Continuous Monitoring During Haemodialysis



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To my beautiful wife Jennifer and our precious daughter Sophia

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Abstract

Intradialytic Hypotension (IDH) is the commonest complication of maintenance haemodialysis and is associated with increased morbidity and mortality. However, there is no standardised definition of IDH, making comparisons between studies difficult.

This observational study with a total of 80 patients and over 600 dialysis sessions showed a poor correlation between symptoms and hypotension. Importantly, patients experienced low blood pressure without symptoms, so continuous intradialytic blood pressure monitoring is required to identify this asymptomatic group. In light of these findings, a revised definition of IDH is suggested. This study also aimed to identify predictors of IDH that could be detected in sufficient time to allow a mitigating intervention.

A novel non-invasive alternative for continuous blood pressure monitoring is introduced which uses intra-fistula pressure data from the sensors sited in the extracorporeal circuit of the dialysis machine. Results show that in the majority of patients, changes in intra-fistula pressure correlate with blood pressure measurements obtained by a standard oscillometric device.

To investigate whether IDH can be predicted, a photoplethysmogram (PPG) waveform was obtained from a pulse oximeter attached to the finger or ear. Continuous PPG monitoring of patients with IDH during dialysis demonstrated that some IDH episodes were predictable using the variation in the PPG baseline with respiration as a surrogate for low blood volume. Additionally, the area under the curve of the PPG waveform can be used as a surrogate for cardiac output and peripheral vascular tone, resulting in a reasonable predictor for potentially critical changes in blood pressure during dialysis.

Individually, the novel metrics described here are limited in their identification of IDH in all patients affected, but in combination they may be used to develop a multi-parameter predictive model. The relative merits of personalised versus population-based models are explored and a conclusion is drawn that personalised multi-parameter data fusion modelling for haemodialysis patients would be an important area for future work.

Ars Longa, Vita Brevis

Hippocrates

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List of Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
AGC	Automatic Gain Control
AUC	Area Under the Curve
AVF	Artero-Venous Fistula
BHS	British Hypertension Society
BP	Blood Pressure
CVP	Central Venous Pressure
DBP	Diastolic Blood Pressure
EBPG	European Best Practice Guidelines
ECG	Electrocardiogram
EQ	Equivital
ESRD	End Stage Renal Disease
FFT	Fast Fourier Transform
GCP	Good Clinical Practice
HD	Haemodialysis
IDH	Intra-Dialytic Hypotension

IDWG	Intra-Dialytic Weight Gain
KDOQI	Kidney Disease Outcomes Quality Initiative
LBNP	Lower Body Negative Pressure
MAE	Mean Absolute Error
MAP	Mean Arterial Pressure
NIBP	Non-Invasive Blood Pressure
OB	Observational Study
PD	Peritoneal Dialysis
PPG	Photoplethysmogram
PTT	Pulse Transit Time
RBV	Relative Blood Volume
RIIV	Respiratory-Induced Intensity Variation
RRT	Renal Replacement Therapy
SBP	Systolic Blood Pressure
SEM	Sensor Electronic Module
SVR	Systemic Vascular Resistance
TMP	Trans-membrane Pressure
UF	Ultrafiltration
UFR	Ultrafiltration Rate

Chapter 1

Introduction

1.1 Background

In the United Kingdom (UK), 794 patients per million population (49,080) receive dialysis or have a kidney transplant (collectively termed Renal Replacement Therapy (RRT)) as treatment for end stage renal disease (ESRD)[1]. Of those receiving RRT, the prevalent number of dialysis-dependent patients continues to rise year-on-year, despite a concurrent increase in the number of prevalent patients with a kidney transplant (Figure 1.1). Figure 1.2 shows the rates of incident RRT patients and reflects not only the increasing incidence of ESRD with age but also the delivery of RRT to a population with ESRD and increasing life expectancy[1][2]. In the UK, haemodialysis (HD) is the modality for 77% of dialysis patients; peritoneal dialysis (PD), the alternative modality, sustains the remainder[1]. Aside from patients choosing HD as their preferred modality, others have defaulted to HD due to social or co-morbid factors that have precluded transplantation or rendered predominantly home-based treatment with PD unfavourable, impractical or impossible.

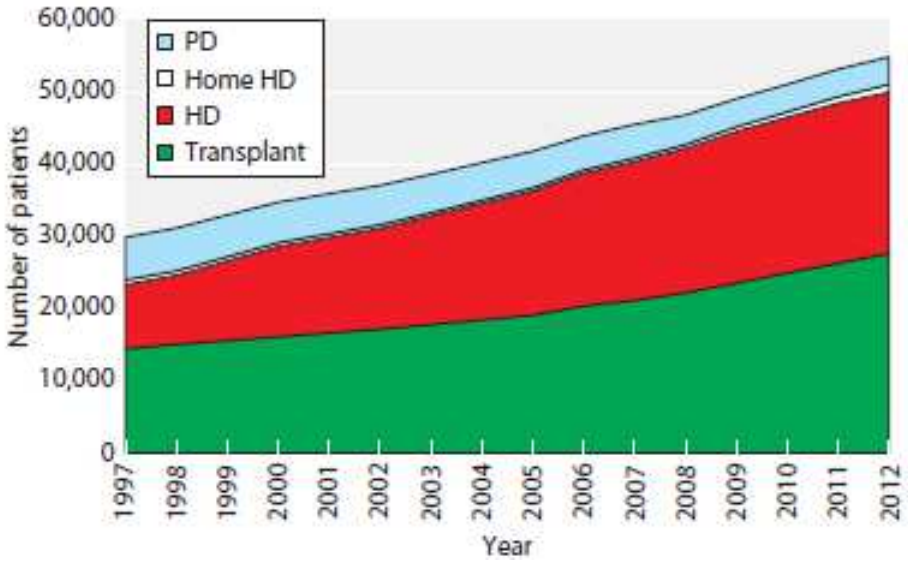


Figure 1.1: Growth in prevalent RRT patients by treatment modality
Taken from: The UK Renal Association, Renal registry report, 2013[1]

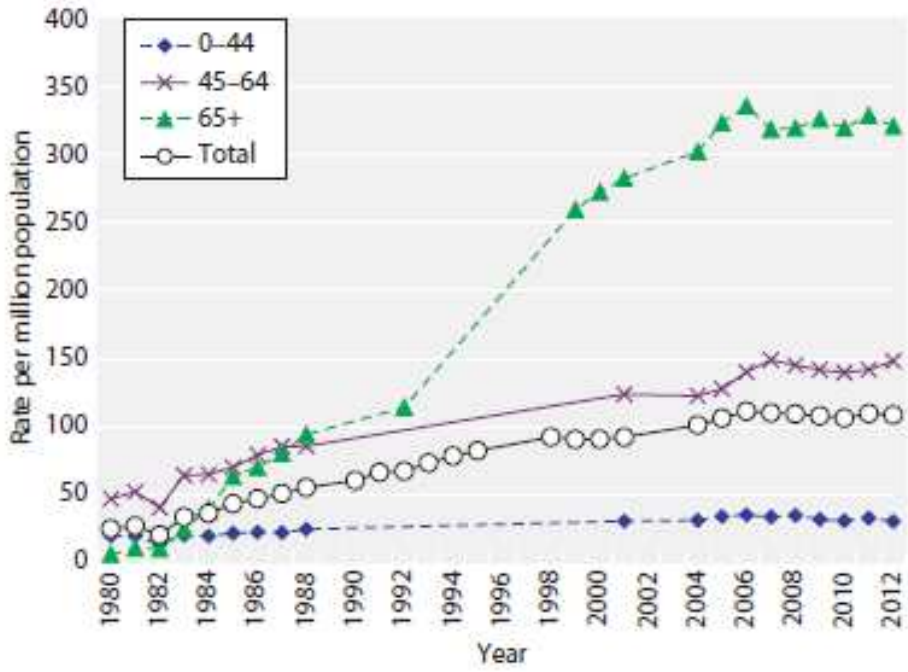


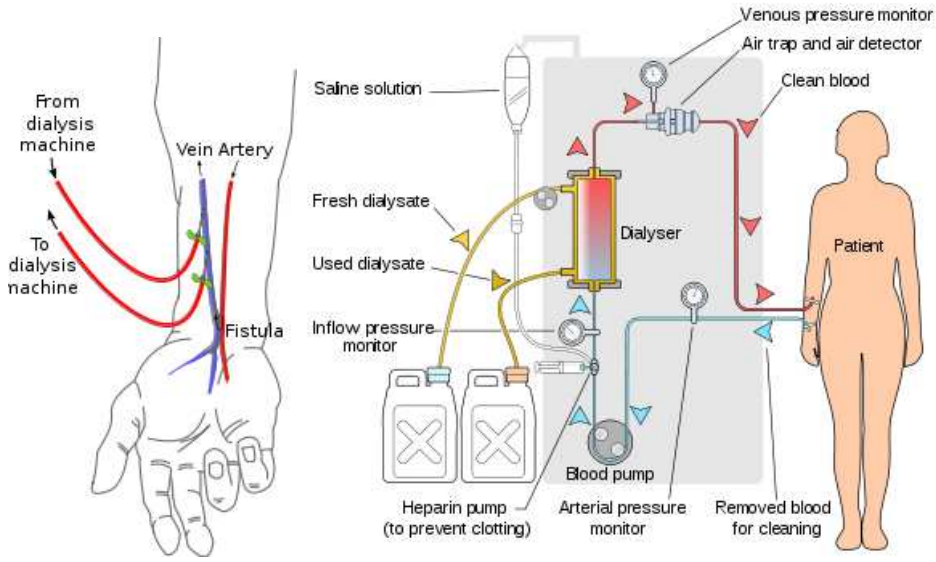
Figure 1.2: RRT incident rates in the UK: 1980-2009
Taken from: The UK Renal Association, Renal registry report, 2013[1]

1.2 Haemodialysis (HD)

Haemodialysis is the process by which blood is removed from the patient,filtered, and replaced. Blood is extracted via a surgically-formed vascular conduit (the Artereovenous Fistula, or 'AVF'), and pumped through a synthetic filter, the dialyser, integrated into the extracorporeal circuit of the dialysis machine (see Figure 1.3 on page 4). Arteriovenous fistulae are the gold standard for vascular access for haemodialysis and are formed from a surgical 'anastamosis' between the venous system and the radial or brachial artery in the distal or proximal forearm, respectively. The anastomosis allows arterial blood to bypass the capillary bed and pass directly into the venous system. The increased venous pressure and flow promote thickening or 'arterialisation' of the vascular wall which results in fistula 'maturation' suitable for needling after about 6 to 8 weeks. An AVF blood flow around 1000 to 1500 millilitres per minute ensures that blood can be extracted from the fistula, filtered, and returned downstream, without significant mixing ('recirculatation') within the fistula of non-dialysed and dialysed blood. Functioning as an interface between the patient's extracorporeal blood and the dialysis fluid (dialysate), the dialyser permits diffusion and ultrafiltration (UF).

1.2.1 Diffusion

The dialyser regulates blood biochemistry using a semi-permeable synthetic membrane through which solutes can move down their respective concentration gradients by diffusion. Twelve hours of treatment per week (four hours thrice-weekly) is typically the minimum time (t) required to achieve the therapeutic target of $\frac{K_{urea}t}{V} \geq 1.3$, where ($K_{urea}$) is the clearance of urea from the blood, normalised by the patient's body water volume (V). Urea is a product of protein breakdown and is used as a surrogate for a multitude of waste products of metabolism excreted in urine. A clearance of urea below the $\frac{Kt}{V}$ target of 1.3 is associated with increased morbidity and mortality[3][4].



(a) Arterio-Venous Fistula (b) Schematic Dialysis Circuit

Figure 1.3: An Arterio-venous Fistula and a schematic haemodialysis circuit
Taken from:http://www.thefullwiki.org/Hemodialysis

The vascular anatomy of a radial fistula is shown in (a). The outflow ('arterial') needle is inserted distal to the inflow ('venous') needle to prevent recirculation of filtered blood. A typical set up of a dialysis machine is shown in (b). The blood pump generates a negative pressure within the arterial line (measured by the arterial pressure monitor) to remove blood from the patient at a prescribed rate. The anticoagulant Heparin is continuously infused to prevent blood clotting in the dialyser. Blood passes in an opposing direction to the dialysate solution within the dialyser. The venous line is checked for air before filtered blood is returned to the patient. The blood pump is suspended by alarms which are activated either by line pressure sensors, or by the entrained air detector.

1.2.2 Ultrafiltration

A hydrostatic pressure gradient across the dialyser membrane, the Transmembrane Pressure (TMP), shifts extracellular fluid from the blood into the dialysate. The TMP is proportional to the pre-programmed ultrafiltration rate (UFR). (mls/min), which is determined by the volume of fluid to be removed (mls) and the prescribed duration of treatment (mins).

1.2.2.1 Dry weight

Ultrafiltration restores the patient to their clinically-determined 'dry weight' by removing excess sodium and water from dietary gains in the interdialytic period. Dry weight is currently defined as the lowest weight a patient can tolerate without the development of symptoms or hypotension[5][6]. Dry weight is set below what

is usually considered a 'normal' extracellular volume for the healthy adult to allow for ongoing refilling of the extracellular space (detailed in Section 1.3.4), which may continue for some hours following cessation of dialysis. In practice, dry weight determination is an inexact science and often estimated clinically on a trial-and-error basis. Dry weight may vary with changes in nutritional status so should be reassessed regularly to avoid under-ultrafiltration of patients whose dry weight has been overestimated, and over-ultrafiltration of patients whose dry weight has been underestimated[7]. During a session of fixed duration (typically four hours), large interdialytic fluid gains will require a proportionally greater rate of UF to achieve dry weight. High UF rates can precipitate symptoms or signs of hypotension, discussed later, necessitating a temporary suspension in UF or termination of the dialysis session. If UF is interrupted, dry weight may not be achieved during the allocated time and a vicious-circle is established for the following session – hence why meticulous attention to fluid balance by both patient and clinical staff is considered of prime importance to patient well-being.

1.3 Physiological response to hypovolaemia

Tissue perfusion with oxygen and nutrients is dependent on an adequate blood pressure (BP) to overcome the opposing forces to blood flow, such as gravity and the variable resistance of the vasculature supplying the tissue bed ('afterload'). However, blood pressure is also *dependent* on vascular resistance, as it is the product of cardiac output and systemic vascular resistance (the sum total of vascular resistance of all tissue beds). The interdependence of cardiac output, vascular resistance and blood pressure is outlined below.

1.3.1 Cardiac output

Cardiac output is defined as the product of heart rate (chronotropy) and stroke volume, the latter determined by the volume of blood returned to the heart from the venous system ('preload') and the contractility (inotropy) of the heart muscle. Figure 1.4 demonstrates the interrelationship between cardiac output and venous return, and the effect of interdependent changes in systemic vascular resistance

(SVR), central venous capacitance, and blood volume. Figure 1.4 shows that a reduction in blood volume (e.g. during ultrafiltration on HD) would result in a shift in the venous return curve to the left and a reduced cardiac output (and blood pressure) at equipoise. However, cardiac output could be restored by an upwards shift in the cardiac output curve, either by an increase in heart rate or an increase in contractility. In healthy adults, the regulation of cardiac output and vascular tone is tightly controlled by the 'Baroreflex'.

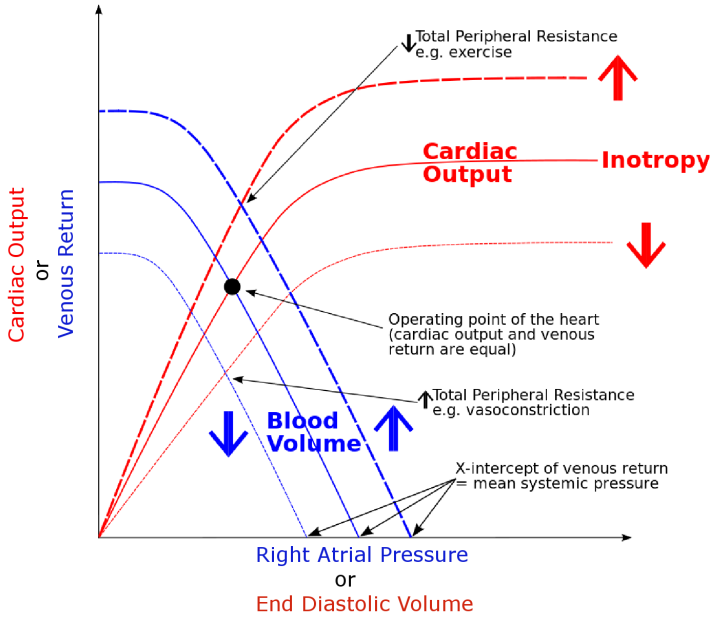


Figure 1.4: The relationship between Cardiac Output and Venous return

The operating point is defined as the equipoise at which cardiac output matches venous return. This operating point may be shifted primarily due to changes in cardiac output (eg. heart rate or contractility/inotropy) or primarily due to changes in venous return, governed by changes in peripheral vascular (arteriolar) resistance, changes in the capacitance of the central venous system, or changes in blood volume. The pressure within the arterial and venous systems equilibriates at cardiac arrest and is dependent on blood volume - a theoretical value known as the mean systemic pressure. Haemodialysis patients with an AVF will have an operating point similar to that of patients with a low systemic vascular resistance e.g. during exercise in the figure above. A relatively rapid reduction in cardiac output (indicated by the gradient of the upper dashed red line) results from a given reduction in blood volume compared with the solid red curve associated with a normal operating point (solid black dot).
Figure produced and released into the public domain without copyright by Huckfinne, 2010.
Sourced from: http://en.wikipedia.org/wiki/Frank-Starling_law_of_the_heart

Table 1.1: The Major Cardiovascular Reflexes

Reflex	Receptors	Afferent limb	Efferent limb
Baroreflex	Stretch receptors in the vessel wall of the aortic arch and carotid sinus	Fibres in glossopharyngeal nerve to medulla	Autonomically mediated control of arterial Bp via changes in cardiac output and systemic resistance
Bainbridge reflex	Stretch receptors in junction of vena cava and right atrium, and at junction of pulmonary vein and left atrium	Fibres in vagus nerve to medulla	Inhibition of vagal outflow and augmentation of sympathetic outflow to sinoatrial node, causing tachycardia
Bezold-Jarisch reflex	Mechanical and chemosensitive receptors in ventricular walls	Nonmyelinated vagal C-fibres to medulla	Inhibition of sympathetic outflow causing bradycardia, vasodilation, and hypotension

1.3.1.1 The Baroreflex

The compensatory 'Baroreflex' is one of the three major cardiovascular reflexes (see Table 1.1) and is considered to be the primary homeostatic mechanism that maintains arterial blood pressure. The baroreflex is initiated by an offloading of pressure-sensitive baroreceptors, located adjacent to the arch of the aorta and in the carotid sinus. This results in stimulation of the sympathetic nervous system which increases heart rate and, indirectly, stroke volume by decreasing central venous capacitance and increasing venous return.

1.3.1.2 The Bainbridge reflex

Contrary to the expected rise in heart rate with ultrafiltration, some patients do not exhibit a rise in heart rate from baseline during dialysis. Moreover, studies suggest that removing fluid from *hypervolaemic* patients results in an initial *decline* in heart rate, followed later by a moderate increase in heart rate during the transition from normovolaemia to effective hypovolaemia [8][9]. The presumed

mechanism of the initial tachycardia associated with *increased* central blood volume is the Bainbridge reflex[10]. The Bainbridge reflex was discovered in dogs in 1915 by the British physiologist Francis A. Bainbridge, but its presence in humans has also been established[11]. The Bainbridge reflex causes an increase in heart rate when central blood volume is increased beyond an optimal threshold. In this respect it acts antagonistically with the aforementioned baroreceptor reflex – i.e. when blood volume is increased beyond this optimal threshold the Bainbridge reflex predominates and when blood volume decreases below this optimal threshold the baroreflex predominates. For example, during ultrafiltration of the fluid-overloaded patient, a baseline tachycardia caused by the Bainbridge reflex may normalise as ultrafiltration progresses, and then reappear when hypovolaemia ensues and the baroreflex predominates.

1.3.2 Systemic vascular resistance

In addition to an increased cardiac output, activation of the sympathetic nervous system in response to baroreceptor offloading results in cutaneous and splancnic vasoconstriction. This response mitigates a fall in systemic blood pressure and perfusion of critical tissues (for example, the heart and brain) by selectively increasing the vascular resistance (and decreasing the perfusion) of other tissues, namely the skin and gut[12]. The vasculature of the skin also has a thermoregulatory function; heat can be lost to the environment by the vasodilation of cutaneous vessels and can be conserved by vasconstriction. This duality of function is an important consideration in scenarios where the stimulus to vasoconstrict skin vessels in response to a falling blood volume is in direct conflict with the stimulus to lower core body temperature by vasodilation. It is possible that such a conflict occurs during haemodialysis – this postulated mechanism for hypotension will be explored in detail later.

1.3.3 Central venous capacitance

In the resting state, up to 75% of the systemic blood volume is stored on the venous side of the circulation in low-pressure central capacitance vessels. As a result, sympathetically mediated reflex alterations in venous vasomotor tone and

passive elastic recoil of veins provide a rapidly acting mechanism for the compensatory redistribution of blood – essential for counteracting the gravitational pooling of blood in the lower limbs during standing[13]. A related haemodynamic response is the mobilisation of sequestered blood from capacitance vessels of the gut to the central venous circulation by a process known as the DeJager-Krogh phenomenon (see Figure 1.5). This process is thought to be important in humans in the context of cardiovascular stress due to exercise or high ambient temperatures, but is also likely to be a compensatory response to blood volume reduction during haemodialysis[14].

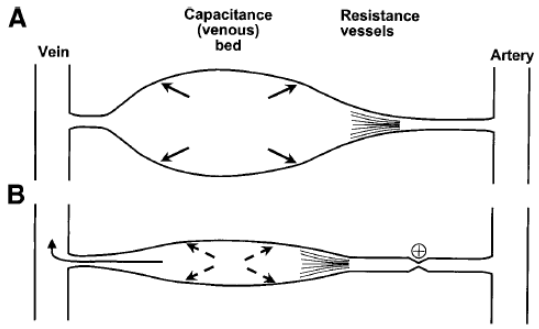


Figure 1.5: The DeJager-Krogh Phenomenon

'A' represents the sequestration of blood within the capacitance vessels of the gut under a normovolaemic state. 'B' represents arteriolar vasconstriction in response to hypovolaemia, the collapse of down-stream capacitance vessels (broken arrows), and the release of sequestered blood to the central venous system
(Adapted from Daugirdas,JT; Pathophysiology of Dialysis Hypotension: An Update, 2001[14]).

If the rate of fluid removed from the intravascular compartment by ultrafiltration approximates the rate of fluid 'refilling' from the expanded interstitium (or if compensatory mechanisms are adequate in the case where removal of fluid exceeds refilling), high volumes of ultrafiltrate, which may exceed the total circulating plasma volume, can be removed in a typical 4-hour session without haemodynamic compromise.

1.3.4 Intravascular refilling during ultrafiltration

A reduction in blood volume by ultrafiltration causes a fall in capillary hydrostatic pressure and a rise in oncotic pressure, the latter exerted by large molecules within

the vasculature. This combination promotes the net transfer of fluid back into the intravascular space to facilitate the restoration of blood volume. The rate of refilling is governed by Starling Forces, described in the equation below:

$$F = L_p S(P_c - P_{int}) - \sigma(\pi_p - \pi_{int}) \tag{1.1}$$

where F is the resultant force, L_p is hydraulic conductivity, S is capillary surface, P_c is capillary hydrostatic pressure, P_{int} is interstitial hydrostatic pressure, σ is the capillary permeability coefficient, π_p is the plasma oncotic pressure, and π_{int} is the interstitial oncotic pressure.

In the hypervolaemic patient, initial reduction in blood volume with ultrafiltration is likely to be minimal, as high interstitial pressures in the expanded extracellular space correspond to high rates of intravascular refilling[15]. As ultrafiltration continues, interstitial pressure falls, and the decline in blood volume appears exponential (see A in Figure 1.6). Approaching normovolaemia, the influence of oncotic pressure increases markedly. This accounts for the flattening out of the curve 'A' as the rate of refilling increases with respect to the rate of ultrafiltration. When refilling ceases, the decline in blood volume becomes linear, as demonstrated by a switch from 'two-pool' to 'single pool' characteristics in a study by Mitra *et al* (see 'B' in Figure 1.6)[16].

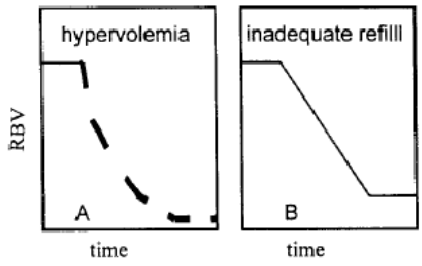


Figure 1.6: Characteristics of relative blood volume decline during UF

'**A**' represents the exponential relative blood volume (RBV) decline in a 'Two Pool' model. '**B**' represents the linear RBV decline in a 'Single Pool' model. Adapted from Mitra, S. et al; Linear decay of relative blood volume during ultrafiltration predicts haemodynamic instability, 2002[16]

1.4 Intradialytic decompensation

If the volume of fluid removed by ultrafiltration during haemodialysis exceeds the patient's capacity for physiological compensation (usually above UF rates of 0.35ml/kg/min)[17], the blood pressure will fall, often precipitously, and/or the patient may experience unpleasant symptoms associated with tissue hypoperfusion. Common symptoms are reported to include muscle cramps, nausea, lightheadedness or temporary loss of consciousness. This complication of haemodialysis is known as Intradialytic Hypotension (IDH). The European Dialysis & Transplant Association (EDTA) and Kidney Disease Outcomes Quality Initiative (K-DOQI) have agreed the following pragmatic definition of IDH: 'a fall in systolic pressure by >20mmHg or mean arterial blood pressure by >10mmHg along with symptoms requiring intervention'[18][19], but this definition is not evidence-based and does not appear to have gained wide acceptance. The numerous previously unstandardised definitions of IDH account in part for the wide range of reported incidence (15 – 50% of dialysis sessions) and as a result, the difficulty comparing results from disparate studies has been subject to much debate[20]. Despite this, recognition that IDH is an independent risk factor for reduced survival[21] has led to recommendations to audit IDH rates, monitor those at risk, and implement reduction strategies[18][19].

1.4.1 Pathophysiology of IDH

All of the implicated pathophysiological mechanisms described in this section lead to at least one of two final common pathways: 1) A critical decline in cardiac output and/or 2) An inappropriately low systemic resistance for the degree of blood volume reduction. However, pathophysiological causes underlying IDH are multifactorial and demonstrate complex interrelationships, the relative importance of which vary between individual patients.

Impaired plasma refilling

A study by de Vries *et al* showed that blood volume reduction relative to UF volume was higher in hypotensive prone patients, implicating impaired refilling in

this group[22]. Referring to the overview of plasma refilling presented in Section 1.3.4, it can be seen that either an increased capillary hydrostatic pressure or a decreased plasma oncotic pressure would result in impaired refilling from the interstitium to the capillary vasculature. An increase in capillary hydrostatic pressure may be due to high venous pressures from poor cardiac function, or from a failure of pre-capillary arteriolar vasoconstriction due to autonomic dysfunction and reduction in the pre-capillary to post-capillary resistance ratio. In addition to a low serum albumin concentration, plasma oncotic pressure is reduced by a rapid efflux of blood urea during dialysis. This increases the ratio of intracellular to extracellular urea, thereby lowering the osmotic gradient that determines fluid transfer from cells to the extracellular compartment. This is discussed later in this section.

Decreased venous compliance

The DeJager phenomenon, shown in Figure 1.5, is thought to play a significant part in maintaining central venous pressure (preload) during blood volume reduction in humans. Hypertensive dialysis patients have been shown to have decreased venous compliance which may reduce this 'vascular reactivity' to blood volume reduction. Decreased venous compliance can lead to steep decreases in central venous pressure for a relatively small decline in blood volume[23][24].

Autonomic neuropathy and dysfunction

Dysfunction of the autonomic nervous system is a recognised complication of uraemia and is thought to be common in patients with renal failure on haemodialysis [25]. Reduced baroreflex sensitivity — i.e. the blunted reflex adjustments in ECG R-R interval in response to an evoked change in blood pressure — is a clinical marker of global autonomic dysfunction and has been linked with age-matched patients prone to intradialytic hypotension[26]. A study of 10 patients by Lilley *et al* showed that hypotension-prone patients mounted less of a compensatory tachycardic response to the vasodilator amyl nitrate than hypotension-resistant patients. However, the vasocontricting response to submersion of a hand in cold water was identical between the two groups, leading the investigators to conclude

that the problem was likely to be found in the afferent limb of the baroreflex arc, rather than the apparently intact efferent limb[27]. This mechanism is supported by others[28], including work investigating the causes of circulatory instability and orthostatic hypotension in the elderly (it is worth recalling that the incidence of HD is increasing among the population aged >65yrs). Gribbin *et al* were the first investigators to examine the relationship between age and the baroreceptor control of heart rate. The authors found that ageing was associated with a decreased Baroreflex sensitivity[29]. Postulated mechanisms included: 1) Arterial stiffening within the segments containing baroreceptors; 2) altered afferent signals from baroreceptors; 3) altered central integration of barosensory information; and 4) impaired cardiac vagal function. In an investigation using similar methods to Lilley *et al* [27], Cleroux and colleagues excluded age-related changes to the efferent limb because the BP, HR and SVR responses to a cold pressor test were the same in young, middle-aged, and elderly subjects[30]. In summary, reduced baroreflex sensitivity and associated autonomic dysfunction appears to be predominantly a defect of the afferent limb of the baroreflex arc or the afferent-efferent coupling. The extent to which this can be attributed to age or uraemia in haemodialysis patients with IDH remains to be elucidated.

Decreased myocardial contractility and myocardial stunning

Early work by Ritz *et al* showed that decreased left ventricular compliance associated with hypertensive cardiomyopathy is a contributory factor to IDH [31]. The dialysate concentrations of electrolytes essential for myocardial function have also been shown to affect myocardial contractility. These electrolytes, particularly calcium and magnesium, are discussed in more detail later. It is well established that haemodialysis can induce global and segmental myocardial ischaemia 'myocardial stunning' due to a reduction in the microcirculatory flow of blood to the heart. Whether the association with hypotension is a cause or consequence of this phenomenon has yet to be elucidated[32][33]; however, work by Burton *et al* reports that repetitive haemodialysis-induced myocardial stunning is also associated with an impaired haemodynamic response to ultrafiltration during dialysis[34].

Anaemia

A direct relationship between haematocrit (i.e. blood viscosity) and vascular resistance exists[35]. It is conceivable that haemodialysis patients, who are prone to anaemia due to insufficient erythropoeitin production and inhibitory effects of uraemia on bone marrow turnover, may be at risk of hypotension due to a low systemic vascular resistance, despite the expected increase in cardiac output. Sherman *et al* reported that patients with a low hematocrit appeared to be inordinately susceptible to IDH and the problem could be ameliorated by an elective 2-unit blood transfusion. Exactly why increasing the haematocrit reduces the risk of IDH has not be clarified, but appears to be independent of blood volume expansion. A postulated mechanism is that patients with low haematocrit have a relatively high plasma volume, so the concentration of plasma protein is lower at any given volume of ultrafiltration than a patient with normal haematocrit. The relatively low plasma protein concentration and, therefore, plasma oncotic pressure, may result in a reduced plasma refilling rate and increased propensity to hypotension with ultrafiltration[36].

Osmolytes: Sodium and Urea

It is well established that isolated ultrafiltration causes less haemodynamic instability for a given volume of fluid removed than standard haemodialysis, in which ultrafiltration and the additional depuration of sodium by diffusion are combined[37][38][39]. This series of observations suggests that diffusive solute transport plays a role in the pathogenesis of IDH. Sodium and urea are the major determinants of plasma osmolality in normoglycaemic dialysis patients. One mechanism leading to IDH during standard dialysis involves the diffusion of plasma sodium down a concentration gradient and into the dialysate. The accompanying shift in fluid from the relatively hypotonic extracellular compartment to the relatively hypertonic intracellular compartment effectively reduces blood volume. It is possible that these fluid shifts are augmented by the urea concentration gradient which is established between the extracellular and intracellular compartments during the first hour of high-efficiency haemodialysis when the rate of removal of urea from the blood is maximal. Falls *et al* and Oh *et al* indicate

that the reduction in plasma osmolality associated with haemodialysis results in a substantial fluid shift approximating 1 to 1.5 litres from the extracellular to the intracellular compartment, exacerbating the reduction in intravascular volume with ultrafiltration[40][41].

Independent of the association with blood volume, plasma sodium and osmolality have been reported to directly affect vascular tone. Increased plasma osmolality is associated with a direct vasoconstrictor effect on the systemic vasculature[42]. Conversely, Schultze *et al* found that low sodium dialysis elevated the plasma concentration of prostaglandin E2, which is known to have vasodilatory properties[43].

Dialysate Calcium

Calcium ions are important in the contractile processes of both vascular smooth muscle cells and cardiac myocytes. Higher dialysate calcium concentrations result in increased stroke volume, cardiac output, and blood pressure in stable patients[44][45], as well as increased haemodynamic stability in cardiac compromised patients when dialysate concentrations were increased from 1.25mmol/l to 1.75mmol/l[46]. The mechanism is presumed to be predominantly related to improved myocardial contractility, but increased vascular reactivity to a vasoconstricting stimulus may play a minor role.

Dialysate Magnesium

Kyriazis *et al* investigated the haemodynamic effects of varying both dialysate calcium and magnesium in a random cross-over study of 8 patients. They found significantly higher rates of IDH, due to impaired myocardial contractility, when the combination of 0.25 mmol/L magnesium and 1.25mmol/L calcium was used in the dialysate. However, they demonstrated that increasing the magnesium to 0.75 mmol/L ameliorated this effect, suggesting that dialysate magnesium concentration may be important with regard to dialysis tolerance[47]. Pakfetrat *et al* support this finding in a case-control study of 58 patients. The authors found that serum magnesium levels taken at baseline showed no significant difference between the IDH and non-IDH group, but magnesium concentration was signif-

icantly lower in the IDH group after 2 hours of treatment and on completion of dialysis[48].

Dialysate Potassium

Dolson *et al* investigated the relationship between three dialysate potassium concentrations (1.0, 2.0 and 3.0 mmol/L) and blood pressure in 11 patients. They found that intradialytic blood pressure was determined by fluid removal rather than dialysate potassium concentration, but a significant 'rebound' hypertension occurred post-dialysis with the 1.0 and 2.0 mmol/L potassium dialysates. They attribute this effect to a systemic arteriolar vasoconstriction associated with a rapid reduction in plasma potassium[49]. However, in a larger cross-over study of 24 patients over 211 sessions using continuous non-invasive haemodynamic monitoring, Gabutti *et al* showed that a lower potassium dialysate was associated with significantly more episodes of IDH than a higher potassium dialysate (72% vs. 17%, $p<0.01$), which was likely to be mediated by an intradialytic decrease in systemic vascular resistance[50].

1.4.2 Patterns of intradialytic hypotension

While the underlying causes of IDH are multifactorial, there appear to be three distinct patterns of decompensation during HD[51]: Type 1 occurs when the rate of UF exceeds the rate of refilling and capacity for compensation — i.e. heart rate, heart contractility, and systemic vascular resistance are appropriately increased at the time of decompensation. Type 2 and Type 3 involve a sudden and unexpected loss of SVR towards the end of dialysis (mean time of occurrence 178 ±20 mins). Type 2 is characterised by an unchanged or moderately increased heart rate and is likely to represent a sudden breakdown of SVR, possibly due to vasodilation associated with cumulative heat stress and attempts to thermoregulate during dialysis[52].

Type 3 is characterised by a combination of vasodilation and bradycardia at the point of haemodynamic collapse. The cause for this is unclear, but it may represent the Bezold-Jarish reflex[53] — see Table 1.1 on page 7. This reflex is in-

titated when an under-filled ventricle causes cardiac mechanoreceptor activation, which leads to a parasympathetic preponderance due to the sudden withdrawal of sympathetic tone[51][54]. Studies on conscious mammals suggest that the combination of bradycardia and vasodilation is an expected physiological response when hypovolaemia reaches a critical level, usually >30% reduction in circulating blood volume[55]. It is unclear from the literature whether differentiating the pattern of IDH into one of these three classes is important prognostically.

1.5 Existing techniques to manage IDH

A description of commonly employed techniques for reducing IDH is presented in Table 1.2 on page 18. Relative blood volume monitoring using a Critline^{TM} is expanded further in the next section because of its role over the last decade as an input to novel biofeedback systems and because of its use as a continuous monitoring device later in this thesis.

1.5.1 Blood volume monitoring using a Critline^{TM}

During dialysis the ultrafiltration rate at which fluid is removed from the circulation is invariably greater than the rate of refilling from the interstitium to the intravascular space. This lag results in a reduction in effective blood volume. In recognition of the fact that hypovolaemia is the primary cause of IDH, importance has been placed on monitoring the blood volume continuously as dialysis progresses. The Critline^{TM} monitor (Hema Metrics, Massachusetts, USA) is reported to be advantageous in this regard because it uses real-time quantification of the patient's haematocrit concentration, as described in detail in Section 2, as a surrogate for changes in blood volume[1]. A key assumption of this method for relative blood volume (RBV) monitoring is that the measured haematocrit concentration is representative of the entire circulation. Recent work casts some doubt on this. Mitra *et al* suggest that during dialysis relatively haemodilute blood is translocated from the microcirculation to the central circulation. This

[1]Direct measurement of blood volume is feasible using dilution of radioactively labelled blood elements (such as ^{131}I albumin or ^{51}Cr red blood cells), but it involves serial blood tests and radiation, and is therefore impractical for the repetitive assessment of blood volume.

Table 1.2: Common strategies to mitigate intradialytic symptoms and IDH

Strategy	Mechanism	Comments
Dialysate cooling	Offset intradialytic warming or active cooling to increase vascular tone/SVR.	Inexpensive. May improve baroreflex sensitivity[26]. Systematic review concludes benefit, but patients experience discomfort at temperatures <35 °C[56].
UF profiling	Tailors maximal UF to early phase of dialysis when interstitial pressure is highest.	Of benefit in reducing IDH when combined with sodium profiling[57]. High initial UF rates may precipitate IDH in those with poor refilling or cardiovascular disease.
Sodium Profiling	Supports UF using a hypertonic dialysate to increase intravascular osmotic pressure.	Of benefit in reducing IDH[58][59],and used in biofeedback systems[60][61], but may cause high intradialytic weight gains and hypertension due to sodium loading and associated thirst[62][63].
Blood volume monitoring using a Critline^{TM}	Provides a continuous visual/numerical assessment of changes in haematocrit concentration (as a surrogate for relative blood volume).	Non-invasive. Informs changes in UF rate[64]. May reduce symptoms during HD[65]. Individual thresholds may be defined to provide input to a biofeedback loop[66][67][68]. However, there appears to be substantial intra- and interpatient variability. Relative blood volume changes may underestimate total blood volume changes in HD[69].

would result in the observed RBV change underestimating the actual total blood volume change during haemodialysis[69][70].

The application of the Critline^{TM} for prediction of IDH falls into two broad categories: The first includes studies investigating the occurrence of IDH with absolute reductions in RBV. Steuer *et al* showed that many patients demonstrated individual thresholds of RBV reduction at which hypotension occurs, coining the phase 'Crash-Crit' to denote these individualized parameters[71]. The second category includes studies investigating the gradient or trajectory of the RBV curve as a marker of refilling status. Mitra *et al* reported that a switch from an exponential to a linear decrease in blood volume, indicating a cessation of plasma refilling, was a better predictor of IDH than absolute blood volume (See Figure 1.6 on page 10). In a large multi-centre prospective study of 123 patients, Andrulli *et al* also found that the irregularity of the RBV curve was more predic-

tive of IDH than absolute values of RBV, which did not differ significantly from non-hypotensive patients[72].

1.6 Biofeedback/intelligent decision systems for HD

The development of online relative blood volume monitoring has been the catalyst for a series of studies investigating the merits of biofeedback strategies on the incidence of IDH or symptoms. Inputs to these systems, usually RBV (see Table 1.2 on page 18) and/or BP[73][74][75], link to actuators that alter the UF rate, the sodium concentration (conductivity) of the dialysate, or deliver a bolus of saline. These biofeedback technologies require a pre-specified threshold to be determined by regular clinical assessment and estimation of dry weight for each patient. Depending on whether RBV or BP serves as the input, the pre-specified threshold is set at the predicted level of BV reduction at which IDH occurs for that particular patient, or a maximum allowable rate of BP decline, respectively. As such, these thresholds are usually defined following a learning phase of several weeks. Existing biofeedback systems appear to be limited by their univariate RBV or BP inputs. For example, the ROC[1] curve for the RBV slope alone has a predictive value of just 0.55 for symptomatic IDH[76]. Despite this, some authors have reported benefits in reducing IDH rates in hypotension-prone[61][66] and non-hypotension prone subgroups[77]. Biofeedback systems using multivariate inputs to define the point at which intervention should occur have not been described in the literature.

[1] A receiver operating characteristic (ROC) curve is a graphical plot of the sensitivity versus false positive rate (1 – specificity) for a binary classifier system as its discrimination threshold is varied.

1.7 Physiological monitoring for patient deterioration

It is routine to measure a patient's weight and BP at the beginning and end of dialysis. In the short term, these measurements serve to ensure that the patient is not at risk of collapse due to hypotension prior to their journey home, and in the longer term serves to inform decisions made by clinical staff about dry weight adjustment and amendment of the dialysis prescription. If there is clinical concern during dialysis, nursing staff may choose to undertake additional monitoring of BP, pulse rate, respiratory rate, peripheral oxygen saturation (S_pO_2), and tympanic temperature. However, as no structured protocol for routine monitoring during dialysis currently exists, these data are collected on an intermittent, usually ad hoc, basis and analysed separately against reference ranges derived from the general medical population with somewhat arbitrary decisions being taken on when and how to intervene.

1.7.1 Track and Trigger Systems

Physiological track and trigger systems rely on periodic observation of selected basic physiological signs ('tracking') with predetermined calling or response criteria ('trigger') for requesting the attendance of staff who have specific competencies in the management of acute illness and/or critical care. Hospital inpatient track and trigger systems have become commonplace in recent years, partly in response to a series of confidential reports and enquiries highlighting the deficiencies in the care of the acutely unwell. A key finding of the 2005 National Confidential Enquiry into Patient Outcome and Death[78] was that in many cases of suboptimal care, the cause was either a failure to recognise patient deterioration or a failure to appreciate the importance of the clinical findings in cases where patient deterioration *was* recognised. Despite obvious differences between acutely unwell hospital inpatients and otherwise-well outpatient haemodialysis patients, there are clearly some parallels in the need to avoid, or recognise and respond quickly to, an acute deterioration. With high intradialytic event rates and an increasingly elderly dialysis population accruing multiple co-morbidities, it is conceivable

that such a system is required to assist the monitoring of haemodialysis patients during their treatments.

Applicability of Track and Trigger Systems to HD

There are several major difficulties that potentially preclude the implementation of existing track and trigger systems to monitor haemodialysis outpatients. Firstly, this approach assumes that haemodialysis patients share the same baseline physiological ranges as the general medical population. The effect on blood pressure, pulse, body temperature, and potentially oxygen saturation, of a repeating 2-3 day cycle of intradialytic fluid acclumulation followed by a 4-hour ultrafiltration to sub-normovolaemia indicates why this is unlikely. By design, existing track and trigger systems (outlined in Table 1.3 on page 22) do not take into account the dynamic physiological changes associated with an expected compensatory response to ultrafiltration. Lastly, and an extension of the previous point, is the underlying assumption that staff using the track and trigger system will be able to recognise a deterioration. The heterogeneity of physiological values observed in maintenence dialysis patients undergoing uneventful haemodialysis brings into question what range of physiological parameters would be considered 'normal' or 'expected' and what values would be indicative of imminent deterioration or decompensation such as the intradialytic events described in Section 1.4.2.

Table 1.3: Existing Track and Trigger Systems

System	Comments	Advantages	Disadvantages
Single Parameter	Periodic observation of selected vital signs that are compared with a simple set of criteria with predefined thresholds. A response algorithm is activated when any criterion is met. Not widely adopted in the UK	Simple to use. Better reproducibility.	Does not allow a patient's progress to be tracked. Does not allow a graded response strategy. Current evidence suggests that system has low sensitivity, low positive predictive value, but high specificity.
Multi-parameter	Response algorithm requires more than one criterion to be met, or differs according to the number of criteria met. Widely used in UK hospitals.	Allows monitoring of clinical progress and for a graded response strategy.	May lack reproducibility and reliability because systems are prone to human calculation errors. These systems have high sensitivity but low specificity when one abnormal observation is present, but sensitivity reduces and specificity increases as the number of abnormal variables increase.
Aggregate-Scoring	Weighted scores are assigned to physiological values and compared with predefined trigger thresholds. Widely used in UK hospitals	Allows monitoring of clinical progress and for a graded response strategy.	May lack reproducibility and reliability because systems are prone to human calculation errors. A range of sensitivities and specificities depending on the cut-off score used, but it is possible to achieve high sensitivity and specificity at defined cut-off point.

(Adapted from National Institute of Clinical Excellence. Acutely ill patients in hospital. Recognition of and response to acute illness in adults in hospital (2007)[79])

1.8 Continuous monitoring during HD

Continuous physiological monitoring might allow the early identification of trends preceding adverse events and is commonplace in high-dependency settings. It is intuitive that a similar approach may be beneficial for monitoring patients during haemodialysis. A review of existing research utilising continuous physiological monitoring of patients during haemodialysis is presented in Table 1.4. The requirement of additional technical equipment, the unfamiliarity of some staff with the use of additional monitoring, and the uncertainty around how compensatory physiology can be distinguished from a deterioration predictive of IDH (as discussed in Section 1.7.1), currently limits the utility of continuous monitoring during outpatient haemodialysis. In addition, any potential clinical benefit versus patient discomfort from the additional sensors/electrodes is clearly marginal in a subgroup of 'stable' dialysis patients. For those less stable, such an intervention may be justifiable, indeed preferable.

A prolific area of published research using continuous monitoring involves the quantification of autonomic activity using variables derived from spectral analysis of R-R intervals in the ECG[1]. Recent work analysing the waveform of the photoplethysmogram (PPG), outlined in Table 1.4, is of huge interest given the possibility that autonomic status, an assessment of change in blood volume during HD, and surrogates for changes in vascular tone can be derived from the same non-invasive source.

[1]Spectral analysis takes a signal from the time domain (time series) and, using a transformation algorithm (usually a Fourier transform), displays the magnitude/'power' of frequencies from which the signal is composed. This allows the quantification of numerous biologically important frequencies, including those used for estimating autonomic nervous system activity.

Table 1.4: Continuous monitoring on HD: A catalogue of existing research

Sensor/Input	Method
PPG	Spectral analysis of extractable features from the Finger PPG waveform[80]
	Spectral analysis of extractable features from the Ear PPG waveform[9][81]
Oximeter	Statistical analysis of envelope amplitude changes[82]
	Analysis of central venous oxygen (S_cvO_2) changes with blood volume depletion during UF [83]
	Analysis of S_pO_2 variability during dialysis (finger probe) [84][85]
ECG	Analysis of heart rate response to ultrafiltration[9][86]
	Holter monitoring for arrythmias during dialysis[87]
	Spectral analysis of Heart Rate Variability[88][89][90][91][92][93]
	Impedence Cardiography as a surrogate for changes in cardiac output[94][95][96]
Critline^{TM}	Identification of a critical BV threshold[71][97]
	Analysis of RBV curve/slope as an IDH predictor[16][72]
	Correlation of RBV with other cardiovascular parameters (e.g Heart Rate, Vena Cava diameter, BP)[98][99]
	Correlation of RBV with intradialytic symptoms[65]
	Blood volume tracking in biofeedback systems[66][67][68][100][101]
Blood Thermal Monitor (BTM)	Continuous analysis of blood temperature with dialysate temperature regulation[102][103][104][105][106][107] and systematic review in [56]
Finapres/Finometer^{TM}	Beat-to-beat non-invasive BP monitoring and derivation of surrogates of CO, SVR and Baroreflex activity/ sensitivity[26][32][108][109][110]

1.9 Motivation for this research

In an attempt to improve the experience of haemodialysis for patients, my interest in reducing the frequency of intradialytic hypotension developed during my training as a Specialist Registrar in Nephrology. In October 2008, I audited the frequency of IDH in the Oxford Kidney Unit[1] and found this to be higher than IDH rates quoted in the literature (occurring in 47% cf. 20-30% of sessions over one month[111] — see poster in Appendix A on page 171). The results of this audit propagated my interest in dialysis physiology in an attempt to explain the factors leading to high rates of IDH in our unit. Ultimately, this led to the formation of my research question: *Can continuous patient monitoring with the integration of dialysis-machine parameters help identify intradialytic events?*

1.10 Overview of this Thesis

A comprehensive review of the current literature shows that there is no universal agreement on exactly what the term IDH represents or how it is best defined. This has implications for future research because of the difficulties comparing results of studies using non-standardised outcome measures. In order to test the efficacy of monitoring strategies to identify or predict IDH, an important objective of this thesis was to clearly define IDH so that an outcome measure could be established for subsequent analyses.

