

Invited article for Eur Heart Journal Suppl

**HYPERTENSION AND CARDIOVASCULAR RISK IN YOUNG ADULT LIFE:
INSIGHTS FROM CAVI**

Paul Leeson, PhD, FRCP

Address for correspondence:

Professor Paul Leeson, Oxford Cardiovascular Clinical Research Facility, Division of
Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, John
Radcliffe Hospital, Oxford. OX39DU. e-mail: paul.leeson@cardiov.ox.ac.uk.

Tel:+44(0)1865572846, Fax:+44(0)1865572840

ABSTRACT

1 in 17 adults below the age of 40 years are hypertensive with higher rates in those with particular predispositions such as a familial history or developmental exposures to pregnancy hypertension or preterm birth. Hypertension in early life significantly increases the risk of stroke and cardiovascular disease before the age of 50 years and, to reduce this disease burden, interventions that target the distinct physiological mediators of blood pressure control in young people are required. This review highlights recent studies that have used a deep phenotyping approach to characterise the key phenotypic differences in vascular structure and physiology in young people that may be amenable to intervention.

HYPERTENSION AND THE YOUNG ADULT

Recent randomised trials have demonstrated that there is benefit for stricter control of blood pressures and that the lower the level the better the risk reduction¹, an observation supported by recent meta-analyses². As a result, the concept that the risk associated with high blood pressure is a continuum is increasingly recognised and current trends are for guidelines to encourage lower levels for diagnosis of hypertension, while aiming for tighter control³. This changing practice is of particular relevance to younger individuals who are being diagnosed as hypertensive at younger ages and who will need appropriate advice on blood pressure management over many decades^{4,5}. Current guidelines for diagnosis of hypertension propose systolic blood pressures greater than 140mmHg and/or diastolic pressures greater than 90mmHg based on repeated clinic readings³. Home or ambulatory monitoring has lower thresholds for diagnosis of stage 1 hypertension of a daytime average greater than 135mmHg systolic or 85mmHg diastolic^{3,6}. Based on these criteria it has been estimated that 1 in 17 young adults below the age of 40 years have blood pressures that exceed the diagnostic thresholds with this number rising to 1 in 5 if there are specific predisposing factors, such as a family or developmental history⁷.

Traditionally, awareness of blood pressure levels in young people has been suboptimal due to lower levels of interaction with health services and reduced opportunities for blood pressure management⁸. When diagnosed there has been a tendency to manage the higher levels suboptimally because it is not considered relevant to the immediate health concerns of the individual or because it is felt it can be well managed with lifestyle changes^{5,9}. However, recent systematic review demonstrates that lifestyle interventions are effective when initially introduced but fail to sustain benefits for blood pressure reduction beyond a few months⁵.

The net effect of these problems is that there is a proportion of young people with poorly controlled blood pressure with a substantial lifetime risk for cardiovascular disease and stroke when older⁴. However, there are also immediate health concerns for these young people, particularly women, who will be more likely to have complications and hypertension during their pregnancies¹⁰, with resultant relevance to the long term health of their offspring¹¹. Research on optimal management of this age group is hampered by an underrepresentation of young people in clinical studies of hypertension so that there is a lack of evidence base with regard the nature of the hypertension in this young population or in relation to the most effective lifestyle or therapeutic interventions¹².

DEEP PHENOTYPING TO STUDY DEVELOPMENT OF HYPERTENSION IN YOUNG ADULT LIFE

Our approach to understand disease development in early life, identify key pathways of interest in predisposition to hypertension and develop specific preventive approaches has been to use multi-modality imaging to capture information on cardiovascular structure and function ‘from heart to capillary’. With this approach it becomes possible to model the interrelationship between features of the cardiovascular system and, with longitudinal data, study the progression of disease across vessel and heart¹³. By extending the data collection to other organs such as brain and liver, a holistic view of disease development can be captured¹⁴. Such multi-modality, multi-organ imaging provides unprecedented insight into disease development, which is recognised through its use within several landmark epidemiological studies, such as UK Biobank¹⁵ and guidance on future, disease-specific research strategies¹⁶.