Chapter 3 starts by investigating the relationship between intradialytic blood pressure and symptoms using data from this large observational study conducted over a year (80 patients participating in a total of 600 dialysis study sessions). Importantly, it is established that many patients experience critically low levels of blood pressure during dialysis but without symptoms. These patients would not have otherwise been identified using the conventional intermittent monitoring strategies, which use symptoms as a prompt for blood pressure measurement and intervention. Using evidence from the literature suggesting that morbidity and

[1] defined as a fall in SBP by >20mmHg to <100mmHg or a symptomatic fall in SBP by >10% of predialysis baseline

mortality was blood pressure related (regardless of symptoms), Chapter 3 argues that patients' blood pressure should be continuously monitored to identify the significant proportion of patients who experience, and may be at increased risk of harm from, asymptomatic hypotension. As a result, an alternative evidence-based IDH definition is suggested and used as the outcome measure for later work. This outcome measure is further described, stratified and compared to outcomes defined by existing guidelines in Chapter 4.

After establishing the importance of continuous blood pressure monitoring, this thesis introduces alternative non-invasive ways in which blood pressure could be tracked continuously during dialysis without the need for additional (invasive) sensors. Chapter 5 introduces a novel mathematical algorithm that uses the information from the sensors incorporated within the external circuit of the dialysis machine. These pressure sensors were originally designed to monitor needle dislodgement or clotting within the blood line, but this chapter describes the incorporation of these pressure data into a bespoke algorithm to monitor pressure changes that occur at the tip of the needles that are sited within a major blood vessel (the arteriovenous fistula), which acts as the interface between the patient and the extracorporeal circuit of the dialysis machine. Results show that in the majority of patients this technique produces a continuous blood pressure trend that correlates with blood pressure measurements obtained using a standard oscillometric device with inflatable brachial cuff. This algorithm is tested in patients with radial and brachial arteriovenous fistulae and reasons for differences in performance of the technique for these two groups are discussed.

While identification of symptomatic and asymptomatic hypotension is clearly beneficial in identifying patients prone to intradialytic hypotension, it is arguably more desirable to be able to accurately predict these events before they occur. An analysis of the literature presented earlier in this chapter shows that the methods used by many studies in pursuit of this elusive goal have been limited by their restriction to the analyses of univariate or bivariate inputs.

The multifactorial pathophysiology of IDH discussed earlier in this chapter in-

dicates that any future predictive model is likely to involve multivariate inputs. The identification of which of the multiple permutations of physiological inputs would provide the optimum predictor of IDH is recognised to be a process of trial and error, but this thesis builds on established physiological principles and clinical experience to determine which physiological parameters are likely to be most informative. Later chapters investigate novel metrics that may be used as early indicators of critical hypovolaemia and/or inappropriate vasodilation, which have already been shown in the introduction to be important determinants of IDH.

For a model to have utility in the prediction of IDH, any alerts generated by the model need to have a high sensitivity, specificity for abnormal physiological patterns that precede overt hypotension, and need to occur in sufficient time to allow a mitigating intervention. The physiological monitoring used to generate timely alerts will need to be real-time or near real time. As dialysis is predominantly an outpatient therapy and therefore constrained to non-invasive monitoring both in terms of practicality, economy and patient acceptability, the focus of this work in a later chapter are on non-invasive methods of continuous real-time monitoring.

Chapter 6 introduces the use of the PPG waveform for the identification of IDH episodes during dialysis. The PPG is obtained from a commonly-used pulse oximeter sensor attached to a finger or an ear. This chapter explores the use of the PPG as a non-invasive way of tracking hypovolaemia, building on earlier work using the pulse oximeter-derived PPG waveform for monitoring of blood loss in patients undergoing surgery. This chapter describes how the mechanical influence of respiration on central venous pressure (and therefore the ear PPG waveform) during hypovolaemia has potential benefits over existing strategies used for cardiovascular status monitoring, especially those using the autonomic nervous system as a surrogate for an adequate physiological compensatory response to hypovolaemia.

Chapter 7 investigates whether the area under the curve of the ear and finger PPG waveform (a proxy for continuous cardiac output and peripheral vascular resistance, respectively) could identify 'increased risk' periods during dialysis

when a hypotensive event was likely to occur. The assumption is that an increasing cardiac output or peripheral resistance would have an overall protective effect and reduce the risk, but a decreasing cardiac output or vascular resistance would render a patient at risk of hypotension.

The Conclusion chapter (Chapter 8) summarises results of the Observational Study, evaluates the merits of the novel metrics described above, and considers how these may be used to construct a multivariate predictive model. In describing the requirements for a future predictive model, this chapter also considers important concepts such as the distinction between physiological patterns that are normal or expected during dialysis, and physiological patterns predictive of deterioration. In the Future Work section, several approaches to multivariate probabilistic modelling are introduced and discussed in the context of their potential use as models to predict intradialytic hypotension. Finally, this thesis concludes by suggesting that individualised multi-parameter data-fusion modelling for haemodialysis patients would be an important area for future research because a reliable means of identifying and reducing IDH for our patients is of upmost importance in advancing the tolerability of haemodialysis.

Chapter 2

General Methods

2.1 Overview

The broad aims of predictive model development fall into three overall phases: Phase 1 is data collection and model building; Phase 2 is model testing on a different patient cohort to which it had been developed; and Phase 3 involves a subsequent clinical trial to test the utility of the model-guided pre-emptive interventions described previously. An observational study was designed to address phase 1 of the overall plan.

2.2 Study Design

Multi-parameter model for predicting IDH has not been previously explored (see Section 1.6), so the relative merits of a population-based approach (where normality and abnormality of physiological parameters are defined across a population) versus a personalised approach (where normality and abnormality of parameters are defined against a stereotypical physiological pattern for a particular individual) were unknown. The pragmatic approach to study design outlined in Section 2.2.1, culminated in a dataset that comprised of cross-sectional data from a limited number of dialysis sessions in a diverse patient group (typical of the prevalent dialysis population of the Oxford Kidney Unit), and data from a longitudinal group, where individuals were studied over multiple dialysis sessions.

2.2.1 Patient numbers and target event rates

Ethical Approval was granted to study 80 patients over 320 dialysis sessions (each patient studied over four treatments each separated by four weeks). To allow development of a longitudinal dataset and offset any potential data loss from patients moving out of the area to satellite units or from patients receiving a kidney transplant during the study period, it was agreed that patients could undergo further monitoring sessions if they wished to do so. The number of participants was decided using an approximation of predicted monitored events, and was calculated as follows: Assuming that each patient is studied on a minimum of four occasions and that these sessions are subject to the lowest rates of IDH as reported in the literature (minimum of 15% of sessions affected), the aim was to capture at least 48 (320×15%) episodes of IDH. This approximates the number of events on which similar models have been trained in the general medical population[112].

2.2.2 Eligibility Criteria and Recruitment

All adult haemodialysis patients undergoing dialysis at the Oxford Kidney Unit were considered for this Observational Study. Patients under 18, patients unable to tolerate additional monitoring, patients choosing not to participate, and prisoners were excluded. Patients were given information leaflets approved by the research ethics committee and were recruited and consented by staff that had undertaken Good Clinical Practice training[1] within the preceding 6 months. Both prevalent and incident haemodialysis patients were required to achieve the 80 patient target over the designated study period.

2.2.3 Validity of the study population

The UK dialysis population is known to be a heterogenous group, in terms of patient ages, ethnicity, and co-morbidities. During the planning phase of the observational study, it was recognised that patients may have been more likely

[1] Good Clinical Practice (GCP) training is a key requirement for anyone involved in the conduct of clinical research. GCP sets standards and guidelines to which all research is conducted

to partake if they had concerns about their health or stability on dialysis. This may have resulted in a selection bias towards patients in whom symptoms or events were more likely to occur, and limited the availability of data from healthy controls that routinely experienced an uneventful dialysis. Conversely, those motivated to partake in this research may have been generally younger with an interest in maintaining their health. As such, a selection bias towards a more stable group that was not representative of the population may have occurred. To investigate these possibilities and establish the validity of the study population, basic demographics of the non-participants were included (see Table 3.2 on page 44), and a comparison of study participants health and social welfare status —which may affect symptom reporting—was made with haemodialysis patients external to the study. This assessment was conducted using the Short Form 'SF-36' health survey. The SF-36 is a multi-purpose questionnaire comprising 36 questions. SF-36 outcomes are widely cited and validated for patients with end-stage renal disease[113][114][115]. Each of eight categories is assessed on a 0 to 100 scale from weighted averages of related question responses[116]. In addition, analyses of baseline demographics were performed to establish whether or not results from this study can be considered typical and broadly applicable to the wider haemodialysis population.

2.2.4 Patient physiological monitoring equipment

Hidalgo EQ02^{TM}: Multi-parameter sensor and recording device

In order to integrate multiple physiological parameters as a time-series, it is essential that data from multiple sources/sensors can be time-synchronised. A multi-channel recording device was required not only to overcome this time-synchronisation problem, but also to minimise the burden of sensors, leads and recording devices to the patient. Following extensive research and development meetings with Hidalgo UK, including a visit to the company's Cambridge headquarters, a non-invasive, multi-parameter recording device (EQ-02^{TM}) was custom built to meet the requirements of this study. The EQ-02 belt incorporated a strain gauge to monitor respiratory rate and a series of electrodes that provided a 2-lead ECG. A pocket within the belt held the sensor electronic module (SEM)

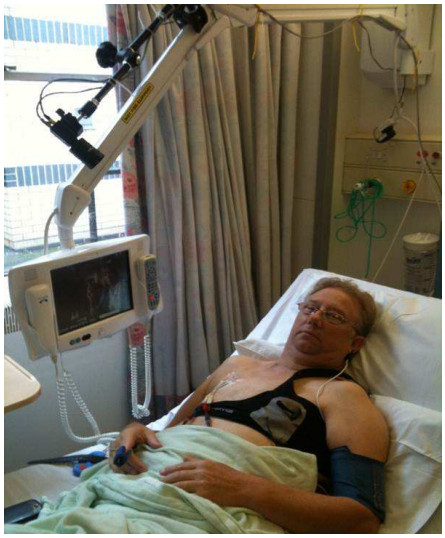


Figure 2.1: Study patient and monitoring equipment
Photograph taken and reproduced with the patient's permission

recording device, into which optional external probes, such as the Nonin peripheral pulse oximeter, were attached. The SEM recording device also included a three-dimensional accelerometer and an infrared skin-surface thermometer. The belt is shown on a study patient in Figure 2.1.

Non-invasive assessment of blood pressure

During the design phase of the study, patients were asked to complete a questionnaire to establish a tolerable frequency of non-invasive blood pressure measurement. These considerations were subsequently incorporated into the study protocol. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) measurements were taken on the non-fistula arm using an appropriately sized cuff-oscillometric device that was integrated into the dialysis machine.

2.2.5 Dialysis monitoring equipment

Nexadia

B.Braun's Nexadia software is an add-on package to the Dialog+ dialysis machine. It time-synchronises the intermittent Non-invasive blood pressure (NIBP) recordings with specific dialysis machine data, such as ultrafiltration rate; cumulative ultrafiltration volume; blood pump speed; and arterial and venous needle pressures. These machine parameters are recorded at one minute intervals and stored in an internal database. At the end of each session this database was downloaded and interrogated 'off-line'.

Critline^{TM} haematocrit monitor

The Critline^{TM} (Hema Metrics, Massachusetts, USA) monitor is used widely in haemodialysis research and practise, as described in Section 1.2. It provides a continuous measurement of absolute haematocrit and oxygen saturation. A cuvette is attached to the extracorporeal circuit at the arterial side of the dialyser. A sensor uses the reduction in transmitted near-infrared light to determine the hematocrit concentration of blood in the circuit according to the following formula:

$$\%\Delta RBV_t = (\frac{HCT_0}{HCT_t} - 1) * 100 \tag{2.1}$$

where $\%\Delta$ represents percentage change, and HCT_0 and HCT_t represent haematocrit concentrations at baseline and time 't', respectively.

Assuming that the red blood cell mass stays constant during dialysis (e.g., in the absence of blood transfusion or blood loss), the change in haematocrit will be directly proportional to the change in plasma volume during ultrafiltration — a characteristic that is useful in determining fluid status. The output display on the monitor is the percent change in haematocrit compared to baseline haematocrit, which is expressed inversely as the percent change in blood volume (i.e. the 'relative blood volume'). The Critline^{TM} device samples the percentage haematocrit, percentage change in blood volume, and oxygen saturation at twenty-second intervals. These time-synchronised Critline^{TM} data are stored in

the device's internal memory but can be downloaded to a computer following dialysis.

2.2.6 Symptom questionnaires

Symptom questionnaires were included in the design of this observational study for the following reasons: Firsty, there is uncertainty in the literature about the relationship between patient symptoms and hypotensive events, so it was hoped that analysis of intradialytic symptoms and blood pressure would provide new insights into which symptoms were associated with hypotension on dialysis. This would form the basis of an evidence-based definition that was required to form a robust outcome measure for subsequent analyses. Secondly, it was considered important to establish the extent of this relationship because any dissociation may highlight symptoms that were themselves associated with predictable and potentially preventable physiological changes regardless of blood pressure status. In terms of the patient experience of dialysis, such an outcome was considered a viable application of a predictive model, even if abrupt changes in blood pressure could not be predicted or prevented.

To minimise the impact of the study on a patient's propensity to report symptoms during dialysis, participants were asked to complete the post-dialysis symptom questionnaire immediately following the treatment – see Appendix C on page 181. The questionnaire included symptoms considered synonymous with a reduction in blood volume or blood pressure, such as nausea, dizziness[65] and cramps[117]. Each of the specified symptoms was stratified by severity: none, trivial, mild, moderate, severe and scored 0, 1, 2, 3 or 4, respectively. Nursing documentation was collated and transcribed for each study session so that it could be compared with patients' post-dialysis questionnaire responses.

2.3 The Observational Study

The observational study was conducted between October 2011 and October 2012. The dialysis environment, the dialysis prescription, and the patients' usual medication were not changed for the purposes of this study. Our unit does not restrict eating or drinking on haemodialysis, and fluid intake during dialysis was not incorporated into the calculation for prescribed ultrafiltration volume. Haemodialysis was carried out by Dialog+® Machines using high-flux dialysers (B.Braun, Melsungen, Germany). Room temperature was typically 19 °C at the start of the morning session, rising to 22 °C by the end of the afternoon. Dialysate temperature was 37 °C. Dialysate solutions were bicarbonate-based with a concentration of 35mmol/L and an acetate concentration of 2meq/L. Dialysate composition for each patient is detailed in Appendix C on page 181. Dialysate conductivity ranged between 13.8 and 14.3 mS/cm depending on the prescribed sodium profile. Both patient and dialysis nurse were blinded to the blood pressure and Critline interface display on the dialysis machine monitor; however, these data could be readily accessed if there were sufficient clinical concern mandating closer haemodynamic monitoring.

2.3.1 Research protocol

Four patients were monitored simultaneously[1]. The following data was gathered from each study participant:

1. Basic demographic details (age, sex, co-morbidities, months on dialysis).
2. Treatment details (prescribed dry weight, dialysis prescription, medication list).
3. Dialysis machine parameters using the B.Braun Nexadia^{TM} software package.
4. Critline^{TM} relative blood volume monitoring (see Table 1.2 on page 18), incorporating oximetry of the arterial line of the dialysis machine.

[1] A 1:4 nurse-to-patient ratio is representative of usual dialysis care in the UK

5. Continuous monitoring of surface body temperature, 3D accelerometer, ECG, respiratory rate (strain gauge), PPG waveform/oximetry at 2 of 3 potential sites (index finger of non-fistula arm, index finger of fistula arm, pinna of ear on contralateral side to fistula).

6. Intermittent monitoring of non-invasive blood pressure every 15 mins, including a pre- and post-dialysis orthostatic challenge.

7. Pre- and post-HD body weight.

8. Pre- and post-HD tympanic temperature.

9. Pre- and post-HD symptom questionnaire, including appraisal of the monitoring equipment.

10. Pre- and post-study SF-36 validated quality of life questionnaire (see Section 2.2.3).

2.3.2 Minor amendment to protocol

A significant uptake in the option of additional monitoring sessions and lower than expected drop-out rates meant that mid-way through the observational study data collection had far exceeded the conservative expectations for Phase 1. Moreover, it was envisaged that an extension to the study end-date by 12 weeks for 20 patients would not only provide sufficient data to construct a model, but would allow stratification of the cohort so that the model can be retrospectively tested on different subgroups without the need for an additional (Phase 2) study. This in-house model testing was considered beneficial because it avoided the complexities of finding a different cohort of dialysis patients from other hospitals or community satellite dialysis units. A minor amendment was agreed by the Ethics Committee to extend the study by 12 weeks. An outline of the final study is illustrated in Figure 2.2 on page 37. Population-based and personalised model development using this dataset is described in detail in the doctoral thesis of Yasmina Borhani[118] and is also outlined in Chapter 8 of this thesis.

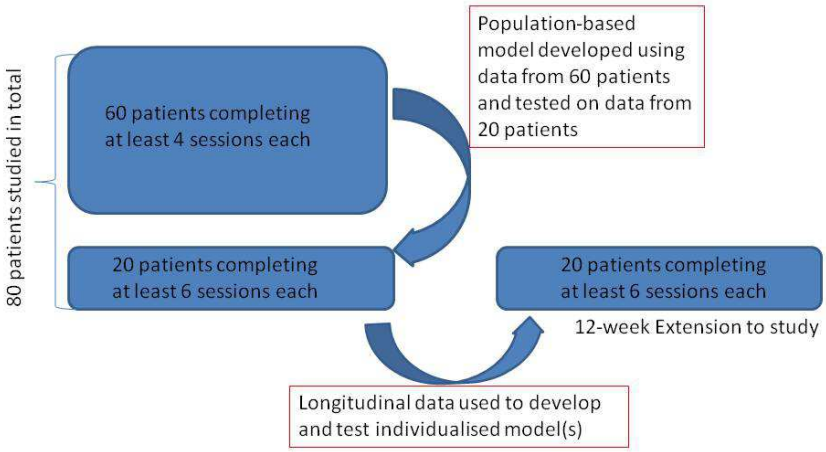


Figure 2.2: An outline of the Observational Study

2.4 Assimilation, sorting, and storage of the observational data

Following each study dialysis session, a computer was linked in turn to the Dialog+ machine and Critline. Time-synchronised data from the Nexadia and Critline databases were assimilated with the raw waveform and summary data files downloaded from the EQ-02 into unified session-specific files using Matlab R2012a (Mathworks Inc., Natick, Massachusetts, U.S.A). Date-labelled session files were gathered and stored securely in patient-specific folders which were coded and labelled to maintain participant anonymity.

Chapter 3

Identifying Intradialytic Hypotension

3.1 Introduction

Intradialytic hypotension is recognised as a detrimental complication of maintenance haemodialysis, but how it is defined and reported varies widely in the literature (see Chapter 1.4). This variation results from different blood pressure thresholds at which hypotension is classified and inconsistency as to whether associated symptoms such as nausea, vomiting, dizziness, and cramp are a prerequisite to a diagnosis of IDH[119]. Some definitions go further and require an intervention to have taken place (such as the reduction of ultrafiltration rate or blood pump speed, tilting of the bed, or the administration of a saline bolus) to fulfil the diagnosis. Current European Best Practice Guidelines (EBPG) and Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines are explicit in this regard[19][120]. However, an increasing number of studies whose diagnostic criteria do not include the presence of symptoms or an intervention demonstrate morbidity and/or mortality associated with a critical reduction in intradialytic blood pressure[21][32][34].

It is usual practice to measure BP before and after dialysis, unless the patient appears or feels unwell during the treatment. As such, the measurement of intra-

dialytic blood pressure, and any subsequent intervention, is usually initiated by a patient's report of symptoms or overt signs of hypoperfusion. This sequence of events means that little is known about the incidence of asymptomatic hypotension in the maintenance dialysis population. This is of potential importance because it is conceivable that patients with recurrent asymptomatic hypotensive events and cumulative sub-clinical hypoperfusion injury may go undetected and, therefore, not benefit from strategies reported to those identified as IDH prone. Such mitigating strategies are reported to be beneficial in asymptomatic patients with hypotension during dialysis[26].

This chapter explores the propensity for a patient to report symptoms during dialysis, outlines the association between nausea, dizziness, cramp and intradialytic blood pressure, and establishes the relative frequency of asymptomatic hypotension (defined using commonly cited BP thresholds) for patients participating in the observational study.

3.2 Methods

The selection, recruitment and protocol for this observational study is outlined in Chapter 2. Additional methods to those already outlined, and specific to this chapter, are described here:

3.2.1 Blood pressure descriptors of IDH

After assigning the blood pressure reading immediately following bleed-out into the extracorporeal circuit as 'baseline', the following commonly cited descriptors of IDH were defined for SBP, DBP and MAP: a) The lowest recorded value (minimum) for the session (mmHg); b) The maximum difference ('delta') from baseline blood pressure i.e. baseline - minimum (mmHg); c) The maximum difference from baseline value as a percentage of the baseline value i.e. $\frac{Baseline-Minimum}{Baseline} * 100($ %); d) The maximum change between two consecutive 15-minute measurements i.e. $BP_{t-15} - BP_t$ (mmHg), where t = time of current blood pressure measurement in minutes; e) The maximum change between two consecutive 15-minute

measurements as a percentage of the baseline value i.e $\frac{BP_{t-15}-BP_t}{Basline} * 100$ (%). Data for the intervention group was also censored at the time of the first intervention for subgroup analyses.

Session-specific data sourced from the B.Braun Nexadia®package were used to assess total ultrafiltration volume for each treatment and this was also expressed as a percentage of the patient's dry weight, which was reassessed clinically at least every three months. Using Critline data, the lowest achieved relative blood volume (%) was recorded for each session.

3.2.2 Assignment of categories for analysis

The study sessions were divided in to one of three categories according to post-dialysis symptom questionnaire responses and/or any intervention received by the patient during dialysis: Firstly, sessions scoring zero for all symptoms (nausea, dizziness and cramp) were assigned to the Asymptomatic group. Secondly, sessions scoring one or more for any of these IDH-suggestive symptoms but not receiving an intervention were assigned to the Symptomatic group. Finally, an Intervention group was created for sessions in which symptoms or signs of hypoperfusion (e.g. excessive sweating, sudden change in skin tone/cyanosis, or cognitive impairment/reduced consciousness) prompted an immediate intervention such as the reduction of ultrafiltration rate or blood pump speed, tilting of the bed, or the administration of a saline bolus. Interventions due to vascular access problems or clotting of the extracorporeal circuit were excluded from the analysis.

3.2.3 Statistical Analysis

Descriptive statistics such as mean (standard deviation/standard error) or median (inter-quartile range) were used in the analysis of the demographic data of the study subjects. Analysis of SF-36 scores for the study patients versus the remaining haemodialysis patients affiliated to our renal unit but not partaking in the study were conducted using non-parametric Mann-Whitney U tests, as the data for the eight SF-36 outcome measures were not normally distributed. Re-

peated measurements during a dialysis session, over repeated sessions, for more than one patient, represent a multi-level data structure. The hierarchical nature of our three-level data was taken into account using mixed (fixed and random errors) modelling, and standard errors/confidence intervals were adjusted accordingly. The mixed-model analyses were carried out independently by a medical statistician using Stata 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). Multilevel analyses of the three groups (Asymptomatic, Symptomatic, and Intervention) incorporated covariates at the session level (functions of SBP, DBP, and MAP; Total UF; UF adjusted for weight; and maximum decrease in relative blood volume for the session) whilst adjusting for repeat measurements on the same patient. For logistic regression analyses of symptoms in a generalised mixed model, scores were dichotomised i.e. Symptom score of 0 (Asymptomatic) compared with symptoms of any severity (1-4). Covariates at the patient level (presented in Table 3.1) included age, gender, months on dialysis, and the number of antihypertensives taken by the patient. At the session level, covariates were derived from the pre-defined functions of blood pressure for SBP, DBP and MAP. The resulting probabilities allowed the calculation of Odds Ratios. In order to obtain a probability of a patient from a particular group reaching a pre-determined blood pressure threshold, each blood pressure value for every session was coded as 0 if it was below the threshold or 1 if it was above the threshold. This binary variable at the session level was also analysed using logistic regression in a generalised mixed model. Findings were reported as significant at the 5% level ($p<0.05$).

3.3 Results

At this stage of the analysis, 77 patients had been recruited to the study and had completed 469 dialysis sessions. To inform the stratification of the descriptors for IDH which would be used in the remainder of the study, multilevel analysis was therefore undertaken on the 469 sessions. This chapter reports the findings from this analysis.

Participant characteristics are detailed in Table 3.1 on page 43 and reflect our dialysis population, which is predominately Caucasian and male with a median age of 65 years. Basic demographics of the 20 non-participants are shown in Table 3.2 on page 44 and show non-significant differences when compared to study participants. Table 3.3 on page 45 shows non-significant differences in both the demographics and responses for each of eight categories of the SF-36 questionnaire when study respondents were compared with patients dialysing in regional satellite units. Each patient was studied for a mean of 5.9 sessions (range 1-19) over 12 months (see Figure 3.1).

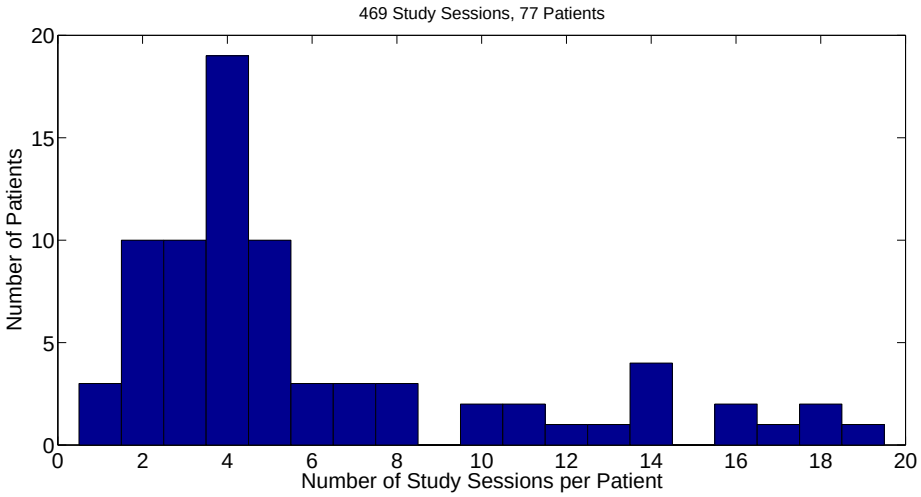


Figure 3.1: Total number of sessions studied for each of 77 patients

Table 3.1: Patient Characteristics of Study Participants

Variable		***n*=77**	**%**
Male:Female	55:22		
Age, years (Median, IQR)	65 (51-75)		
RRT Vintage, months (Median, IQR)	30 (14-66)		
HD Vintage, months (Median, IQR)	26 (11-49)		
Ethnicity			
White		68	88.3
Black		3	3.9
South Asian		3	3.9
Other		3	3.9
Primary Diagnosis			
Glomerulonephritis		24	31.2
Diabetic Nephropathy		16	20.8
Hypertensive/Renovascular		9	11.7
Pyelonephritis/Reflux		5	6.5
Polycystic Disease		4	5.2
Renal Dysplasia		3	3.9
Other		7	9.1
Unknown		9	11.7
Smoker		15	19.5
Diabetes		31	40.3
Type 1		6	7.8
Type 2		25	32.5
Insulin		18	23.4
Ischaemic Heart Disease		30	39.0
PCI		19	24.7
known LVH		16	20.8
Listed for Transplant		19	24.7
Medication			
ACEi		16	20.8
A2RB		16	20.8
B-Blocker		29	37.7
Alpha Blocker		12	15.6
Ca-Channel Blocker		26	33.8
Other		8	10.4
Antihypertensives per patient			
0		23	29.9
1		14	18.2
2		31	40.3
3		5	6.5
4		4	5.2

Table 3.2: Patient Characteristics of Non-Participants

Variable		***n*=20**	**%**	**p-value***
Male:Female	16:4			0.58
Age, years (Median, IQR)	73 (60-81)			0.07
HD Vintage, months (Median, IQR)	17 (7-26)			0.07
Ethnicity				
White		15	75.0	0.15
Black		3	15.0	0.10
South Asian		1	5.0	0.99
Other		1	5.0	0.99
Primary Diagnosis				
Glomerulonephritis		5	25.0	0.79
Diabetic Nephropathy		6	30.0	0.38
Hypertensive/Renovascular		3	15.0	0.71
Pyelonephritis/Reflux		0	0.0	0.58
Polycystic Disease		1	5.0	0.99
Renal Dysplasia		0	0.0	0.99
Other		0	0.0	0.34
Unknown		5	25.0	0.16
Diabetes		7	35.0	0.80
Type 1		2	10.0	0.67
Type 2		5	25.0	0.60
Listed for Transplant		4	20.0	0.77

The superscript (*) shows p-values for comparison with the Study Participants in Table 3.1 using Fisher's exact test or Mann-Whitney test (Age, and HD Vintage) at the 5% level.

Table 3.3: Results from Unit-wide SF-36 Health Survey

Results are expressed as Median(Inter-Quartile Range).
The superscript (†) indicates non-significant differences on comparison using Mann-Whitney Test at the 5% level.

	SF-36 Respondents in Study n = 50	Non-Study SF-36 Respondents n = 73
Age (yrs)	67(51-77)	71(52-77)†
Months on HD	24(12-46)	26(12-49)†
Male:Female	34:16	46:27
	SF-36 Health Survey Score	
	Respondents in Study	Non-Study SF-36 Respondents
Physical functioning	30(6-50)	25(5-45)†
Role limitations due to physical health	0(0-46)	0(0-25)†
Role limitations due to emotional problems	33(0-100)	33(0-100)†
Energy / Fatigue	33(16-45)	35(15-55)†
Emotional well-being	68(56-80)	72(52-88)†
Social functioning	69(50-84)	63(50-88)†
Pain	55(43-78)	55(23-90)†
General Health	40(33-56)	38(25-34)†

SF-36 Categories: 1) Physical functioning (0=very poor physical functioning to 100=excellent physical functioning); 2) Role limitations due to physical function (0=no limitation to 100=extremely limited); 3) Role limitation due to personal/emotional problems (0=no limitation to 100=extremely limited); 4) Energy/fatigue (0=low energy/high fatigue to 100=high energy/low fatigue); 5) Emotional well-being (0=very poor emotional well-being to 100=excellent emotional well-being); 6) Social functioning (0=very poor social functioning to 100=excellent social functioning); 7) Bodily pain (0=no pain to 100=continuous pain); and, 8) General health perceptions (0=general health perceived as very poor to 100=general health perceived as excellent)

3.3.1 Symptom Reporting

Of the 298 sessions assigned to the Asymptomatic group on the basis of the post-dialysis questionnaire, there were the *expected* absence of patient-reported symptoms in the dialysis session notes. However, all 113 sessions assigned to the Symptomatic group on the basis of the post-dialysis symptom questionnaire were also without corresponding documentation of the patient's symptoms in the dialysis notes. Conversely, 38 of the 45 Intervention sessions accurately documented patient-reported symptoms, and the remaining 7 sessions documented that an intervention had occurred due to signs of hypoperfusion in an otherwise asymptomatic patient.

3.3.2 Symptoms, Patient-specific covariates, and Session-specific covariates

Table 3.4 on 47 shows that the percentage of sessions in which the patient experienced cramp, dizziness or nausea was 22.1%, 12.3% and 7.5%, respectively. For each symptom, the frequency of occurrence was inversely related to the graded severity. The mixed model logistic regression analysis showed that the occurrence of nausea was not significantly related to any function of blood pressure, but was significantly associated with a lower age (Odds Ratio for 10 years increment in age of 0.52 [0.30 to 0.91], p=0.023). The occurrence of dizziness was significantly associated with change in blood pressure from baseline (Odds Ratio for 10 mmHg delta was 1.25 [1.06 to 1.48], p=0.03 for SBP; and 1.37 [1.08 to 1.74], p=0.01 for MAP), but not patient-level covariates (age, gender, months on dialysis, and number of antihypertensives). Cramps were significantly associated with change in SBP from baseline (Odds Ratio for 10mmHg delta SBP was 1.19 [1.02 to 1.38], p=0.03) but not associated with changes in MAP or patient-level covariates.

Table 3.4: Number of sessions reporting symptoms, categorised by symptom severity

Group	Severity Score	All Patients		
		Nausea	Dizziness	Cramp
Asymptomatic	0 (Asymptomatic)	298	298	298
Symptomatic	0 (Asymptomatic)	84	67	39
	1 (Trivial)	14	22	38
	2 (Mild)	9	20	18
	3 (Moderate)	3	2	16
	4 (Severe)	2	1	2
	Not Recorded	1	1	0
Intervention	0 (Asymptomatic)	38	34	18
	1 (Trivial)	3	4	7
	2 (Mild)	1	3	9
	3 (Moderate)	1	3	5
	4 (Severe)	1	1	6
	Not Recorded	1	0	0
	Total	456	456	456
	%Sessions reporting symptoms	7.5	12.3	22.1

Table 3.5 on page 49 shows a non-significant difference between the total UF volume of the Asymptomatic and Intervention groups but a significant difference between the Asymptomatic and Symptomatic groups. Despite this, the maximum decrease in relative blood volume achieved during dialysis was not significantly different between the three groups. Baseline blood pressure was equivalent amongst the Asymptomatic, Symptomatic, and Intervention groups; but Symptomatic and Interventions sessions experienced significantly lower minimum SBPs than the Asymptomatic group. These findings remain highly significant when the delta (baseline-minimum) BP is adjusted for baseline. Moreover, logistic regression analysis showed the odds of an intervention increased significantly for every 10mmHg increment in delta SBP (1.41 [1.17 to 1.70], $p<0.0001$). These findings were generally not true of diastolic blood pressures, apart from significant difference between Asymptomatic and Intervention DBP (23% vs. 29%, $p<0.01$). Maximum fall in SBP between consecutive measurements (i.e. delta over 15 minutes) was significantly lower in both the Symptomatic and Intervention group; however, delta SBP over 15 minutes, delta DBP over 15 minutes, and delta MAP over 15 minutes were all non-significant when adjusted for baseline values. The differences between the three groups for rate of change of SBP and DBP over the first hour of dialysis were not significant. There were no significant changes in any reported outcome when the intervention session data was censored at the time of the (first) intervention.

Table 3.5: Dialysis variables for Asymptomatic, Symptomatic, and Intervention Sessions

Values adjusted for the repeat measurements on the same patient
(Mean, SEM, p-value for comparison with Asymptomatic group). Symptomatic vs. Intervention comparisons were all non-significant at the 5% level.

Variable	Asymptomatic Sessions (n=298)	Symptomatic Sessions (n=112)	Sessions with an Intervention (n=45)
UF Volume (L)	2.23 (0.11)	2.43 (0.13) p=0.02	2.24 (0.14) p=0.91
UF Volume as % Dry Weight	3.00 (0.15)	3.24 (0.17) p=0.03	2.99 (0.19) p=0.98
Maximal decrease in Blood Volume (%)	-9.32 (0.45)	-9.69 (0.64) p=0.57	-8.53 (0.85) p=0.36
Baseline SBP (mmHg)	139.5 (2.6)	139.4 (3.1) p=0.97	141.1 (3.7) p=0.62
Minimum SBP (mmHg)	111.2 (2.3)	104.8 (2.8) p=0.006	102.4 (3.4) p=0.003
Delta SBP as % of Baseline SBP	0.20 (0.01)	0.24 (0.02) p=0.007	0.27 (0.02) p<0.0001
Delta SBP over 15 mins (mmHg)	26.1 (1.2)	28.5 (1.3) p<0.0001	28.3 (1.3) p<0.0001
Delta SBP over 15 mins as % of Baseline SBP	0.19 (0.01)	0.2 (0.01) p=0.70	0.2 (0.02) p=0.80
Baseline DBP (mmHg)	78.2 (1.8)	78.4 (2.1) p=0.90	82.0 (2.5) p=0.08
Minimum DBP (mmHg)	59.4 (1.5)	59.7 (1.8) p=0.29	57.5 (2.2) p=0.29
Delta DBP as % of Baseline DBP	0.23 (0.01)	0.25 (0.02) p=0.21	0.29 (0.02) p<0.01
Delta DBP over 15 mins (mmHg)	20.6 (1.3)	20.7 (1.8) p=0.98	22.9 (2.3) p=0.32
Delta DBP over 15 mins as % of Baseline DBP	0.28 (0.02)	0.27 (0.03) p=0.73	0.27 (0.04) p=0.81
Pre-dialysis MAP	98.6 (1.8)	98.7 (2.2) p=0.94	101.7 (2.6) p=0.17
Minimum MAP	79.1 (1.9)	75.4 (2.0) p=0.023	74.3 (2.8) p=0.021
Delta MAP as % of Baseline MAP	0.19 (0.01)	0.23 (0.02) p=0.021	0.27 (0.02) p<0.0001
Delta MAP over 15 mins (mmHg)	18.8 (1.1)	20.4 (1.5) p=0.29	22.9 (2.3) p=0.32
Delta MAP over 15 mins as % of Baseline MAP	0.19 (0.01)	0.21 (0.02) p=0.32	0.2 (0.02) p=0.90
Rate of change in SBP over first hour (mmHg/hour)	-7.1 (0.5)	-7.1 (0.5) p=0.76	-7.2 (0.5) p=0.08
Rate of change in DBP over first hour (mmHg/hour)	-3.9 (0.2)	-3.8 (0.2) p=0.76	-4.0 (0.2) p=0.16

Table 3.6: Patients starting Haemodialysis with a Baseline SBP <100mmHg

Patient (n=9)	**No. of Sessions with Baseline SBP <100mmHg** (n=17)
20	2 of 28 (7.1%)
21	1 of 18 (5.6%)
22	2 of 11 (18.2%)
24	3 of 3 (100.0%)
34	2 of 3 (66.7%)
35	3 of 12 (25.0%)
36	2 of 10 (20.0%)
38	1 of 3 (33.3%)
71	1 of 2 (50.0%)

Figures 3.2(a) & 3.2(b) show that a minimum SBP <100mmHg is the threshold with greatest discrimination between Asymptomatic and Intervention sessions (35% vs. 64% respectively, or probability of SBP <100mmHg = 0.22 vs. 0.55 respectively, when analysed using logistic regression in a generalised mixed model). Likewise, Figures 3.2(c) & 3.2(d) show maximal separation between the proportion of Asymptomatic and Intervention groups occurred when delta (baseline-minimum) SBP, expressed as a percentage of baseline, was 25% (maximum discrimination is estimated at 20% using mixed model logistic regression). Figures 3.2(e) & 3.2(f) show the change in Systolic BP over 15 minutes as a percentage of the baseline SBP and illustrate the non-significant differences between groups. Figure 3.3 illustrates comparable trends for MAP, but here the ability to discriminate between groups is less than that shown in Figure 3.2 for SBP.

Table 3.6 shows that only 17 of 469 sessions (3.6%) had a baseline SBP of <100mmHg on starting Haemodialysis. These 17 sessions were identified from a total of 9 patients, showing a tendency for some patients, such as OB24, to start dialysis with a systolic blood pressure below the 100mmHg threshold. However, only sessions where SBP fell by 20% from this sub-threshold baseline were considered to have an IDH event for the purposes of subsequent analyses.

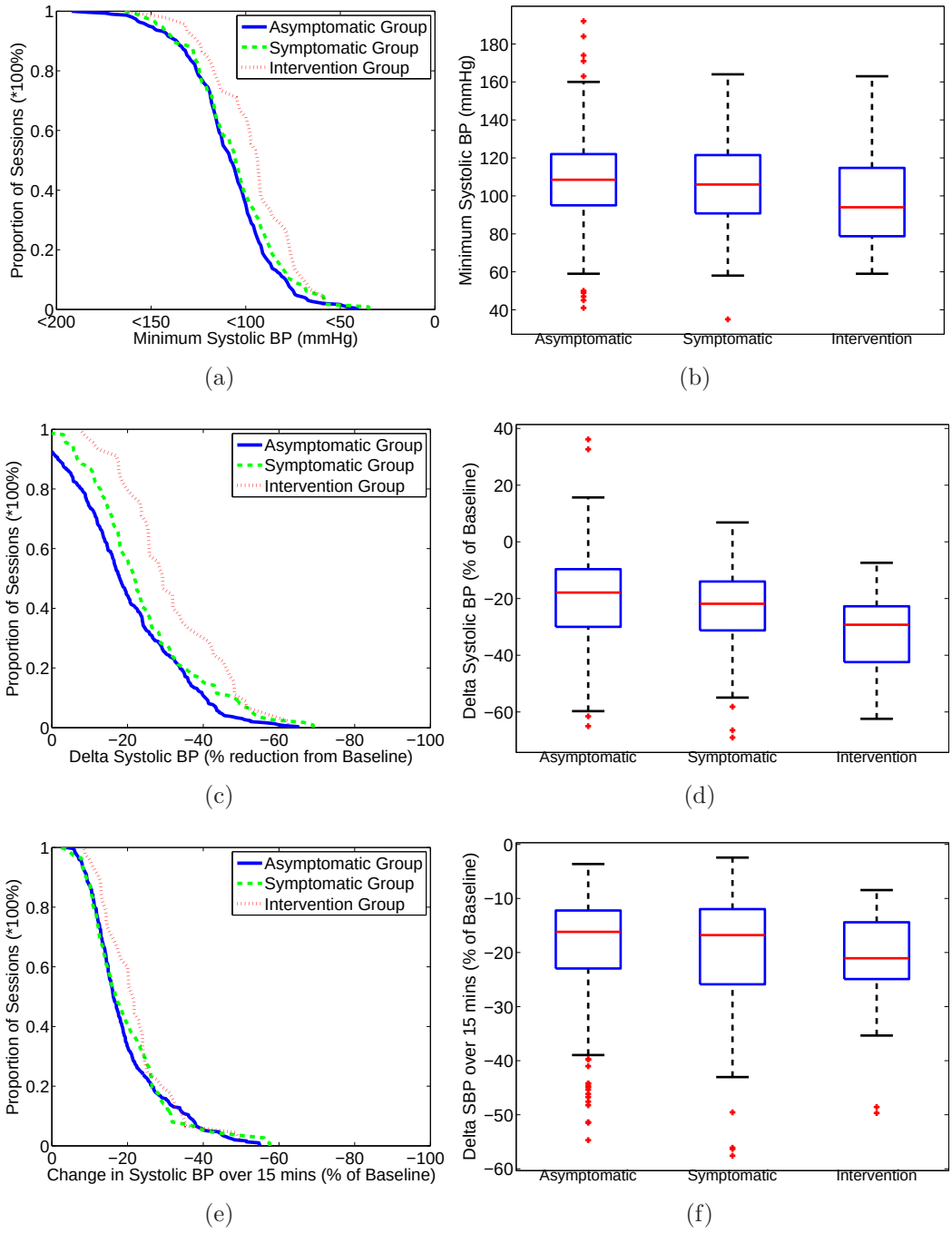


Figure 3.2: Systolic blood pressure profiles for Asymptomatic, Symptomatic, and Intervention groups

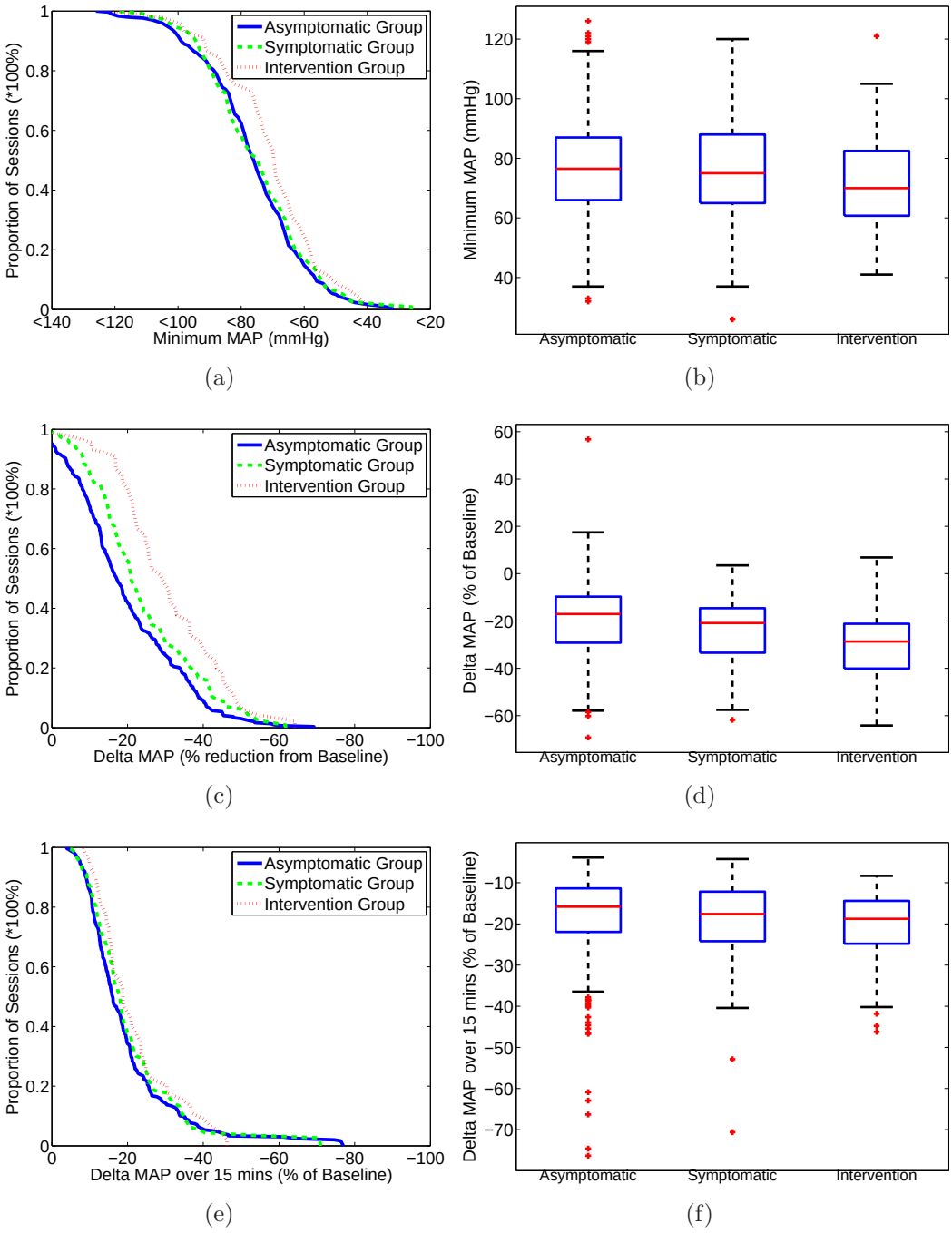


Figure 3.3: Mean arterial blood pressure profiles for Asymptomatic, Symptomatic, and Intervention groups

3.4 Discussion

It is clear that for purposes of clinical audit or research, a standardised evidence-based approach to the definition of IDH is required if the burden of intradialytic adverse events are to be compared within a particular dialysis unit over time, or between units (inter-)nationally. In this chapter, results are presented which may help to refine this definition. Firstly, the issue of symptom reporting is considered. When nausea, dizziness or cramp were reported to the nurses and documented during dialysis, an appropriately documented intervention inevitably followed. However, in all 113 of the sessions labelled symptomatic on the basis of the post-dialysis questionnaire (∼25% of total), an intervention did not occur. Possible reasons are speculative: 1) Symptoms were not reported to the dialysis staff by the patient during the session. This could represent a research effect, with patients over-reporting symptom severity on the post-dialysis questionnaire that would have otherwise been dismissed as (less than) trivial during the dialysis. Alternatively, patients may have experienced non-trivial symptoms but then either opted not to report these because symptoms were considered inevitable or unlikely to be improved with nursing intervention, or the patient had not been given the opportunity to report symptoms to a member of staff at the time of occurrence. 2) Symptoms were reported by the patient but these were deemed not to warrant an intervention by nursing staff, and this decision was not documented. This may be the case for symptoms graded as trivial or mild by the patient, but symptoms reported as moderate or severe (of which there are 25 such reports in the Symptomatic group in Table 3.4 on page 47) would have been expected to result in an intervention to reduce severity, regardless of the blood pressure. 3) The patient reported symptoms warranting intervention during dialysis but these were not appropriately documented or acted upon. This scenario is considered unlikely, especially given the delivery of pre-study training to participating dialysis nurses, but cannot be excluded as a possibility.

The potential disconnect between the occurrence of symptoms and the reporting of these symptoms during dialysis is important when contemporary definitions of IDH are considered. The under-reporting of symptoms in association

with hypotension, as suggested by patients in the Symptomatic group reaching SBP levels <100mmHg, could lead to a false reduction in IDH rates according to current guidelines, especially when it appears that the additional diagnostic requirement – an intervention – is dependent on symptom reporting. Another potential source of inconsistency is that there is no universal agreement as to what symptoms should be deemed indicative of IDH. Other symptoms are commonly reported during dialysis and may be associated with changes in blood pressure (for example; headache and abdominal pain). Moreover, Caplin *et al* highlight variations in dialysis-associated symptoms attributable to gender and ethnicity, as well as unexplained inter-regional differences[121]. For the purposes of this thesis, selection of symptoms were limited to those in which it was anticipated would have the highest sensitivity and specificity for hypotension; however, this pragmatic approach is a potential limitation.

These results demonstrate a strong relationship between the intradialytic reduction of blood pressure, dizziness and cramp. However, this does not necessarily imply causation as potential confounders such as ultrafiltration rate, dialysate tonicity, and patient versus dialysate temperature were not taken into account in these analyses. Of interest was the finding that nausea during dialysis was more likely to be a function of age than of blood pressure, with younger patients reporting nausea more frequently than older patients. If these results are corroborated it would suggest that nausea should not be considered if symptoms are required to make a diagnosis of IDH, at least for younger members of dialysis populations with comparable demographics to those in this observational study.

The metric most strongly associated with dizziness and cramp appears to be SBP, especially if adjusted to pre-dialysis baseline. The association between DBP and symptoms is poor, and the inferiority of MAP to SBP in the association with symptoms seems likely to be due to the DBP variable in the MAP equation. A SBP <100 mmHg or reduction in SBP of 20% of baseline were the thresholds which maximised the probability that a session would result in an intervention rather than remain asymptomatic. The utility of this finding is limited but may serve to justify IDH definitions incorporating these values.

Of particular importance is our finding that a larger than anticipated proportion of asymptomatic patients reach blood pressure thresholds which potentially render them at risk of hypoperfusion injury. If a fall in SBP >20% to <100mmHg is considered, the probability of an asymptomatic patient reaching this threshold is 0.22 using mixed-model logistic regression, alternatively interpreted as systolic hypotension affecting up to a quarter of all asymptomatic sessions. Given that there was a 15 minute interval between blood pressure measurements during this study, it is probable that our results represent an underestimate of the true incidence of asymptomatic hypotension —i.e. it is possible that a patient experienced a critical reduction in blood pressure that was followed by recovery within a 15 minute period.

The stipulation that symptoms are required in the definition of IDH seems to be an attempt to improve diagnostic accuracy, but what is the rationale behind this association? The coupling of symptoms to blood pressure for the diagnosis of IDH serves one of two functions: 1) Either symptoms identify the occurrence of hypoperfusion in a particular individual at a blood pressure threshold that may vary over time or between patients (i.e. reflects individual (organ) variation in the BP threshold at which hypoperfusion occurs and, therefore, of limited utility when extrapolated to the wider population); or 2) Symptoms act as a surrogate for hypotension and are used to identify individuals that may be crossing a pre-defined population-based threshold (i.e function as a 'red flag' to trigger blood pressure assessment). If the former, then identification of risk of intradialytic hypoperfusion injury should perhaps be solely symptom-based and decoupled from a pre-defined BP threshold; and if the latter, then the risk of hypoperfusion injury should perhaps be defined against a population-based blood pressure threshold and not symptoms. When considering which of these distinctions is most appropriate, it is worth recalling that current, although limited, evidence indicates that there is a stronger association between symptoms and blood volume than symptoms and blood pressure[65][71]; and it is the absolute blood pressure, rather than blood volume reduction or intradialytic symptoms *per se*, that determines morbidity and mortality in haemodialysis patients[21][32][34].

Clearly, this unmasks some practical difficulties: How do we establish when the dynamic fluctuations of intradialytic blood pressure cross a pre-defined threshold in outpatients? Frequent NIBPs are one approach, but how frequent? The pre-study questionnaire suggests that NIBP more frequent than every 15 minutes would be intolerable to most patients, but if seeking to establish the frequency of asymptomatic hypotension, any interval would be sub-optimal compared to continuous BP monitoring. Other considerations arise: While there may be evidence to suggest that potentially detrimental outcomes are associated with low intradialytic blood pressure, there is little to suggest that intervening and reducing hypotension in asymptomatic patients reduces morbidity and mortality. Further, if asymptomatic hypotension was readily identified, would the propensity to intervene be such that detrimental increases in inter-dialytic weight gain (IDWG) result from interrupted ultrafiltration and/or the overzealous administration of saline? Or, would a timely, graded intervention in response to sub-critical hypotension improve dialysis adequacy and reduce IDWGs by avoiding interrupted dialyses caused by an unforeseen decline to critical hypotension?

The remainder of this thesis incorporates current evidence with the results presented here to formulate the outcome measure for future analyses: A reduction in SBP by >20% from baseline to <100mmHg is used to define those at risk of significant intradialytic hypoperfusion injury, regardless of symptoms.

Chapter 4

Stratification of Intradialytic Hypotensive Events

4.1 Using the modified definition to score hypotension on dialysis

For the purposes of audit, the binary response of whether or not a patient has met IDH criteria is sufficient for the monitoring of event rates. However, for the purposes of this thesis, dialysis hypotension was further stratified so that each study session could be labelled according to the extent to which the systolic blood pressure (shown to be the most useful metric in Chapter 3) was perturbed. The reason for doing so requires recognition that blood pressure is a clinical surrogate for the perfusion of critical tissues such as the brain, heart, liver (and kidneys). Accepting that tissue damage due to hypoperfusion is not dichotomous and likely to be determined by a continuum of risk, a stratification of this risk seems appropriate. Moreover, this continuum of risk is likely to be determined not just by the degree or magnitude of hypotension, but also by the rate at which the blood pressure falls, and the duration of the hypotensive event; for example, a non-sustained dip in blood pressure to a SBP of 60mmHg in an individual is conceivably less likely to result in hypoperfusion injury than a assymptomatic but rapid fall in blood pressure to 80mmHg which is then sustained for an hour. As discussed in Chapter 3, it is difficult to place an arbitrary cut off in blood pres-

sure at which hypoperfusion occurs, especially when considering a heterogeneous dialysis population. Some patients will experience tissue hypoperfusion at blood pressure levels that are considered to be normal in other patients. It is for these reasons that both relative and absolute blood pressure reductions should used to define risk of hypoperfusion in cases of hypovolaemic compromise[122].

Stratfication according to risk allows the use of the extremes of this spectrum as a way of efficiently assessing the performance, and potential utility, of the predictive techniques introduced in later chapters. For instance, a particular technique is not likely to have any clinical utility if it manages to detect relatively low-risk events, but fails to detect high-risk events. However, conversely, it may have some utility if it manages to detect high-risk events but not low-risk events.

4.1.1 Stratification of a hypotensive episode

The stratification levels are outlined in Table 4.1. The 1 to 10 grading of this stratification is arbitrary and non-evidence based but serves to reflect both the magnitude and rate of fall in systolic blood pressure during dialysis and, therefore, the perceived risk of hypoperfusion injury (a score of 10 is representative of the highest risk). It should be noted that these stratifications do not take into account the duration of the hypotensive event. This limitation is in part to reflect the lack of this consideration in the contemporary dialysis literature, which is possibly due to the requirement of tracking non-invasive blood pressure continuously. There are notable exceptions that have used continuous non-invasive blood pressure monitoring and included duration of event in their definition of IDH[110]. Blood pressure was assessed at 15-minute intervals in this study, so the duration of the event could have an error range of up to 30 minutes.[1] This potential error range was deemed to be unacceptable, so duration of hypotension was omitted from the following analyses.

[1]For example, consider 3 consecutive blood pressure measurements, 15 minutes apart. Blood pressure could fall immediately following the first measurement and recover just prior to the third measurement – a duration of up to 30 minutes.

4.1.2 The subgroup for event rate analyses

Of the total dataset of 603 study sessions, 591 were complete – see Figure 4.1. Only the first four sessions for each patient were considered, which was the optimal number that maximised the data available for analysis but minimised the potential 'weighting' bias from the analysis of a different number of sessions from each patient. Event rates (percentage of study sessions in which an event defined by a particular stratification was observed) were calculated for each level.

4.1.3 Magnitude and rate of change of systolic BP

The first intradialytic systolic blood pressure was taken as 'baseline' and the deviation from baseline was calculated for each session. The magnitude of change for SBP during dialysis was assessed as the difference between the baseline reading and minimum intradialytic SBP and expressed as a percentage of baseline i.e. $\frac{BaselineSBP-MinimumSBP}{BaselineSBP} * 100(\ \%)$. The rate of change of SBP was assessed as the maximum change between two consecutive 15-minute measurements as a percentage of the baseline value i.e $\frac{SBP_{t-15}-SBP_t}{BaslineSBP} * 100$ (% where t = time of SBP measurement in minutes). On the basis of these results, a stratification label was assigned to each study session. If more than one hypotensive episode occurred during dialysis, the session was labelled according to the episode with the highest risk score for hypoperfusion.

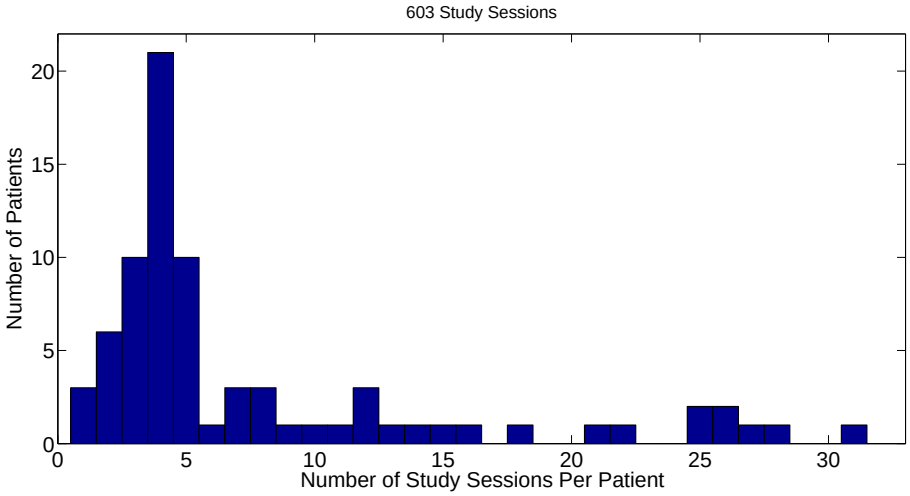
4.1.4 IDH rates according to KDOQI and EBPG

For comparison, and so that the stratified event rates can be interpreted in context, the rate of IDH according to KDOQI and EBPG guidelines was also calculated as the percentage of sessions in which SBP decreased by ≥20mmHg or MAP decreased by ≥10mmHg, associated with symptoms and an intervention[19][120].

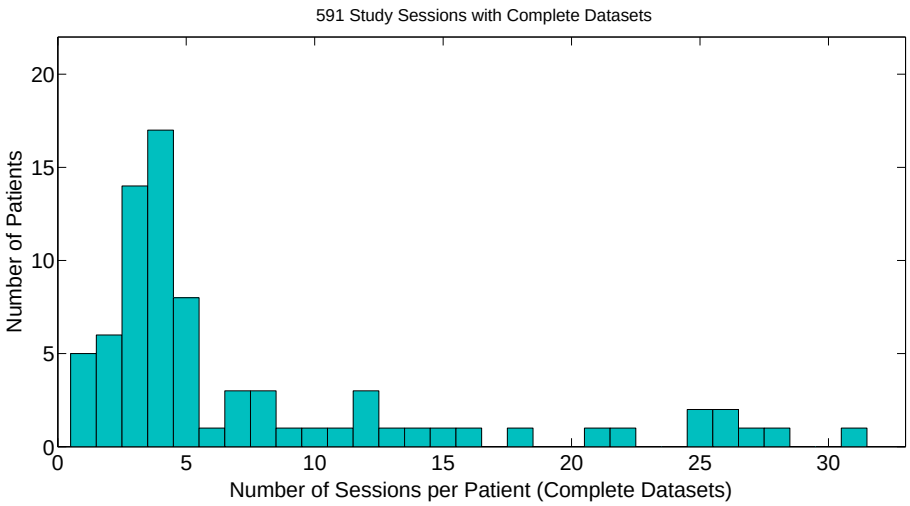
4.2 Results

In total, 52 of the 77 patients had at least four complete session datasets. Event rates were analysed for the first four sessions from each of these 52 patients (a

total of 208) and are presented in Table 4.2. For the purposes of this thesis, and according to findings presented in Chapter 3, IDH is defined as a fall in SBP by >20% of baseline to <100mmHg, with or without accompanying symptoms. According to this definition (which relates to stratification grades 7, 8, 9 & 10), the event rate for the study patients was 28.9%, but reduces to 10.6 % if only symptomatic episodes are considered. By comparison, the event rate of IDH according to KDOQI and EBPG guidelines for these 208 sessions was $\frac{17}{208} = 8.2\%$. Alternatively, $\frac{14}{52} = 26.9\%$ of patients experienced at least one event.



(a)



(b)

Figure 4.1: Total number of study sessions per patient (a). Number of complete datasets per patient (b).

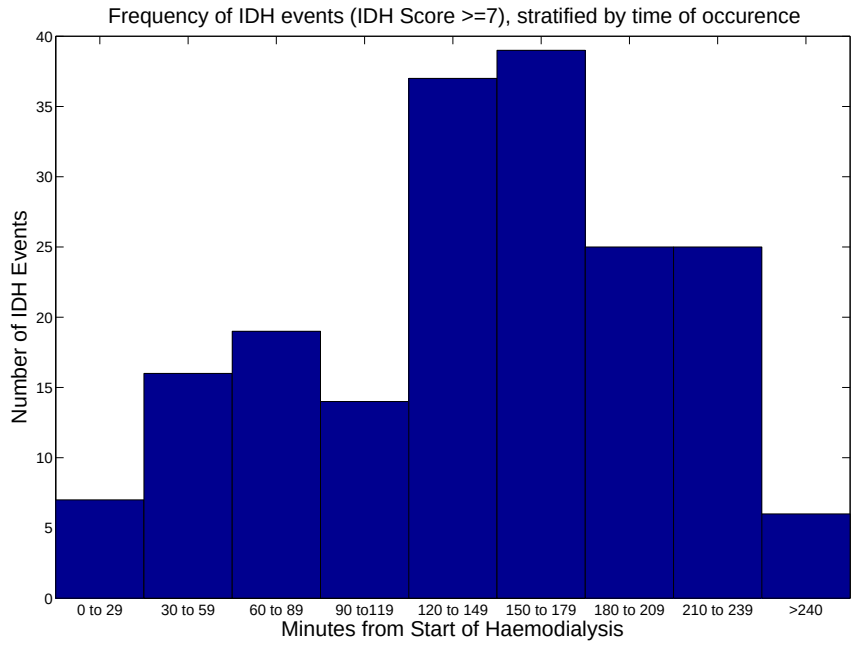
Table 4.1: Stratification score according to change in systolic BP

Score	Description
1	Fall in SBP by >20% of baseline without symptoms
2	Fall in SBP by >20% of baseline with symptoms
3	Abrupt fall* in SBP by >20% of baseline without symptoms
4	Abrupt fall* in SBP by >20% of baseline with symptoms
5	Fall in SBP to <100mmHg without symptoms
6	Fall in SBP to <100mmHg with symptoms
7	Fall in SBP by >20% of baseline to <100mmHg without symptoms
8	Fall in SBP by >20% of baseline to <100mmHg with symptoms
9	Abrupt fall* in SBP by >20% of baseline to <100mmHg without symptoms
10	Abrupt fall* in SBP by >20% of baseline to <100mmHg with symptoms

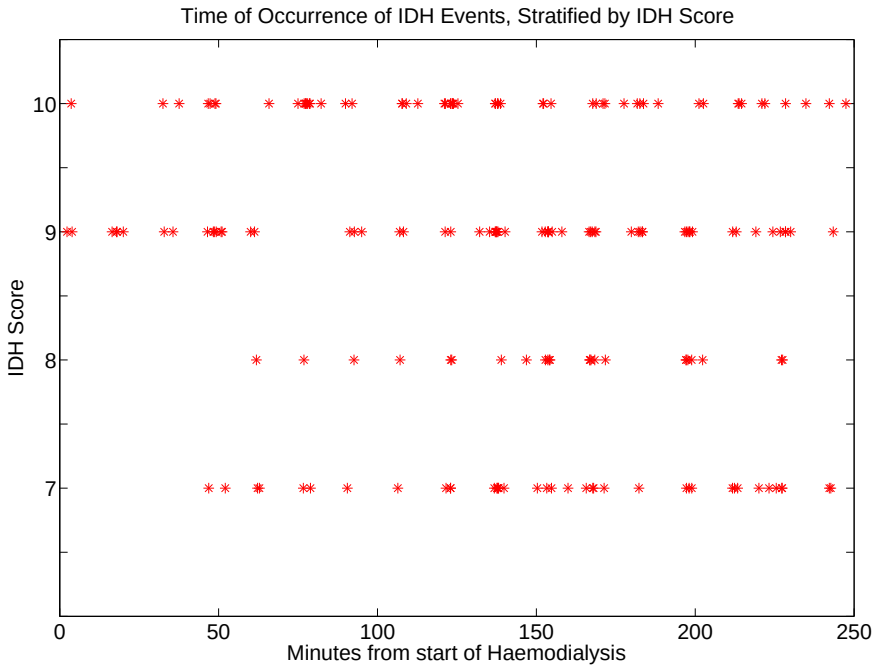
*Abrupt is defined as >20% reduction in SBP over ≤15 minutes

Table 4.2: Intradialytic event rates according to stratification score

Extent of fall in SBP	**Score Combination** (All sessions)	**%**	**Score Combination** (Symptomatic Subgroup)	**%**
Fall in SBP by >20% of baseline	1,2,3,4,7,8,9,10	62.0	2,4,8,10	17.8
Abrupt fall in SBP by >20% of baseline	3,4,9,10	33.2	4,10	12.0
Fall in SBP to <100mmHg	5,6,7,8,9,10	32.2	6,8,10	11.1
Fall in SBP by >20% of baseline to <100mmHg	7,8,9,10	28.9	8,10	10.6
Abrupt fall in SBP by >20% of baseline to <100mmHg	9,10	18.8	10	7.2



(a)



(b)

Figure 4.2: IDH Events: Time of IDH Occurrence (a), and Time of Occurrence Stratified by IDH Score (b).

4.3 Discussion

This chapter emphasised the reasons for considering dialysis-induced hypoperfusion and not just hypotension, which essentially serves as a convenient surrogate for the former. Hypoperfusion is unlikely to be an all or nothing condition as perfusion to some tissues may well be compromised while perfusion to other tissues remains sufficient. These hypoperfusion threshold(s) are likely to vary significantly between patients, and the use of symptoms as a surrogate marker for hypoperfusion appears to be unreliable, at least on a population-basis. This chapter stratified each IDH episode so that the effect of predictive or future intervention strategies could be assessed according to magnitude and rate of change of blood pressure, and therefore the perceived risk of hypoperfusion. The duration of the hypotensive episode is also likely to play an important part in this stratification, since ischaemia related injury is a function of time, but the intermittent nature of the NIBP assessments meant that the assessment of this parameter was likely to be subject to a large degree of error and was therefore considered too unreliable for inclusion in this study.

Incorporating results from Chapter 3, IDH scores $\geq$7 appeared to represent those at significant risk, with 10 representing the highest risk of intradialytic hypoperfusion. Figure 4.2 showed that IDH was more frequent in the third hour of dialysis (120 to 180 minutes from bleed-out), which supports the findings of other investigators[52] as discussed on page 16. Analysing episodes by stratifying according to IDH score did not alter these findings. Interesingly, despite more stringent blood pressure criteria, the inclusion of asymptomatic patients in this stratification identified significantly more at-risk dialysis sessions than were identified according to the KDOQI and EBPG definition of IDH (28.9% vs 8.2%). As stratification levels 7 and 9 included asymptomatic sessions, the identification of events during these sessions is dependent on continuous blood pressure monitoring not just to establish when or how often these episodes occur, but also, importantly, the duration of an episode within a particular individual. Methods for continuous blood pressure estimation during dialysis are presented in the following chapter.

Chapter 5

Continuous Blood Pressure Monitoring

5.1 Introduction

Results from Chapter 3 demonstrated that patients' systolic blood pressure often falls by >20% baseline to <100mmHg during dialysis. These potentially detrimental hypotensive episodes may or may not be accompanied by symptoms traditionally associated with hypoperfusion, such as nausea, dizziness, or cramp. As symptoms are therefore not a reliable indicator of hypotension, these asymptomatic episodes would not be detectable without more frequent and ideally continuous blood pressure monitoring during haemodialysis. Continuous monitoring in this context is defined as a beat-to-beat estimation of blood pressure approximating a sampling frequency of one Hertz (i.e. every second in a patient with a heart rate of 60 beats per minute). The need for continuous monitoring is important when considering the untested hypothesis that intervention to mitigate these asymptomatic episodes during dialysis may have a positive impact on the morbidity and mortality associated with dialysis.

5.1.1 Existing strategies for continuous BP monitoring

5.1.1.1 Arterial catheter: The gold standard

An indwelling intra-arterial catheter with pressure transducer is the most accurate and widely established means of obtaining beat-to-beat blood pressure[123]. The arterial pressure transduced from a peripheral site, such as the radial artery, is used as a surrogate for systemic arterial blood pressure, assuming that the vascular tree is of uniform distensibility and free from atheromatous disease or strictures which may result in readings subject to error. Arterial lines are invasive and are usually reserved for the monitoring of hospital inpatients in high dependency areas, not only due to the critical nature of the patient mandating close physiological monitoring, but also because of the skills and expertise required to insert the catheter, monitor for signs of infection or dislodgement and recognise potential complictions such as emboli, vascular ruptures or fistulae, and any potentially critical compromise of the distal circulation[124]. For these reasons, the widespread use of this type of monitoring for dialysis outpatients is impractical and not without risk in a patient population where blood vessel patency is of prime importance because of the limited sites available for the surgical formation of arterio-venous fistulae (henceforth referred to as AVF) as vascular access for haemodialysis.

Non-invasive alternatives

Non-invasive alternatives for continuous blood pressure monitoring have been piloted in haemodialysis patients with varying degrees of success. The utility of these devices as clinical tools has not yet been established as most of the experience using these devices has been within the research arena. Techniques using the Finapres device and pulse transit time are discussed here as examples, as these are the only methods with literature pertaining to their validation for use in haemodialysis.

5.1.1.2 The Finapres device

The Finapres is a beat-to-beat haemodynamic monitor that uses a finger cuff and a volume-clamp method to obtain a continuous pulse waveform. The volume-clamp method involves variable finger cuff pressures to offset the changes in finger artery diameter detected by infra-red photoplethysmography[1]. Using an extremely rapid servo control system with a finger cuff actuator, the Finapres adjusts the pressure in a finger cuff to keep a reference photoplethysmogram flat throughout systole and diastole. The waveform of the applied pressure exerted to maintain a constant finger artery diameter correlates with the intra-arterial pressure waveform of the finger. Continuous beat-to-beat blood pressure is estimated using transfer functions that are generalised for all patients and physiological states, leading to concerns about performance in certain sub-populations. A later model of the Finapres, the Finometer, uses advanced waveform analysis algorithms to estimate cardiac output and total peripheral resistance in addition to blood pressure.

Finapres: Validation for blood pressure

To date there has been limited work validating the use of the Finapres for blood pressure estimation in haemodialysis, but validation has been reported in some small studies of other patient groups[125][126][127]. The applicability of these studies, some of which contain pregnant women[126], may be limited in the context of haemodialysis, because assumptions used in the device's algorithms regarding the vascular elasticity of these groups may not hold true for dialysis patients known to be at risk of hypertensive arterial intimal hyperplasia and vascular calcification. However, studies validating the technique in patients with vascular disease and in the elderly[127] may be more applicable to the dialysis population. In his thesis[110], Hakim compared pre- and post-dialysis blood pressure measurements between the Finometer and an oscillometric NIBP monitor in 25 patients (of 33 patients recruited, four withdrew consent due to the burden of additional monitoring equipment and waveforms were not detectable in four

[1]This is based on the Penaz Principle which states 'a force exerted by a body can be determined by measuring an opposing force that prevents physical disruption'

of the remaining 29 patients). Hakim found no significant difference between the Finapres and NIBP estimates for pre- and post-dialysis SBP, DBP and MAP, and showed a significant correlation between the Finometer and NIBP (r^2=0.64, 0.35, and 0.5 for SBP, DBP, and MAP, respectively). Using Bland-Altman plots, the estimated bias for SBP, DBP and MBP at 0.6, 1.44 and -1.12 mmHg respectively and the 95% limits of agreement (mean difference ± 1.96 SD) were 31 to -30, 24 to -22 mmHg, and 21 to -23, for SBP, DBP and MAP respectively. Interestingly, of the 7 of 25 dialysis patients who experienced a hypotensive episode (defined as <90mmHg for a duration of at least 10 minutes) none were symptomatic, leading to his conclusion that continuous blood pressure monitoring has major benefits over the existing protocol of pre- and post-dialysis NIBP with additional measurements only if the patient experiences symptoms of hypotension.

5.1.1.3 Pulse transit time

Pulse Transit Time (PTT), a function of the related Pulse Wave Velocity, is time taken for the incident pressure wave to travel from the heart following systole to the peripheral circulation, usually the artery supplying the finger tip. PTT is calculated as the time lag from the 'R' wave of the ECG to the start of the upslope in the corresponding PPG waveform of the finger. Changes in PTT result from dynamic changes in arterial compliance which are thought to be strongly correlated with blood pressure i.e. a rise in blood pressure is associated with decreased arterial distensibility and a more rapid propagation of the pressure wave, measured as a reduced PTT. The PTT has been described in the dialysis literature as an independent metric for the assessment of cardiovascular morbidity and predictor of mortality[128] but little work has been done on investigating PTT trends as a surrogate for blood pressure changes during haemodialysis. Progress in this area to date is outlined below.

Pulse transit time: Validation for blood pressure

Ahlstrom *et al* showed that there was good correlation between the PTT and SBP for 'normal subjects' undergoing induced hypotension using lower body negative pressure to reduce venous return (r = 0.80 ± 0.06 [mean ± SD]), but did

not present correlative findings when using the same technique on four dialysis patients because they report that blood pressure variability during dialysis was minimal and that group statistical analysis was therefore inappropriate[129]. Mambelli and colleagues investigated the correlation of estimated blood pressure ('Esys') from the commercial HASTE[1] device with blood pressures obtained from both an intra-arterial catheter and a NIBP cuff in 18 dialysis patients. The HASTE device uses the principles of PTT to generate the Esys estimate. The authors report a good correlation between the HASTE device and the radial arterial catheter measurements (mean difference between invasive SBP values and Esys was 0.7±13 mm Hg ($p < 0.01$; $r = 0.80$) but the correlation between the HASTE device and the NIBP cuff was not significant[130].

5.2 Intra-fistula pressures: An alternative method for BP monitoring

As the gold standard for continuous blood pressure monitoring involves intra-arterial catheterisation for pressure transduction, a logical alternative involves the use of the indwelling fistula needles to transduce the intra-fistula pressure for use as a near-arterial surrogate. However, there are important variables which need to be considered with this approach — see Figure 5.1 on page 73. Firstly, the flow of blood through a fistula is dependent on the calibre of the artery used for the surgical anastomosis, the patency of the anastomosis post surgical formation of the fistula, and the inflow of venous blood returning from the hand downstream of the AVF. The flow of blood through the anastomotic conduit is unlikely to be representative of the laminar flow typical of integral arterial vessels, and the presence of needles within the fistula withdrawing and returning blood using a peristaltic pump at potentially variable rates is likely to introduce further turbulence. The fistula needles are sited within the venous side of the capillary circulation, so pressure fluctuations within the fistula may be subject to changes in both systemic arterial pressure and, to a greater or lesser extent, fluctuations in central venous pressure. Structural changes associated with maturation of

[1] Acronym for Harmonised Alert Sensing Technology

the AV fistula post creation, and the formation of impeding strictures which commonly complicate the established fistula, may also result in changes to intra-fistula pressure over time. Finally, step changes in cardiac performance status or hydration status may occur over a period of weeks or months and also affect intra-fistula pressure.

5.2.1 Intra-fistula pressure monitoring: Previous work

Nakane and colleagues investigated the use of intra-fistula pressure as a surrogate of systemic arterial pressure in a study of 9 dialysis patients[131]. They punctured the blood tubing of the outflow (arterial) dialysis needle with a 25 gauge fine needle and advanced this through the lumen of the 15 gauge fistula needle. The tip of the pressure transducer was then secured about 5 mm beyond the tip of the fistula needle, from which intra-fistula pressure was measured continuously. For this experiment, the return (venous) dialysis needle was not sited in the fistula; blood was returned to an alternative large vein but the exact location was not specified. Systemic arterial pressure was concomitantly measured, although again, exact methods are not described. The authors found that the ratio of intra-fistula blood pressure to mean systemic arterial pressure was 65%±6% for the group, and this ratio did not change significantly when censored at start of HD, after 1 hour, after 2 hours, after 3 hours, and on completion of HD at 4 hours. However, Nakane *et al* describe some patients in whom the mean intra-fistula blood pressure decreased more than the relative systemic mean arterial blood pressure and attributes these findings to changes in central venous pressure, although this was not measured directly[131]. A study by Agishi *et al* in 1979 used a double-lumen cannula inserted into the distal segment of a fistula between the femoral artery and femoral vein in dogs to investigate 'fistulated venous pressure'. One lumen was used as an outflow port to the dialysis machine and the other lumen was connected to an external pressure transducer. The authors report a 'strict', statistically significant ($p \leq 0.01$) correlation between fistulated venous pressure and systemic arterial pressure, but detailed results were not presented, apart from an example in a figure, in which the r value was 0.918. The technique was also applied to a single haemodialysis patient, but again, data were not

presented in the manuscript[132].

5.3 Transduction of AVF pressure: A novel approach

The methods described by Nakane *et al* would not be practical for use as a clinical tool. As dialysis machines are routinely fitted with arterial and venous line pressure sensors for detecting needle dislodgement or clotting within the extracorporeal circuit, it is conceivable that this extracorporeal system could be additionally used for tracking changes in intra-fistula pressure at any given constant blood pump speed. The rationale behind this hypothesis is described below and uses Figure 5.2 on page 74 as an illustrative example.

5.3.1 Using pressure sensors in the extracorporeal circuit

During haemodialysis, blood is extracted, filtered and returned to the patient. The pressure differential required to move blood along the extracorporeal circuit is generated by a peristaltic pump. The pump revolves at variable speeds, according to the prescribed blood flow rate, which is typically set between 300-400 ml/min depending on fistula maturity. The circuit upstream of the pump is under negative pressure and this is monitored using the arterial pressure sensor. This negative pressure extracts blood from the fistula through the arterial needle. The circuit downstream of the pump is under positive pressure. This positive pressure is used to push blood through the dialyser and then back through the venous needle to the patient. The venous side of the circuit is monitored using the venous pressure sensor. An additional pressure sensor is situated at the inflow to the dialyser, but this is not of relevance to this section and is not discussed further.

It can be seen from Figure 5.2 on page 74 that any clotting or dislodgement of the needle on the arterial side only would result in a reduction of pressure (i.e. more negative) at the arterial pressure sensor; however, assuming the venous side is not momentarily affected, the pressure would remain unchanged on the venous side of the extracorporeal circuit. If the disruption resulted in the

arterial pressure being lower than the 'guard' threshold then the pressure alarm would sound and the pump would stop, pending investigation of the problem by the clinical staff. Likewise, any clotting or dislodgement on the venous side of the circuit would result in an increase in pressure (i.e. more positive) detected by the venous pressure sensor but the arterial pressure would remain unaffected. It should be noted, however, that in theory, pressure changes occurring anywhere patient-side of the venous bubble trap could be attenuated by the small volume of compressible air within the bubble trap. This is relevant to a later discussion regarding choice of sensor from which to estimate intrafistula pressure. Nevertheless, if a disruption resulted in a venous pressure above the 'guard' threshold, the venous pressure alarm would sound and the pump would stop pending an intervention to rectify the problem.

5.3.2 Hypothesis Generation

In summary, any mechanical problem or disruption to blood flow within the needles or tubing of the extracorporeal circuit would result in a divergent trend (one blood pressure trend has positive gradient and the other trend has a negative gradient) when the arterial and venous pressures are monitored continuously, plotted as a time series, and compared. However, concordant (both positive or both negative gradients) changes in arterial and venous pressure trends could only be attributable to pressure changes within the AV fistula itself. This realisation is pivotal to the proposed hypothesis that fistula pressure, as a surrogate for systemic arterial pressure, can be monitored using the dialysis machine pressure sensors without the need for additional, more invasive monitoring equipment.

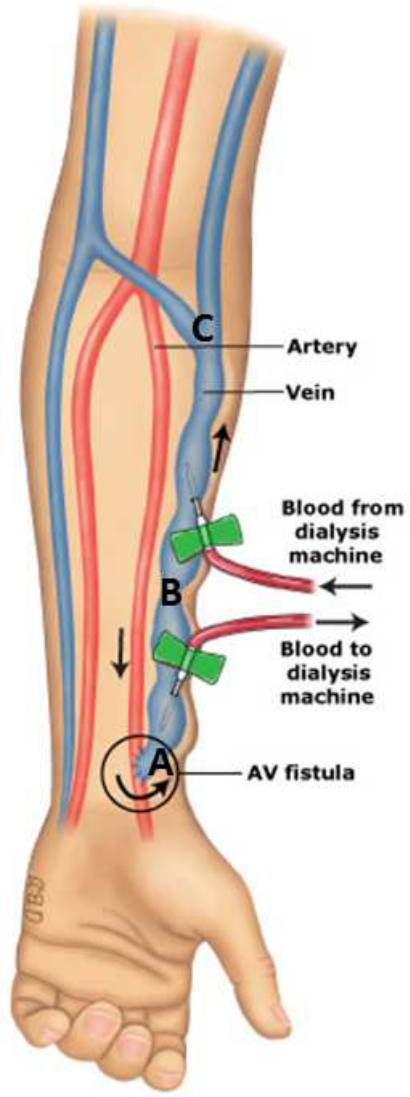


Figure 5.1: Schema of an arterio-venous fistula (AVF)

A venous stenosis at the anastamosis (labelled 'A') will result in reduced blood flow, and therefore pressure drop across the fistula. This scenario may lead to a low signal-to-noise ratio (discussed later) when correlating changes in intrafistula pressure with changes in systemic blood pressure. A fixed pressure difference between the arterial and venous pressure sensors will occur at the point labelled 'B' if the patient is undergoing ultrafiltration, when the volume of blood returned by the venous needle is lower than the volume of blood removed from the AVF by the arterial needle. Changes in the UF rate may be seen as step changes in this pressure differential. An anatomical venous stenosis at point B would also result in a fixed pressure difference between the arterial and venous sensors. Proximal venous stenoses (labelled 'C') typically cause high AVF pressures, which would be detectable in both sensors as a fixed increase in pressure. Image adapted from a figure courtesy of Dr Pradip Chakrabarti

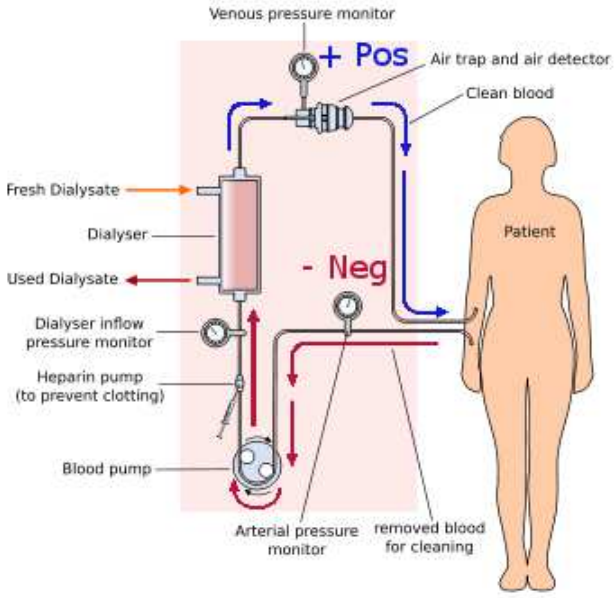


Figure 5.2: Schema of a dialysis circuit showing pressure sensors

The peristaltic blood pump generates a negative pressure in the arterial line/needle (in red) which is measured by the arterial line pressure sensor, and a positive pressure in the venous line/needle (in blue) which is sensed by the venous line pressure sensor located at the dialyser side of the venous bubble trap. Adapted from http://www.renalmed.co.uk/database/haemodialysis-hd

5.4 Methods

5.4.1 Patient Selection

Patients with a functioning AV fistula were selected from the Observational Study (OB) dataset for analysis. These patients were divided into two subgroups, those with a radial AVF and those with a brachial AVF, to test whether the anatomical position of the fistula had an influence on the ability to monitor intrafistula pressure. In total 24 patients with a radial AVF (177 sessions) and 40 patients with a brachial AVF (325 sessions) were selected for further study (the remaining 13 patients without a functioning AVF were excluded from the analysis).

5.4.1.1 Dialysis Needle Size

Resistance to blood flow, and therefore the fall in pressure across a dialysis needle, is proportional to the size (gauge) of the needle. Of the 64 patients above, 56 (87.5%) dialysed using 15 gauge needles, and 8 (12.5%) dialysed using 16 gauge needles. These are detailed in Appendix D on page 185. Dialysis needle size was not varied during the Observational Study.

5.4.2 Extracting raw pressure data from the HD machine

As described in Section 2.2.5 on page 33 of General Methods, B.Braun's Nexadia software is an add-on software package to the Dialog+ dialysis machine. It time-synchronises the intermittent Non-invasive blood pressure (NIBP) recordings with specific dialysis machine data, including blood pump speeds and arterial and venous line pressures. At present the arterial and venous line pressure data have limited clinical utility and are usually accessed only by specialist renal technicians to monitor the performance and efficiency of the dialysis machine during service. These machine parameters are sampled every 10 seconds and stored in an internal database. While sampling every 10 seconds (0.1 Hz) is not equivalent to continuous (beat-to-beat) sampling, it was considered to be of sufficient resolution to detect any clinically significant changes in systemic blood pressure.

Nyquist sampling theory[1]states that the sampling frequency should be twice the maximum frequency in the signal of interest, so the sampling frequency used in this study would be able to detect changes in blood pressure occurring over 20 or more seconds. At the end of each session, blood pump speed and pressure data were extracted from the database and converted into Matlab files.

5.4.3 Signal Processing

Extraction of the signal of interest

As discussed in Section 5.3.2 on page 72, concordant arterial and venous pressure changes were likely to represent intrafistula blood pressure variation and, therefore, these concordant changes were the signal of primary interest. Discordant pressure changes would be expected on initiating the blood pump at the start of dialysis, stopping the blood pump at the end of dialysis, or changes to the blood pump speed during dialysis. Discordant pressure changes would also be expected if needles were dislodged or if clotting occurred within the extracorporeal circuit. These discordant changes represented 'noise' in the signal and were removed to enable further analysis. This was done by iterating through the first derivatives for both the arterial and venous pressure signals and excluding any values where the gradients had opposite signs at the same sampling time point (i.e. one positive and one negative). Missing values were then estimated using linear interpolation - an example of these processes is illustrated in Figure 5.3 on page 79.

Filtering the data for correlation with NIBP

Although concordant pressure changes are, by definition, evident in both the arterial and venous pressure series, the arterial needle is sited most distally (closer to the anastomosis between the vein and the supplying artery) and was, therefore, the series that was deemed to be most representative of systemic arterial pres-

[1]The Nyquist sampling theorem states that for a limited-bandwidth signal with maximum frequency 'fmax', the equally-spaced sampling frequency 'fs' must be at least twice the frequency of fmax, (i.e. fs > 2*fmax) in order to have the signal reconstructed without a form of distortion known as aliasing.

sure. In addition, Section 5.3.1 on page 71 highlighted a potential for intrafistula pressure changes to be buffered by the compressible air in the bubble trap positioned between the venous needle and venous pressure sensor. For these reasons, while inclusion of the venous pressure data was important to help identify the signal of interest, it was not required after this methodological step and further analysis was conducted on the arterial pressure data only. To allow comparison with NIBP, the arterial pressure data was smoothed using a 7-point (one minute) median filter window which advanced by 3 points on each iteration — see Figure 5.4 on page 80. The value for the arterial pressure waveform that was correlated with NIBP was selected as the median value that immediately preceded the time of the NIBP measurement. Smoothing with a median filter prior to correlation was deemed appropriate because the NIBP reading itself represents an average pressure reading over time (typically 30 to 60 seconds is taken to inflate and deflate the cuff). Both SBP and MAP were used for initial comparison against the arterial pressure data because at this stage it was not known which of these blood pressure metrics, if any, would show superior correlation with intra-fistula arterial needle pressures. An example of a scatter plot of SBP vs median-filtered arterial needle pressure data is shown in Figure 5.5 on page 81.

5.4.4 NIBP cuff accuracy: Comparison with manual sphygmomanometry

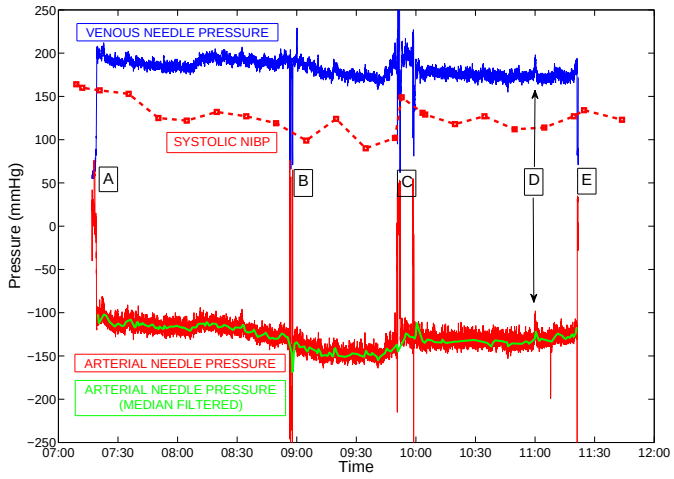
Comparing arterial line pressures with NIBP assumes that NIBP measurement using an oscillometric cuff is itself an accurate way of determining blood pressure. Oscillometric devices are required to meet standards defined by the British Hypertension Society (BHS) and/or the United States Association for the Advancement of Medical Instrumentation (AAMI)[133]. BHS criteria state that at least 50 % of the measurements from the test device should be $\leq$5mmHg difference from the standard (manual syphygmomanometry); 75% of the measurements should be $\leq$10mmHg difference; and 90% of the test device measurements should be $\leq$15mmHg difference from the standard[134]. AAMI criteria state that a test device must not differ from the standard by a mean difference $<$5mmHg or a standard deviation $>$8mmHg[133]. In order to validate the accuracy of the NIBP

cuff used for correlation with arterial line pressures, a series of 25 NIBP measurements were taken using an appropriately sized cuff sited at heart-level on the upper arm of a healthy volunteer. NIBP measurements were repeated on four different days (i.e. 100 total), and compared with a simultaneous assessment using a manual syphygmomanometer cuff placed at the same level on the contralateral upper arm. The assessor was blinded to the digital output of the NIBP device for the duration of the experiment — see figure 5.6 on page 82. The mean absolute error (average absolute difference between the manual sphygmomanometer and the oscillometric NIBP) and standard deviation of this error was calculated. Bland-Altman plots[1] were used to illustrate the agreement and any fixed bias between the two measurement techniques[135].

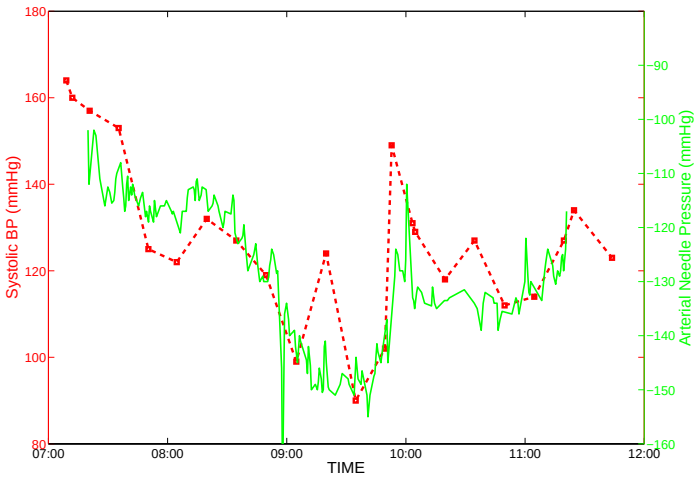
Increasing the signal-to-noise ratio

Prior to analysis, it was recognised that a low signal-to-noise ratio may adversely attenuate any correlation between the signals of interest (arterial needle pressure and non-invasive SBP). For this reason correlation analyses were performed not only on the whole dataset, but also for a censored subset, in which sessions with a low signal-to-noise ratio were excluded. For the censored subset, dialysis sessions were excluded from the correlation analysis if the variation of blood pressure during a session was within the range that was subject to error because of inaccuracies introduced by the use of a non-invasive oscillometric cuff. For example, if blood pressure were to remain relatively constant during dialysis and vary by only, say, a few millimetres of mercury (mmHg), this variation would be within the range of error of most non-invasive cuff devices for measuring blood pressure. In such cases, the signal-to-noise ratio would be low and correlation analysis would be unrepresentative due to the limitations of the NIBP device. For this study, the potential error resulting from use of the B.Braun NIBP device was estimated using the data from the comparison of manual BP measurements with automated B.Braun NIBP measurements, as described in Section 5.4.4. Dialysis sessions for which the maximum minus minimum intradialytic SBP was $\leq$ 20

[1] The mean difference between two measurement techniques is the estimated bias, and the SD of the differences measures the random fluctuations around this mean. If the differences within mean $\pm$ 1.96 SD are not clinically important, the two methods may be used interchangeably.



(a)



(b)

Figure 5.3: Arterial needle pressure signal processing for correlation with SBP

Panel (a) shows the SBP (dashed red line), raw data for arterial (solid red line), and venous (solid blue line) needle pressures for a typical dialysis session. 'A' and 'E' represent discordant pressures due to the pump starting up and slowing down at the beginning and end of dialysis, respectively. 'B' and 'C' represent discordant pressures due to temporary suspension of the blood pump, in response to the patient experiencing episodes of IDH. 'D' shows a concordant change in arterial and venous pressure at 11:00, which is likely to represent a true fluctation in systemic blood pressure. The solid green line shows the median filtered arterial needle pressure time series after removal of the discordant trends (A,B,C & E).
Panel (b) illustrates the visual correlation between the median filtered arterial needle pressure data and SBP.