Figure 1 demonstrates the range of measures that can be performed with appropriate equipment and infrastructure in young people for observational studies or clinical trials^{13, 17}. Such investigations, in experienced hands, can be performed within a few hours, or split over a couple of days, making them acceptable for the majority of participants. Typically, to assess cardiac structure and function, cardiovascular magnetic resonance allows for the most robust and detailed measures of left and right ventricular mass and geometry. Combined with echocardiography the imaging protocol allows a comprehensive study of systolic and diastolic function as well as valvular function^{18, 19}. During the magnetic resonance scan it is also possible to image the aorta directly to measure aortic size, geometry and function, in the form of distensibility or pulse wave velocity^{20, 21}. The ability to undertake regional assessment allows more specific study of the differential impact of variables, such as ageing, gender^{22, 23} or risk factor such as cholesterol levels²⁴ on structure of different parts of the aorta. This is of importance as the structure of the aorta and composition of collagen differs significantly from ascending aorta to bifurcation so that it can function as a conduit for pulsatile cardiac flow.

Other arterial stiffness parameters can capture information on broader vascular beds including conduit vessels. These include tonometer and cuff-based measures of pulse arrival time at peripheral vessels such as the carotid, femoral or radial artery²⁵. In addition, measures that use the peripheral waveform and transform this to extract interpretations of features of pulse wave analysis can provide additional information²⁶. Cardiac ankle vascular index (CAVI) provides an additional global measure of arterial pathophysiology. Figure 2 demonstrates how the device uses both a microphone to identify the time of aortic valve closure and limb cuffs to identify the timing and character of the pulse wave^{27, 28}. The calculation used to derive the index means it is independent of blood pressure at time of

measurement²⁸. Imaging also allows assessment of a further, vascular bed important in determining blood pressure levels, the smaller vessels that extend from resistance arterioles to the capillary bed²⁹. Techniques exist to study density of small vessels within tissue including the skin^{30 31} or at accessible visible beds such as the retina³¹. Functional differences in these vascular beds can also be measured based on responses to different stimuli and stimuli-induced measures incorporate those that study conduit function such as flow mediated dilatation³² and reactive hyperaemic flowmetry measures along with tests of microvessel oxygenation or perfusion²⁹.

There are limitations to this deep phenotyping approach. Only a limited number of centres have the complex infrastructure required to support multiple modalities from cardiovascular magnetic resonance through to microvascular assessment, alongside the individual technical expertise across modalities to maintain and process the imaging data to a high standard. As a result, a deep phenotyping approach, although potentially of value in selected patients, is unlikely to form part of population-based clinical care. Rather, its value lies in investigation of currently poorly defined areas of cardiovascular diseases to refine understanding and to help focus future studies and clinical trials into pathways of specific interest; akin to an omics-style investigation with an ‘imaging probe’. Once the infrastructure is established in a centre, the per participant cost for a combination of investigations is in the order of £500-£1000, with larger studies introducing economies of scale. The cost of logistical organisation and time required for identification and recruitment of participants for observational studies is significant and, therefore, the investment in deep phenotyping ensures maximum scientific value is obtained from these studies. The costs associated with clinical trial failure due to inappropriate selection of a limited set of endpoints are also substantial and could be mitigated by collection of a more detailed cardiovascular evaluation.

CAVI AS TOOL TO INVESTIGATE CARDIOVASCULAR PATHOPHYSIOLOGY

Previous studies have shown that associations between cardiac and vascular measures differ between younger people and older individuals^{23, 33, 34}. This may be relevant to how cardiovascular changes emerge during adolescence. What have studies that incorporate a broad range of measures told us about cardiovascular predispositions to hypertension in young people? The number of studies with a comprehensive assessment of the cardiovascular system ‘from heart to capillary’ are limited. However, some of our examples are presented below to highlight the potential value of this approach.

Longitudinal studies that have followed individuals from adolescence to adulthood with multiple vascular measures have shown that vascular measures during adolescence can predict both cardiovascular phenotype in young adulthood and changes in blood pressure. Interestingly, those individuals with reduced endothelial responses in adolescence, independent of other risk factors such as their body size, cholesterol level or smoking history, tended to have an accelerated increase in their blood pressure over the next five years³⁵. Furthermore, they had greater cardiac mass in young adulthood than their contemporaries with better endothelial function during adolescence³⁵. These findings raise the possibility that there may be value in specific interventions to protect vascular responses during early life to reduce more widespread adverse changes in cardiovascular growth and development³⁶.