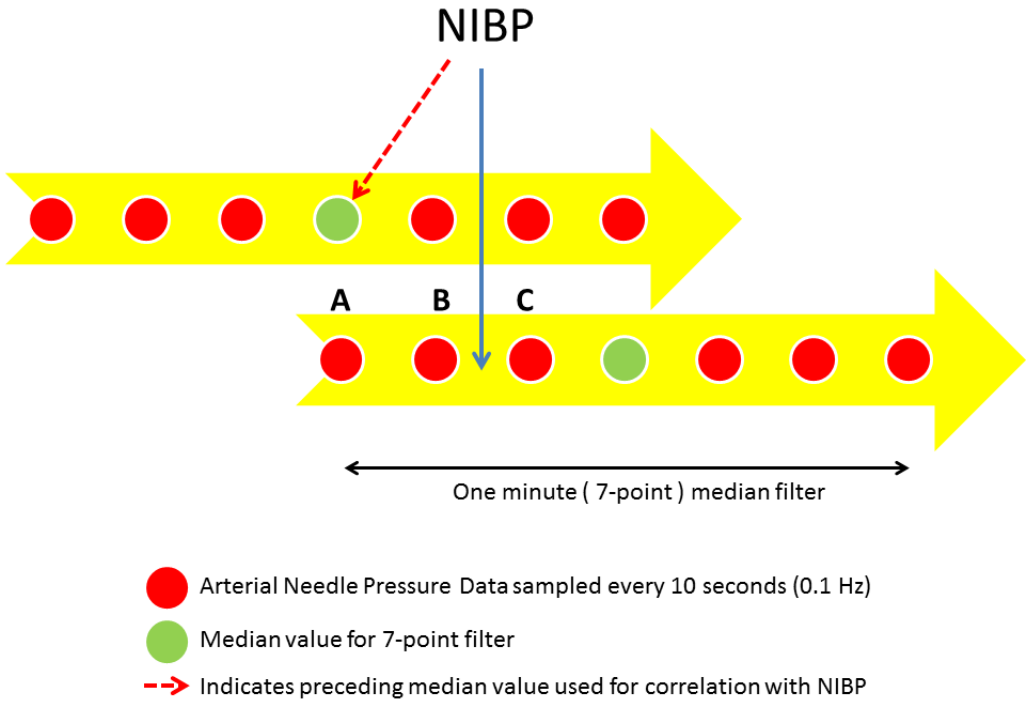
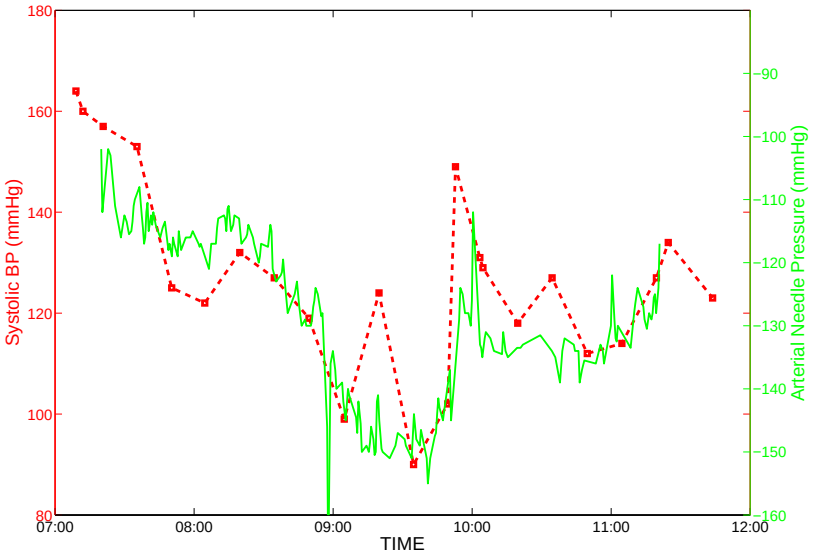
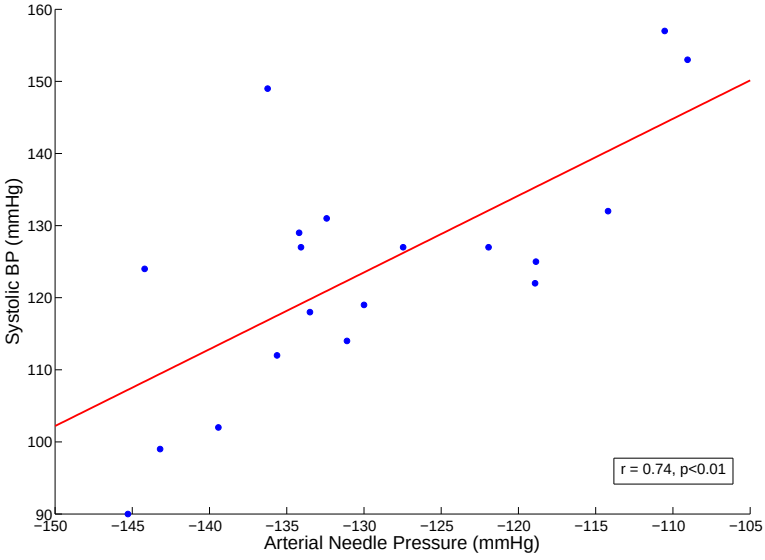


Figure 5.4: Correlation of median-filtered arterial needle pressures with NIBP
The red circles represent arterial needle pressure data sampled at 0.1Hz. The yellow arrows represent a 7-point median filter which overlaps by 4 points on each iteration. In this illustrative example, the NIBP measurement was reported at a time between 'B' and 'C' (solid blue arrow). However, the median value which immediately precedes the NIBP at time 'A' was selected for the correlation analysis (as indicated by the dashed red arrow).



(a)



(b)

Figure 5.5: Correlation of arterial needle pressure and SBP
Panel (a) shows the SBP (dashed red line) and median-filtered arterial needle pressure (solid green line) data. Panel (b) shows the correlation between SBP and arterial needle pressure at the times when NIBP was measured (i.e. correlation using a total of 18 intradialytic NIBP measurements)



Figure 5.6: Validation of the B.Braun integrated oscillometric NIBP device
Photograph taken and reproduced with subject's permission

mmHg or where the standard deviation was $\leq$ 5 mmHg were excluded from the correlation analysis. To investigate whether variance of blood pressure was indeed a significant contributor to the postulated signal-to-noise ratio, correlation analyses were performed for sessions grouped according to the standard deviation of NIBP for each dialysis session i.e. σ >5 mmHg, σ >10 mmHg, σ >15 mmHg, and σ >20 mmHg.

5.4.5 Using arterial line pressures to identify IDH episodes

The ability to track blood pressure continuously is important but the primary reason for blood pressure monitoring during dialysis is so that episodes of IDH may be readily identified. The utility of arterial pressure monitoring in detecting IDH was tested by assessing whether sessions that experienced an episode of IDH (defined as an IDH stratification score of $\geq$7) had a concomitant (occurring within a 15 minute window preceding the event[1]) nadir in arterial line pressure. The nadir was defined as the pressures occupying the lowest decile of all pressures recorded during the session rather than the minimum value because the minimum value assumes that only one event occurred in a particular session. The number

[1]The width of the window was 15 minutes because it was difficult to establish exactly at what time following the preceding NIBP measurement, taken 15 minutes previously, the IDH event occurred.

of sessions with IDH episodes that occurred contemporaneously with the nadir in arterial pressure were expressed as a percentage of the total number of sessions experiencing IDH. For sessions in which more than one IDH event occurred, the event with the lowest associated blood pressure was considered.

5.5 Results

5.5.1 Validity of the B.Braun Oscillometric NIBP device

Following 100 blood pressure measurements using both the NIBP cuff and a manual sphygmomanometer simultaneously, the mean (±SD) absolute difference between the two techniques was 4.5 (±3.7)mmHg for SBP and 6.2 (±5.9)mmHg for DBP. The agreement between the methods is demonstrated in the Bland-Altman plots shown in Figure 5.7 on page 84.

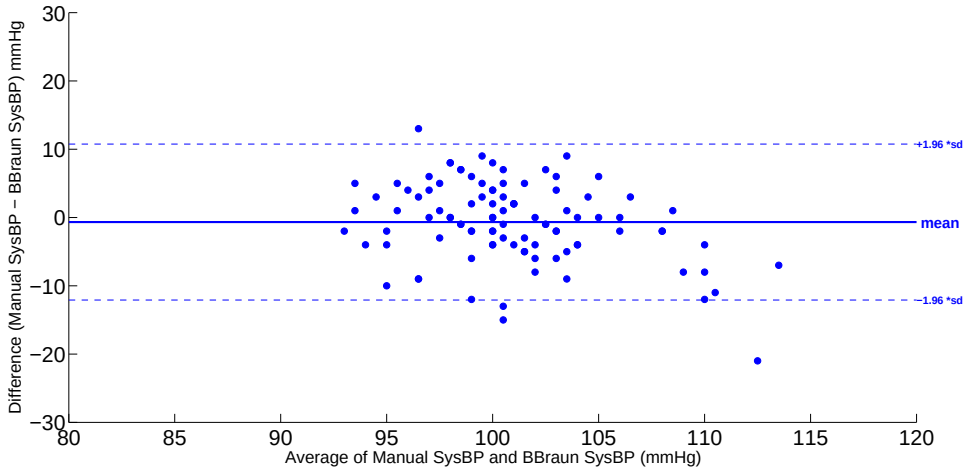
5.5.2 Analyses of the study population

SBP vs. MAP for correlation with arterial needle pressures

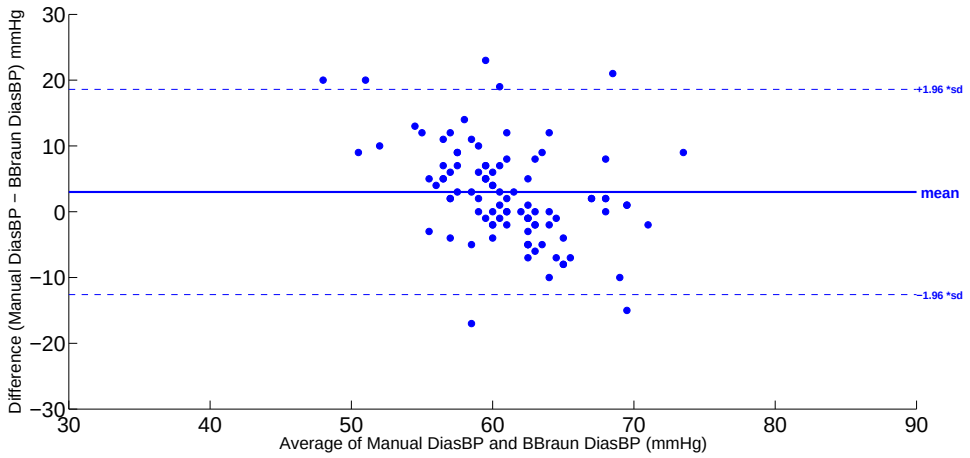
Firstly, the comparison of SBP with MAP for correlation with the arterial needle/line pressure is considered. Histograms of all sessions representing MAP (red dotted line) and SBP (blue dashed line) show no significant difference in the distribution of r-values for both radial AVFs (upper pair labelled (a) in Figure 5.8 on page 86), and brachial AVFs (lower pair labelled (b) in Figure 5.8)(p=0.48 for comparison of r-value distributions using a two-tailed t-test). Given that SBP is shown in Chapter 3 to be the most useful BP metric for defining episodes of intradialytic hypotension, this non-inferiority of SBP to MAP allowed simplification of the following analyses by consideration of correlation between arterial needle/line pressure and SBP only.

Radial vs. Brachial AVF needle pressures for correlation with SBP

A comparison of arterial needle/line pressures from radial AVFs and brachial AVFs for correlation with SBP is considered next. Figure 5.8 also demonstrates that the arterial needle/line pressure from a brachial AVF correlates with SBP



(a) Systolic: Mean absolute difference = 4.5 mmHg, SD of the difference = 3.7mmHg



(b) Diastolic: Mean absolute difference = 6.2 mmHg, SD of the difference = 5.9mmHg

Figure 5.7: B.Braun NIBP Vs. Manual Sphygmomanometer: 100 measurements

better than the arterial needle/line pressure from a radial AVF (p=0.002 for comparison of r-value distributions using a two-tailed t-test). This is represented numerically in Table 5.1 on page 87 as the percentage of sessions achieving an r-value greater than 0.5, arbitrarily defined as the lowest value associated with a good correlation. For both the uncensored and censored data, it can be seen that the proportion of Brachial AVF sessions achieving an r-value >0.5 is higher than radial AVF sessions and that this difference is statistically significant for sessions where σ >10mmHg.

Stratification of the dataset according to variance of SBP

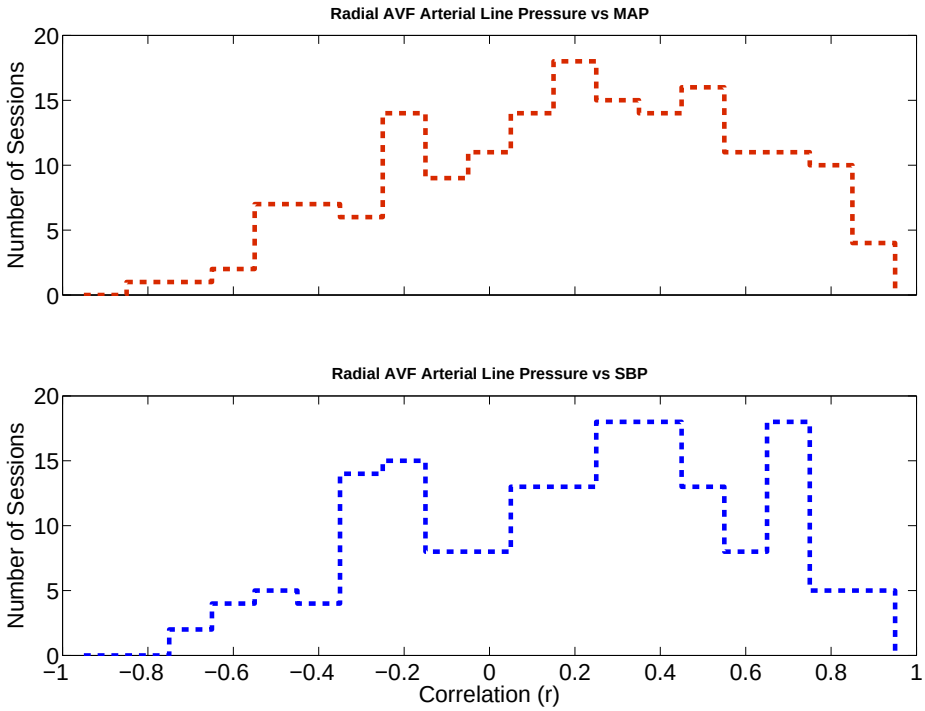
Table 5.1 on page 87 shows that the proportion of dialysis sessions with an r value $\geq$0.5 is significantly greater for sessions with high SBP variance than sessions of lower SBP variance (69.6% vs 33.6% [χ^2=10.038, p<0.005] for brachial AVF sessions with σ >20mmHg and σ >5mmHg, respectively.) In general, a high SBP variance is associated with a better correlation with arterial needle pressure, but there are some notable exceptions where sessions with a high SBP variance correlate poorly with arterial needle pressures – examples are illustrated in the patient-based analyses in Section 5.5.3.

Identification of IDH episodes

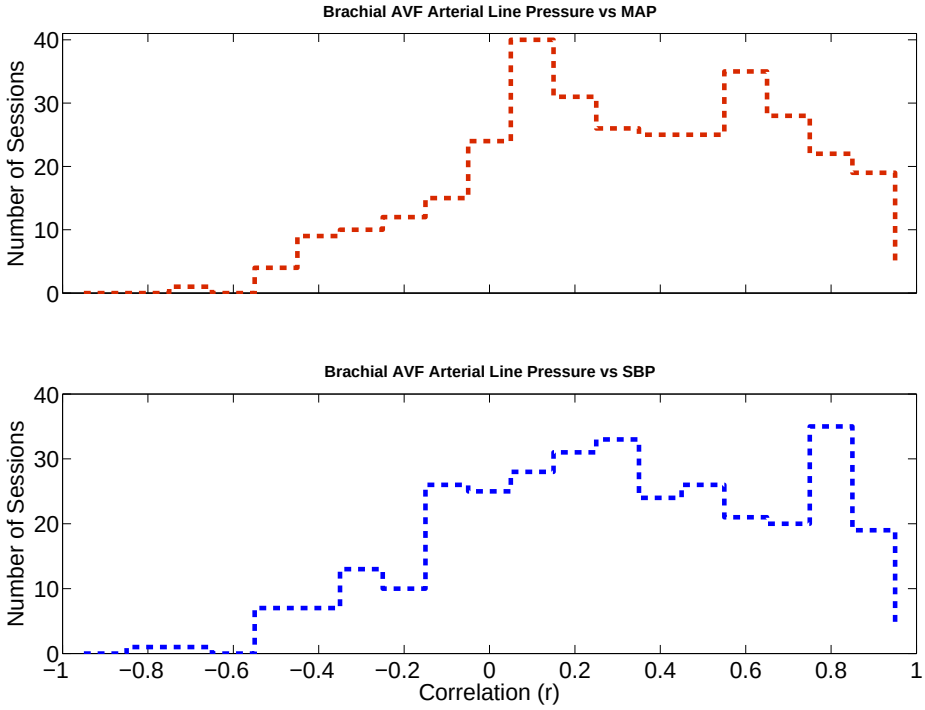
Table 5.2 on page 88 shows that the lowest decile of brachial arterial needle pressures coincided with IDH events in 60% of all sessions in which patients experienced IDH. Pressures from the arterial needle of radial AVFs performed less well, detecting only a third of the most severe IDH episodes (categories 9 & 10).

5.5.3 Patient-based analyses

On stratifying arterial pressure vs. SBP correlation analyses at the patient level, it is clear that some patients' arterial needle/line pressures correlate more strongly with SBP than other patients. Table 5.3 on page 88 presents correlation data for the top three and bottom three patients, ranked according to median r-value over all sessions for that particular patient. To put this performance data in context,



(a)



(b)

Figure 5.8: Histograms of Radial AVFs vs. Brachial AVFs for SBP and MAP

Table 5.1: Percentage of sessions with arterial needle vs. SBP correlation $\geq$0.5

	% r $\geq$0.5, stratified by standard deviation of SBP				
	All Sessions	σ >5mmHg	σ >10mmHg	σ >15mmHg	σ >20mmHg
Brachial AVF Sessions (n=325)	$\frac{88}{325}$=27.0%	$\frac{87}{313}$=27.8%	$\frac{69}{188}$=36.7%‡	$\frac{44}{85}$=51.8%‡	$\frac{16}{29}$=55.2%‡
Censored Sessions† (n=220)	$\frac{74}{220}$=33.6%	$\frac{74}{220}$=33.6%$^{\diamond}$	$\frac{60}{145}$=41.4%‡	$\frac{38}{64}$=59.4%‡	$\frac{16}{23}$=69.6%‡§
Radial AVF Sessions (n=177)	$\frac{39}{177}$=22.0%	$\frac{39}{177}$=22.0%	$\frac{29}{122}$=23.8%	$\frac{17}{65}$=26.2.8%	$\frac{7}{34}$=20.6%
Censored Sessions† (n=110)	$\frac{26}{110}$=23.6%	$\frac{26}{110}$=23.6%	$\frac{21}{79}$=26.6%	$\frac{14}{50}$=28.0%	$\frac{7}{27}$=26.0%

†Sessions with Maximum minus Minimum SBP $\leq$ 20 mmHg and standard deviation $\leq$ 5 mmHg were omitted from the analysis
‡indicates a significant (p<0.05) difference between Brachial AVF and Radial AVF proportions using Chi-Squared Test
χ^2=10.038 between $\diamond$ and § (p<0.005)

Table 5.2: IDH events and nadir arterial needle pressure

	Percentage of sessions in which nadir of arterial needle pressure is within 15 minutes of an IDH event		
Max. IDH Score	All AVFs	Brachial AVFs	Radial AVFs
7 or 8	$\frac{39}{66}$=59.1%	$\frac{33}{54}$=61.1%	$\frac{6}{12}$=50.0%
9 or 10	$\frac{58}{110}$=52.7%	$\frac{48}{80}$=60.0%	$\frac{10}{30}$=33.3%

Table 5.3: Arterial Needle Pressure vs. Systolic NIBP Correlations
Performance data from top three (a) and bottom three (b) Brachial AVF patients

(a)

Patient	Number of Sessions	Min r	Max r	Median r	% r>0.5	Median σ SBP	Median σ Art.needle pressure
10	21	0.18	0.93	0.70	80.0	17.7	12.5
32	4	0.23	0.91	0.68	75.0	13.7	12.8
59	4	0.59	0.73	0.68	100	18.7	16.9

(b)

Patient	Number of Sessions	Min r	Max r	Median r	% r>0.5	Median σ SBP	Median σ Art.needle pressure
60	5	-0.74	0.61	-0.23	20.0	20.8	4.7
53	3	-0.42	0.28	-0.30	0.0	5.2	2.87
51	4	-0.53	0.37	-0.45	0.0	6.15	7.20

examples from two patients who correlate well (OB10 and OB32) and two patients who correlate poorly (OB51 and OB60) are shown in Figures 5.9 to 5.14 on pages 91 to 96).

Patient OB10 (shown in Figures 5.9 to 5.11) underwent 21 study sessions. 17 of these sessions (80.9%) were associated with an r-value >0.5. The median r value was 0.70 (range 0.18 to 0.93). Likewise, patient OB59 (shown in Figure 5.12) demonstrates good correlation between arterial needle pressures and SBP (median r-value 0.68, ranging between 0.59 and 0.73) over a wide-range of SBP values (i.e. high SBP variability). Conversely, patient OB51 had a median r-value of -0.45 and in none of this patient's study sessions did the SBP correlate well with arterial needle pressure. It may appear non-physiological that a SBP should have a negative correlation with arterial needle (i.e. intra-fistula) pressure; speculative reasons for these results are discussed later in Section 5.6. As noted previously during the population-based analyses in Section 5.5.3, Table 5.3 also shows that patients with a stronger correlation between SBP and arterial needle pressure tend to have a higher median standard deviation for SBP. A notable exception is patient OB60 (median r = -0.23 despite median σ SBP = 20.8 mmHg). Here, however, there is a relatively large discrepancy between median σ SBP and median σ arterial needle pressure in comparison with other patients. Again, a possible explanation for these results is discussed later.

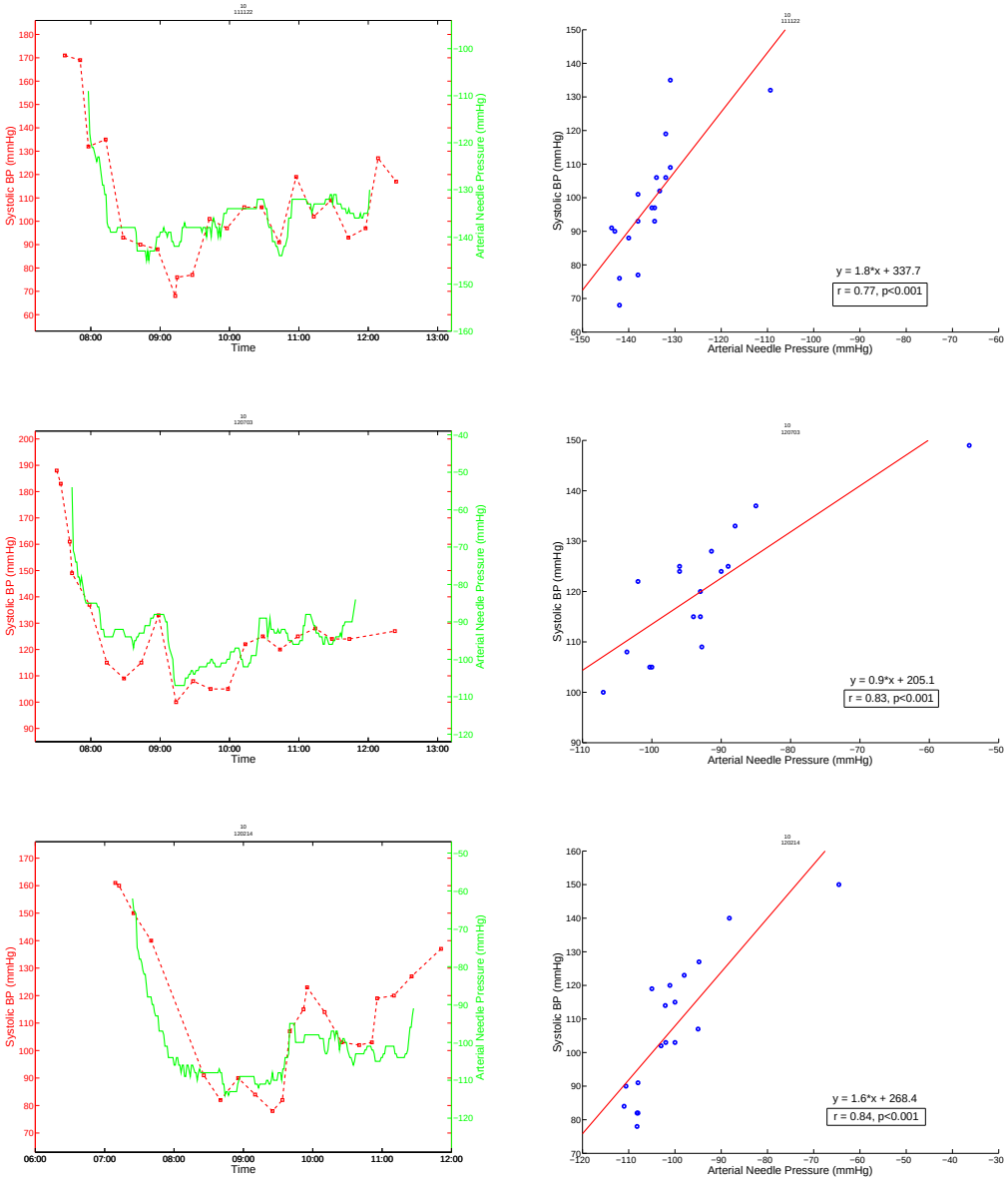


Figure 5.9: Arterial needle pressures vs. SBP for patient OB10 (1 of 3)

Patient OB10 demonstrates a high variability for SBP and experiences frequent episodes of IDH. Variability of the arterial needle pressures are similarly high (indicated by the gradient coefficient of the line of best fit of between 1 and 2), and for the majority of sessions correlation between SBP and arterial needle pressure is excellent.

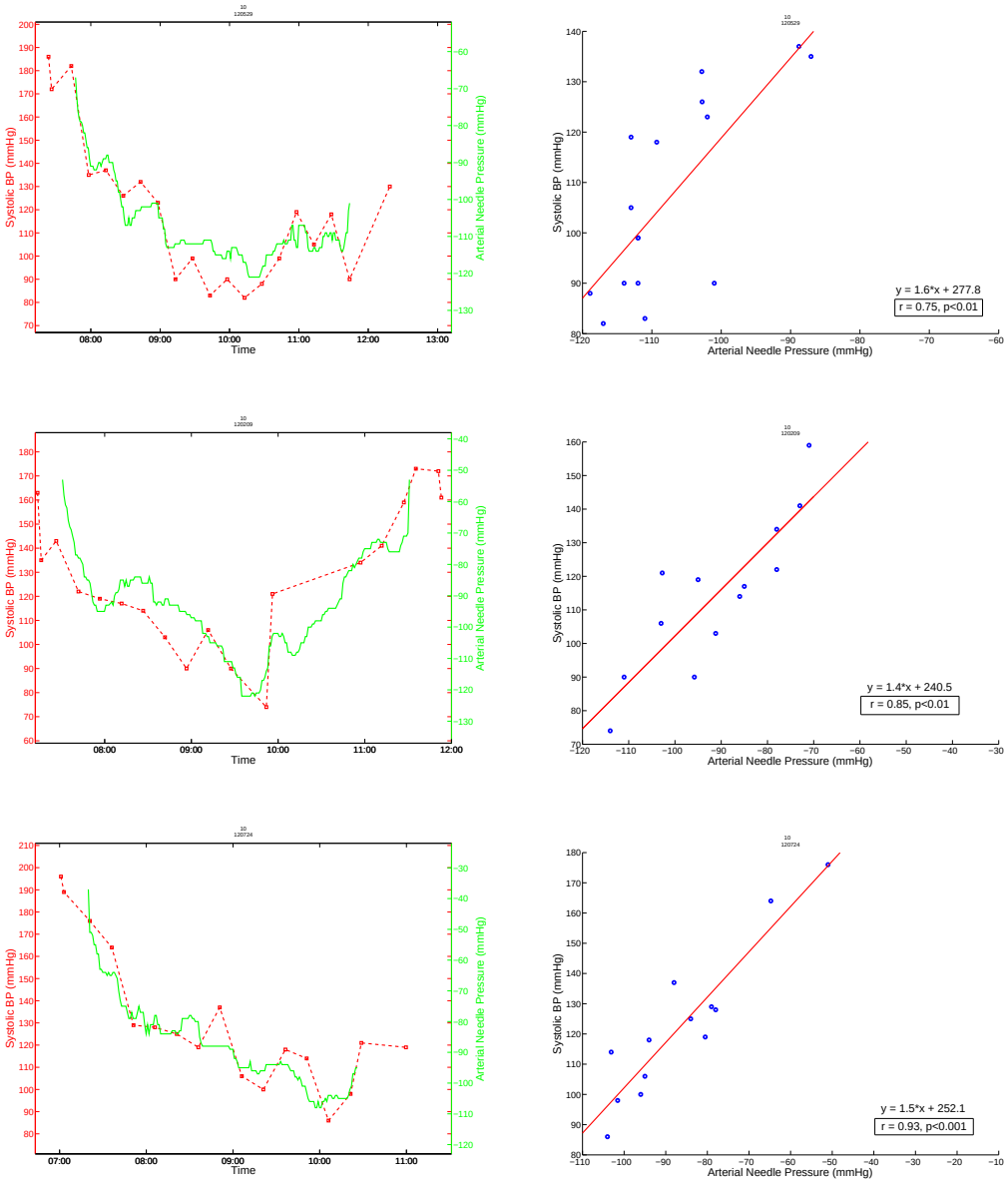


Figure 5.10: Arterial needle pressures vs. SBP for patient OB10 (2 of 3)

Patient OB10 demonstrates a high variability for SBP and experiences frequent episodes of IDH. In the examples shown here, the nadir (lowest decile) arterial needle pressure is within 15 minutes of the lowest intradialytic SBP, indicating the potential utility of this method for the monitoring of IDH in this patient

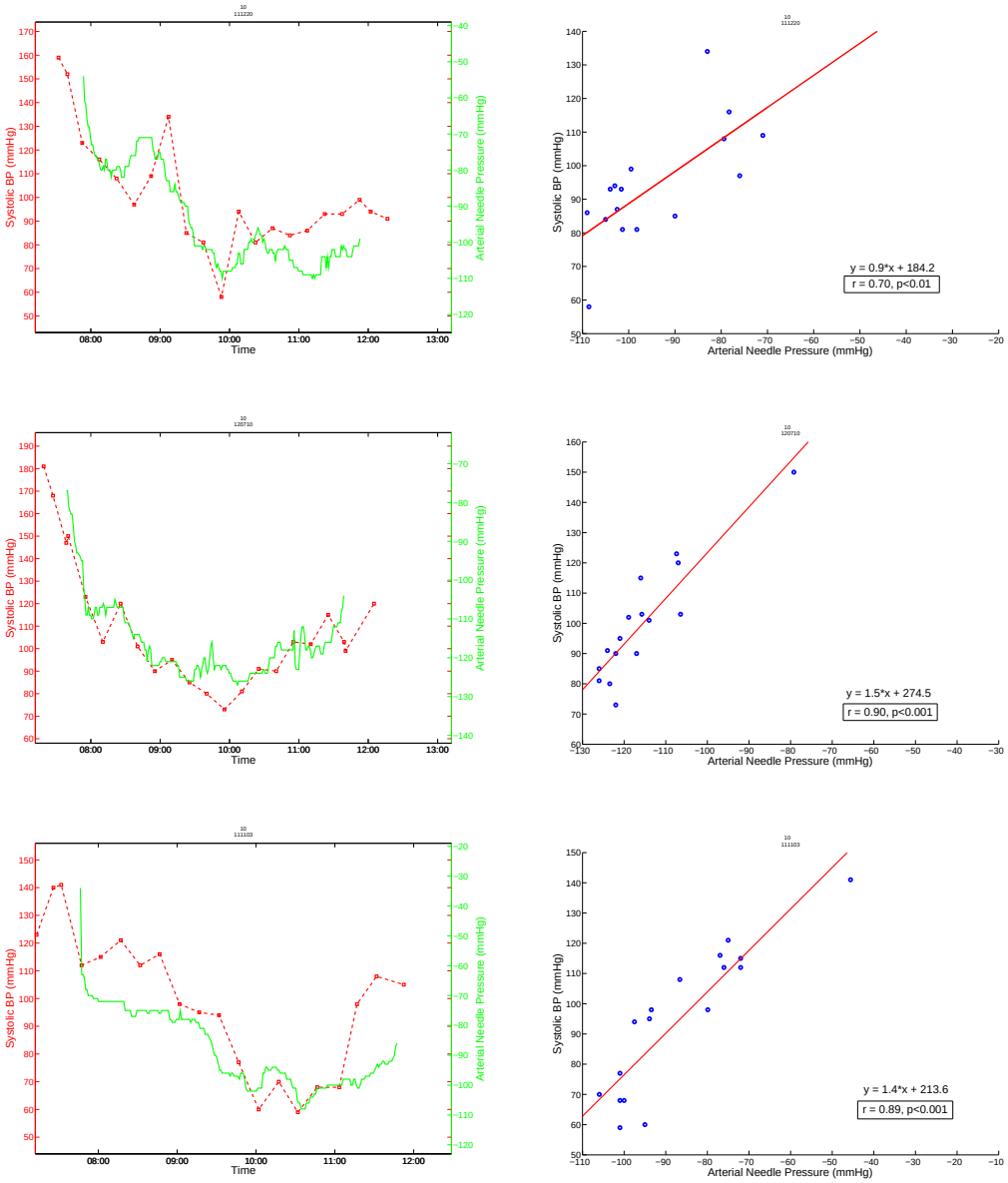


Figure 5.11: Arterial needle pressures vs. SBP for patient OB10 (3 of 3)

Patient OB10 demonstrates a high variability for SBP (maximum minus minimum SBP approximates 80 to 100 mmHg) and experiences frequent episodes of IDH. Variability of the arterial needle pressures are similarly high, and for the majority of sessions correlation between SBP and arterial needle pressure is excellent.

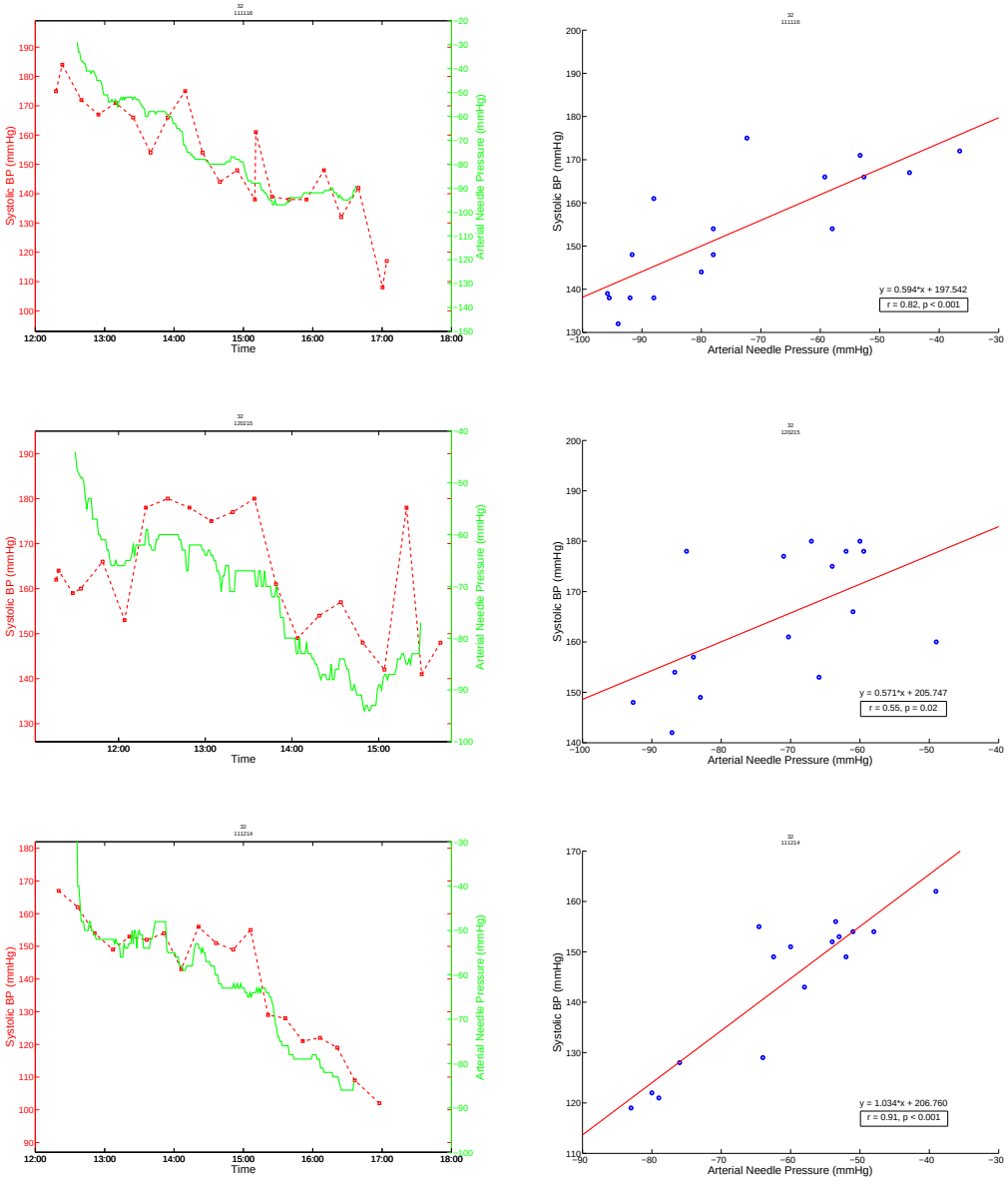


Figure 5.12: Arterial needle pressures vs. SBP for patient OB59

Three of OB59's 4 study sessions are shown here. OB59 demonstrates high SBP variability, and for the majority of sessions correlation between SBP and arterial needle pressure is good.

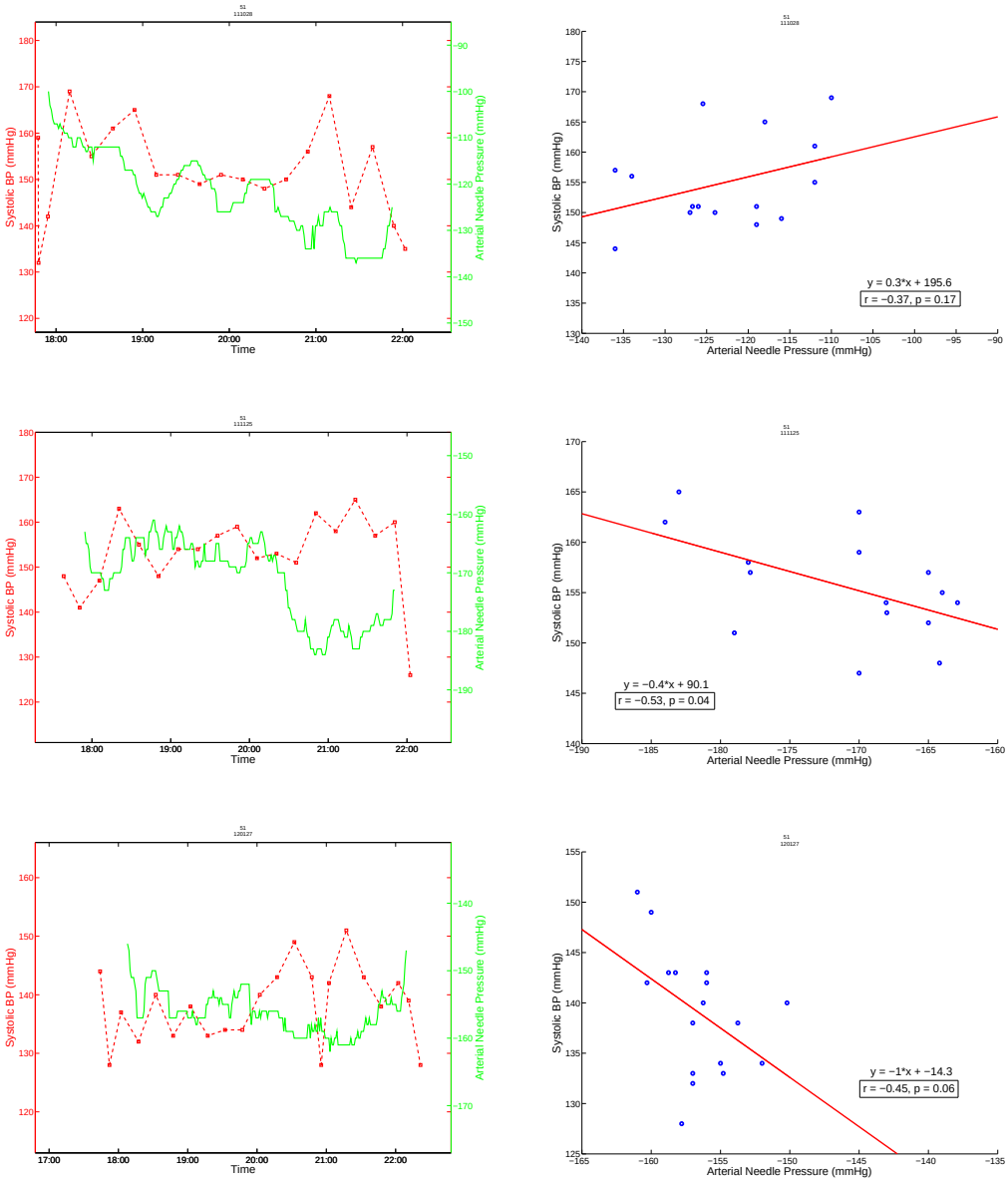


Figure 5.13: Arterial needle pressures vs. SBP for patient OB51

Three of OB51's 4 study sessions are shown here. Note the reduced intradialytic SBP variability when compared to OB10 and OB59. As expected, the variability of the arterial needle is correspondingly low. There appears to be a low signal to noise ratio and a poor correlation between SBP and arterial needle pressure.

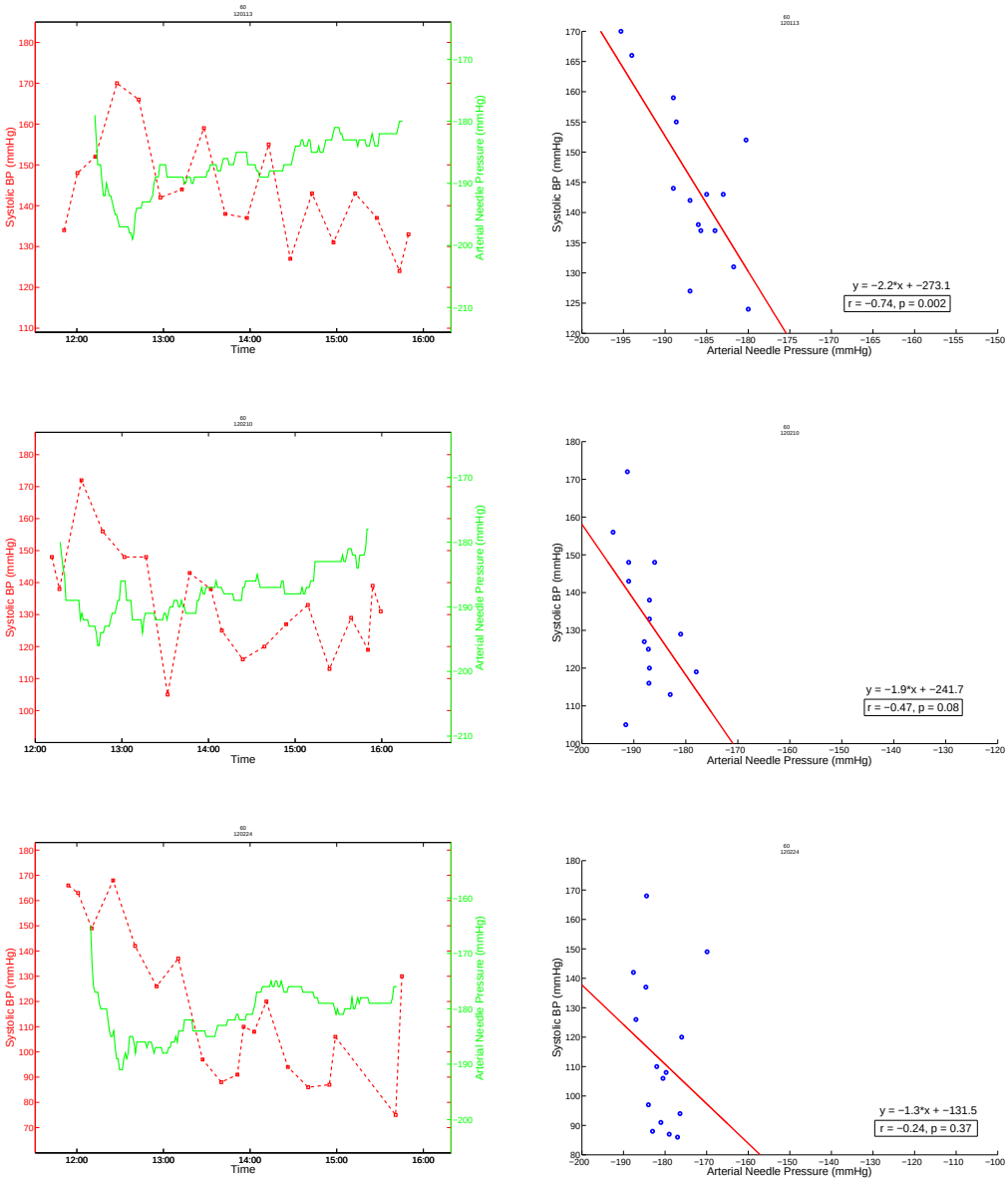


Figure 5.14: Arterial needle pressures vs. SBP for patient OB60

OB60 demonstrates high SBP variability but relatively low arterial needle pressure variability. There may be an anatomical reason for this discrepancy (e.g. poor AV fistula flow) as systemic pressure variation does not appear to be detectable by the arterial needle pressure sensors that report intra-fistula changes in blood pressure.

5.6 Discussion

It is probable that this represents the first time that the approximation of systemic blood pressure has been studied using the method described in this chapter. There is an absence of literature on the subject, and anecdotal reports from the technical research team at B.Braun confirm the lack of prior data.

The results presented here show that arterial line pressures derived from brachial AVFs correlate better with systolic blood pressure than those derived from radial AVFs. Reasons for this are speculative, although it is likely that this is due to the larger calibre of artery and vein used in the surgical formation of the AVF, resulting in relatively greater blood flow. As such, these AVFs would be less likely to be influenced by factors that would complicate the approximation of systemic blood pressure such as tortuosity of the vessels, turbulent flow, and significant stenoses impeding the outflow. It is, however, worth noting that current best practice is to form a fistula as distally as possible, i.e. the radial site as the primary option, reserving more proximal (e.g. brachial) vessels for later procedures if further access surgery is required. Approximately two-thirds of the patients in this study had brachial fistulae, but this proportion is likely to differ significantly among other dialysis populations.

Population-based analyses show that the correlation between SBP and arterial needle pressure is stronger for sessions with high blood pressure variability than for sessions with low blood pressure variability. Moreover, when stratified at the patient level, these results show that some patients correlate consistently well while others correlate consistently poorly — i.e. the variation of r-values for the population is predominately determined by between-patient rather than within-patient variability. This trend implies that patients with better correlation coefficients are likely to have the most variable BP and are, by definition, those most likely to experience blood pressures associated with intradialytic hypotension.

The analysis of patients OB51 and OB60, two of the worst performers, pro-

vides some insight that may help explain why the method does not work for a sub-set of patients. OB51 is generally very stable during dialysis (no IDH events recorded during 5 study sessions) and this is reflected by an intradialytic blood pressure with minimal variability (median σ SBP = 6.2mmHg). As discussed in the methods section, this is close to the threshold below which measurement errors of the NIBP device were likely to adversely impact the signal-to-noise ratio. OB60, however, had a median σ SBP = 20.8mmHg which would be expected to be representative of a high signal-to-noise ratio. However, this variability did not translate to the intra-fistula pressures as shown by the relatively low arterial needle pressure variability (median σ Arterial needle pressure = 4.7mmHg) and illustrated by the vertical scatterplots in Figure 5.14 on page 96. Reasons for this discrepancy are speculative, but this is most likely explained by an anatomical stenosis impeding blood flow within the fistula, a common problem for dialysis patients. Indeed, retrospective analysis of blood flow through the fistula using the Transonic ultrasound dilution method showed that fistula flow for OB60 at the time of the study was 900ml/min compared to 2050ml/min for OB32, for whom median σ SBP and median σ arterial needle pressure were broadly equivalent (13.7 mmHg and 12.8 mmHg, respectively) and correlation coefficients were consistently high (median r = 0.68).

An unexpected feature of the results was the presence of negative correlation coefficients, implying that intra-fistula pressure was changing in an opposite direction to systemic blood pressure. While some of these results may be explained by low pressure variability and a low signal-to-noise ratio, it should be remembered that the needles are actually sited in the venous side of the circulation and that central venous pressure does not necessarily positively correlate with arterial pressure. Burton *et al* describe myocardial stunning during haemodialysis, where blood flow to the myocardium is reduced and detected by regional wall motion abnormalities (RWMAs) on echocardiography. They postulate that this may be a common cause of intradialytic hypotension and present results suggesting that 64% of dialysis patients may be 'significantly' affected[34][136]. For these patients, the reduction in systemic blood pressure would be expected to be associated with a relative increase in central venous pressure due to the temporary,

reversible, decrease in myocardial contractility and therefore inefficiency of the heart as a pump. Clearly, investigation of this hypothesis requires monitoring of central venous and intrafistula pressures in tandem, but this was outside the scope of this observational study.

The major limitation of this study was the use of intermittent NIBPs as a comparator in the analysis. Despite results presented here showing that the accuracy of the NIBP is within an acceptable range when compared to manual syphygmomanometry, the intermittent measurements meant that much of the continuous arterial needle pressure data representing the 15-minute windows between NIBP readings were effectively redundant and did not contribute to the analysis. As correlation analysis was performed on an average of 16 pairs of data per session (16 measurements x 15 mins. = 4 hours), the sample sizes were relatively small and the significance of the findings were consequently attenuated. This limitation is relevant to the analysis of IDH events also. The results showed that the lowest decile in arterial pressures corresponded to the time of IDH event in just 60% of sessions in which IDH occurred. However, given the intermittent NIBP readings, it is difficult to establish whether or not IDH events were occurring (and BP then recovering) in the 15-minute window between otherwise normal (SBP $\geq$100mmHg) measurements; i.e. it is possible that 'true' events, occurring contemporaneously with the nadir in arterial needle pressure, were not being captured using the NIBP device. Such an abrupt fall in blood pressure followed by recovery is certainly plausible when the patterns and pathophysiology of IDH are considered, as discussed in Chapter 1. If this is proven to be the case, then inclusion of these uncaptured events will increase the proportion of events occurring contemporaneously with the lowest decile in arterial needle pressure.

For arterial needle pressures to be of utility in identifying IDH episodes prospectively, an absolute threshold for arterial needle pressure would need to be determined for identifying hypotension because the use of a decile defined by entire session data would be meaningless when monitoring dialysis sessions in real-time. Pre-defined thresholds are already used for the identification of dislodged needles or blocked lines, but the level of a threshold at which hypotension can be identi-

fied is likely to be patient-specific.

To address the limitations described above, the assessment of this method against a validated technique for continuous blood pressure monitoring would be beneficial. However, as described in the introduction to this chapter, at present there are limited data validating non-invasive techniques. The alternative would require a comparison using an invasive intra-arterial catheter with pressure transducer, but this study would carry an inherent risk to vascular integrity in a population where lack of options for vascular access for dialysis could be life threatening.

Chapter 6

Photoplethysmography during Haemodialysis

6.1 Introduction

6.1.1 Photoplethysmography

Photoplethysmography (PPG) is an optical technique that exploits the wavelength dependent variation in light absorption coefficient for different tissues. It is typically performed using a pulse oximeter, which uses light sources (usually light emitting diodes) at two wavelengths: red (660 nm) and near-infrared (940 nm). The light intensity is modulated by the increase in haemoglobin content and expansion of the vascular and tissue volume between the light source and the detector (i.e. increased optical path length) such that there is a reduction of signal with each cardiac systole. The Beer-Lambert law (below) is often used to model this process but is an oversimplification because this equation assumes a homogeneous tissue and considers only absorption of light:

$$\%T = 100 \times e^{-\alpha l c} \tag{6.1}$$

where $\%T$ is the percentage transmission of light; α is the absorption coeffieient of the material; l is the length of the layer; and c is the concentration of the absorbing material (in this case haemoglobin).

In fact, cutaneous tissue is heterogeneous and the relationship between blood volume and the fraction of emitted photons that pass through the skin to the detector is reduced by scatter, refraction and reflection.

Most manufacturers invert the waveform, such that a reduced transmission of light is displayed as a positive deflection. In addition, post-processing of the waveform amplitude in most commercial devices, described later, results in a unitless output waveform; hence, comparisons between waveforms and their amplitudes cannot be made between different subjects.

The PPG waveform

The PPG waveform is essentially volumetric. At first sight, the pulsatile component of the PPG waveform is similar in morphology to the waveform obtained from arterial blood pressure monitoring. This demonstrates the relationship of change in volume with change in pressure, given by the equation below:

$$\Delta V = \Delta P \times D \tag{6.2}$$

where ΔV is the change in blood vessel volume; ΔP is the change in intravascular pressure, also known as the pulse pressure; and D is the distensibility of the vascular walls. Indeed, when distensibility is constant, the height of the PPG waveform is proportional to the pulse pressure (difference between systolic and diastolic pressure)[137]. However, the exact origin of the PPG waveform is not clear. Blood flow at capillary level is generally continuous and unlikely to produce a pulsatile waveform, and the low distensibility of the distal arterioles is such that changes in vessel diameter are likely to be minimal during the cardiac cycle. An alternative explanation is that the waveform represents pulsatile venous distension (at the cardiac frequency) from cutaneous arterio-venous anastamosis[1] [138, 139]. In general, an increase in the diameter of any vessel within the

[1] The majority of arterial blood passes through a dense capillary network before entering the venous system. Cutaneous arterio-venous anastamoses refer to small shunts within the skin vasculature, where arterial blood enters the venous system directly.

monitored region results in a reduction in transmitted light and a corresponding positive deflection of the (inverted) PPG waveform. Thus, vasodilated or easily distensible vessels, such as veins, correspond to relatively higher PPG amplitudes than vessels of smaller diameter. It should be noted that although increased PPG amplitude may represent increased tissue perfusion, it is not necessarily synonymous with a high blood pressure: peripheral cutaneous vasoconstriction will cause a reduction in PPG amplitude[140] but may concurrently lead to an increase in systolic blood pressure.

PPG waveform components

Pulse oximetry relies on the assumption that the PPG signal at both the red and infra-red wavelengths consists of two components only: the a.c. 'pulsatile' component and the d.c. 'baseline' component.

a.c. component

The pulsatile (a.c.) component represents cardiac-synchronous changes in blood volume at a frequency generally between 0.5 Hz and 4 Hz, corresponding to 30 beats/min and 240 beats/min, respectively. For patients in normal sinus rhythm with a normal stroke volume, the PPG peak-to-peak interval approximates the R-wave to R-wave ('R-R') interval of the ECG (see Figure 6.1 on page 104). As autonomic modulation of the ECG R-R interval with respiration (known as 'Respiratory Sinus Arrhythmia' – RSA) can be used to assess respiratory rate, a similar process can be used to estimate respiratory rate from the PPG peak-to-peak (or 'P-P') tachogram (i.e. plot of change in P-P interval over time)[141]. The estimation of respiratory *rate* is not a feature of this work *per se*, so is not discussed further.

d.c. component

Figure 6.3 on page 107 shows that the amplitude of the PPG waveform also varies in synchrony with the respiratory cycle. This phenomenon can be described either as amplitude modulation of the cardiac-synchronous pulsatile waveform or

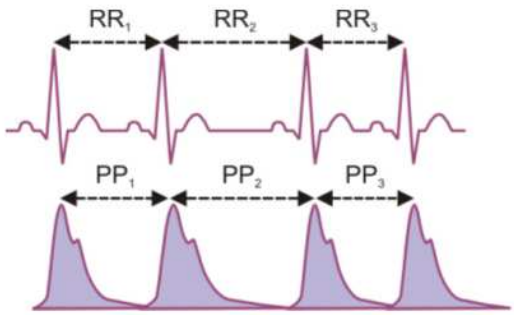


Figure 6.1: PPG a.c. component

respiratory-induced intensity variation (RIIV) in the baseline. Which description is adopted depends on the choice of cut-off frequency for the filters used to separate the baseline and pulsatile components.[1] A low-pass filter extracts the baseline component (frequencies below the cut-off frequency being let through) and a high-pass filter extracts the pulsatile component (frequencies above the cut-off frequency being let through).[2] If the cut-off frequency is chosen to be 0.5 Hz (as with most pulse oximeters), the baseline component will include the RIIV, for all values of respiratory rate (see panel (a) in Figure 6.2 on page 105). If the cut-off frequency is chosen to be 0.1 Hz instead, the respiratory-induced variation will appear as amplitude modulation of the pulsatile component, for respiratory rates above 6 breaths/min (see panel (b) in Figure 6.2). This distinction is further complicated by the fact that most equipment manufacturers include some form of automatic gain control (AGC) to ensure that the amplitude of the pulsatile component is minimally unaffected by anatomical variations such as finger width (larger fingers will therefore have relatively more light shone through them). The AGC circuitry is driven by monitoring the variations in the amplitude of the baseline component; if the latter includes the respiratory-induced variations (as with a cut-off frequency of 0.5 Hz), then the AGC will attempt to 'compensate'

[1] This is rarely made explicit by the manufacturers of pulse oximeters or PPG instrumentation.

[2] This simple explanation assumes an infinitely sharp transition between the pass-band and stop-band of the filters; in practice both the low-pass and high-pass filters will have gradual roll-offs in their frequency response.

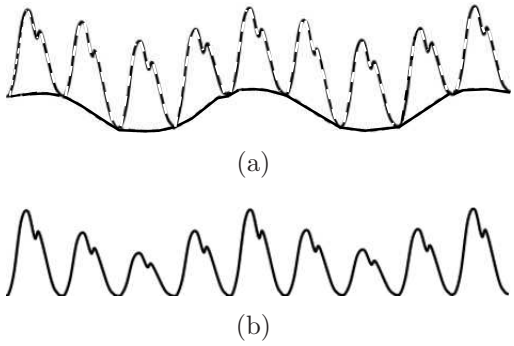


Figure 6.2: Variation in the PPG with respiration

This figure shows a PPG recording over two respiratory cycles. Panel (a) shows respiratory-synchronous variation (i.e. RIIV) in the d.c. 'baseline' component for a filter cut-off of 0.5 Hz. Panel (b) shows respiratory-synchronous amplitude modulation of the a.c. 'pulsatile' component for a filter frequency cut-off of 0.1 Hz

for these variations, thereby making it impossible to extract the RIIV reliably from the PPG waveform.

Physiological explanation for the RIIV in PPG

There are several possibilities as to the origin of respiration-synchronous amplitude changes in the PPG Baseline (approximately 0.15 to 0.5 Hz). Firstly, inspiration results in a momentary reduction in stroke volume and, therefore, a corresponding reduction in cardiac output, which should in turn have an effect on the pulsatile component of the PPG waveform. Also, there will be tissue blood volume changes during the respiratory cycle due to the transmitted changes in thoracic pressure: a reduction in intra-thoracic pressure during inspiration is transmitted through the venous system, effectively siphoning blood from the vascular bed within the tissue. In addition, it has been argued that sympathetically-mediated vasoconstriction from ventilatory-synchronous discharge of the autonomic nervous system also plays a part. The evidence for this comes mostly from a study monitoring the PPG waveform obtained from a finger probe placed distal to an artery occluded by a blood pressure cuff inflated above systolic pressure. A variation in the baseline of the PPG waveform was evident during a deep inspiratory gasp but not during normal respiration[142]. The occlusion of the vasculature in the limb excluded the possibility that the change in waveform was transmitted intravascularly from mechanical changes in the thoracic cavity. The link suggests

a coupling of the respiratory system to the autonomic nervous system, which can affect the PPG waveform independently of the changes resulting from the mechanical effects of the respiratory cycle. In summary, the implication from studies to date, including those timing the onset of the RIIV throughout the central and peripheral venous system, is that RIIV is closely associated with a reduction in arterial pressure, rather than a backward transmission of reduced venous pressure. Whether the association with reduced arterial pressure is mediated through forward transmission of reduced stroke volume or through an autonomic relay to the skin microvasculature that accompanies the reduction in blood pressure is yet to be elucidated. Finally, it should be noted that there are also baseline fluctuations in the PPG waveform which are attributable to physiological processes independent of ventilation.

Other waveform components of the PPG

Lower frequency (≈ 0.1 Hz) baseline fluctuations are evident in humans as part of a separate vascular response to the sympathetic nervous system[143][144]. These fluctuations are often referred to as Mayer waves and are thought to represent the baroreflex mediated oscillation of arterial blood pressure. Very low frequency (0.01-0.08 Hz) sympathetically-mediated variations in the baseline may also be apparent as a vascular response in the regulation of body temperature[145].

6.1.2 Modes of PPG and choice of site for monitoring

Transmission and reflectance PPG

Two modes of photoplethysmography are commonly utilised in clinical practice. In Transmission-mode photoplethysmography, the light source is situated opposite the receiving photodetector, which senses the proportion of non-absorbed light passing through the tissues. The requirement for opposing sensors limits the attachment of the probe to sites on distal extremities such as the fingertip, toe, or pinna (ear lobe). Reflectance-mode photoplethysmography uses a photodetector adjacent to the emitting light source and is, therefore, not as restricted in

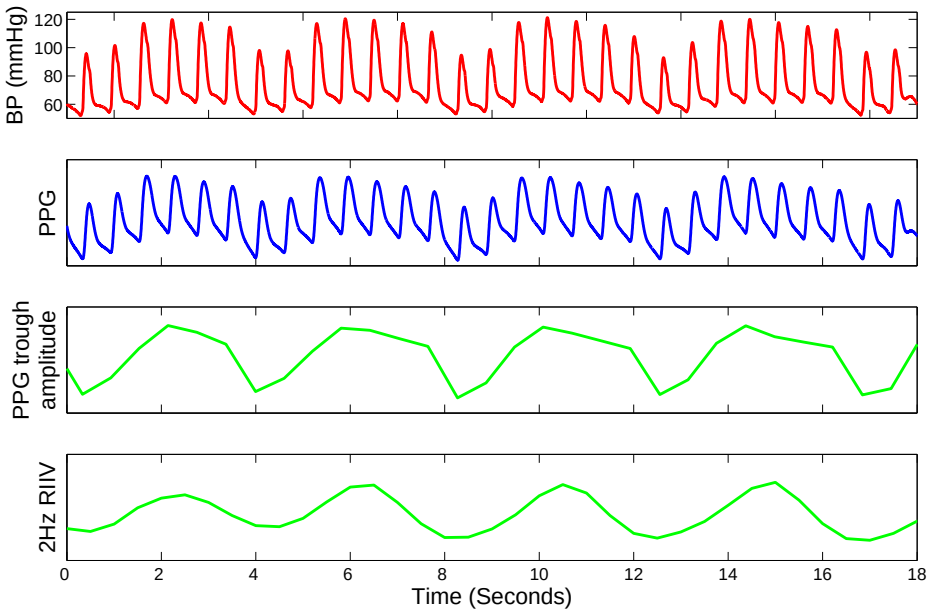


Figure 6.3: Variation in the PPG waveform components with respiration.

This recovering ICU patient was breathing spontaneously with minimal non-invasive respiratory support (CPAP at 5cmH_2O). CVP(blue) was measured with a central venous (jugular) catheter, PPG (black) was measured using a transmission-mode index finger probe, and BP (red) was measured continuously with a radial arterial line and transducer. The PPG envelope is derived by tracking the troughs of the PPG waveform and re-sampling the linearly interpolated time series at 2 Hz. The RIIV waveform is a low-pass filtered version of the PPG amplitude.

the anatomical sites at which it may be employed. The reflectance method has been reported to be more sensitive to the oscillations in venous pressure during the respiratory cycle because the transmission method usually involves using a clip or similar device to secure the probe, which can result in external venous compression[146]. The reflectance method limits this artefact when securing the probe with an adhesive sticker, but the trade-off may be a reduction in overall signal quality due to the possibility of inferior contact with the skin. Despite the differences in the way that these two methods detect light, the morphologies of the PPG waveforms are very similar[146].

Choice of anatomical site for the probe

In addition to choice of mode, the choice of anatomical site for PPG monitoring is important. For those wanting to acquire the RIIV components of the PPG, the avoidance of distal extremities may reduce the vasconstricting influence of the sympathetic nervous system on peripheral vessels. However, investigators wishing to assess compensatory autonomic function may find evidence of peripheral vasoconstriction useful. Shelley *et al*[147] investigated whether the finger, ear, or forehead is best suited to acquire the respiratory signal from the PPG waveform in a study carried out in spontaneously breathing and mechanically ventilated patients. Results from spectral analyses indicated that variations in the PPG waveform acquired from a site on the head (either the forehead or an ear) were more than 18 times larger in magnitude than the variations in the PPG waveform acquired from a finger in the ventilated patient, and 12 times larger in the spontaneously breathing patient. The authors suggest that this difference can be explained by the proximity of the head to the chest and that the vessels in the head have fewer sympathetic innervations and so are not as likely to express an attenuated signal due to vasoconstriction, when compared with vessels in the extremities[147]. This hypothesis is supported by the work of Awad *et al*[148], who tested the sympathetic response of the finger and ear to a cold-water immersion stimulus (4°C) in 12 healthy volunteers. The authors report a 48% reduction in the amplitude of the PPG waveform acquired from a contralateral finger, but just a 2% reduction in the amplitude of the PPG waveform acquired from the ear.

6.1.3 Utility of photoplethysmography in HD

During ultrafiltration-induced hypovolaemia, haemodialysis patients may defend arterial pressure by initiating compensatory physiological mechanisms. As such, impending cardiovascular collapse can be masked by a maintained BP right up until the point of decompensation. For this reason, the use of blood pressure alone as an indicator of critical hypovolaemia often proves to be unhelpful and does not allow for an early intervention to mitigate the situation. Recalling that BP is a function of cardiac output and systemic vascular resistance, important physiological clues to potential decompensation may become apparent if the trends of these BP-components are tracked continuously.

The above exploration of the physiology underpinning the various components of the PPG waveform, and the realisation that the waveform from different anatomical sites may represent different underlying physiological processes, demonstrates the potential utility of the PPG waveform for continuous physiological monitoring of cardiovascular status. An overview of these potential derivations, of particular relevance to haemodialysis, is presented in Table 6.1 on page 111. The potential for a single waveform to track important components of the compensatory response to hypovolaemia enables unprecedented opportunities to further the understanding of these physiological or pathological responses during haemodialysis. Moreover, the dialysis process offers a controlled environment in which the degree of hypovolaemia can be stratified, the same patient can be studied on multiple occasions, i.e. function as their own control, and the patients themselves can be further stratified according to known autonomic defects or the likely effects of their cardiovascular medication. In theory, the study of dialysis patients could allow the elucidation of physiological and pathophysiological compensatory responses to hypovolaemia. This may involve any component of the baroreflex arc from the afferent detection of hypovolaemia by baroreceptors, through the baroreceptor-effector coupling, to the efferent dynamic vascular response or chronotropic response of the heart.

In addition to tracking the compensatory response to hypovolaemia — which is introduced in the following chapter — the PPG can also serve to quantify central blood volume. The underlying principle requires quantification of the mechanical influence of ventilation on the PPG waveform, the RIIV, which is known to increase in amplitude, or power, with increasing hypovolaemia[81]. This phenomenon was inferred by Perel *et al* during their experiments studying the haemodynamic effects of graded haemorrhage in dogs. They noted that 'systolic pressure variation' with ventilation was a sensitive indicator of hypovolaemia, and that this variation was significantly more sensitive than heart rate, blood pressure and central venous pressure for identifying blood loss[149][150]. As introduced in Section 1.4.1, central blood volume is considered to be an important determinant in cardiovascular stability of a patient undergoing haemodialysis, so it is hypothesised that reliable quantification of central blood volume would be important in the monitoring of haemodialysis.[1] The use of the RIIV component of the PPG waveform as a surrogate for central blood volume is, therefore, considered here.

6.1.4 PPG RIIV as a surrogate of central blood volume

The PPG has been promoted as a non-invasive indicator of intravascular volume status, as first described by Partridge in 1987[154]. Of particular interest is the use of the PPG waveform amplitude variation for detecting mild to moderate hypovolaemia [137][152] and in the optimisation of patient fluid status for patients undergoing surgery[155][156]. For these studies, the confounding influence of peripheral vasoconstriction on the PPG waveform has been partially circumvented using probes attached to the ear, which is less sensitive to sympathetically mediated changes in vasomotor tone than the fingertip[147][157].[2] This anatomical variation in vascular response to a sympathetic stimulus is explored further in the next chapter.

[1] The same premise is used by advocates of the Critline relative blood volume monitor

[2] The reduced sensitivity of the cutaneous vessels of the ear to the sympathetic nervous system is attributed to a lower density of alpha adrenoreceptors, the stimulation of which causes vasoconstriction.

Table 6.1: Possible derived variables from continuous PPG waveform monitoring

Derived Variable	Method
Heart Rate Variabilty	Spectral analysis of peak-to-peak tachograms and quantification of spectral power in the Low frequency (LF) region (0.1 to 0.15 Hz) and High Frequency (HF) region (0.15 to 0.5 Hz). For ECG analysis, the LF/HF ratio is widely used as a surrogate marker of intradialytic autonomic tone, where LF represents sympathetic activity and HF represents parasympathetic activity, respectively[90][93].
Respiratory Rate[141]	If RSA exists, the respiratory rate can be estimated from PPG peak-to-peak tachograms. Alternatively, respiratory rate can be estimated from amplitude modulation of the a.c. or d.c. component (see Section 6.1.1)
Surrogate of Central Blood Volume (using the ear probe)[81][151][152]	The relative (to total) power of the peak corresponding to respiration in the respiratory region (0.15 to 0.5 Hz) on spectral analysis of PPG trough-to-trough or trough-to-peak amplitude may correspond to intravascular volume status.
Surrogate of Vascular Tone (using the finger probe)[80]	Low frequency (<0.15 Hz) spectral power may correspond to sympathetic nervous system modification of vascular tone.
Area under curve (AUC) of the PPG a.c. component as a composite measure of blood volume and vascular tone[153]	Area beneath the curve of each pulse wave is increased with increased blood volume and/or vasodilation but decreased with reduction in blood volume and/or vasoconstriction.

PPG and blood volume: Existing work

The majority of work in this area, as cited above, has been focussed on ventilated patients during surgery. The investigation of spontaneously breathing patients is limited to a few studies of healthy volunteers undergoing blood donation[151][158]. It should be noted, however, that reduction in blood volume due to blood donation and the reduction in blood volume by ultrafiltration during dialysis are not synonymous. Blood donors experience whole blood loss and a transient reduction in haematocrit, whereas dialysis patients undergo pure fluid removal from the blood space, resulting in haemoconcentration. This difference may have fundamental effects on cardiovascular status, given the previously described relationship (in Section 1.4.1) between haematocrit, viscosity, and vascular resistance. Also, many subjects in these studies are normovolaemic prior to a reduction in blood volume. The transition from hypervolaemia, due to fluid overload in the dialysis patient, to relative hypovolaemia during ultrafiltration is again fundamentally different in terms of haemodynamics.

The potential utility of the PPG as a non-invasive tool for monitoring blood volume changes during HD of spontaneously breathing haemodialysis patients is the focus of a single published manuscript in the literature to date: Javed *et al* study this relationship using an ear probe on just ten participants[81]. The authors compared a group of seven fluid removal patients (mean UF volume of 3.5 litres) with three non-fluid removal patients. Six minutes of PPG were recorded at 20 minute intervals throughout dialysis. The authors found a significant difference in PPG amplitude variation at a frequency band between 0.145 and 0.45 Hz, consistent with the mechanical effects of respiration on the ear PPG waveform. They also noted a modest correlation ($r = 0.64$) with percentage change in relative blood volume. However, this small study included only haemodynamically stable patients and, therefore, did not consider patients with hypotensive episodes.

6.2 Hypothesis generation

Javed *et al*'s investigation into the relationship of PPG RIIV to blood volume did not include haemodynamically unstable patients, so the utility of PPG RIIV as a tool to identify or predict episodes of hypotension during dialysis was considered an important focus for work in this area. This was based on the underlying hypothesis that IDH can, at least in part, be attributed to low blood volume, and that a quantifiable threshold in the amplitude of RIIV might exist, beyond which IDH is likely to occur. A similar concept was described by Steuer *et al*[65] when they proposed the idividualised 'Crash Crit' value when monitoring dialysis sessions using a Critline^{TM} relative blood volume (RBV) monitoring device (introduced in Section 1.5.1). The theory behind the 'Crash Crit' value was based on the observation that patients often experience hypotension at a certain degree of blood volume reduction. This threshold value is predictable for a patient undergoing repeated dialysis sessions but may vary significantly between individuals. RBV monitoring is widely used in U.K. dialysis units as it is the only method for continuously and non-invasively estimating the change in blood volume during haemodialysis, and it is therefore used primarily for the avoidance of IDH. For this reason, individualised Critline thresholds were used in this study as the standard against which the performance of PPG RIIV in identifying or predicting intradialytic hypotension was assessed.

6.3 Methods

The patient cohort

In order to perform sensitivity analyses for the PPG and Critline techniques for the identification or prediction of IDH, only patients who experienced frequent IDH events (defined as an IDH score $\geq$7 for one or more intradialytic NIBP measurement) were included. Eleven individuals experienced IDH in five or more sessions (see Figure 6.4 on page 114), so further analyses were based on these patients' PPG data (a total of 159 sessions).

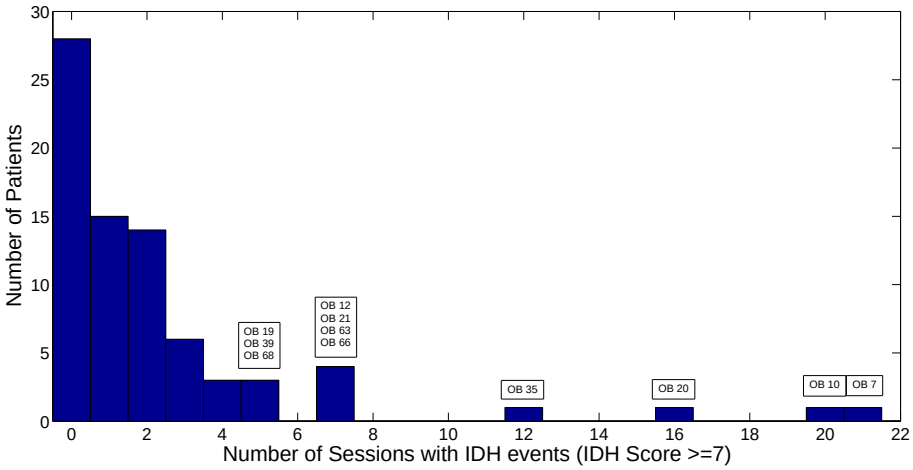


Figure 6.4: Number of sessions with an IDH Score of 7 or greater

PPG data acquisition

A Nonin reflectance pulse oximeter, with a sampling frequency of 75Hz, was attached using a spring-loaded clip to the right ear. This anatomical site was most likely to be influenced by the mechanical effects of ventilation on tissue blood volume and least likely to be influenced by sympathetically-mediated changes in vascular tone. Where possible, patients were encouraged to recline at 45 degrees with their head resting against the bed to relax sternocleidomastoid muscles and maintain patency of the jugular veins. Patients generally opted to read or watch television during dialysis, which helped to minimise artefact caused by movement of the head. The probe's wire was clipped to the lapel and fed into the sensor electronic module of the Equivital EQ02 belt, which functioned as a data logger. Raw PPG files were downloaded from Equivital's Sensor Electronic Module (SEM) at the end of each session and uploaded to a Matlab file for analysis.

Segmenting the PPG timeseries into windows for signal processing

Five-minute windows of PPG waveform were analysed, a duration over which an average UF volume between 50 and 100mls is removed for a typical dialysis

prescription.[1] Assuming no refilling takes place, this was considered to be below the blood volume from which a significant variation in cardiovascular parameters could be detected i.e. satisfying the assumption that the signal analysed by spectral analysis is stationary or time-invariant. These 5-minute PPG windows were shifted iteratively every minute: e.g. window one from minute 0 to 5, then window two from 1 to 6 etc.

Signal processsing of the PPG waveform

An open-source peak/trough detector using a threshold-based technique was applied to the PPG waveform within a 5-minute window. The troughs were identified and then linearly interpolated and re-sampled at 2 Hz.[2] The data was detrended by subtracting the mean from each window and then a Hamming windowing function was applied.[3] On average, 240 spectra were produced for each session using a 1024pt[4] FFT (over a frequency range between 0 and 1Hz), and then the power at each frequency was normalised so that the sum of the squared output values from each spectrum was equal to 1.0. This normalisation allowed the spectral content of each PPG segment to be standardised with respect to the other segments for the session, enabling easy visualisation on a three-dimensional plot of any shifts in relative power over the range of specified frequencies as dialysis progressed. The power corresponding to the respiratory frequencies (i.e. between 0.15 and 0.5Hz, or between 9 and 30 breaths/min) was calculated by integration of the power spectrum between 0.15 and 0.5Hz. The area under the FFT for this 'respiratory' region was plotted for all segments as a time series, so that power changes occurring in the respiratory frequency band could be tracked throughout dialysis.

[1] For example, an average total UF volume of 3500mls over 4 hours equates to 73 mls over 5 minutes.

[2] The use of the FFT requires a series evenly sampled in time.

[3] A FFT assumes an infinitely repeating signal. When a finite signal is analysed, discontinuities can appear between the start of one repetition and the beginning of the next. A Hamming window is a mathematical transform which avoids high frequency noise or 'spectral leakage'[159] from these discontinuities by mathematically 'splicing' the segments such that they appear contiguous.

[4] This was calculated using a next power of 2 method from the length of the interpolated time series.

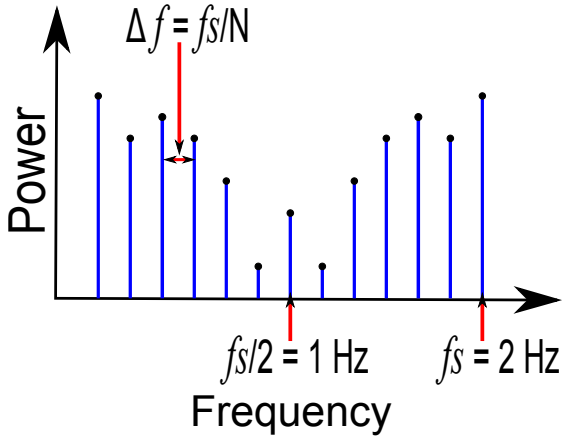


Figure 6.5: Fast Fourier Transform (FFT): Frequency resolution for the spectral plot

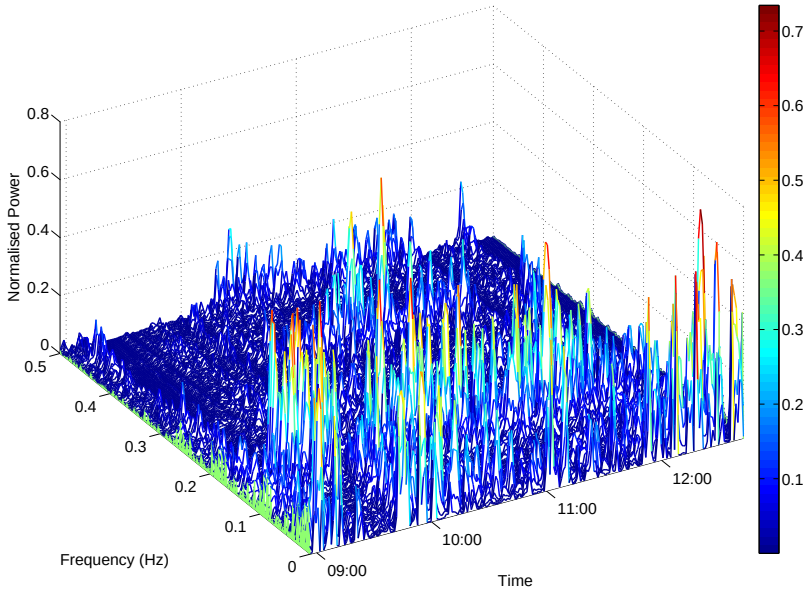
For a sample frequency ('fs') of 2 Hz and 1024pt FFT ('N' = 1024), the resolution ('Δf') = 2/1024 Hz, equivalent to 0.12 breaths per minute. Note the symmetry around 1Hz ($fs/2$), also known as the Nyquist frequency.

Visualisation of frequency spectra in two-dimensions

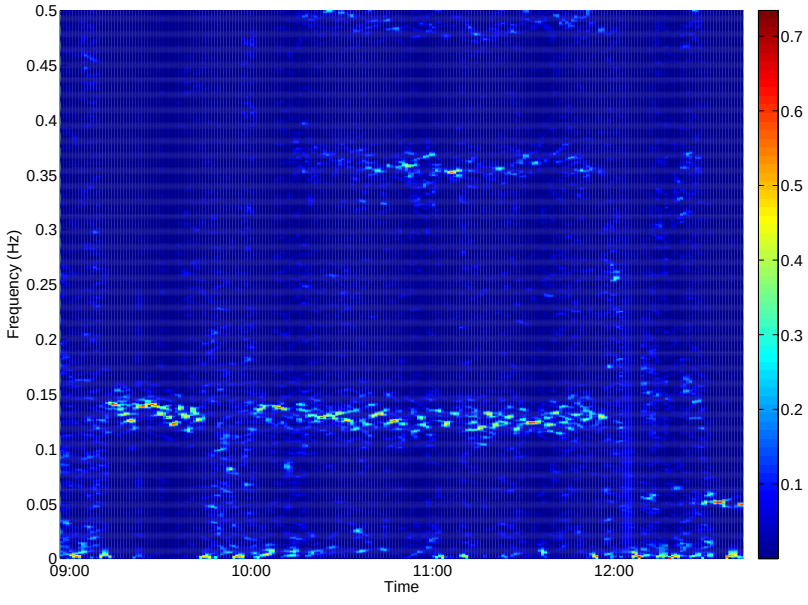
The three-dimensional spectral plots were converted to two-dimensional plots so that the relative (to total) power could be easily visualised at each frequency. For the two-dimensional plots, the y-axis shows the frequency content of the signal and the x-axis shows the time (start to end of the dialysis session). For each plot, colour replaces the z-axis in the three-dimensional plot. The colour axis ranges from blue to red indicating low and high spectral power, respectively – see Figure 6.6 on page 117.

Using area in the 'respiratory region' of FFT to identify NIBPs with an IDH Score ≥7:Sensitivity and Specificity

NIBP measurements were taken at least every 15 minutes, resulting in an average of 16 NIBP assessments over the four-hour dialysis session. An IDH score was assigned to each measurement according to the stratification presented in Chapter 4. Sessions complicated by intradialytic hypotension were identified as those with an IDH score ≥ 7 for one or more of the NIBP assessments during the session. Sensitivity and specificity analyses were conducted to establish whether the area under the FFT in the respiratory region of the spectra (0.15 to 0.5Hz) could be



(a)



(b)

Figure 6.6: FFT spectral plots of PPG Baseline RIIV

The colour bar in panel (a) indicates the normalised power of the frequency spectra (i.e. the z-axis of the 3-dimensional plot shown here). Blue indicates low spectral power and red indicates high spectral power. Panel (b) is a two dimensional representation of panel (a), showing time (start to finish of dialysis session) on the x-axis and frequency content of the signal (Hz) on the y-axis.

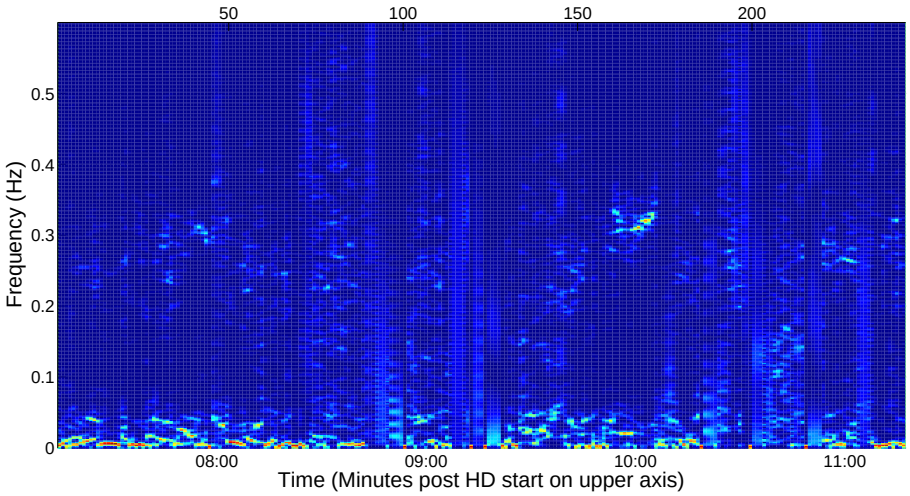
used to discriminate between NIBPs that were not diagnostic of IDH (i.e. NIBP IDH Score <7) and NIBPs that were diagnostic of IDH (i.e. NIBP IDH Score ≥7). A 'True Positive' (TP) marker was assigned if the FFT area exceeded a pre-defined threshold value within 15 minutes of a NIBP assessment with an IDH Score ≥7. If this pre-defined threshold was crossed in association with an NIBP IDH Score <7, then a 'False Positive' marker was assigned. A 'True Negative' (TN) marker was assigned if FFT area in the respiratory region did not exceed a pre-defined threshold value in the preceding 15 minutes of a NIBP assessment with an IDH Score <7. Conversely, a 'False Negative' marker was assigned if the area under the FFT in the respiratory region did not exceed a pre-defined threshold value within 15 minutes of a NIBP assessment with an IDH Score ≥7 — see Figure 6.7 on page 119. A sensitivity and specificity score was obtained for each pre-defined threshold using the formulae below:

$$Sensitivity = \frac{TP}{TP + FN} \tag{6.3}$$

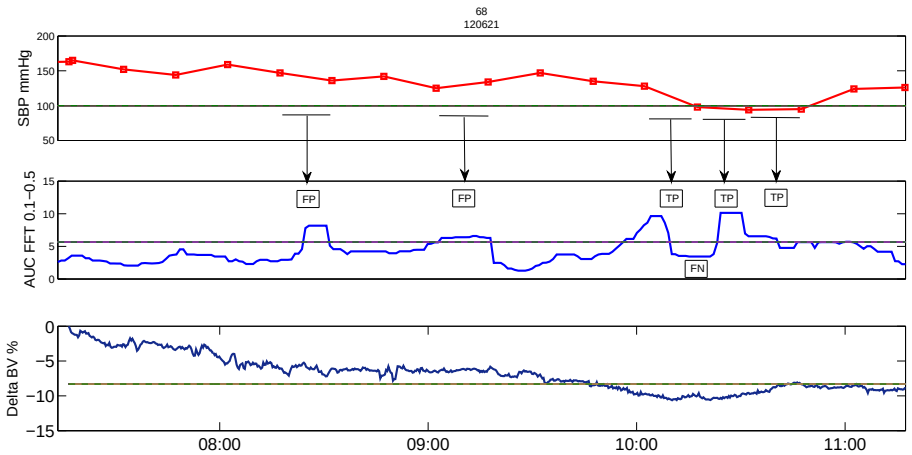
$$Specificity = \frac{TN}{TN + FP} \tag{6.4}$$

Using the Critline's %change in blood volume to identify NIBPs with an IDH Score ≥7: Sensitivity and Specificity

Similar to the process described above for the PPG, a 'True Positive' (TP) marker was assigned if the %change in blood volume exceeded a pre-defined threshold (ranging between 0 and -20%) within 15 minutes of a NIBP assessment with an IDH Score ≥7. If this threshold was crossed in association with an NIBP IDH Score <7, then a 'False Positive' marker was assigned. A 'True Negative' (TN) marker was assigned if %change in blood volume did not exceed a pre-defined threshold value in the preceding 15 minutes of a NIBP assessment with an IDH Score <7. A 'False Negative' marker was assigned if %change in blood volume did not exceed a pre-defined threshold value within 15 minutes of a NIBP assessment with an IDH Score ≥7.



(a)



(b)

Figure 6.7: Classification for Sensitivity and Specificity analysis

Plotting Receiver Operating Curves (ROC) for each patient

In order to establish whether a patient-specific threshold could be defined for both area under the FFT in the respiratory region and for percentage change in blood volume (i.e. synonymous with the previously described 'Crash Crit'), the sensitivity and specificity scores were averaged at each threshold across all of the IDH sessions for each patient. The optimum threshold was defined as that corresponding to the highest mean specificity and sensitivity. Receiver operating curves were constructed to compare the performance of the area under the FFT technique with that of the Critline's output of percentage change in blood volume — i.e. the existing gold standard for non-invasive intradialytic blood volume monitoring.

6.4 Results

Spectral plots and associated AUC estimates for the PPG FFT are shown here as illustrative examples for two sessions from each of four patients (OB10, OB12, OB30, OB34). Sensitivity and specificity analyses are presented later.

6.4.1 Spectral Analyses

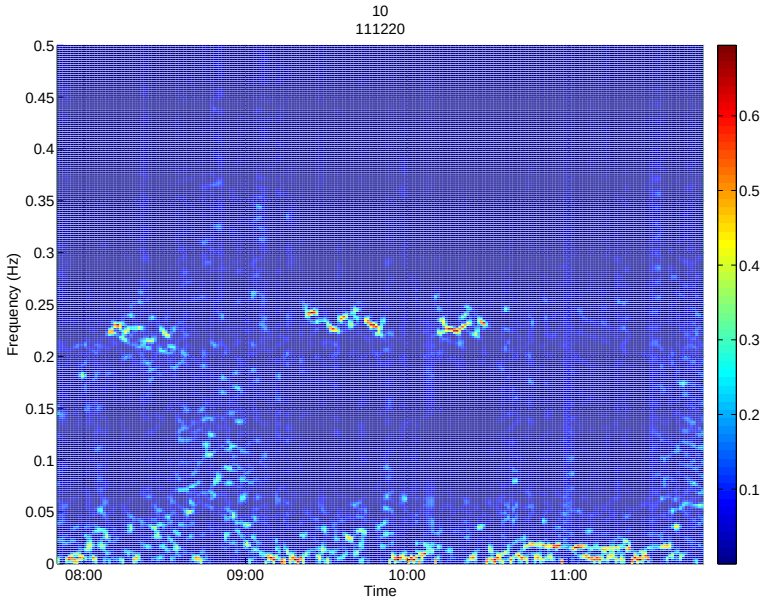
Spectral plots from the first two patients (OB10 and OB12) show high power within the respiratory region (at approx. 0.25Hz, or 15 breaths per minute) that are associated with episodes of IDH. This would suggest that blood volume was low at this time. The Critline's trend in relative blood volume from OB10 is decreasing which would support this, but interestingly this is not the case with one of OB12's sessions, whose RBV trend in Figure 6.11 on page 125 is reasonably static at the point of hypotension. OB30 shows high spectral power at approximately 0.25Hz for most of the latter half of the two dialysis sessions, when SBP tends to fall to $\leq$100 mmHg (Figures 6.12 and 6.13 on pages 126 and 127, respectively). This corresponds to a Critline value indicating a change in relative blood volume of approximately -10%, which again supports the likelihood that the patient was hypovolaemic for the latter part of dialysis. OB34, however, has high spectral power in the respiratory region for much of both dialysis sessions

(Figures 6.14 and 6.15 on pages 128 and 129, respectively). Additionally, SBP tends to fall below 100mmHg early in the session and remain low throughout. Interestingly, the change in relative blood volume recorded by the Critline is ≤-5%, suggestive of a relatively small change from the starting value. This may represent a patient who is starting dialysis relatively dehydrated (i.e. under their appropriate 'dry weight').

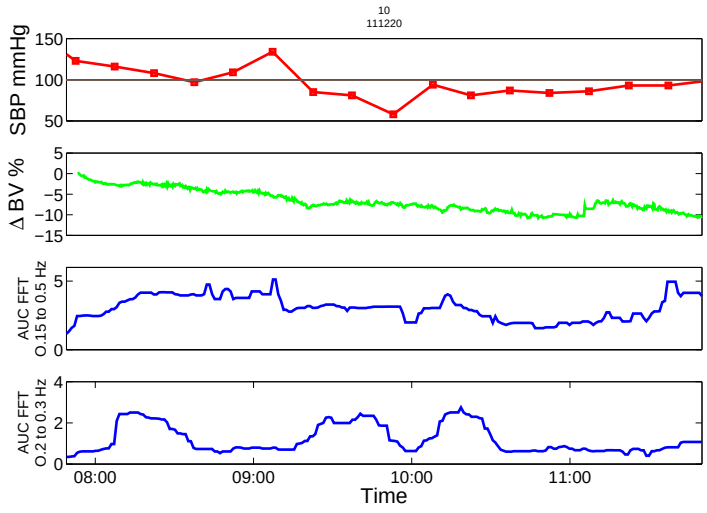
6.4.2 Area under the curve of the respiratory region of the PPG FFT

The sub-figures labelled (b) in Figures 6.8 to 6.15 on pages 122 to 129 show AUC estimates for the respiratory region (i.e. 0.15 to 0.5 Hz) as well as AUC estimates for a region of 0.1 Hz bandwidth that is centred around the frequency with highest power (i.e. representative of the average respiratory rate for the session). This proved to be more representative of the spectral plot because it reduces the influence of the broadband noise associated with a poor PPG signal. This is illustrated in Figure 6.8 on page 122 where centering the 0.1Hz band around the respiratory signal (i.e. between 0.2 and 0.3 Hz) reduces the influence of the broadband noise that occurred between 08:00 and 09:00. As this process requires some prior knowledge of the likely respiratory rate,[1] the subsequent sensitivity and specificity analyses do not utilise this individualised centering technique and are performed on the respiratory region defined for the population (0.15 to 0.5Hz, or 9 to 30 breaths per minute). Figure 6.11 on page 125 shows a peak in AUC around 08:00, which is associated with an episode of IDH (SBP < 100mmHg), and subsequent peaks at 09:00, 09:30 and 09:45, which result from broadband noise that is visible on the spectral plot. Sessions of this type are likely to result in a large number of false positives (peaks above the threshold value) — and therefore low specificity — in the following performance analyses.

[1] Although respiratory rate was estimated for all dialysis sessions, the method of acquisition (using a strain-gauge chest band) proved to be unreliable and respiratory rate was therefore not used in these analyses.

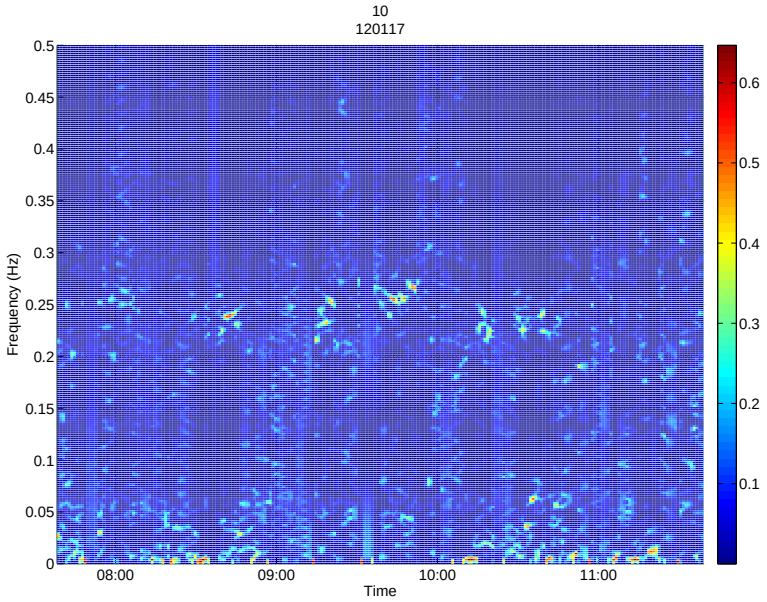


(a)

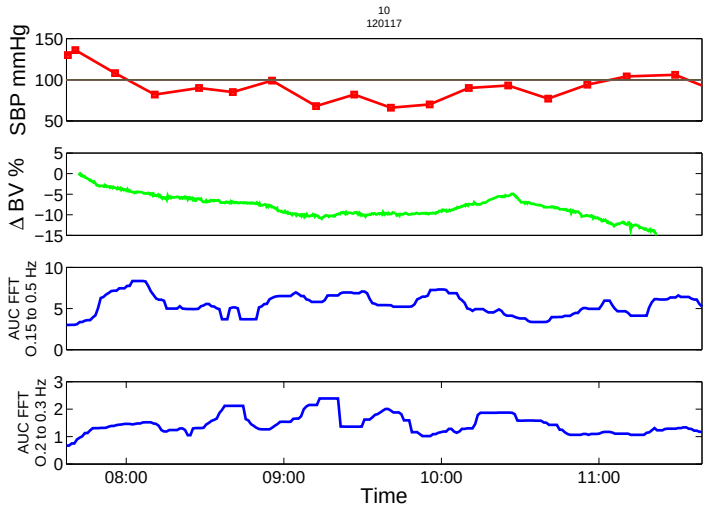


(b)

Figure 6.8: AUC estimates for OB10 (1 of 2)

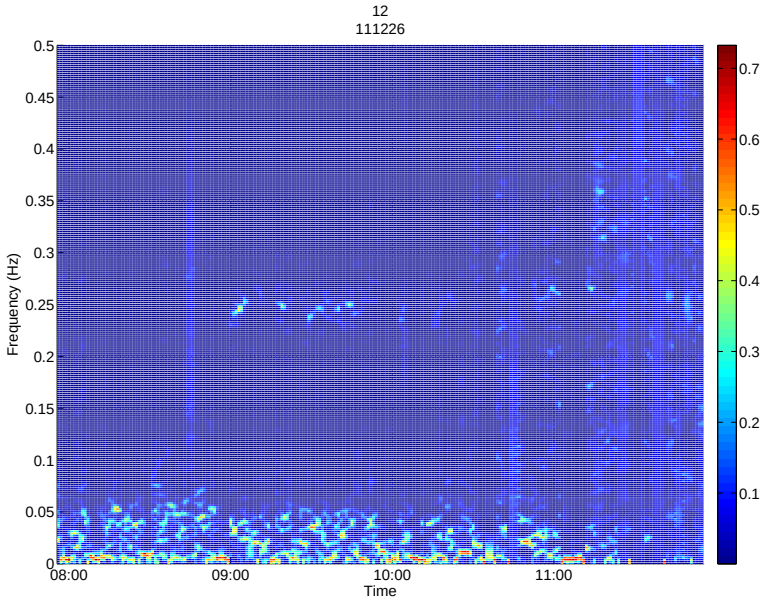


(a)

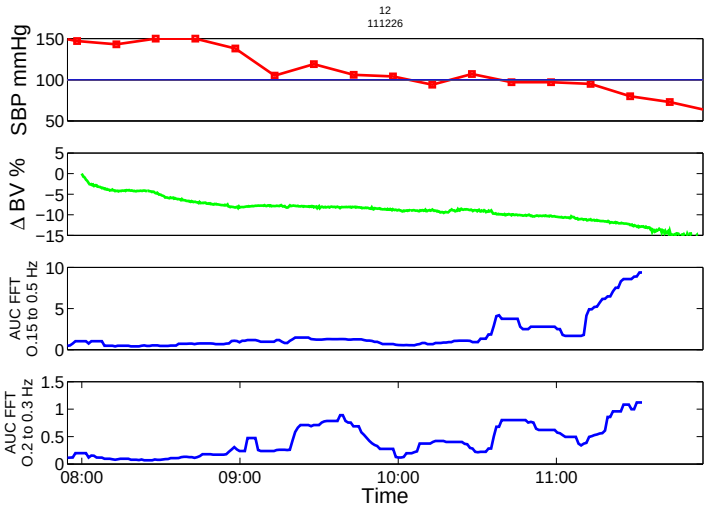


(b)

Figure 6.9: AUC estimates for OB10 (2 of 2)

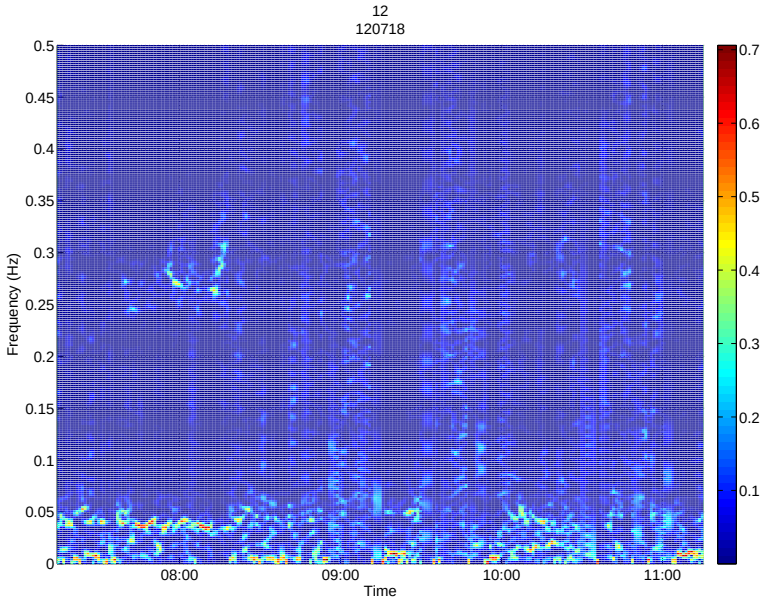


(a)

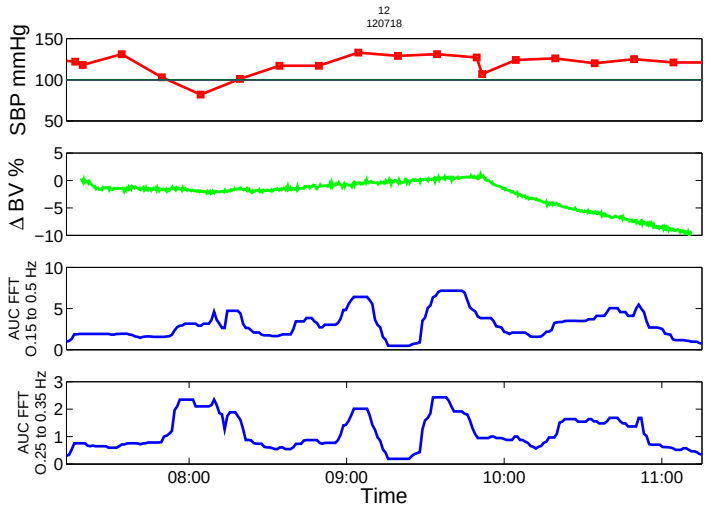


(b)

Figure 6.10: AUC estimates for OB12 (1 of 2)

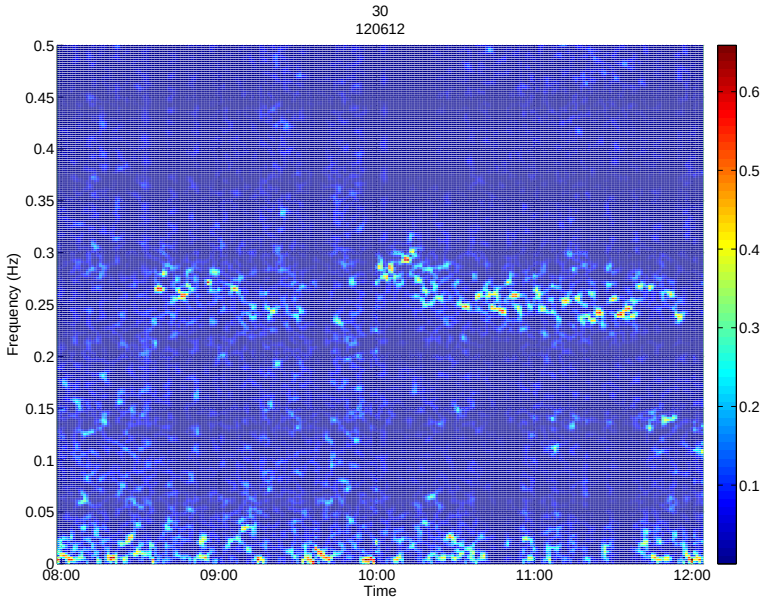


(a)

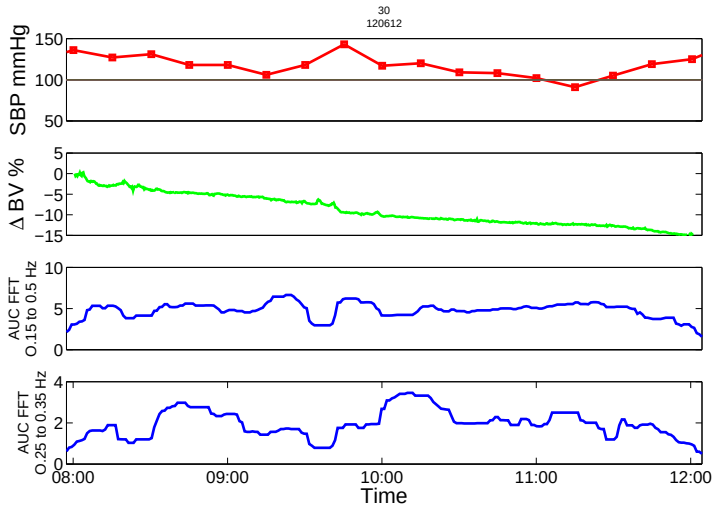


(b)

Figure 6.11: AUC estimates for OB12 (2 of 2)

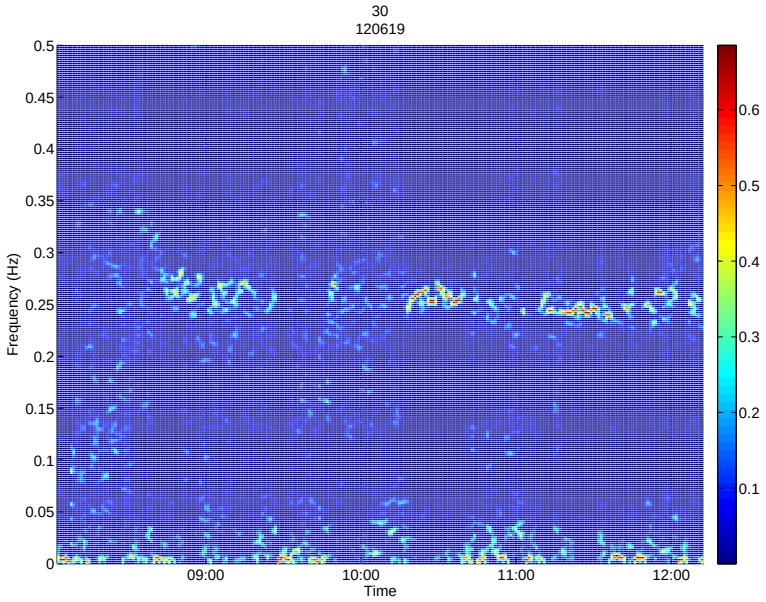


(a)

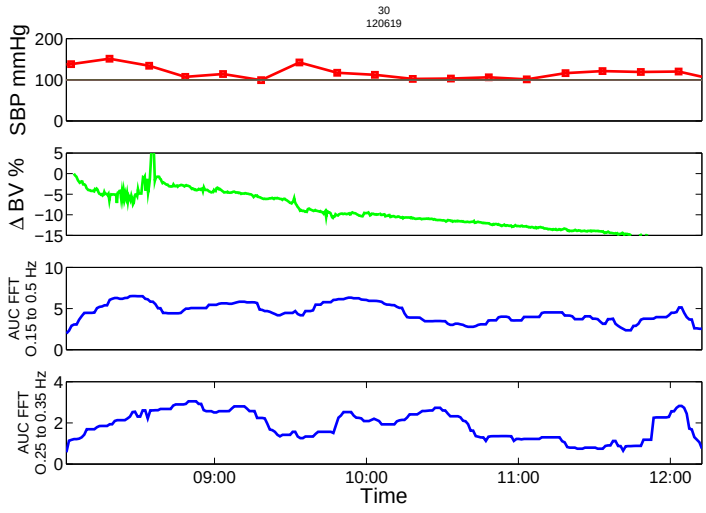


(b)

Figure 6.12: AUC estimates for OB30 (1 of 2)

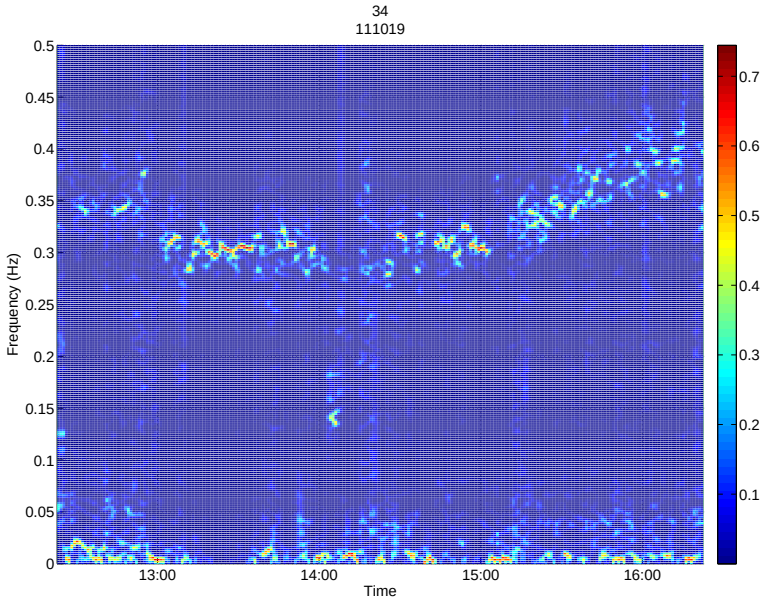


(a)

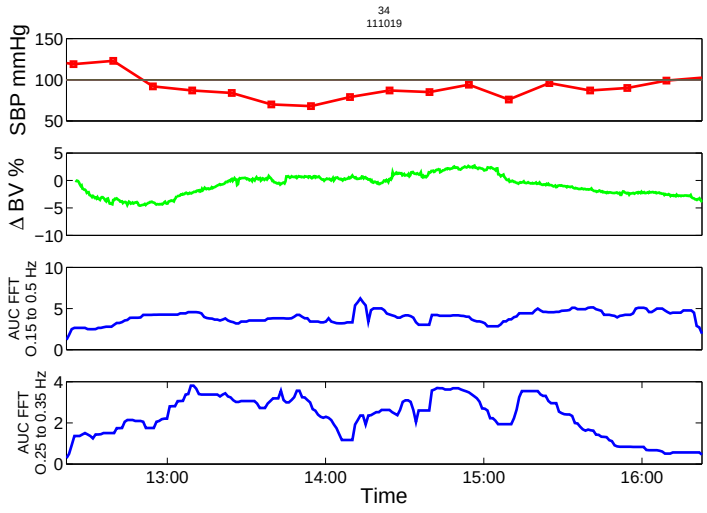


(b)

Figure 6.13: AUC estimates for OB30 (2 of 2)

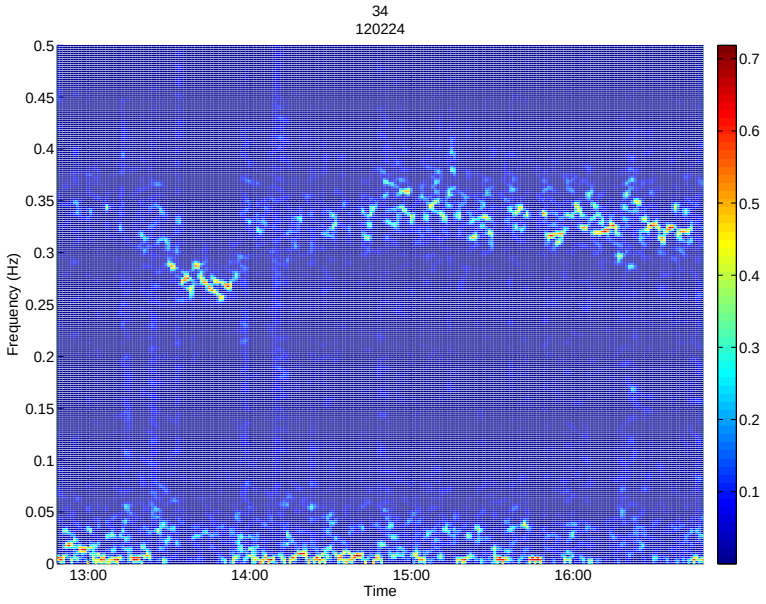


(a)

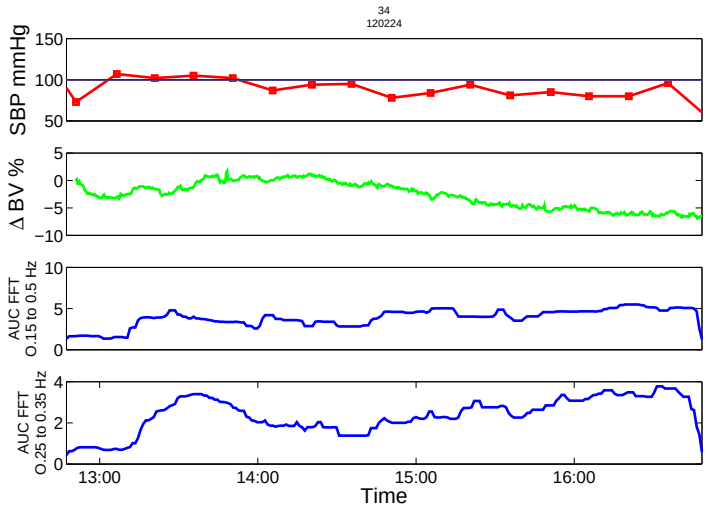


(b)

Figure 6.14: AUC estimates for OB34 (1 of 2)



(a)

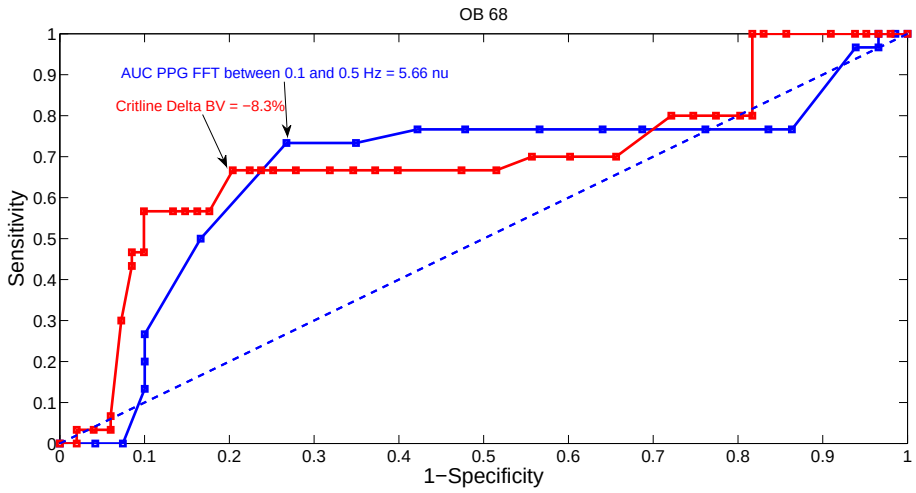


(b)

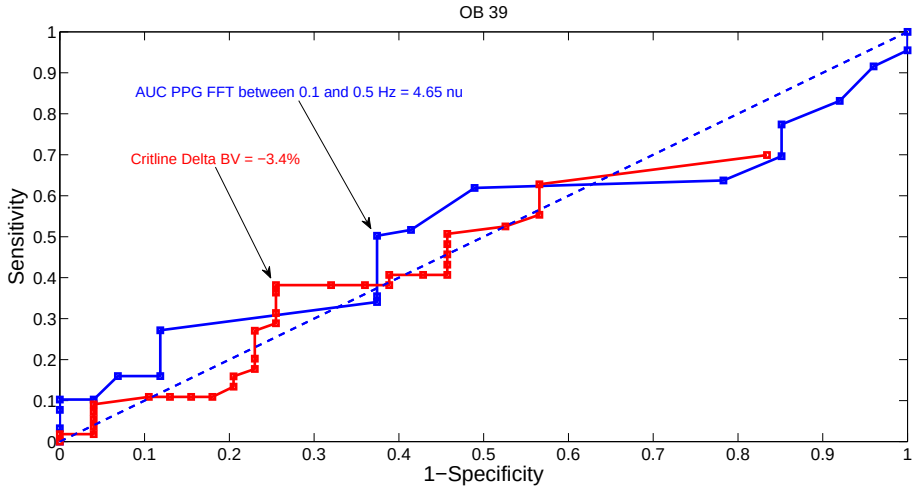
Figure 6.15: AUC estimates for OB34 (2 of 2)

6.4.3 Sensitivity and specificity analyses

Table 6.2 on page 132 shows sensitivity and specificity data for the eleven patients with ≥5 sessions with IDH. In 8 out of 11 patients there was predictive value (i.e. sensitivity and specificity both > 0.5) when defining the optimal threshold using the FFT AUC method, compared to 5 out of 11 patients when the Critline method was used. Three out of 11 patients (OB7, OB12, OB68) had an optimum FFT AUC threshold that resulted in both sensitivity and specificity ≥0.60 compared to 4 out of 11 patients (OB10, OB12, OB19, OB68) where the optimal threshold was defined using relative blood volume measured by the Critline. The ROC curves in Figure 6.16 on page 131 illustrate sensitivity and specificity results from patients OB68 (panel 'a') and OB39 (panel 'b'). Patient OB68 is shown as an example where IDH can be predicted with high sensitivity and specificity using either the Critline or PPG method: at a Critline RBV of -8.3%, sensitivity and specificity were 0.67 and 0.80, respectively; and for a FFT AUC threshold of 5.66 (normalised units), both sensitivity and specificity were 0.73. This suggests that blood volume reduction is a significant contributor in the pathogenesis of IDH for this patient. For patient OB39, blood volume monitoring by either method appears to have no predictive value for identifying episodes of IDH, suggesting that other factors (outlined in Section 1.4.1) play a more significant role in IDH pathogenesis for this patient.



(a)



(b)

Figure 6.16: Receiver Operating Curves (ROC) for the determination of IDH episodes in patients using Critline and PPG Spectral Analyses

For patient OB68 (panel 'a'), sensitivity and specificity were 0.67 and 0.80, respectively at a Critline RBV of -8.3%; and for a FFT AUC threshold of 5.66 (normalised units), both sensitivity and specificity were 0.73. This suggests that blood volume reduction is a significant contributor in the pathogenesis of IDH. For patient OB39 (panel 'b'), blood volume monitoring by either method appears to have no predictive value for identifying episodes of IDH, suggesting that other factors play a more significant role in IDH pathogenesis for this patient.

Table 6.2: Sensitivities and Specificities for PPG and Critline methods of detecting IDH

Patient	No. IDH Sessions	Optimum Critline Threshold	Sensitivity	Specificity	Optimum PPG Threshold	Sensitivity	Specificity
7	21	-4.8	0.59	0.60	4.85	0.71	0.61
10	20	-7.3	0.71	0.63	4.85	0.60	0.52
12	7	-9.0	0.71	0.71	5.66	0.61	0.69
19	5	-3.2	0.60	0.70	6.46	0.40	0.89
20	14	-3.4	0.36	0.71	4.65	0.55	0.39
21	7	-10.9	0.33	0.92	4.65	0.58	0.48
35	12	-7.7	0.44	0.71	4.85	0.59	0.57
39	5	-3.4	0.38	0.75	4.65	0.62	0.51
63	7	-8.7	0.43	0.90	5.25	0.82	0.59
66	7	-4.2	0.30	0.77	4.85	0.56	0.59
68	5	-8.3	0.67	0.80	5.66	0.73	0.73

IDH is defined as sessions with an IDH Score of 7 or greater. PPG optimum threshold represents area under the FFT of the PPG baseline between 0.15 and 0.5 Hz which maximises sensitivity and specificity for identifying IDH. Critline optimum threshold is the percent change in blood volume from baseline which maximises sensitivity and specificity.

6.5 Discussion

To our knowledge, this is the first study to use the PPG for blood volume monitoring where the primary focus is on haemodynamically unstable dialysis patients.

Results from spectral analyses showed that in some patients (e.g. OB12) an increase in spectral power in the respiratory region precedes or accompanies a fall in systolic blood pressure during haemodialysis. Moreover, patients with high spectral power in the respiratory region throughout dialysis (e.g. OB34) tended to have prolonged episodes of hypotension (i.e. SBP <100mmHg). This may be an indicator that a patient is below their optimal 'dry' weight and that a check of fluid balance and nutritional status would be indicated. Interestingly, OB34's prescribed dry weight was increased incrementally from 61 to 63kg at clinical review over the duration of the study period.

While one of the strengths of this work was the use of unedited 'raw' data in the analysis of continuous PPG data (as may be expected for prospective data analysis in a clinical context), episodes of poor quality data introduced into the analysis from artefact during signal recording could also be viewed as a major limitation. The spectral plots in Figures 6.8 to 6.15 on pages 122 to 129 showed how heavily influenced the AUC metric was by episodes of broadband noise introduced by poor signal quality. As a result, sensitivity and specificity analyses presented here are likely to vary considerably depending on how much artefact is present in the PPG signal. The introduction of a (near) real-time signal quality index may be beneficial in this regard. Arbitrary thresholds could then be defined below which incoming PPG data is censored from the analysis, so that only good-quality data is kept for prospective analyses. This type of signal processing is commonplace in the realm of biomedical engineering and would be an important focus of future work in this area.

The fact that variations in the PPG waveform are primarily due to the mechanical effects of respiration rather than mediated by the nervous system is another potential strength of this technique. Dialysis patients may have autonomic defects

which render methods reliant on an intact nervous system, such as the analysis of heart rate variability as a surrogate for autonomic tone, difficult to apply to this patient population[25]. Additionally, the PPG method is not subject to some of the assumptions used for RBV monitoring: for example, that uniform mixing of haematocrit and plasma occurs throughout the whole circulation. Section 1.5.1 discussed how these assumptions may lead to a significant source of error when estimating RBV during ultrafiltration on haemodialysis [70][160].

Regardless of whether the Critline-based RBV measurement or PPG-based AUC measurement is used, the estimation of blood volume *per se* appears limited in its ability to accurately identify episodes of IDH in all patients at risk. While the PPG FFT AUC method described in this chapter may be improved by reducing the bandwidth of the respiratory region as outlined in Section 6.4.2, these results are likely to be limited by the fact that while low blood volume is contributory to the pathogenesis of IDH, blood volume status in isolation remains a poor predictor of IDH. Indeed, it should be remembered that although hypovolemia is considered a major determinant in the pathogenesis of IDH, the relationship between blood volume reduction and hypotension is not linear. Despite positive findings by Steuer *et al*[65], a specific threshold in blood volume reduction at which hypotension will invariably occur does not seem to exist, even in an individual patient.

It is likely that the maximal benefit of blood volume monitoring would not be achieved from its use in isolation as a univariate predictor of IDH, but as one of several inputs to a model designed to consider other important determinants of IDH, such as cardiac output and peripheral vascular tone. This aspect of future work is discussed further in Chapter 8.

Chapter 7

Dual PPG Monitoring

7.1 Introduction

7.1.1 Monitoring haemodynamic status with the PPG

The introduction to Chapter 6 outlined how the PPG can be used as a surrogate for important components of the circulation, namely blood volume, stroke volume, and peripheral vascular tone. With knowledge of how each of these components is changing with respect to the other, it is in theory possible to exploit the physiological content of the PPG waveform to establish a predictable *trend* for blood pressure in real-time. The proposed method of BP-component tracking is made possible by the fact that physiological differences exist between arterioles at different anatomical sites and that these differences are evident in the morphology of the PPG waveform from sensors attached to these sites. The relationship of PPG morphology to haemodynamic status is demonstrated in the following examples.

Examples from surgical patients

Nijboer and Dorlas compared plethysmograms taken simultaneously from the finger and ear of 500 patients during surgery. They discovered the following stereotypical responses: On induction of anaesthesia they noted an increase in the amplitude of the finger PPG which did not occur in the ear. As pulse pressure

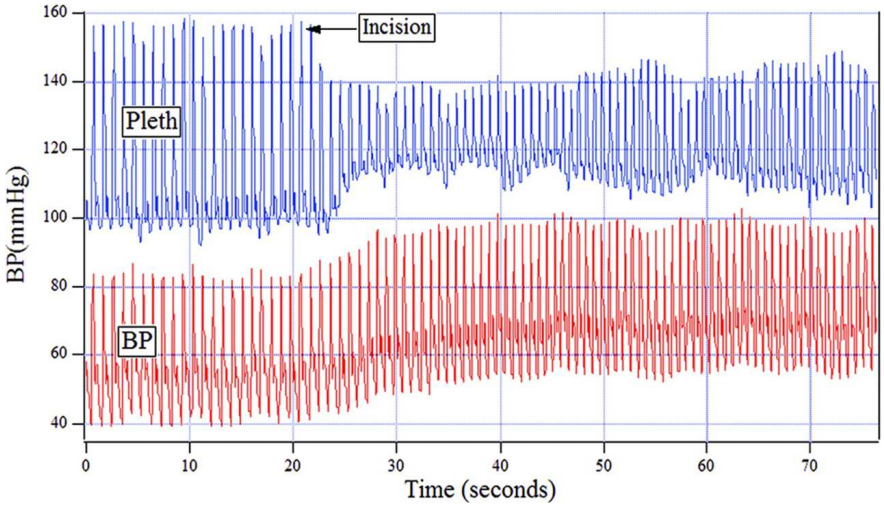


Figure 7.1: Finger PPG waveform during vasoconstriction

A scalpel incision during surgery under general anaesthesia is associated with a reduction in PPG amplitude and, therefore, area beneath the pulsatile component of the waveform. A subsequent rise in systemic blood pressure (monitored continuously through a radial arterial cannula) despite constant pulse pressure suggests this is the result of an increase in peripheral vascular tone. Reproduced from Shelley K.H. Anaes Analg 2007;105:S31-S36.

(a surrogate for stroke volume) did not change, they attributed this finding to a reduction in sympathetic tone and relative vasodilation during anaesthesia – so called 'induction sympatholysis'. During endotracheal intubation, a decrease in finger PPG amplitude was evident despite anaesthesia and, given that this was not accompanied by a decrease in pulse pressure, this was attributed to stress-induced sympathetic vasoconstriction. A similar vasomotor response was demonstrated on initiation of surgery and continued throughout surgery (see Figure 7.1). The finger PPG amplitude reduction was abolished when an adreno-receptor blocking agent was administered to the patient, at which point the morphology of the finger PPG matched that of the ear PPG. The amplitude changes in the ear PPG varied only with changes in pulse pressure (i.e. stroke volume). Drawing on similar experiments of others, the authors concluded that there was little evidence of sympathetically-mediated constriction of vessels located within the 'blush area' of the head and upper thorax[140][161].

Examples from non-ventilated, conscious adults

In their 2011 study, McGrath *et al*[162] were the first to assess the relationship between features of PPG morphology (pulse amplitude, pulse width, and area under the curve[1] of the waveform) and reductions in central blood volume in awake, non-ventilated adult volunteers. The reduction in blood volume was achieved using lower body negative pressure (LBNP), which reduces venous return, and therefore stroke volume, by sequestering blood in the lower extremities. LBNP is an established technique for modelling the physiological changes attributable to haemorrhage in conscious humans. Using PPG obtained from the finger, forehead and ear in 18 healthy adults, the investigators assessed changes at each anatomical site for each of the morphological PPG features listed above at incremental levels of LBNP until the point of cardiovascular collapse (defined as a precipitous decrease in SBP $\geq$15mmHg with concurrent symptoms associated with pre-syncope). Of interest, and of relevance to the study of haemodialysis patients described in this thesis, was their choice of Nonin pulse oximeters because they claim that the raw PPG from these devices is minimally affected by automatic gain control,[2] unlike other similar commercially available sensors. McGrath *et al* showed progressive reduction in pulse amplitude and width (and therefore AUC) with increasing LBNP. These trends were true of all monitored sites, but correlation with stroke volume was strongest with the forehead and ear as opposed to the finger ($R^2 = 0.97, 0.91$, and 0.44 respectively).

This important result supports the hypothesis behind the methods used later in this chapter that sympathetically mediated vasoconstriction in response to hypovolaemia predominates in cutaneous vessels of the distal extremities such as the finger, rather than in those located centrally such as the ear. During hypovolaemia in spontaneously breathing adults, changes in PPG amplitude and width in the ear accurately reflect changes in stroke volume but morphological changes in the finger PPG can reflect either changes in stroke volume or changes

[1] The AUC of the PPG waveform was calculated in McGrath's study by subtracting the integral of the d.c. component of the PPG from the integral of the a.c. component. A similar technique is used in this study and is described in detail in Section 7.2.

[2] Automatic Gain Control is discussed in Chapter 6. If active, this would have a major confounding influence on methods using metrics such as PPG waveform amplitude or AUC.

in sympathetically-mediated vessel tone. In isolation, each have limited utility in establishing a predictable trend for blood pressure, but when used simultaneously, differences between the morphology of the PPG waveforms at these anatomical sites harbour important physiological information from which a patient's haemodynamic status may be deduced.

7.1.2 Multi-site PPG to quantify IDH Risk

Background concepts

A review of the pathological mechanisms of IDH in Chapter 1 showed that hypovolaemia due to ultrafiltration causes an expected reduction in stroke volume. The consequential reduction in blood pressure can be offset by a compensatory increase in heart rate to maintain total cardiac output, and/or by increasing systemic vascular resistance. Of these two responses, the increase in vascular resistance is considered most important, because little is to be gained by increasing the heart rate if the primary problem is related to cardiac under-filling. Therefore, to maintain haemodynamic stability, a normal response to ultrafiltration would be a progressive and sustained vasoconstriction until blood volume can be restored either by a reduction in UF, increased plasma refilling, or a combination of the two. Any failure of vasoconstriction in this context could be considered inappropriate and render the patient at risk of hypotension. As outlined in Chapter 1, haemodialysis patients are at risk of disorders of the autonomic nervous system and these usually manifest as a failure of baroreceptor detection of hypovolaemia. In addition to an impaired vasoconstrictory response from autonomic neuropathy, vasodilatory responses also occur during dialysis and are considered to be an important cause of IDH. The postulated cause is a thermoregulatory controlled vasodilation induced by the rise in core temperature during haemodialysis. The cause of this warming is unclear but may relate to an initial phase of vasoconstriction as part of an appropriate pressure-preserving response, but at the expense of a reduced capacity for heat loss. Either way, the use of a cooled dialysate, shown in a systematic review to reduce the incidence of IDH[56], presumably mitigates the risk of hypotension by cooling the body sufficiently to increase vascular tone.

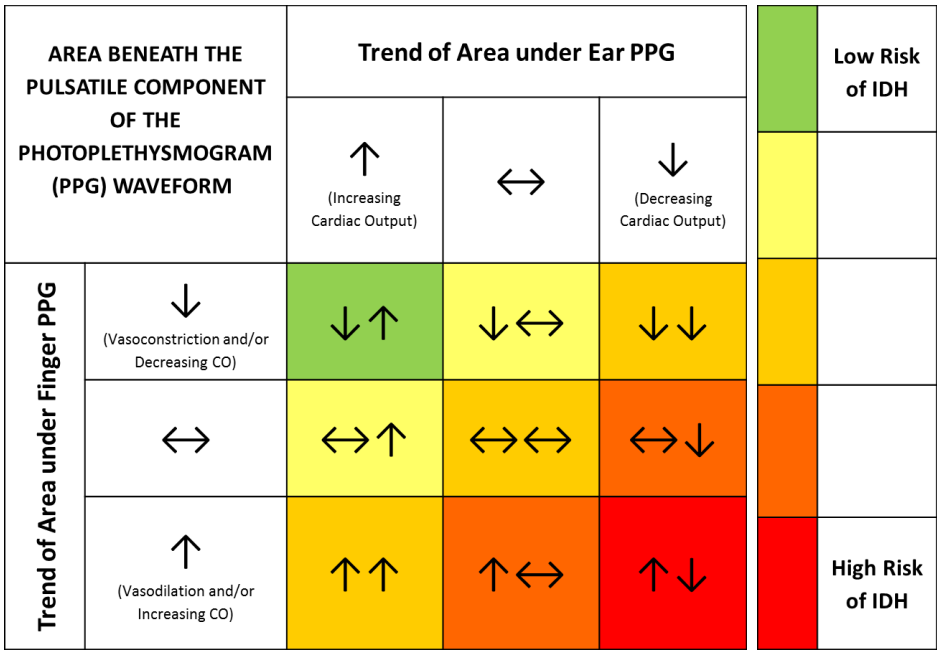


Figure 7.2: Stratification of IDH Risk using trends of area beneath PPG waveform

Hypothesis generation

With these concepts in mind, if cardiac output and peripheral vascular diameter decrease concordantly, the risk of hypotension is considered less than if the decrease in cardiac output is associated with a discordant increase in peripheral vascular diameter. In the latter higher-risk case, this discordance would be evident if the area under the pulsatile component of the ear PPG was decreasing as the area under the pulsatile component of the finger PPG was increasing — i.e. the output of the area from the PPG of the two sites were trending in opposite directions — see Figure 7.2. Therefore, it is hypothesised that monitoring the trends from these two anatomical sites could provide real-time physiological information about haemodynamic status that can be used to assess the risk of intradialytic hypotension.

7.2 Methods

Simultaneous ear and finger PPG monitoring

Seventy-six sessions were simultaneously monitored with finger and ear oximeter probes during the observational study. A Nonin reflectance-mode pulse oximeter, with a sampling frequency of 75Hz, was attached using a spring-loaded clip to the right ear, and a Nonin transmission-mode pulse oximeter with a sampling frequency of 75Hz was attached to the index finger of hand of the arm without the AV Fistula/Graft. Data from the ear probe was stored in the Hidalgo Equivital EQ02 sensor electronic module, and data from the finger probe was stored on an external computer placed adjacent to the dialysis machine. Both the EQ02 SEM and the external computer were time-synchronised to within one second.

Identification of IDH Sessions

NIBP measurements were taken at least every 15 minutes during dialysis, so an average of 16 intradialytic NIBP measurements were obtained for each four-hour session. An IDH score was assigned to each measurement according to the stratification presented in Chapter 4. Sessions complicated by intradialytic hypotension were identified as those with an IDH score ≥ 7 for one or more of the NIBP assessments during the session. Of the 23 dual-PPG monitored IDH sessions, 9 sessions had incomplete datasets so were excluded. The remaining 14 dual-PPG monitored IDH sessions were analysed.

Segmenting the PPG timeseries into windows for analysis

As the area under the pulsatile component of the ear PPG has been shown to correlate strongly with cardiac stroke volume, a window of one minute of the ear PPG timeseries was analysed over which 80 to 120 cardiac cycles would provide a representative estimate for total cardiac output.[1] In order to produce a continuous cardiac output trend over time, this one-minute window was advanced by 30 seconds each iteration such that a total of 480 windows were analysed for

[1]This is usually expressed in ml/min (Cardiac Output = Stroke Volume (ml) x Heart Rate (beats/min), but in this context it is expressed as an area beneath the ear PPG waveform over the one-minute window.

each four-hour session. An identical technique was used for deriving the area under the pulsatile component of the finger PPG waveform.

Calculation of the Area Under the Curve (AUC) of the PPG waveform

For each of the 480 windows the total AUC (a.c. and d.c. components combined) was calculated by trapezoid numerical integration. An open-source peak/trough detector[163] was then used on the non-filtered raw PPG waveform data to isolate the troughs that, when linearly interpolated, would define the d.c. component of the non-detrended waveform. The area beneath the pulsatile component of the PPG (a.c.) was obtained by subtracting the the AUC of the d.c. component from the total AUC. These methodological steps are illustrated in Figure 7.3 on page 144. When area values for each of the windows had been obtained, these were combined to form a series of values representing the change in AUC over time for the duration of dialysis.

Normalisation of the PPG AUC for ear and finger

Despite the use of the same hardware for PPG acquisition, it was recognised that PPG waveform data from different anatomical sites may have different distributions in terms of both mean and variance. Indeed, many studies using data from the PPG waveform rely on a form of normalisation procedure to allow comparable analyses. For this study, the AUC values for each site, recorded over a four-hour dialysis, were normalised by a zero-mean, unit variance transformation because the area under the curve values for a session were shown to approximate a normal (Gaussian) distribution. After normalisation, a unit change in PPG AUC represents a change by one standard deviation. Central to this procedure is the assumption that over the course of a session complicated by hypotension, the blood vessels in the ear and finger would vary over the same physiological dynamic range. Without this assumption, it would be difficult to know to what extent differences in variance were due to the dynamic physiological range of the vasculature rather than differences introduced by using independent sensors on different anatomical sites. The limitations associated with this assumption are discussed later.

Using difference in Ear and Finger PPG AUC trend as an indicator of IDH risk

Section 7.1.2 presented the hypothesis that an increasing trend in finger PPG AUC with respect to a decreasing trend in ear PPG AUC was likely to represent an inappropriate increase in vascular tone in the context of a falling cardiac output. This situation would therefore be deemed high risk for IDH. Conversely, a decreasing trend in finger PPG AUC with respect to an increasing trend in ear PPG AUC was likely to represent a period of low IDH risk. Using the previously described assumption that over the course of dialysis the blood vessels in the ear and finger change calibre over a similar dynamic range, then at any one time point, the difference between the finger PPG AUC and the ear PPG AUC will provide an indication of risk for IDH — i.e. low risk when Finger PPG AUC minus Ear PPG AUC is low (or negative), and high risk when Finger PPG AUC minus Ear PPG AUC is high (or positive).

Median filtering of the output of the Finger AUC - Ear AUC difference

The timeseries of the difference between the finger PPG AUC and ear PPG AUC was smoothed so that for each 15-minute NIBP assessment, a representative (median) value for AUC difference could be assigned. An 11-point (approximating 10-minute) median filter was required to adequately smooth the series finger-ear AUC values. This process was required so that representative finger PPG AUC minus ear PPG AUC difference values could be compared with IDH scores that were assigned to each of the 15-minute NIBP assessments as part of a sensitivity and specificity analysis for the detection of IDH.

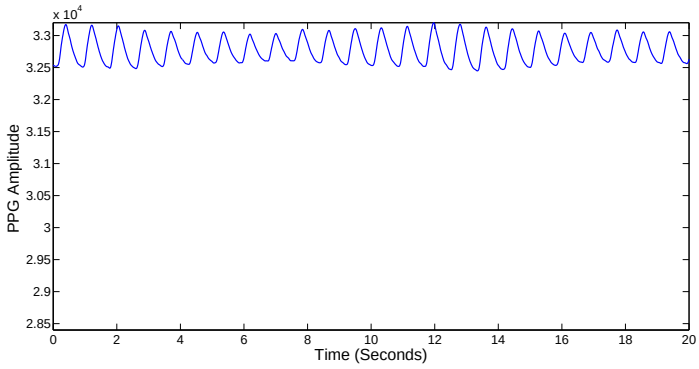
Using AUC to identify of NIBPs with IDH Score $\geq$7:Sensitivity and Specificity

As each of at least 16 NIBPs taken during a dialysis session were assigned an 'IDH Score', sensitivity and specificity analyses were conducted to establish whether the difference between finger and ear PPG AUC could be used to discriminate between NIBPs that were not diagnostic of IDH (i.e. NIBP IDH Score $<$7) and NIBPs that were diagnostic of IDH (i.e. NIBP IDH Score $\geq$7). 'True Positive'

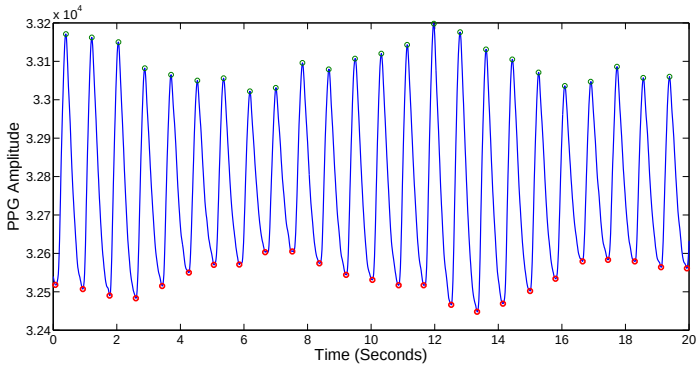
(TP), 'False Positive', 'True Negative', and 'False Negative' markers were assigned in an identical manner to that described in Section 6.3 of the previous chapter. For each of the 14 IDH sessions, a sensitivity and specificity score was obtained for each pre-defined threshold using the formula outlined in Section 6.3. For each of the 14 dialysis sessions, an optimum threshold value was obtained that maximised both sensitivity and specificity.

Incorporating Blood volume monitoring techniques from Chapter 6

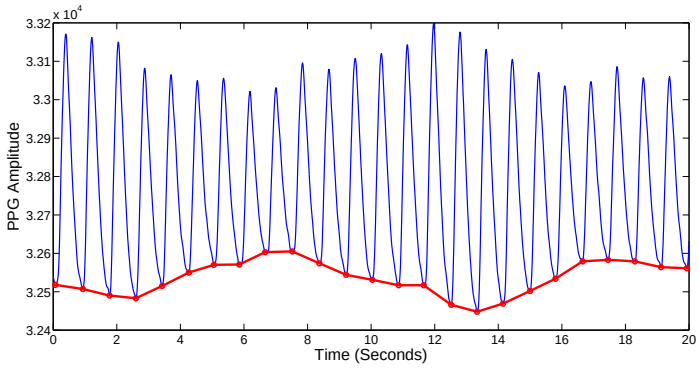
Spectral plots of the d.c. component of the Ear PPG, as described in Chapter 6, were also performed for the dialysis sessions that are illustrated as examples in this chapter. These spectral plots are presented alongside the Critline RBV plots for each session so that blood volume status can be used to interpret the Finger minus Ear PPG AUC plots in context, enabling a comprehensive analysis of a patient's haemodynamic status during dialysis.



(a)



(b)



(c)

Figure 7.3: PPG signal processing to extract area beneath pulsatile component

Figure (a) shows the raw PPG waveform. Figure (b) shows detection of troughs in the non-detrended PPG using a threshold-based technique. Figure (c) shows interpolation of the troughs of the non-detrended PPG to delineate the d.c. component. The area under the a.c. component of the PPG waveform is given by the subtraction of the integral of the d.c. component from the integral of the total area (a.c. + d.c.).

7.3 Results

Illustrative examples are shown in Figures 7.4 to 7.8 on pages 147 to 151 for 5 of the 14 sessions complicated by intradialytic hypotension. For each example, the IDH event can be attributed to either a decrease in the area under the ear PPG, an increase in the area under the finger PPG, or a combination of the two. Of interest is the similarity between the SBP plot (top panel) and the 'filtered difference' plots (bottom panel). As the filtered difference plots represent the risk of low blood pressure, they are positive when SBP tends to be low and negative when SBP tends to be high, so appear in several of these examples as reflections of the SBP plot in the x-axis. This finding is most evident in Figures 7.4, 7.5, and 7.6.

7.3.1 Results of sensitivity and specificity analyses

The optimum threshold for finger-ear AUC difference for the identfication of IDH Scores ≥ 7 is shown in Table 7.1 on page 146, along with associated sensitivities and specificities. It can be seen that in 4 of the 14 sessions (OB2 120523, OB20 120622, OB22 120509, and OB33 111116) the finger-ear difference does not help discriminate NIBP measurements with an IDH Score ≥ 7 from non-IDH NIBP measurements. However, in 10 of the 14 sessions (71%) both sensitivity and specificity are $\geq$0.50, indicating diagnostic benefit with this technique. Moreover, in 8 of the 14 sessions (57%) both sensitivity and specificity are $\geq$0.60; and in 4 of the 14 (29%) sessions (OB7 120925, OB23 120928, OB66 120628, and OB71 120510), both sensivity and specificity are $\geq$0.70.

Table 7.1: Finger-ear AUC difference for identifying IDH Scores $\geq$ 7:Sensitivity and Specificity analyses

Patient	Session	Optimum Threshold	Sensitivity	Specificity
1	120727	1.5	1.00	0.62
2	120523	0.5	1.00	0.15
7	120522	1.0	0.50	0.54
7	120724	3.0	0.67	0.80
7	120925	3.0	0.83	0.78
10	120117	3.0	0.66	1.00
10	120619	3.5	1.00	0.63
20	120622	0.0	0.50	0.10
22	120509	1.0	1.00	0.25
23	120928	3.0	1.00	0.76
33	111116	2.0	1.00	0.23
66	120628	2.0	1.00	0.72
68	120531	0.5	0.50	0.60
71	120510	4.0	0.71	0.80

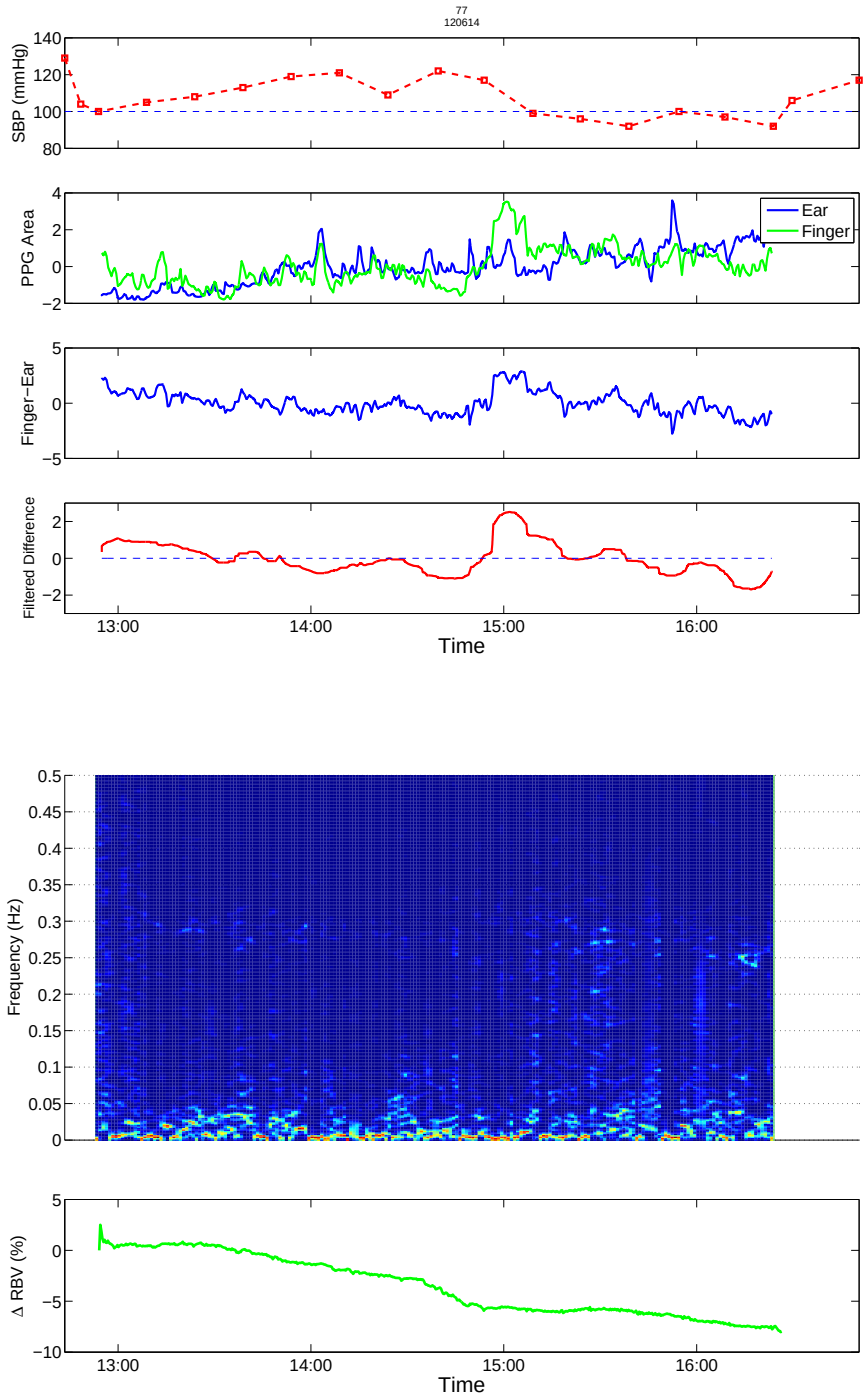


Figure 7.4: OB77 120614 Dual PPG Monitoring: IDH

The hypotensive event around 15:00 appears to be associated with a rapid increase in area beneath the pulsatile component of the finger PPG, suggesting a rapid reduction in vascular tone. This is associated with a marked increase in the finger-ear difference at 15:00. This 'vasodilatory' hypotension is also suggested by the relatively low power in the respiratory region of the Ear PPG FFT, and the modest reduction in RBV, both of which would indicate that blood volume reduction is not critical at this time. Note that the filtered difference plot approximates a reflection of the SBP plot in the x-axis.

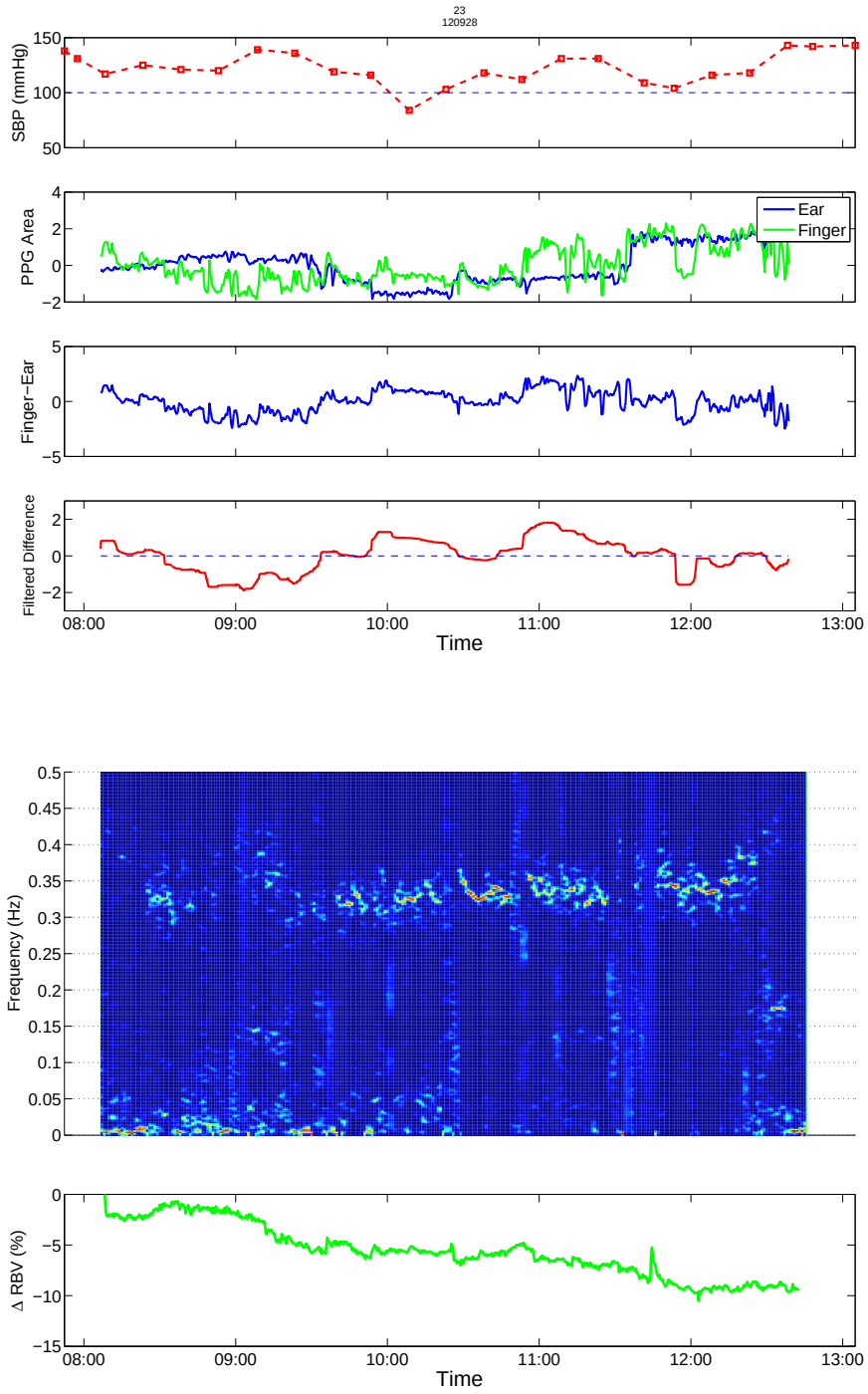


Figure 7.5: OB23 120928 Dual PPG Monitoring: IDH

The increase in area beneath the pulsatile component of the ear PPG, and decrease in the area beneath the finger PPG (between 08:00 and 09:00) suggests a compensatory response to ultrafiltration and is accompanied by a stable BP and negative finger minus ear values, indicating low risk of IDH. The hypotensive episode at 10:00 is indicated by a reduction in cardiac output (positive finger minus ear values) and the appearance of high power in the respiratory region of the ear PPG FFT spectral plot. Note that the filtered difference plot approximates a reflection of the SBP plot in the x-axis.

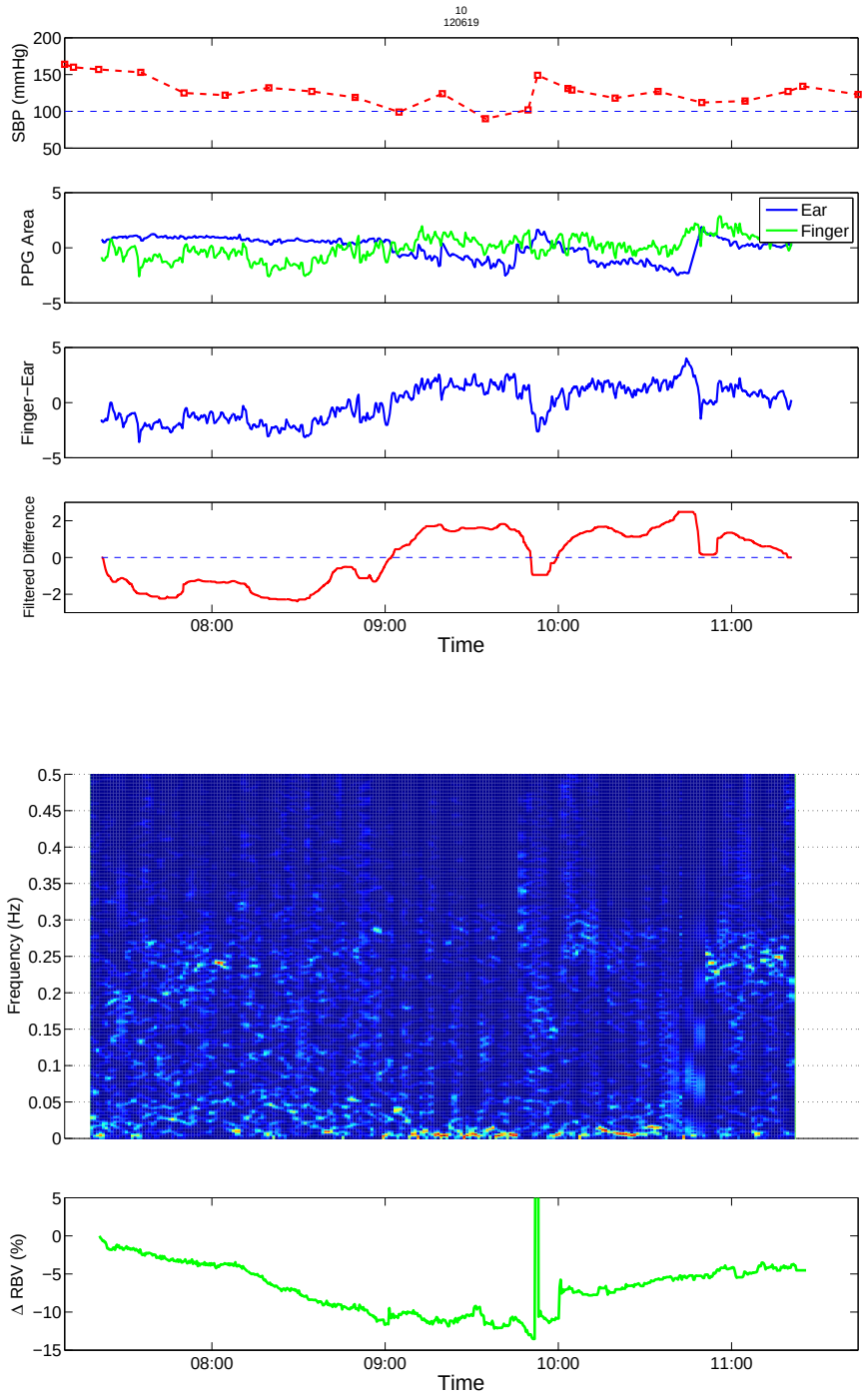


Figure 7.6: OB10 120619 Dual PPG Monitoring: IDH

The area beneath the pulsatile component of the ear PPG is stable between 08:00 and 09:00. The fluctuation in SBP during this hour is explained by changes in peripheral vascular tone, as demonstrated by the area beneath the finger PPG. At 09:30, a decrease in vascular tone is associated with a decrease in cardiac output, which appears to precede the hypotensive episode. The finger-ear values are positive at this time. Recovery of BP at 09:50 is due to administration of a fluid bolus (an artefactual spike is visible in the RBV plot), which is associated with an increasing area beneath the ear PPG (i.e. cardiac output). Note that the filtered difference plot approximates a reflection of the SBP plot in the x-axis. The spectral plot appears unhelpful in this example.

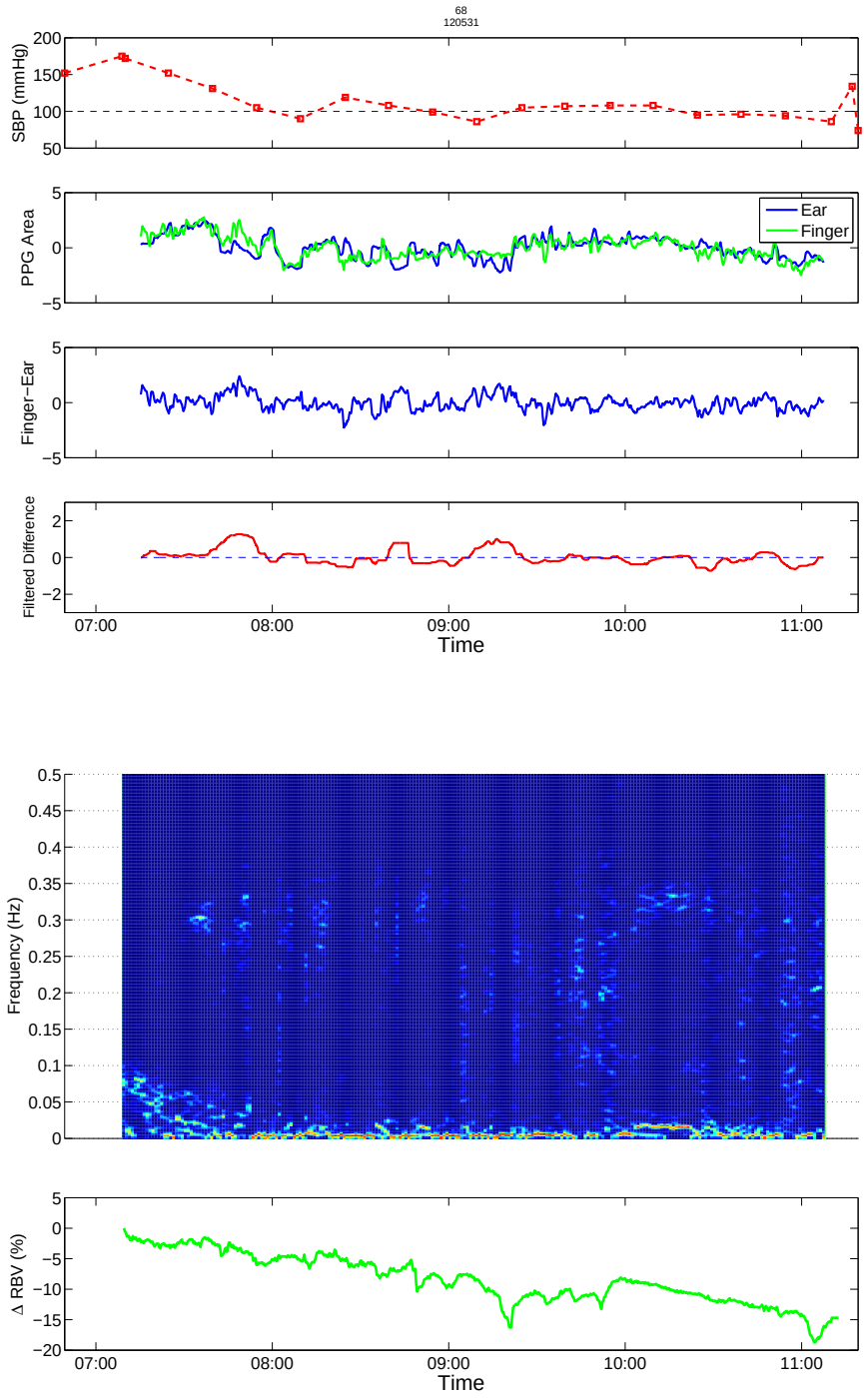


Figure 7.7: OB68 120531 Dual PPG Monitoring: IDH

The high correlation between the pulsatile components for the ear and finger PPG waveforms suggests that the BP is predominantly dependent on cardiac output for this patient during this session, but renders the finger minus ear value close to zero. If cardiac output was blood volume dependent, we would expect to see high power in the respiratory region of the Ear PPG FFT spectral plot, but this is not present in this example. However, the hypotensive event around 09:10 may be due to a relatively low cardiac output with respect to vascular tone, as indicated by positive finger-ear values and low RBV values around this time.

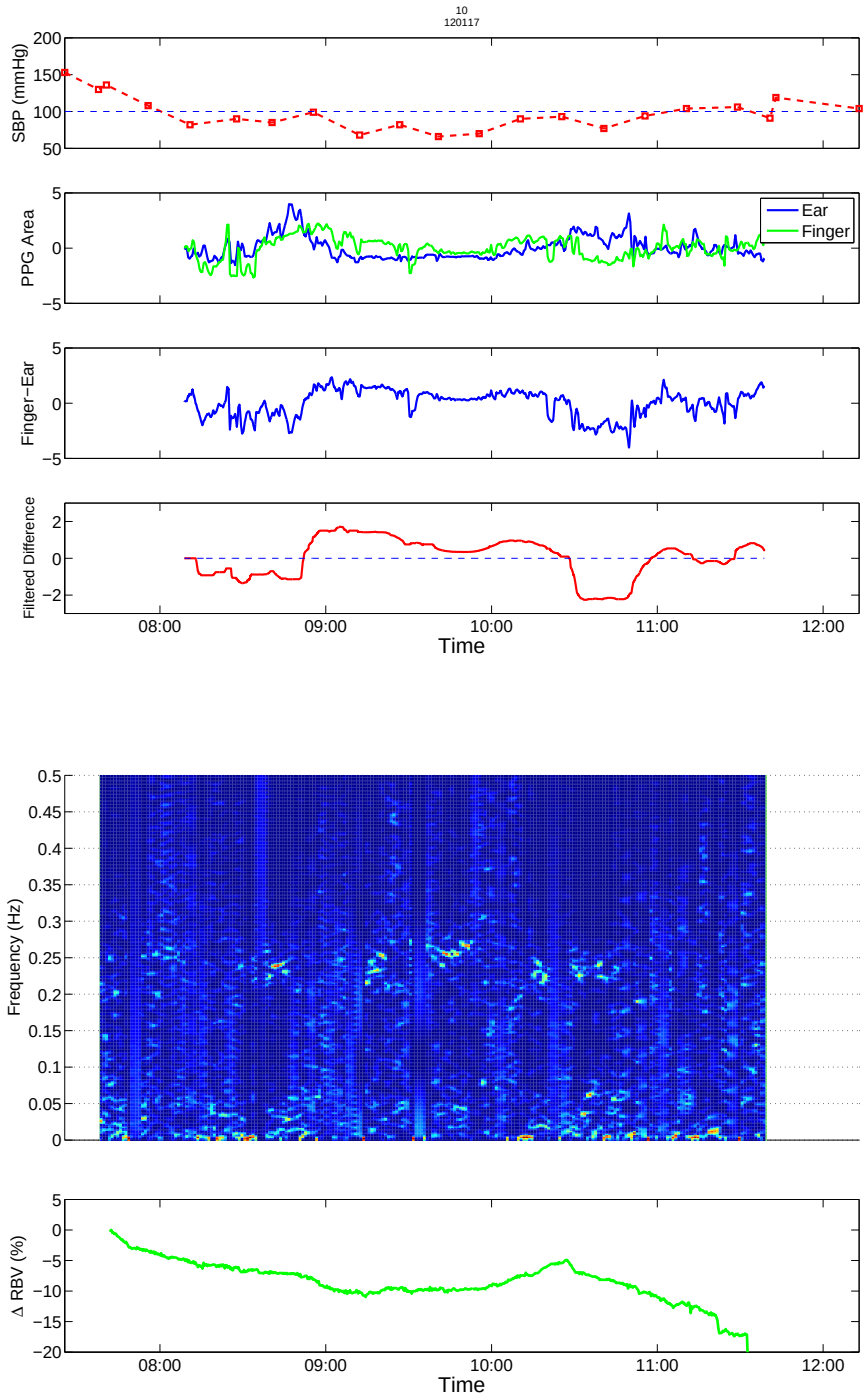


Figure 7.8: OB10 120117 Dual PPG Monitoring: IDH

This patient appears to have a sub-optimal compensatory response to ultrafiltration. The prolonged period of hypotension between 08:00 and 11:00 is associated with positive finger-ear values and high power in the respiratory region of the Ear PPG FFT spectral plot. The modest increase in SBP around 10:30 appears to coincide with an increase in RBV and, therefore, cardiac output (indicated by negative finger-ear values around this time).

7.4 Discussion

To our knowledge, this is the first time that dual PPG continuous monitoring has been used in haemodialysis patients to estimate the time during dialysis that IDH is most likely to occur by tracking AUC estimates of changes in the calibre of the ear PPG waveform with respect to the finger PPG waveform. The results presented here show that there appears to be merit in this approach (i.e. in over half of the 14 dialysis sessions studied, the 15-minute window preceding IDH was identified with a sensitivity and specificity both $\geq$0.6). A major strength of this work is that the metric of interest (the calibre of resistance blood vessels[1] that influence haemodynamic status) is estimated directly, rather than using surrogates of autonomic tone,[2] such as heart rate variability, to predict the likely haemodynamic response. This is of importance because, as outlined in Section 1.4.1, the benefits of heart rate variability monitoring has not been established in the dialysis population and HRV may itself be attenuated as a result of end-stage renal failure[25] or the ageing process[29]. A surprising aspect to the results presented here was the extent to which the trend blood pressure could be estimated using dual finger and ear PPG monitoring. This is evident in Figures 7.4 to 7.6 on pages 147 to 149 in the similarity between the plot for SBP and the plot finger-ear difference, with the latter appearing as a reflection in the x-axis of the former in the cases illustrated.

The methods presented in this chapter were used to estimate the change in ear PPG AUC with respect to the finger PPG AUC as a means of quantifying haemodynamic status and, therefore, the risk of IDH. Section 7.2 highlighted the need for a methodological assumption to be made prior to analysis of the PPG data. The assumption was that the calibre of the blood vessels within the dermis of the ear and the finger change within a similar physiological dynamic range during dialysis. Without normalisation of the data, it would be difficult to determine to what extent differences in the PPG AUC were due to differences in the calibre

[1] The generic term 'blood vessels' is used because there is uncertainty about the exact origin of the PPG waveform[138, 139], as discussed in Section 6.1.

[2] 'Autonomic tone' describes the balance between sympathetic and parasympathetic autonomic components.

of vessels (i.e. explained physiologically) or due to the acquisition of PPG data from two different sites (i.e. introduced by the sampling method). Zero-mean, unit-variance normalisation of PPG data from each probe allowed comparison of the PPG datasets, with the mean AUC representing the calibre of a blood vessel that was neither maximally vasoconstricted nor maximally vasodilated. Given that patients with IDH often experience relatively large fluctuations in blood volume during dialysis, and given that peripheral vasodilation to offset warming on dialysis is considered to be common and an important determinant of IDH[52], the assumption that the blood vessels of the finger and ear may change over a similar dynamic range over the course of dialysis (i.e. between vasoconstricted and vasodilated) seems plausible. There are, however, important caveats to this assumption, an example of which is given in the following scenario: A patient who attends dialysis below his/her dry weight (i.e. relatively dehydrated) may already be vasoconstricted as a compensatory response to defend blood pressure in the context of relative hypovolaemia. Assuming that any IDH episode during dialysis in this patient is purely volume-related rather than due to sudden peripheral vasodilation, it is unlikely that the change in calibre of the already vasoconstricted blood vessels of the finger will be of the same magnitude as the change in calibre of the (non-vasoconstricted) blood vessels of the ear. Whether or not the calibre of ear and finger vessels in patients with autonomic neuropathy or patients taking sympatho-inhibitory medication (e.g. alpha-blockers) would occupy the same physiological dynamic range is not clear. As vessels of the ear are known to be sparse in adrenoreceptors, it is possible that alpha-blockers and autonomic neuropathy result in very similar dynamic ranges between blood vessels within the dermis of the ear and finger[140][161].

It is important to emphasise that only sessions that were known to have IDH were analysed in this chapter. This meant that sensitivity and specificity analyses in this chapter was based upon the ability of the proposed method to correctly identify the 15-minute window preceding IDH. To extend this method to the wider population so that IDH risk could be estimated in all (i.e. including non-IDH) dialysis sessions would require an absolute rather than normalised AUC metric. The acquisition of an absolute metric would require a training period for each

individual patient where data from each probe site was gathered over a range of experimental conditions that included vasoconstrictory and vasodilatory stimuli. Only in the absence of other confounding factors, such as automatic gain control (AGC), could the amplitude of the PPG waveform (and therefore the AUC) become an absolute rather than relative physiological variable that could be used prospectively to represent blood vessel calibre.

As discussed in the introduction to this chapter, the application of AGC is a potential confounder to any AUC analysis of the PPG. Review of the raw PPG data used for this analysis suggests that AGC was not obviously active,[1] and this premise is supported by McGrath *et al* who performed similar AUC analysis with identical Nonin pulse oximeters[162]. Moreover, if AGC was active, it would have presumably predominantly affected the early phase of PPG recording when the probe was being attached to the patient, and not the intradialytic period which started after the probes were securely attached. The dialysis patients were seated in a reclined position throughout PPG recording and, as mentioned previously in Chapter 6, this limited any potential motion artefact that may activate AGC. Similarly, although not controlled during this study, there was no obvious change in levels of ambient light in the dialysis unit during the hours of the study that may have activated AGC.

As indicated above, further work should explore how ear PPG AUC changes with respect to finger PPG AUC under laboratory conditions. Peripheral vasoconstriction and vasodialation may be achieved with cold and warm thermal stimuli[27], respectively. Results of these experiments could then be used to quantify vessel calibre for an individual in absolute rather than relative terms, which could then form the basis for monitoring haemodynamic status prospectively using the ubiquitous non-invasive pulse oximeter.

[1]This issue was not clarified by contacting the manufacturers of the device because this information is considered confidential and is not available to persons external to the manufacturing company.

Chapter 8

Conclusion

8.1 Summary of Results

The introduction to this thesis highlighted the exponential increase in patients requiring Renal Replacement Therapy for End-Stage Kidney Disease. This is partly explained by an ageing population at increased risk of kidney failure, and partly explained by RRT being offered to an increasingly older patient group: At the turn of the millennium, the median age of the incident population was 63 years but results from the 2012 renal registry indicate that this has now increased to 67 years[164].

However, this increasingly elderly cohort of patients often present with extensive medical co-morbidities in addition to renal failure. While some of these co-morbidities have no relevance to dialysis treatment, others, in particular cardiovascular disease, can manifest as a challenge to dialysis staff when trying to ensure that treatment targets (the clearance of toxic metabolites and restoration of a body salt-water content compatible with normotension) are achieved. In a significant proportion of patients, treatment is interrupted by IDH, the most common complication of haemodialysis. The introductory chapter demonstrated the multi-faceted nature of IDH and examined the potential pathophysiological pathways that could result in a decompensation to hypotension during ultrafiltration. The pathophysiology of IDH was emphasised because of its importance

in determining which biological signals or 'vital signs' would be most informative when trying to predict these adverse events. Differentiating the normal physiological response to ultrafiltration from the pathophysiological patterns of IDH is an essential requisite for any potential predictive model, and this distinction was fundamental to the work of later chapters.

8.1.1 The relationship of symptoms to intradialytic blood pressure

In order to test the efficacy of monitoring strategies to identify or predict IDH, it was important to clearly define IDH as the outcome measure. Chapter 3 identified that many definitions exist in the literature, making direct comparisons between studies difficult and leading to confusion about the true extent or burden of this phenomenon. While consensus guidelines exist to try and address this issue, there has been variable uptake of the suggested definition, and Chapter 3 highlighted that there were some fundamental flaws to this approach. Firstly, the EBPG definition requires a symptomatic fall in blood pressure with an intervention to satisfy the IDH criteria. However, results from the observational study of continuous blood pressure monitoring and symptom questionnaires showed that patient symptoms were not a reliable surrogate for an acute fall in blood pressure, and some patients remained asymptomatic regardless of low blood pressure during dialysis. This finding uncovered the second problem with the current definition. The limited data on morbidity and mortality to date are predominately based upon absolute blood pressure levels and do not distinguish between symptomatic and asymptomatic hypotension.

IDH: Defining the outcome measure

To maintain continuity with the current evidence, a blood pressure-only definition was required as an outcome measure for this thesis. A SBP <100mmHg or reduction in SBP of 20% of baseline were decided upon as an outcome measure going forward, because at these thresholds the probability that a session would result

in an intervention rather than remain asymptomatic was maximised. Of interest was the finding that approximately 1 in 4 asymptomatic sessions fulfil these IDH criteria. This highlighted that continuous blood pressure monitoring was required to identify asymptomatic patients at risk of intradialytic hypoperfusion.

8.1.2 Continuous blood pressure monitoring

Chapter 3 introduced a novel approach to the problem of continuous blood pressure monitoring during haemodialysis. Without any additional sensor equipment, this technique used existing pressure transducers in the arterial and venous lines of the extracorporeal circuit to detect relative changes in intra-fistula blood pressure. The algorithm developed in this thesis exploited the duality of continuous arterial and venous pressure monitoring to identify and exclude artefactual changes in pressure caused by shifts in the needle position or temporary reductions in flow through the circuit. Results from this technique demonstrated that once these artefacts are removed by a filtering process, which could occur in near real-time with the power of conventional computer processors, the resulting continuous pressure trace correlated strongly with results from intermittent non-invasive blood pressure measured through an inflatable cuff over the upper arm. When stratified at the patient level, the results in Chapter 3 show that some patients correlate consistently well while others correlate consistently poorly. These differences were attributed both to the variability of blood pressure during dialysis and the calibre of the blood vessels forming the A-V fistula. The strongest correlations occurred in patients with brachial A-V fistulae, and those with a large dynamic range of intradialytic blood pressures — i.e. a larger signal-to-noise ratio, typical of the patients experiencing large blood pressure fluctuations with IDH. The superiority of brachial over radial fistulae when fistula pressures were correlated with SBP was likely to be related to the increased calibre of the underlying blood vessels and, therefore, related to increased blood flow through the underlying fistula.

8.1.3 The ear PPG as an indicator of low intravascular volume

While continuous blood pressure monitoring *per se* was considered vital in identifying episodes of hypotension during dialysis, especially in otherwise asymptomatic patients, it had little *predictive* value other than conveying a decreasing blood pressure trend that would inevitably progress to hypotension in a patient unable to compensate. However, as BP is often maintained by compensatory physiological mechanisms until the point of cardiovascular collapse, the prediction of IDH before its occurrence required tracking of the magnitude of the disequilibrium (i.e. progressive hypovolaemia with ultrafiltration) or tracking of the magnitude of the compensatory response to this perturbation. Chapter 6 considered non-invasive ways of tracking hypovolaemia, building on earlier work using the pulse oximeter-derived PPG waveform for monitoring of blood loss in patients undergoing surgery. This chapter described how the mechanical influence of respiration on central venous pressure (and therefore the ear PPG waveform) during hypovolaemia had potential benefits over heart rate variability when used for cardiovascular status monitoring.

Javed *et al* are to be credited with recognising the utility of the PPG waveform as a tool to assess haemodynamic status in haemodialysis patients, but their study of 10 patients excluded those with haemodynamic instability – i.e. patients with significant intradialytic hypotension[81]. The work presented in Chapter 6 addressed this by investigating the use of respiration-induced variations in the ear PPG waveform of patients experiencing IDH. These variations were quantified using the area under the curve of the respiratory region of the fast fourier transform of the PPG waveform. The performance of this technique in identifying thresholds predictive of subsequent adverse hypotensive events was found to be comparable with the 'Crash-Crit' threshold of the current gold-standard for continuous relative blood volume monitoring: the Critline^{TM}[65]. Overall, there was some predictive value for 8 out of 11 patients (i.e. sensitivity and specificity both >0.5) when defining the optimal threshold using the FFT AUC method, compared to 5 out of 11 patients when the Critline^{TM} method was used.

8.1.4 Dual ear and finger PPG monitoring

Chapter 7 investigated whether the area under the curve of the ear and finger PPG waveform (a proxy for continuous cardiac output and peripheral vascular resistance, respectively) could identify when during a dialysis session a hypotensive event was likely to occur. The assumption was that an increasing cardiac output or peripheral resistance would have an overall protective effect and reduce the risk, but a decreasing cardiac output or vascular resistance would render a patient at risk of hypotension. Results from Chapter 7 demonstrated a striking similarity between the plots of the finger-ear AUC difference, and the blood pressure profiles obtained by interpolating the intermittent NIBP measurements. Using 'dual' pulse oximeters attached to the ear and finger, this novel technique for deconstructing blood pressure into its determinants — cardiac output and vascular resistance — allowed tracking of the compensatory response to ultrafiltration and an indication of when an inappropriate response (such as a falling cardiac output or vasodilation) was occurring. At the optimal threshold for Finger-Ear AUC difference, the 15-minute window preceding IDH was identified with a sensitivity and specificity both $\geq$0.6 in 8 of the 14 dialysis sessions studied.

8.2 Future Work

This thesis presented results from univariate analyses of several novel potential predictors of IDH. However, given the multi-faceted pathogenesis of IDH, described in the introduction to this thesis, it is reasonable to suggest that multivariate analysis may be a more informative approach. By definition, multivariate analysis takes into account more than one variable simultaneously. This type of analysis may allow the distinction between abnormal physiology from an appropriate compensatory cardiovascular response to UF on dialysis and abnormal physiology representative of an imminent cardiovascular decompensation and collapse. Distinguishing normal from abnormal physiological responses requires a pre-determined distinction between which physiological patterns are normal or expected during dialysis and which patterns are predictive of deterioration. The description of how such a multivariate model may be constructed to assess multi-

source inputs in near real-time is the focus of this section on Future Work.

8.2.1 Defining 'normal' physiology during dialysis

In order to distinguish between an appropriate and inappropriate physiological response to ultrafiltration on dialysis, the training data set for a potential model should comprise 'normal' dialysis physiology, against which comparisons are drawn and abnormality is defined. This data set is likely to differ from those used in other studies because the physiology comprising the normal group is *expected* to be abnormal if the patient is mounting an appropriate compensatory response. For example, a rising heart rate may be an early warning indicator for deterioration in a general medical patient, but may be expected as a compensatory response to ultrafiltration in a dialysis patient and, going further, may be a paradoxical indicator of those *less likely* to deteriorate and experience symptoms associated with hypoperfusion or hypotension. In addition, the dynamic response to cumulative ultrafiltration means that 'normal' physiology in the first hour of dialysis may be significantly different from 'normal' physiology in the last hour. This nuance implies that a dialysis-specific model should define 'normal' as the expected degree of physiological derangement in UF volume-matched controls undergoing a symptom-free and event-free dialysis. These parameters of normality may need to shift as dialysis progresses, in-line with the expected change in compensatory physiology for a patient undergoing cumulative ultrafiltration during an uneventful dialysis.

8.2.2 Patient-based vs. Population-based models

As dialysis is a repetitive treatment, the difficulties with trying to predict IDH by comparing a particular individual's physiology with others in a heterogeneous population can be overcome with the development of personalised models. Indeed, work by Dr. Yasmina Borhani on the same observational study dataset showed that differentiating IDH sessions (using the same abrupt 20% fall in SBP to <100mmHg criterion suggested in this thesis) from non-IDH sessions using Neuroscale multi-dimensional visualisation techniques (described below) was not possible when using data from the dialysis population as a whole, but was possible

when using patient-based models. These patient-based models were constructed from a training data set of 7 'normal' dialysis sessions from the same patient using the standard four vital signs (BP, HR, $Sp0_2$ and RR)[165]. The difficulty distinguishing IDH from non-IDH sessions on a population basis is obvious when means and standard deviations of these vital signs for the IDH and non-IDH groups are considered, as demonstrated in Table 8.1.

Table 8.1: Means(μ) and Standard deviations (σ) for standard vital signs recorded during IDH and non-IDH sessions

	μIDH	μNon-IDH	σIDH	σNon-IDH
Heart Rate (beats per min.)	79.0	76.9	14.1	16.3
SpO_2(%)	94.3	93.6	4.7	5.2
Mean Arteral Pressure (mmHg)	100.9	104.0	19.1	18.6
Respiratory Rate (breaths per min.)	21.6	23.1	7.6	9.8

Analysis performed by Dr. Yasmina Borhani[165]

This table indicates that if 'normal' dialysis physiology was defined using the parameters of the non-IDH group, it would invariably include physiological parameters that would be considered extreme and undoubtedly abnormal for some patients. Defining normality by repeated assessments of an individual rather than the population reduces the influence of the marked heterogeneity of the dialysis population, because the patient becomes their own control. Moreover, this approach allows ongoing data collection for repeated dialysis sessions over time and therefore allows increased confidence in the estimation of what represents a normal physiological pattern for a particular individual during their treatment — i.e. this approach introduces the possibility of 'machine learning' algorithms that refine parameter estimates with ongoing cumulative data collection. For these compelling reasons, the future development of patient-specific models are considered here:-

8.2.3 Developing a predictive model

Two potential approaches are presented here — Novelty modelling and Supervised learning. The most suitable technique will depend on the number of observed

events for a particular patient. Both approaches use multivariate probability density distributions of candidate physiological variables to form a multi-dimensional model.

Novelty Modelling

The 'training group' for novelty patient-specific modelling is made up of the session data from a patient undergoing a 'normal' dialysis, which may be defined as the achievement of dry weight[1] without intradialytic symptoms or hypotensive events. Any multidimensional input to this model that is outside the 'expected' limits is considered to be novel with respect to a pre-designated threshold in the probability density function. In this respect, the model defines the probability that the physiological input at a given point in time belongs to that 'expected' for a 'normal' dialysis. This type of modelling is particularly suitable when rare events are considered and has been used extensively in general medical and high-dependency settings[112]. An example of a two-dimensional probabilty density function (for two standard vital signs, heart rate and respiratory rate) is shown in Figure 8.1 on page 163. In this illustrative example, courtesy of Dr. David Clifton, the red circumferential band indicates a pre-designated probability threshold at which an alert may be generated for a 'novel' or unexpected combination of heart rate and respiratory rate. This process in not just limited to two vital signs but each additional vital sign (or other derived physiological parameter) requires an increase in dimensionality of the model.

Supervised learning

Supervised learning takes the reverse approach and requires abnormality to be defined as well as normality — i.e. a two-class problem. For this reason, numerous events will need to be monitored in order to generate the 'training' data for the abnormal class, which in this case represents the data from physiological variables just prior to intradialytic symptoms or hypotensive events. Alerts representing a higher probability of deterioration are generated when the pattern of physiological variables is similar to those defining the abnormal class in the training group. This

[1] This assumes an accurate setting of dry weight

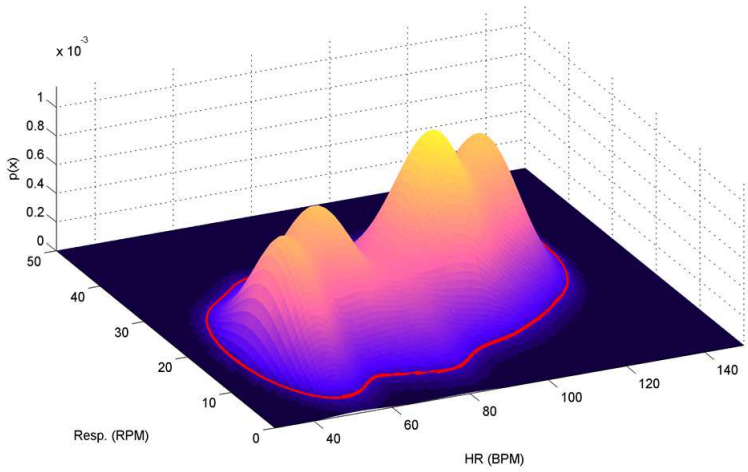


Figure 8.1: Novelty Modelling

A probability density function incorporating two physiological parameters – heart rate and respiratory rate. A pre-designated probability threshold is depicted by a red circumderential band, below which the heart and respiratory rate combinations have been judged to be improbable or abnormal. Note that the heart rate is shown as a near-bimodal distribution. It is possible that this is due to the use of beta-blocker or similar chronotropic medication for the patient population shown here.

is illustrated in Figure 8.2, where the red spheres represent abnormal physiological patterns, the blue spheres represent normal physiological patterns and the green spheres represent inconclusive patterns that border the classifier (shown here as a solid black line in a two-dimensional representation).

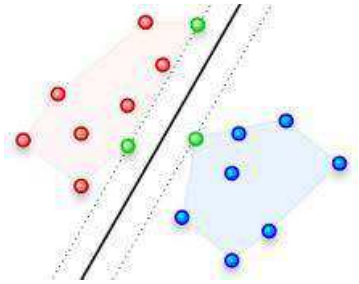


Figure 8.2: Supervised Learning

A schematic two-dimensional representation of a Supervised Learning Algorithm. The red and blue spheres represent different populations divided by a classifier (solid black line). The green spheres represent data points whose proximity is too close to the classifier to be discriminated with confidence. The Supervised Learning algorithm may represent a multi-dimensional structure, depending on the number of input variables.

On balance, given the relatively low event rate seen in the Observational Study conducted for this thesis, Novelty detection seems the more suitable technique for the prediction of potential IDH episodes. An overview of this technique is presented here, but an in-depth review and demonstration can be found in the doctoral theses of Dr Alistair Hann[166] and Dr Yasmina Borhani[165], the latter applied specifically to haemodialysis patients but limited only to the standard four vital signs: HR, NIBP, $Sp0_2$, and RR. Future work should extend these analyses to include derived variables identified in this thesis as good candidate predictors of IDH, such as the area beneath the respiratory component of the spectral plot of the ear PPG waveform (Chapter 6) and the dynamic assessment of area under the curve of the PPG waveform for both finger and ear PPG (Chapter 7).

8.2.4 Neuroscale as a visual aid to model development

As computational requirements increase exponentially with every additional dimension in which the data lie, deciding how many and which physiological input variables are optimal for a model using physiological data to predict adverse events is an iterative process of trial and error, guided by physiological principles and clinical experience. The typical number of input variables is four or five (i.e. four-dimensional or five-dimensional models) for these types of analyses[112],[118],[166].

The neuroscale map is a tool for reducing the dimensionality of complex high-dimensional data sets so that the data can be visualised in two dimensions. In essence, a multidimensional training dataset of normal or expected values is used to define a zone of normality. This zone of normality is represented in a two-dimensional space such that the distance between each point on the neuroscale map is proportional to the euclidean distance in the multi-dimensional space. Once this zone of normality is defined, any new data points can be visually assessed to see whether they are representative of normal data (i.e. lie within the zone of normality), or whether they represent abnormal data (i.e. lie outside of the zone of normality). If data from a combination of four input variables from a session with IDH lie within the zone of normality, it is unlikely that this combi-

nation of variables will be predictive of intradialytic adverse events. However, if a combination of variables is found that distinguishes IDH sessions (data points falling outside of the zone of normality) from non-IDH sessions (data points falling within the zone of normality), then it is likely that this combination of input variables will have some predictive power when used as part of a probabilistic model, such as novelty detection.

The Neuroscale concept is illustrated in Figure 8.3 and Figure 8.4, courtesy of Dr Yasmina Borhani. The grey zone of normality has been trained from 7 'normal' sessions from patient OB20, and this is identical for both figures. In Figure 8.3 data from an additional normal session (not used as part of the training process) has been overlaid in colour. The change in colour spectrum from blue to red represents progress in time during dialysis from 0 to 240 minutes, respectively. In Figure 8.4 vital sign data from an IDH session has been overlaid. It can be seen that although the start of the session is within the limits defined by the zone of normality, the latter part of the session is associated with a combination of vital sign parameters that is clearly abnormal when compared to the training data.

8.2.5 Novelty detection: an overview of the technique

Novelty detection is the identification of new data that has not been experienced by a machine learning system during its training phase[167]. These techniques are increasingly used throughout industry, such as the prediction of engine failure in jet aircraft[168], but also there are applications of these techniques in the healthcare setting, including the continuous monitoring of patients in the Intensive Care Unit and general medical and surgical wards[166]. In the latter example, there are some obvious parallels with continuous monitoring for adverse events during haemodialysis. Unlike supervised learning which requires abnormal and normal classes of equal size, novelty detection is suited to monitoring for adverse events in the healthcare setting because usually there are many more examples of the normal condition available than the abnormal condition – especially when it is considered that the abnormal condition may take many different forms and is not necessarily a stereotypical response. In this respect, abnormalities may be

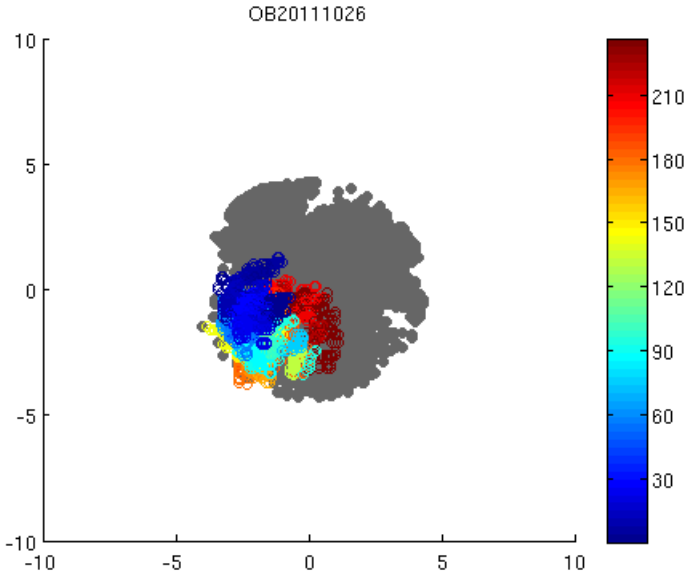


Figure 8.3: Neuroscale plot from a non-IDH session

The grey zone of normality has been trained from 7 'normal' sessions from patient OB20. Data from a 'test' session (not used as part of the training process) has been overlaid in colour. The change in colour spectrum from blue to red represents progress in time during dialysis from 0 to 240 minutes, respectively. IDH did not occur during this test session, and this is shown by the confinement of the coloured projection within the zone of normality

identified for which there are no previous examples in the training phase of model development.

The statistical approach to novelty detection is to construct a probability density function for the normal data and to apply a threshold to the probability of a new pattern coming from this distribution. There are parametric and non-parametric approaches to probability density function estimation. The parametric approach assumes that the data come from a known form of probability distribution, and the training data are used to learn the parameters of that distribution. Non-parametric methods do not make assumptions about the statistical distributions underlying the data: the density function and model parameters are all derived from the training data itself.

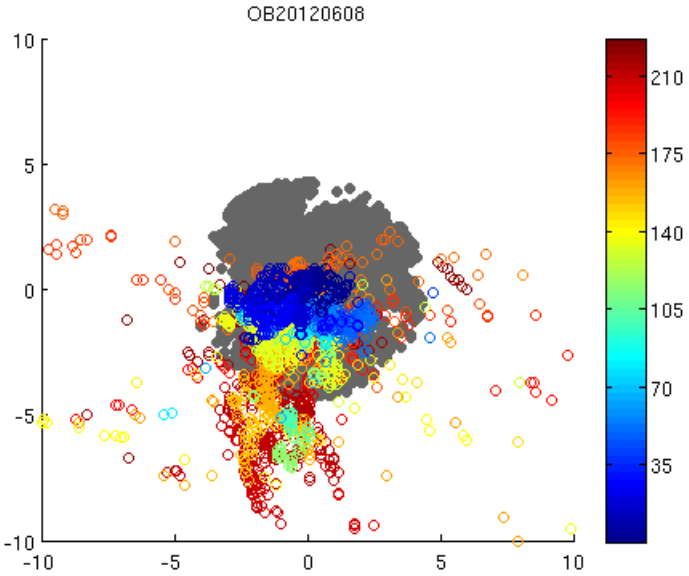


Figure 8.4: Neuroscale plot from a session with IDH

The grey zone of normality has been trained from 7 'normal' sessions from patient OB20. Data from a 'test' session (not used as part of the training process) has been overlaid in colour. The change in colour spectrum from blue to red represents progress in time during dialysis from 0 to 240 minutes, respectively. This test session was complicated by an episode of IDH occuring approximately one hour into dialysis. The coloured projection is clearly visibile outside the boundary defined by the zone of normality and represents an abnormal constellation of vital signs that were not observed during the non-IDH training sessions.

In order to construct this multi-dimensional PDF of the normal data for each patient, a sequence of pre-filtering (excluding physiologically implausible results that are likely to be a result of artefact or error) followed by zero-mean, unit variance normalisation of the training dataset is performed. As a result, each parameter (i.e. vital sign or derived physiological variable) has equal importance/equal 'weight' in the model. A legitimate probability density function must be non-negative and integrate to one.

A kernel density estimator known as Parzen windows is one commonly used example of a non-parametric method for assessing the probability that a new data pattern is represented in the training data set of 'normal' observations[169]. For example, suppose that we want to estimate the value of the probability density function (PDF), $P(X)$, for a single variable at point x. Then, we can place a

mathematical window function at x and determine how many observations x_i from the training data set fall within this pre-defined window. The PDF value $P(x)$ is then the sum total of the contributions from the observations in the training data set to this window, normalised by the volume of the window. In other words, the more densely populated a particular window at point x, the higher the probability that this data represents a normal pattern. In this way, a bespoke (i.e. non-parametric) probability-density function is developed without the requirement of an *a priori* (parametric) assumption about its distribution. A variety of mathematical window functions can be chosen for Parzen window estimates, but details are beyond the scope of this chapter and therefore not expanded further.

8.2.6 Future testing of a predictive model

While it is hoped that the introduction of a predictive model would greatly enhance the care of patients on haemodialysis, there is a possibility that even the development of a robust, predictive model will not translate into clinical benefit. For example, while a predictive model may be sensitive and specific in identifying subsequent intradialytic events, it may only identify a group of patients in whom comorbidity is so great that intervention is unlikely to be effective. Alternatively, an alert may be correctly generated in patients likely to respond, but in insufficient time to allow for effective intervention. If the model is sensitive but lacks specificity, the number of false-alarms may reduce its acceptability or may potentially lead to unnecessary interventions during dialysis.

Answers to these queries can only be addressed through a future trial where a patient-based model is used as generator of alerts to potential IDH and graded interventions are initiated in response to these alerts. Simple interventions may include a reduction of ultrafiltration rate or a bolus of saline administered to increase plasma volume. Outcome measures should not only include the frequency of symptoms, hypotensive events, and quality of life, but also assess whether the prescribed $\frac{Kt}{V}$ was achieved and dry weight attained during dialysis. Frequent interventions may lead to reduced time on dialysis and an inability to achieve dry

weight within the allotted four hours. Related to this is whether any additional intervention results in increased intra-dialytic weight gain and blood pressure from over zealous saline administration. Other considerations are whether the additional alerts and interventions have negative impacts on nursing/clinician workloads or are seen to cause anxiety among patients considering the option of haemodialysis.

The heterogeneity of the population and the limited number of patients that can be continuously monitored at any one time suggests that a prospective cross-over trial design using a patient-specific model developed following a 'training' period of observation would be most informative. The influence of confounding covariates is reduced for this design because each cross-over patient serves as his or her own control. In addition, the cross-over design tends to be more statistically efficient when participant numbers are low. Study periods could alternate continuous monitoring and responding to model-based alerts (A) with periods of usual dialysis care (B) in an A-B-A-B-A-B type pattern, each lasting several months. In addition to hard outcomes such as morbidity and mortality and the other quantitative analyses described here, any future study should include qualitative assessments of patients' dialysis experience. This will help to ensure an holistic approach to further understanding the problem of IDH by investigating patients' symptoms, patients' quality of life, and patients' perceptions of the interventions used to reduce the frequency and/or severity of intradialytic hypotension.

Appendix A

Oxford Kidney Unit IDH Audit

Oxford Radcliffe Hospitals NHS
NHS Trust

Intradialytic Hypotension:
Moving Towards The Individualised Haemodialysis Prescription

Meredith D, Pugh C, Sharples E, Thornley A, Turner C
On Behalf of the Oxford Kidney Unit, Churchill Hospital, Oxford

Introduction

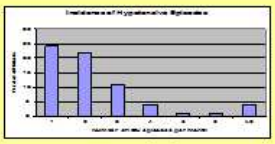
Intradialytic Hypotension (IDH) is the most frequent complication of maintenance haemodialysis (HD), occurring in between 20-30% of treatment sessions[1]. The causes of IDH are multi-factorial and vary widely between patients with differing co-morbidities. Recognition that IDH is an independent risk factor for reduced survival[2] has led to recommendations by the Renal Association in March 2007[3] to audit IDH rates and implement reduction strategies.

Our aim was to discover the incidence of IDH in our patients, and to identify whether there were differences between the stable patients (No IDH) and the unstable patients (≥1 IDH per month) that were amenable to simple intervention by changing the dialysis prescription.

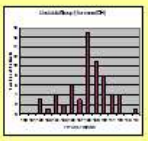
Methods

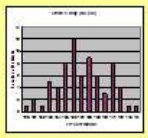
We studied all of our HD patients (n=142) for one month – a total of 1723 dialysis sessions. IDH was diagnosed if SBP fell by >20mmHg to ≤100mmHg, or the patient experienced hypotension-associated symptoms with a >10% fall in SBP from the pre-dialysis baseline. Data was collected prospectively, and the following was obtained: Delta Sodium (dialysate Na – average pre-dialysis serum Na), Delta Temperature (Pre – Post Temperature), Weight loss (Pre – Post weight), weight loss as a percentage of the Dry Weight (%DW), and Ultrafiltration rate (total UF in mls /session length in minutes). Analysis was performed using simple statistics and either Student's t-test or Mann-Whitney test, depending on whether or not the raw data exhibited a normal distribution. Missing data was omitted from the analysis. P-Values of <0.05 were taken as significant.

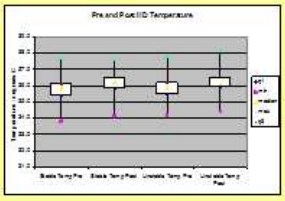
Results



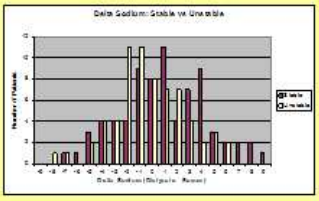
Demographics	Stable Group (No IDH)	Unstable Group (≥1 episode IDH)
Number of Patients	75	67
Median Age	63	63
Males	49	55
Females	26	12







	Stable Group	Unstable Group	p Value
Mean Pre HD Temp (°C)	36.8	36.8	>0.05
Mean Post HD Temp (°C)	36.3	36.3	0.8
Mean Delta Temp (°C)	0.50	0.50	0.58
Median Delta Na (mmol/L)	1	2	0.03
Mean UF (mls)	2200	2200	0.53
Mean UF/kg (ml/kg)	3.6	3.4	0.1
Mean Delta Wt (as %DW)	1	1.5	0.41



Conclusion

Our unit has rates of IDH that are higher than those quoted in the literature. Our results show that many of our patients have average pre-HD serum sodium levels above the standard 137mmol/L that is used in our dialysis prescriptions. This difference appears to be important in the stability of our patients, with significantly more IDH documented in those with negative to neutral delta sodium. It is known that HD is a warming therapy, and patients in both of our groups warmed significantly. There was no difference in the degree of warming between the groups. The volume or rate of UF was not a significant factor in determining the stability of our patients; indeed, more UF was achieved in the stable group, which could be explained by more uninterrupted sessions without the requirement of additional saline for IDH. We aim to use these results to change our practice. We aim to use an individualised dialysis prescription that avoids negative Delta Na values by matching dialysate sodium to the average pre-HD serum Na. We will also reduce our dialysate temperatures, in line with growing evidence[4], and re-audit our rates of IDH, hoping to demonstrate a significant improvement.

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Appendix B

Observational Study Patient Data

Table 2: Observational study patients: RRT vintage

Patient	HD This Episode (months)	Total HD (months)	Total PD (months)	No of Tx	Total Tx (months)	Total RRT (months)
1	49	49	17	0	0	66
2	65	65	0	0	0	65
3	19	37	0	1	63	100
4	157	155	0	0	0	155
5	18	18	0	0	0	18
6	27	27	0	1	279	306
7	56	56	7	0	0	63
8	13	13	0	0	0	13
9	92	92	0	0	0	92
10	18	18	0	0	0	18
11	10	10	0	0	0	10
12	62	62	0	0	0	62
13	47	47	8	0	0	55
14	18	18	0	0	0	18
15	26	26	0	0	0	26
16	-	-	-	-	-	-
17	75	75	0	0	0	75
18	30	30	0	0	0	30
19	9	9	0	0	0	9
20	32	32	0	0	0	32
21	38	104	0	2	240	344
22	52	66	0	1	208	274
23	55	55	0	0	0	55
24	30	30	0	0	0	30
25	29	29	0	0	0	29
26	14	14	0	0	0	14
27	26	26	0	1	103	129
28	13	19	0	3	298	317
29	53	53	3	0	0	56
30	17	23	19	1	7	49
31	27	27	0	0	0	27
32	76	117	0	1	75	192
33	33	33	0	0	0	33
34	29	29	0	0	0	29
35	98	98	0	0	0	98
36	75	75	0	2	220	295
37	11	11	0	0	0	11
38	26	26	0	0	0	26
39	23	23	0	0	0	23
40	24	24	0	0	0	24
41	52	52	0	0	0	52
42	59	59	0	0	0	59
43	18	21	2	0	0	23
44	7	7	0	1	289	296
45	69	69	0	0	0	69
46	38	38	0	0	0	38
47	11	11	90	0	0	101
48	7	22	21	1	52	95
49	17	17	0	0	0	17
50	28	33	0	1	399	432
51	55	55	0	0	0	55
52	11	11	0	0	0	11
53	56	56	0	1	210	266
54	30	30	0	0	0	30
55	26	26	0	0	0	26
56	8	8	0	0	0	8
57	41	41	0	0	0	41
58	20	20	0	0	0	20
59	26	19	0	0	0	19
60	75	75	0	0	0	75
61	48	48	0	0	0	48
62	39	39	0	0	0	39
63	5	5	0	0	0	5
64	5	5	0	0	0	5
65	31	31	0	0	0	31
66	2	2	16	0	0	18
67	5	5	0	0	0	5
68	1	1	0	0	0	1
69	1	1	0	0	0	1
70	8	8	0	0	0	8
71	7	7	0	0	0	7
72	-	-	-	-	-	-
73	2	2	1	0	0	3
74	1	1	0	0	0	1
75	12	12	0	0	0	12
76	7	7	0	0	0	7
77	25	25	0	0	0	25
78	5	5	0	0	0	5
79	0	0	0	0	0	0
80	-	-	-	-	-	-

Table 3: Observational study patients: Ethnicity and Diagnosis

Patient	Ethnicity	Ethnicity Code	Diagnosis Free Text	Diagnosis Category	Tx Waiting List
1	White British	White	Hereditary Amyloid	GN	0
2	White British	White	MPA Vasculitis	GN	0
3	White British	White	Hypertensive Nephropathy	Renovascular	1
4	Whtie British	White	Nephrolithiasis	Other	0
5	White British	White	Membranous	GN	0
6	White British	White	Renal Dysplasia	Dysplasia	1
7	White British	White	ANCA Vasculitis	GN	0
8	White British	White	Diabetic	Diabetes	0
9	White British	White	Renovascular	Renovascular	0
10	White British	White	Diabetic	Diabetes	1
11	White British	White	Unknown	Unknown	1
12	Other Mixed Background	Other	ANCA Vasculitis	GN	0
13	White British	White	Diabetic	Diabetes	0
14	White British	White	IgA	GN	0
15	White British	White	Retroperitoneal Fibrosis	Other	1
16	-	-	-	-	-
17	White British	White	IgA	GN	0
18	White British	White	Diabetic Nephropathy	Diabetes	0
19	White British	White	ANCA Vasculitis	GN	1
20	White British	White	Diabetic	Diabetes	1
21	White British	White	APKD	PKD	0
22	White British	White	APKD	PKD	0
23	White British	White	Diabetic Nephropathy	Diabetes	0
24	White British	White	Drug induced (Cisplatin)	Other	0
25	White British	White	Unknown	Unknown	0
26	White British	White	Diabetic	Diabetes	1
27	White and Black Caribbean	Other	Renal Dysplasia	Dysplasia	0
28	White Irish	White	IgA	GN	0
29	Caribbean	Black	Diabetic Nephropathy	Diabetes	TS
30	White British	White	HUS	GN	0
31	White British	White	Diabetic	Diabetes	1
32	Indian	South Asian	Unknown	Unknown	1
33	White British	White	ANCA Vasculitis	GN	0
34	White British	White	Unknown	Unknown	0
35	White British	White	Unknown	Unknown	TS
36	White British	White	Renal Dysplasia	Dysplasia	0
37	White British	White	NSAIDs	Other	0
38	White British	White	Chronic Pyelonephritis	Pyelonephritis	0
39	White British	White	Diabetic Nephropathy	Diabetes	0
40	White British	White	Tubulointerstitial Nephritis	GN	0
41	Other Asian Background	Other	Chronic TIN	GN	1
42	White British	White	Renovascular	Renovascular	0
43	White British	White	Diabetic Nephropathy	Diabetes	0
44	White British	White	Glomerulonephritis - unknown type	GN	0
45	White British	White	Diabetic	Diabetes	TS
46	African	Black	Unknown	Unknown	1
47	White British	White	IgA	GN	0
48	White British	White	APKD	PKD	0
49	White British	White	IgA	GN	1
50	White British	White	Reflux Nephropathy	Pyelonephritis	0
51	White British	White	FSGS	GN	1
52	White British	White	Goodpasture's	GN	TS
53	White British	White	IgA	GN	0
54	White British	White	IgA	GN	1
55	White British	White	Renovascular	Renovascular	0
56	White British	White	Unknown	Unknown	1
57	White British	White	Renovascular	Renovascular	0
58	White British	White	Reflux Nephropathy	Pyelonephritis	0
59	White British	White	Unknown	Unknown	0
60	Pakistani	South Asian	Diabetic	Diabetes	1
61	White British	White	Renovascular	Renovascular	0
62	Caribbean	Black	Diabetic Nephropathy	Diabetes	0
63	White British	White	APKD	PKD	0
64	White British	White	IgA	GN	TS
65	White British	White	Reflux Nephropathy	Pyelonephritis	0
66	White British	White	Medullary Sponge	Other	0
67	White British	White	Renal Calculi	Other	0
68	White British	White	Diabetic Nephropathy	Diabetes	0
69	White British	White	Renovascular	Renovascular	0
70	White British	White	Renovascular	Renovascular	0
71	White British	White	Obstructive Nephropathy	Other	0
72	-	-	-	-	-
73	White British	White	Reflux Nephropathy	Pyelonephritis	0
74	White British	White	Cast Nephropathy/MCGN	GN	0
75	Pakistani	South Asian	Renovascular	Renovascular	1
76	White British	White	Unknown	Unknown	0
77	White British	White	ANCA Vasculitis	GN	1
78	White British	White	IgA	GN	0
79	White British	White	Diabetic	Diabetes	0
80	-	-	-	-	-

Table 4: Observational study patients: Blood test results at time of study

Patient	Kt/V	nPCR	Hb (g/dL)	cCa (mmol/L)	PO4 (mmol/L)	PTH (pg/ml)	Alb (g/L)	CRP (mg/L)	Mg (mmol/L)
1	1.30	0.78	13.1	2.30	1.40	46.4	42	3.5	
2	1.78	0.82	10.3	2.29	1.03	60.3	40	5.0	
3	1.26	1.05	11.0	2.54	1.42	170.4	43	1.4	
4	2.08	1.00	9.7	2.36	2.02	111.0	41	0.5	0.83
5	1.34	0.48	12.7	2.25	1.72	39.0	42	11.4	
6	1.64	1.00	12.3	2.46	1.85	65.0	42	16.3	
7	1.54	0.83	11.7	2.13	0.64	3.9	42	80.0	0.82
8	1.44	0.66	11.9	2.27	1.30	12.3	39	3.1	
9	1.39	0.66	10.3	2.50	1.50	49.5	40	8.4	
10	1.22	0.82	9.0	2.55	1.20	38.8	38	0.5	0.93
11	0.99	0.68	11.3	2.44	1.18	29.4	37	2.9	1.03
12	1.87	1.10	12.0	2.46	1.51	45.3	40	7.5	
13	2.04	1.02	11.0	1.91	1.19	54.0	42	0.5	
14	1.17	0.83	11.4	2.34	1.91	26.6	40	11.0	
15	1.71	0.70	10.1	2.37	1.21	16.9	37	18.0	0.75
16	-	-	-	-	-	-	-	-	-
17	2.11	0.84	10.3	2.33	1.04	37.4	42	1.8	
18	1.51	0.87	11.3	2.29	1.77	52.1	38	20.4	
19	1.10	0.80	11.9	2.42	2.09	33.8	42	5.7	
20	1.42	0.89	11.9	2.22	1.47	49.6	45	74.0	1.17
21	1.81	1.16	13.2	2.32	1.63	20.3	37	15.3	1.30
22	1.45	1.05	10.4	2.46	2.25	17.8	35	12.3	
23	1.09	0.92	8.6	2.26	2.85	176.0	40	24.6	0.94
24	1.49	0.73	10.6	2.36	1.31	28.0	32		
25	1.35	0.89	12.0	2.49	1.82	32.4	40	2.9	
26	0.99	0.64	10.5	2.44	1.54	8.0	33	5.5	
27	1.40	1.07	12.4	2.46	2.23	116.0	36	2.8	1.17
28	1.21	0.81	10.9	2.41	1.87	33.1	37	5.8	
29	1.10	0.50	13.0	2.12	1.02	11.9	37	9.5	
30	1.19	0.76	13.4	2.28	1.48	40.0	39	4.2	
31	0.96	0.66	12.5	2.42	2.77	11.4	43	3.1	1.25
32	2.00	1.28	11.7	2.29	1.55	75.0	43	1.0	
33	1.20	0.59	12.2	2.46	1.26	75.0	39	30.8	
34	1.83	1.15	10.7	2.33	1.12	24.6	36	6.3	
35	1.49	0.71	11.8	2.28	1.19	27.3	43	18.0	0.79
36	1.32	1.10	12.0	2.30	1.56	30.2	38	13.6	
37	1.05	0.57	13.4	2.48	1.91	89.4	37	11.0	
38	1.64	0.94	12.0	2.45	1.45	2.3	42	8.0	0.91
39	1.56	1.22	10.9	2.40	0.98	63.8	39	2.3	
40	0.86	0.46	11.1	2.18	1.61	5.7	37	4.5	0.78
41	1.69	0.75	10.0	2.47	0.90	193.0	41	1.5	
42	1.40	0.76	10.8	2.54	1.31	60.1	39		
43	0.80	0.59	10.6	2.53	2.18	24.1	40	35.9	0.88
44	-	-	8.0	2.32	1.65	98.0	38	9.9	
45	1.82	0.89	12.2	2.49	1.70	74.2	40	4.2	
46	1.37	1.03	13.7	2.36	1.55	69.7	13	10.1	
47	1.32	0.89	10.3	2.28	1.34	82.0	39	14.5	
48	1.20	0.97	9.7	2.35	2.24	44.5	36	19.2	0.90
49	1.27	0.81	13.5	2.37	1.49	63.0	39	4.5	
50	1.69	1.14	10.9	2.28	1.53	64.0	39	8.8	
51	1.41	0.97	12.0	2.32	1.80	39.0	44	7.2	
52	1.47	0.89	9.7	2.45	1.80	18.0	44	120.0	
53	1.52	1.81	12.5	2.36	1.16	85.0	40	0.9	
54	1.16	0.83	10.5	2.31	1.79	34.1	42	1.3	
55	1.60	0.51	11.6	2.34	0.82	36.0	38	17.4	
56	1.45	0.56	11.4	2.25	1.19	75.0	35	12.6	
57	1.31	0.65	12.0	2.37	1.34	15.0	46	7.3	
58	1.27	0.77	9.8	2.32	1.12	34.6	37	1.8	
59	1.68	0.76	10.6	2.43	1.96	11.1	33	7.8	0.95
60	1.87	1.01	11.3	2.30	1.34	46.8	36	23.7	1.45
61	1.46	1.02	14.4	2.60	1.77	46.5	41	32.7	
62	1.16	1.59	11.3	2.11	1.53	46.8	44	11.4	
63	1.36	1.05	9.6	2.40	2.70	124.0	41	4.9	
64	0.77	0.71	10.2	2.38	1.72	49.4	38	8.6	
65	1.52	1.70	10.9	2.41	1.60	14.8	43	23.3	
66	1.71	-	8.6	2.29	3.54	33.1	38	29.2	
67	1.84	1.21	9.5	2.30	1.66	93.0	37		
68	1.14	0.81	10.9	2.32	1.63	63.9	34		
69	1.40	0.81	10.6	2.33	1.43	21.6	37	1.8	
70	1.91	0.72	11.8	2.15	2.67	21.7	38	19.2	
71	1.19	1.10	9.2	2.45	2.11	31.6	37	24.7	
72	-	-	-	-	-	-	-	-	-
73	0.94	0.59	9.6	2.37	2.29	17.8	35	14.6	
74	-	-	8.6	2.36	1.20	4.6	33	133.0	0.73
75	1.27	1.02	11.1	1.91	1.93	83.0	40	6.8	1.12
76	1.34	0.75	11.4	2.43	1.58	34.7	37		
77	1.84	1.24	14.0	2.34	1.93	47.4	45	52.0	
78	1.25	0.67	11.7	2.40	0.80	8.3	40		
79	-	-	11.1	2.43	1.44	34.4	38	0.5	
80	-	-	-	-	-	-	-	-	-

Table 5: Observational study patients: Medication details (1 of 2)

Patient	ACEi	A2RB	Ca Ch. Blocker	β-Blocker	α-Blocker	Other	Aspirin	Statin	Insulin	Anticoag.
1	0	0	0	0	0	0	1	1	0	0
2	1	1	0	0	0	0	1	1	0	0
3	1	0	0	1	0	0	1	1	0	0
4	0	0	0	0	0	0	1	0	0	0
5	0	0	0	0	0	0	1	1	0	0
6	0	1	0	1	0	0	0	1	0	0
7	0	1	0	1	0	0	1	1	1	1
8	0	0	1	1	0	0	1	1	0	1
9	0	1	0	1	0	0	1	0	0	1
10	0	0	0	0	0	0	1	1	1	0
11	1	0	0	0	0	0	0	0	0	0
12	0	0	1	1	0	0	1	1	0	1
13	0	0	0	0	0	0	0	1	1	1
14	0	0	0	1	0	0	0	1	0	0
15	0	0	0	0	0	0	0	0	0	0
16	-	-	-	-	-	-	-	-	-	-
17	0	1	1	0	0	0	1	0	0	0
18	1	0	1	0	1	0	0	1	1	1
19	0	1	0	0	0	0	0	0	0	0
20	0	1	1	0	0	0	1	1	1	0
21	0	0	1	1	0	0	1	0	0	1
22	0	0	0	1	1	1	1	1	0	1
23	1	1	0	1	1	0	1	1	1	0
24	0	0	0	1	1	0	1	1	0	0
25	0	0	0	1	0	1	0	1	0	0
26	1	1	0	0	0	0	0	0	1	0
27	0	1	1	1	1	0	0	0	0	0
28	0	0	0	1	1	0	1	0	0	0
29	1	0	1	0	0	0	1	0	0	1
30	0	0	1	0	0	1	0	0	0	0
31	0	1	0	0	0	0	0	0	1	0
32	1	0	0	0	0	0	1	0	0	0
33	0	0	0	1	0	0	1	1	0	0
34	0	0	0	0	0	0	0	1	0	0
35	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	1	0	1
37	0	0	0	0	0	0	0	0	0	0
38	0	0	0	1	0	0	0	0	0	1
39	1	0	0	1	0	0	1	0	1	0
40	0	0	0	0	0	0	1	1	0	0
41	0	0	1	0	1	0	0	0	0	0
42	0	0	0	1	0	0	0	1	0	1
43	0	0	1	1	0	0	1	1	1	1
44	0	0	1	0	0	0	1	0	1	0
45	1	0	1	0	0	0	1	1	1	0
46	0	0	0	0	0	0	0	1	0	0
47	0	0	1	1	1	0	1	1	0	0
48	0	1	0	1	1	0	0	1	0	1
49	0	0	0	0	0	0	0	0	0	0
50	1	0	0	0	0	0	0	1	0	0
51	0	0	1	0	0	0	0	0	0	0
52	1	0	1	0	0	0	0	0	0	0
53	0	0	1	1	0	0	1	1	0	0
54	1	0	1	0	0	0	0	0	0	0
55	1	0	0	0	0	0	1	1	0	0
56	0	0	0	0	0	0	0	1	1	0
57	0	1	0	1	0	0	1	1	0	1
58	0	0	0	0	0	0	0	1	0	0
59	0	0	0	0	0	0	1	0	1	0
60	0	0	1	0	1	0	1	1	0	1
61	1	0	1	1	0	1	1	1	0	1
62	0	0	0	0	0	0	1	1	1	0
63	0	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	1	0	0
65	0	0	0	0	0	0	0	0	1	0
66	0	0	0	0	0	0	0	0	0	0
67	0	1	0	1	0	0	0	0	0	0
68	0	1	1	1	0	1	1	1	0	0
69	0	0	1	0	0	1	1	1	0	0
70	1	0	0	1	1	0	1	1	0	1
71	0	0	0	0	0	0	0	0	0	0
72	-	-	-	-	-	-	-	-	-	-
73	0	0	0	0	0	0	1	0	0	0
74	0	0	1	0	0	0	0	0	0	0
75	0	0	0	0	1	1	0	0	0	0
76	0	1	1	0	0	0	1	0	0	0
77	0	0	1	1	0	0	1	1	0	0
78	0	0	1	0	0	0	0	1	0	0
79	0	0	0	1	0	1	1	1	1	0
80	-	-	-	-	-	-	-	-	-	-

Table 6: Observational study patients: Medication details (2 of 2)

Patient	ACEi	Daily Dose (mg)	A2RB	Daily Dose (mg)	Ca-Ch. Blocker	Daily Dose (mg)	β-Blocker	Daily Dose (mg)	α-Blocker	Daily Dose (mg)	Other	Daily Dose	Aspirin	Statin	Daily Dose (mg)	Insulin	Anticoag.
1													1	Simvastatin	40	0	
2	Ramipril	2.5	Losartan	25									1	Atorvastatin	10	0	
3	Lisinopril	5					Atenolol	25					1	Simvastatin	10	0	
4													1			0	
5													1	Simvastatin	40	0	
6			Losartan	25			Atenolol	25					0	Simvastatin	10	0	
7			Candesartan	2			Bisoprolol	1.25					1	Simvastatin	20	1	Clopidogrel
8					Amlodipine	10	Atenolol	50					1	Ezetimibe	10	0	Clopidogrel
9			Candesartan	2			Bisoprolol	1.25					1			0	Clopidogrel
10													1	Simvastatin	40	1	
11	Lisinopril	10											0			0	
12							Bisoprolol	1.25					1	Simvastatin	40	0	Clopidogrel
13													0	Simvastatin	40	1	Warfarin
14							Atenolol	100					0	Atorvastatin	40	0	
15													0			0	
16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
17			Telmisartan	20	Diltiazem	240							1			0	
18	Lisinopril	10			Diltiazem	240			Tamsulosin	0.4			0	Atorvastatin	20	1	Clopidogrel
19			Losartan	50									0			0	
20			Candesartan	8	Amlodipine	10							1	Simvastatin	20	1	
21					Nifedipine	20	Sotalol	40					1			0	Warfarin
22							Bisoprolol	2.5	Tamsulosin	0.4	ISMN	60	1	Atorvastatin	30	0	Warfarin
23	Lisinopril	40	Losartan	25			Atenolol	50	Doxazosin	8			1	Atorvastatin	40	1	
24							Atenolol	25	Tamsulosin	0.4			1	Simvastatin	40	0	
25							Bisoprolol	2.5			ISMN	40	0	Simvastatin	20	0	
26	Lisinopril	20	Irbesartan	150									0			1	
27			Losartan	100	Nifedipine	90	Atenolol	50	Doxazosin	4			0			0	
28							Sotalol	160	Tamsulosin	0.4			1			0	
29	Lisinopril	40			Amlodipine	10							1			0	Dipyridamole
30					Amlodipine	10	Bisoprolol	10			Minoxidil	20	0			0	
31			Candesartan	8									0			1	
32	Enalapril	NaN											1			0	
33							Bisoprolol	10					1	Simvastatin	40	0	
34													0	Simvastatin	20	0	
35													0			0	
36													0	Pravastatin	40	0	Warfarin
37													0			0	
38							Atenolol	25					0			0	Warfarin
39	Ramipril	2.5					Atenolol	25					1			1	
40													1	Pravastatin	40	0	
41					Amlodipine	10			Doxazosin	12			0			0	
42							Bisoprolol	2.5					0	Simvastatin	40	0	Warfarin
43					Amlodipine	5	Metoprolol	37.5					1	Atorvastatin	40	1	Clopidogrel
44					Amlodipine	5							1			1	
45	Lisinopril	20			Felodipine	5							1	Atorvastatin	10	1	
46													0	Simvastatin	40	0	
47					Amlodipine	15	Metoprolol	100	Doxazosin	16			1	Simvastatin	40	0	
48			Valsartan	80			Atenolol	50	Doxazosin	16			0	Pravastatin	20	0	Warfarin
49													0			0	
50	Lisinopril	10											0	Simvastatin	20	0	
51					Amlodipine	10							0			0	
52	Ramipril	5			Amlodipine	5							0			0	
53					Nifedipine	60	Atenolol	50					1	Atorvastatin	20	0	
54	Ramipril	5			Felodipine	5							0			0	
55	Lisinopril	20											1	Simvastatin	40	0	
56													0	Ezetimibe	10	1	
57			Candesartan	8			Bisoprolol	5					1	Simvastatin	10	0	Dipyridamole
58													0	Simvastatin	20	0	
59													1			1	
60					Nifedipine	90			Doxazosin	2			1	Simvastatin	40	0	Clopidogrel
61	Ramipril	10			Felodipine	10	Atenolol	75			ISMN	60	1	Simvastatin	20	0	Clopidogrel
62													1	Simvastatin	20	1	
63													0			0	
64													0	Simvastatin	20	0	
65													0			1	
66													0			0	
67			Candesartan	32			Atenolol	50					0			0	
68			Valsartan	320	Amlodipine	10	Atenolol	100			Minoxidil	7.5	1	Simvastatin	40	0	
69					Amlodipine	10					ISMN		1	Simvastatin	20	0	
70	Ramipril	10					Bisoprolol	10	Doxazosin	8			1	Atorvastatin	40	0	Dipyridamole
71													0			0	
72	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
73													1			0	
74					Amlodipine	10							0			0	
75									Doxazosin	8	Furosemide	120	0			0	
76			Candesartan	32	Diltiazem	90							1			0	
77					Amlodipine	10	Bisoprolol	5					1	Ezetimibe	10	0	
78					Nifedipine	60							0			0	
79							Bisoprolol	2.5			ISMN	40	1	Atorvastatin	80	1	
80	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 7: Observational study patients: Diabetes and treatment

Patient	Diabetic	Type1	Type2	Diet Only	Oral Rx	Insulin	Retinopathy	Neuropathy	Latest HBA1c (%)
1	0	0	0	0	0	0	0	0	
2	1	0	1	1	0	0	0	0	38
3	1	0	1	0	1	0	0	0	
4	0	0	0	0	0	0	0	0	
5	0	0	0	0	0	0	0	0	
6	0	0	0	0	0	0	0	0	
7	0	0	0	0	0	0	0	0	
8	1	0	1	0	1	0	0	0	
9	0	0	0	0	0	0	0	0	
10	1	0	1	0	0	1	1	1	69
11	0	0	0	0	0	0	0	0	
12	1	0	1	1	0	0	0	0	
13	1	0	1	0	0	1	0	0	38
14	0	0	0	0	0	0	0	0	
15	0	0	0	0	0	0	0	0	
16	-	-	-	-	-	-	-	-	-
17	0	0	0	0	0	0	0	0	
18	1	1	0	0	0	1	1	1	72
19	0	0	0	0	0	0	0	0	
20	1	1	0	0	0	1	1	1	73
21	0	0	0	0	0	0	0	0	
22	1	0	1	0	0	1	0	0	
23	1	1	0	0	0	1	1	1	66
24	1	0	1	0	1	0	0	0	44
25	0	0	0	0	0	0	0	0	
26	1	1	0	0	0	1	1	1	
27	0	0	0	0	0	0	0	0	
28	0	0	0	0	0	0	0	0	
29	1	0	1	0	1	0	0	0	38
30	0	0	0	0	0	0	0	0	
31	1	1	0	0	0	1	1	1	52
32	0	0	0	0	0	0	0	0	
33	0	0	0	0	0	0	0	0	
34	0	0	0	0	0	0	0	0	
35	0	0	0	0	0	0	0	0	
36	0	0	0	0	0	0	0	0	
37	0	0	0	0	0	0	0	0	
38	1	0	1	0	1	0	0	0	
39	1	0	1	0	0	1	0	0	66
40	0	0	0	0	0	0	0	0	
41	0	0	0	0	0	0	0	0	
42	1	0	1	1	0	0	0	0	33
43	1	1	0	0	0	1	1	1	55
44	1	0	1	0	0	1	0	0	35
45	1	0	1	0	0	1	1	1	
46	0	0	0	0	0	0	0	0	
47	0	0	0	0	0	0	0	0	
48	0	0	0	0	0	0	0	0	
49	0	0	0	0	0	0	0	0	
50	0	0	0	0	0	0	0	0	
51	0	0	0	0	0	0	0	0	
52	0	0	0	0	0	0	0	0	
53	0	0	0	0	0	0	0	0	
54	0	0	0	0	0	0	0	0	
55	1	0	1	0	1	0	0	0	
56	1	0	1	0	0	1	0	0	
57	0	0	0	0	0	0	0	0	
58	1	0	1	0	1	0	0	0	64
59	1	0	1	0	0	1	0	0	47
60	1	0	1	0	0	1	1	1	
61	1	0	1	0	1	0	0	0	
62	1	0	1	0	0	1	1	1	53
63	0	0	0	0	0	0	0	0	
64	0	0	0	0	0	0	0	0	
65	1	0	1	0	0	1	1	0	56
66	0	0	0	0	0	0	0	0	
67	0	0	0	0	0	0	0	0	
68	1	0	1	0	1	0	1	0	59
69	1	0	1	0	1	0	0	0	60
70	0	0	0	0	0	0	0	0	
71	0	0	0	0	0	0	0	0	
72	-	-	-	-	-	-	-	-	-
73	0	0	0	0	0	0	0	0	
74	0	0	0	0	0	0	0	0	
75	0	0	0	0	0	0	0	0	
76	0	0	0	0	0	0	0	0	
77	0	0	0	0	0	0	0	0	
78	0	0	0	0	0	0	0	0	
79	1	0	1	0	0	1	1	0	
80	-	-	-	-	-	-	-	-	-

Table 8: Observational study patients: Smoking status at time of study

Patient	Current Smoker	Ex-Smoker	Smoking History (Current OR Ex)	Pack-yr Hx	Average Cigs. per day
1	0	1	1		7.5
2	0	0	0		
3	0	1	1		
4	0	0	0		
5	0	1	1		
6	0	0	0		
7	0	0	0		
8	0	0	0		
9	0	1	1	12	
10	1	0	1		5
11	0	0	0		
12	0	0	0		
13	0	0	0		
14	1	0	1	40	
15	0	1	1		
16	-	-	-	-	-
17	0	0	0		
18	0	0	0		
19	0	0	0		
20	0	0	0		
21	0	0	0		
22	0	0	0		
23	1	0	1		
24	0	1	1	40	
25	0	0	0		
26	1	0	1	20	
27	1	0	1		7.5
28	0	0	0		
29	0	0	0		
30	1	0	1		15
31	1	0	1	15	15
32	0	0	0		
33	0	0	0		
34	0	0	0		
35	0	0	0		
36	0	1	1	35	
37	0	0	0		
38	0	0	0		
39	0	1	1		
40	0	1	1		
41	0	0	0		
42	0	1	1	60	
43	1	0	1	10	10
44	0	0	0		
45	0	0	0		
46	0	0	0		
47	1	0	1	60	
48	0	0	0		
49	0	1	1		
50	0	0	0		
51	0	0	0		
52	0	0	0		
53	0	1	1		
54	0	0	0		
55	1	0	1	30	
56	0	0	0		
57	0	1	1		
58	0	0	0		
59	0	0	0		
60	0	0	0		
61	0	0	0		
62	0	1	1	40	
63	1	0	1		
64	0	1	1		
65	0	0	0		
66	1	0	1	15	
67	0	0	0		
68	0	0	0		
69	1	0	1		
70	1	0	1	40	
71	0	0	0		
72	-	-	-	-	-
73	0	0	0		
74	0	0	0		
75	0	1	1		
76	1	0	1	3	2
77	0	0	0		
78	0	1	1		
79	0	0	0		
80	-	-	-	-	-

Table 9: Observational study patients: Cardiovascular status at time of study

Patient	Hypertension	IHD	Trop Pos/NSTEMI	STEMI	PCI	LVH	LV impairment	LVEF (%)	AS Gradient (mmHg)	LBBB	AF	PVD/CerebroVD	Amputee	Comments/Details
1	1	1	0	0	0	0	0	60	0	0	0	1	0	Cardiac Amyloid on myocardial Bx. 9 minutes on Bruce Protocol. 3 vessel disease. AAA, previous TIAs, claudication.
2	1	1	1	0	0	0	1	35	0	1	0	0	0	Incidental Finding of Inferior Partial thickness MI on Myoview. ECGs show LBBB.
3	0	1	0	0	0	0	0	0	0	0	0	0	0	PPM for 1st Degree block. CTR 16/30
4														
5	1	0	0	0	0	0	0	0	0	0	0	0	0	ECG: Sinus
6	1	0	0	0	0	0	0	0	0	0	0	0	0	
7	0	0	0	0	0	1	0	0	0	0	0	0	0	Moderate LVH. Normal Ejection Fraction. Mild AS+AR+MR on Echo
8	1	1	1	0	1	0	0	0	0	0	0	0	0	NSTEMI. PCI to LAD and RCA. Mild AS on Echo. DDD PPM for 2:1 block with bradycardia.
9	1	1	1	0	0	0	1	0	0	1	0	1	0	Dilated LV and Inferolateral Hypokinesis on Echo. Left Carotid endarterectomy following TIA. AAA repaired. Bilateral RAS. LBBB on ECG
10	0	0	0	0	0	0	0	50	0	0	0	1	1	Normal Myocardial Perfusion Scan. 4.5 Minutes on Bruce Protocol. Left toe amputation. 50% stenosis of Left profunda, SFA, popliteal
11	1	0	0	0	0	0	0	0	0	0	0	0	0	
12	0	1	1	0	1	0	1	0	0	0	0	0	0	PCI to LAD. PCI to RCA. Valves normal on ECHO. Moderate LV impairment
13	1	0	0	0	0	0	0	0	0	0	0	0	0	
14	1	1	0	0	1	1	0	0	0	0	0	0	0	PCI and LCx Stent for stable angina. Hypertrophic Cardiomyopathy on Cardiac MRI
15	0	1	1	0	0	0	0	51	0	0	0	0	0	No inducible ischaemia but old inferior infarct noted on Myocardial Perfusion Scan. Low-normal LV function - 0.51
16	-	-	-	-	-	-	-	-	-	-	-	-	-	-
17	0	0	0	0	0	0	0	0	0	0	1	0	0	Paroxysmal AF. Good LV on Echo
18	0	0	0	0	0	0	0	0	0	0	0	1	1	Stress Scintigraphy shows low probability of significant cardiovascular disease. Right BKA. Lt fem angioplasty
19	1	0	0	0	0	1	0	70	0	0	0	0	0	Severe MR/MVP with LVH on Echo
20	0	1	1	0	1	0	0	0	0	0	0	1	0	PCI with stent to LAD. Normal Myocardial Perfusion Scan following stent. 75% Stenosis to Right Popliteal Artery on Duplex
21	0	1	1	0	1	0	0	0	0	0	0	0	0	History of SVT. Abnormal stress Echo. Angiogram showed blocked RCA and irregular LAD.
22	1	1	1	0	1	1	0	0	0	1	0	0	0	Diffuse LAD disease, L main stem stenosis, osteal stenosis RCA on angio. NSTEMI. ECG shows old LBBB
23	1	0	0	0	0	0	0	0	0	0	0	0	0	
24	0	1	1	1	1	1	0	57	25	0	1	0	0	MI with thrombolysis. Moderate MR/TR and mild AS on Echo.
25	1	1	0	0	1	0	0	0	0	0	1	1	0	History of angina. Paroxysmal AF. Coronary PCI. CVA
26	1	0	0	0	1	0	0	41	0	0	0	0	0	40% Stenosis RCA on PCI done for Tx workup
27	1	0	0	0	0	0	0	0	0	0	0	0	0	
28	1	1	0	0	0	0	0	0	0	0	1	0	0	Paroxysmal Atrial Flutter and isolated V.E.'s on Holter
29	1	1	0	0	0	0	0	0	0	0	0	0	0	Pacemaker for CHB. Stress test OK.
30	1	0	0	0	0	0	0	0	0	0	0	0	0	
31	0	0	0	0	0	0	0	68	0	0	0	0	0	No inducible ischaemia on Myocardial Perfusion Scan.
32	0	0	0	0	0	0	0	0	0	0	0	0	0	Normal Echo.
33	1	0	0	0	0	0	0	0	0	0	0	1	0	Aortic Sclerosis and mild LVH on Echo. Renal artery stenosis on MRA.
34	1	0	0	0	0	0	0	0	0	0	0	0	0	
35	0	0	0	0	0	0	0	60	0	0	0	0		
36	1	1	1	0	1	1	0	0	34	0	0	1	0	PCI for NSTEMI. Moderate LVH but normal LV function. AS. Occluded Ext. Iliac to CFA receiving R to L crossover graft.
37	1	0	0	0	0	0	0	0	0	0	0	0	0	
38	1	0	0	0	0	0	0	0	0	0	1	0	0	
39	1	1	0	0	0	0	0	0	0	0	0	0	0	Fixed ST changes on ECG. RBBB with LAD
40	0	0	0	0	0	1	0	0	0	0	0	1	0	Right carotid endarterectomy following CVA.
41	1	0	0	0	0	0	0	0	0	0	0	0	0	
42	1	0	0	0	0	0	0	0	0	0	1	0	0	NYHA Class 3.. Mild LVF.
43	0	1	1	1	1	1	1	0	0	0	0	1	0	Poor cardiovascular status. NSTEMI with PCI. NSTEMI with multiple stents to LAD.
44	0	1	0	0	0	0	0	0	0	0	0	0	0	Angina
45	1	1	0	0	1	0	0	60	0	0	0	1	0	60-70% LAD stenosis on PCI for medical management. TIAs (April 2010 and Dec 2011). 65% Left carotid stenosis.
46	1	0	0	0	0	0	0	0	0	0	0	0	0	0
47	1	1	0	0	0	0	0	0	0	0	0	1	0	Right external iliac angioplasty. Bilateral carotid disease. Previous CVA right frontal lobe.
48	1	0	0	0	0	0	0	0	0	0	0	0	0	On warfarin for DVT
49	1	0	0	0	0	0	0	0	0	0	0	0	0	Mild LVH only. Aortic Sclerosis on Echo.
50	0	0	0	0	0	0	0	0	0	0	0	0	0	
51	0	0	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0	0	0
53	1	0	0	0	0	0	0	0	0	0	0	0	0	Normal Echo.
54	0	0	0	0	0	0	0	65	0	0	0	0	0	Managed 9.5 minutes/Stage 4 Bruce Protocol.
55	1	0	0	0	0	1	0	59	42	0	0	1	0	Renovascular disease with flash pulmonary oedema. Moderate AS, Normal LV, Moderate LVH with EF 59% on Echo.
56	1	0	0	0	0	0	0	0	0	0	0	0	0	
57	1	1	1	0	1	0	0	0	0	0	0	1	0	PCI for NSTEMI. Endarterectomy for 65% Left ICA stenosis following CVA with expressive dysphasia
58	0	1	0	0	1	0	0	0	0	0	1	0	0	CABG
59	0	0	0	0	0	0	0	0	0	0	0	0	0	
60	1	0	0	0	0	0	0	0	0	0	0	1	0	Normal Myocardial Perfusion Scan. CVA with left hemiparesis.
61	1	1	1	1	1	0	0	0	0	0	0	1	0	CABG. Angioplasty to Right SFA. NSTEMI and PCI.
62	1	0	0	0	0	1	0	0	0	0	0	0	0	LVH Only
63	1	0	0	0	0	0	0	0	0	0	0	0	0	0
64	1	0	0	0	0	0	0	0	0	0	0	0	0	Normal size LV and Normal Function on Echo.
65	1	1	1	0	0	0	0	0	0	0	0	1	0	Bilateral lower limb arterial disease on duplex. NSTEMI. Narrow complex SVT
66	0	0	0	0	0	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0	0	0	0	0	0
68	1	0	0	0	0	0	0	0	0	0	0	0	0	0
69	1	1	0	0	1	1	0	0	0	0	0	1	0	High-risk myoview scan. PCI pending. AAA on Abdominal MRA.
70	1	0	0	0	0	0	0	0	0	0	0	1	0	Occluded infra-renal aorta. Aorto-iliac endarterectomy. Aorto R-fem bypass and fem-fem crossover (Sept 1997)
71	1	1	0	0	0	1	1	0	0	0	0	0	0	
72	-	-	-	-	-	-	-	-	-	-	-	-	-	-
73	1	1	0	0	1	0	0	0	0	0	0	0	0	Small anterioischaemia on MPS. Angio pending
74	1	0	0	0	0	0	0	0	0	0	1	0	0	Paroxysmal AF noted during dialysis. ECG shows RBBB.
75	1	0	0	0	0	1	0	0	0	0	0	0	0	Mild LVH normal LV function on Echo.
76	1	0	0	0	0	1	0	0	0	0	0	1	0	LVH on Echo.. ?Diastolic dysfunction
77	1	1	1	0	1	0	0	73	0	0	0	0	0	Inferior MI with 5 stents to RCA. Nuclear scan shows good LV function. Plan for Tx.
78	1	0	0	0	0	1	1	0	0	0	1	0	0	History of AF precipitating LVF
79	1	1	1	0	1	1	1	0	0	0	0	0	0	MI and CABG. Aortic Stenosis
80	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Appendix C

Observational Study Symptom Questionnaire

Can integrated vital sign monitoring contribute to the care of haemodialysis patients?

Participant identification:
Date of completion:

1. Please indicate on a scale of 1 – 10 (1 being very ill and 10 being very well) how you have felt **since your last haemodialysis treatment** by circling the appropriate number.

1	2	3	4	5	6	7	8	9	10
Very ill				Well					Very well

2. Please indicate whether you had any of the following symptoms **prior to this haemodialysis treatment**, and how severe they were:

1. Fever	None	Trivial	Mild	Moderate	Severe
2. Nausea	None	Trivial	Mild	Moderate	Severe
3. Dizziness	None	Trivial	Mild	Moderate	Severe
4. Chest pain	None	Trivial	Mild	Moderate	Severe
5. Cramp	None	Trivial	Mild	Moderate	Severe
6. Shortness of breath	None	Trivial	Mild	Moderate	Severe
7. Itching	None	Trivial	Mild	Moderate	Severe

3. Please indicate on the attached scale bar how you have felt **during this haemodialysis treatment** by circling the appropriate number.

1	2	3	4	5	6	7	8	9	10
Very ill				Well					Very well

4. Please indicate whether you had any of the following symptoms **during this haemodialysis treatment**, and how severe they were:

1. Fever	None	Trivial	Mild	Moderate	Severe
2. Nausea	None	Trivial	Mild	Moderate	Severe
3. Dizziness	None	Trivial	Mild	Moderate	Severe
4. Chest pain	None	Trivial	Mild	Moderate	Severe
5. Cramp	None	Trivial	Mild	Moderate	Severe
6. Shortness of breath	None	Trivial	Mild	Moderate	Severe
7. Itching	None	Trivial	Mild	Moderate	Severe

5. Overall, was this dialysis: Better than normal? The same? Worse than normal? (Please circle)

6. Please circle whether you experienced any discomfort from:

1. the blood pressure cuff?	None	Trivial	Mild	Moderate	Severe
2. the Hidalgo belt?	None	Trivial	Mild	Moderate	Severe
3. the pulse oximeter?	None	Trivial	Mild	Moderate	Severe
4. temperature probes?	None	Trivial	Mild	Moderate	Severe.

PTO

7. Haemodialysis patients use many different words or statements to describe the symptoms they feel during or after their haemodialysis treatment. Please provide up to 10 words or statements that best describe your experience of this dialysis session or any symptoms you may have experienced at home following your last session:

8. Please make any comments you wish about the use of the camera in this study:

Thank you for your time

Table 10: Dialysate Composition and Dialysate Temperature

Patient	Fresenius^{TM} Dialysate	Dialysate Temperature °C
OB01	A/5	36.5
OB02	A/10	37
OB03	A/5	37
OB04	A/5	37
OB05	A/5	36.5
OB06	A/5	37
OB07	A/27	37
OB08	A/5	37
OB09	A/27	36
OB10	A/10	37
OB11	A/5	37
OB12	A/5	37
OB13	A/5	37
OB14	A/27	37
OB15	Citrasate	37
OB16	Citrasate	37
OB17	A/5	37
OB18	A/27	37
OB19	A/5	37
OB20	Citrasate	37
OB21	A/27	36
OB22	A/27	37
OB23	A/18	37
OB24	A/10	37
OB25	A/9	37
OB26	A/10	37
OB27	A/5	37
OB28	A/27	36.5
OB29	A/5	37
OB30	A/18	37
OB31	A/18	37
OB32	A/27	37
OB33	A/27	37
OB34	A/5	37
OB35	A/5	35.5
OB36	A/5	37
OB37	A/10	37
OB38	A/5	37
OB39	A/27	37
OB40	A/10	37
OB41	A/5	37
OB42	A/27	36
OB43	A/27	37
OB44	A/10	37
OB45	A/27	37
OB46	A/18	37
OB47	A/10	37
OB48	A/18	37
OB49	A/27	37
OB50	A/5	37
OB51	A/5	37
OB52	Citrasate	37
OB53	A/5	37
OB54	A/5	37
OB55	Citrasate	37
OB56	A/10	37
OB57	A/5	36
OB58	A/10	37
OB59	A/10	37
OB60	A/17	37
OB61	A/5	37
OB62	A/5	37
OB63	A/5	37
OB64	A/5	37
OB65	A/5	36.5
OB66	A/10	37
OB67	A/5	37
OB68	A/10	37
OB69	A/10	37
OB70	A/5	37
OB71	A/5	37
OB72	A/10	37
OB73	A/5	37
OB74	A/5	37
OB75	A/5	37
OB76	A/18	37
OB77	A/5	37
OB78	A/10	37

Details of dialysate chemistry available from
http://www.freseniusmedicalcare.co.uk/healthcare-professionals/dialysis-products/

Appendix D

Fistula Needle Sizes

Table 11: Arteriovenous Fistula Needle Sizes

Patient	Needle Gauge
OB01	15
OB02	15
OB03	15
OB04	15
OB05	15
OB06	15
OB07	15
OB08	15
OB09	15
OB10	15
OB11	15
OB12	15
OB13	15
OB14	16
OB15	15
OB16	n/a
OB17	15
OB18	15
OB19	16
OB20	15
OB21	n/a
OB22	15
OB23	15
OB24	15
OB25	15
OB26	15
OB27	15
OB28	15
OB29	n/a
OB30	Tessio
OB31	Tessio
OB32	15
OB33	15
OB34	15
OB35	15
OB36	15
OB37	15
OB38	15
OB39	15
OB40	15
OB41	16
OB42	15
OB43	15
OB44	Tessio
OB45	15
OB46	15
OB47	n/a
OB48	16
OB49	15
OB50	15
OB51	15
OB52	16
OB53	16
OB54	15
OB55	15
OB56	Tessio
OB57	15
OB58	15
OB59	15
OB60	15
OB61	15
OB62	15
OB63	16
OB64	15
OB65	Tessio
OB66	Tessio
OB67	15
OB68	15
OB69	n/a
OB70	Tessio
OB71	15
OB72	n/a
OB73	16
OB74	Tessio
OB75	15
OB76	15
OB77	15
OB78	15
OB79	Tessio

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