The use of multimodality measures have also proved of value for developing insights into variation in cardiovascular pathology related to early life exposures and risk markers, for example, links between a family history of hypertension and the emergence of hypertension in the offspring. Those at risk are most easily identifiable early in life in families where the

stress of pregnancy induces hypertension in the mother¹⁷ or the pregnancy results in preterm birth. The offspring of such pregnancies are known to be more likely to be hypertensive in later life with 1 in 5 born to more complicated hypertensive pregnancies being hypertensive by the age of 20 years⁷. We have undertaken detailed cardiovascular phenotyping of these individuals to define the cardiovascular changes evident in the early stages of hypertension. Using a multimodality approach we showed that a range of early life exposures can be associated with long term variation in vascular function. In preterm infants who had received antenatal steroids³⁷ or were fed with intravenous lipids²⁴ differences in aortic stiffness were evident 20 years later. However, these investigations also showed the overall impact of preterm birth was relatively small¹³. Previous studies had suggested all preterm infants may have stiffer arteries but interpretation of these results has been complicated by the fact those born preterm have higher blood pressure. CAVI provided information on global changes in arterial function independent of blood pressure at time of measurement that supported our observations from other imaging modalities that, in general, those born preterm have very similar arterial stiffness to those born at term. The exclusion of significant effects of arterial stiffness then allowed us to , highlight the importance of differences in the microvasculature to the phenotype observed in those born preterm³⁸. CAVI provided a key validation step in defining the essential phenotypes relevant to disease in these populations.

More recently we have been studying, using deep phenotyping, contributions of the cardiovascular system to blood pressure variability in young adults. Blood pressure variability is known to be an independent determinant of cerebrovascular and cardiovascular risk³⁹ but little has been known about factors that determine blood pressure variability early in life. Through use of multi-modality measures we have been able to establish that the major vascular determinant of blood pressure variability in young adults is central aortic stiffness,

as opposed to more global or peripheral arterial stiffness changes⁴⁰. This was highlighted with cardiovascular magnetic resonance measures of central aortic stiffness and confirmed using CAVI, which also captures central aortic stiffness within its calculation and, in young people, closely relates to the cardiovascular magnetic resonance measures⁴⁰.

Future work has the potential to study how CAVI varies in relation to changes in other organs such as the brain and liver so that we can understand whether changes in CAVI may provide additional prognostic information in young people. However, an important consideration in all these studies is that the current datasets are largely observational and therefore the evidence base for causality, and its direction, will remain limited until randomised trials targeted at phenotypes are completed. We currently have trials in progress to study the impact of interventions on the cardiac and vascular system in young adults to understand the holistic impact of cardiovascular preventive treatments.

FUTURE DIRECTIONS FOR HYPERTENSION MANAGEMENT AND RESEARCH IN THE YOUNG

Clinically relevant hypertension is not restricted to older populations but can present at any age, from infancy to childhood to young adulthood. There is a notable lack of studies that have tested in randomised controlled trials effective treatment options for younger individuals. There is also a lack of detailed observational studies that have sought to define the underlying pathophysiological basis for the variation in blood pressure in young people. Deep phenotyping studies have started to unravel the heterogeneity in cardiac and vascular changes that are present in young people with higher blood pressure³³⁻³⁵. New observations challenge a repeated dogma that high blood pressure in young people is predominantly due to

increased stroke volume and sympathetic hyperactivity. Whereas someone with established cardiovascular disease might be expected to have a consistent reduction in arterial stiffness, endothelial response, microvascular structure and function as well as altered cardiac morphology⁴¹, associations between different vascular components appear to differ with type of risk factor exposure in younger people³⁴. As a result, opportunities for targeted interventions either to ameliorate the dysfunctional features of the cardiovascular system or to protect the normally functioning elements may have particular benefit³⁶.

By using a multi-modality imaging protocol, that incorporates a range of cardiovascular measures including cardiovascular magnetic resonance, ultrasound, microscopy and more unique indices, such as CAVI, we have been able to gain insights into some of the background changes related to specific risk groups in young adulthood. Our initial phase of findings has demonstrated that no single measure provides a complete assessment of cardiovascular risk phenotype in younger people but that changes in specific vascular beds can be identified and characterised. Further work is needed to identify those young individuals who have specific impairments in CAVI and thereby understand the risk and lifestyle features that directly impact on the arterial wall. However, changes in larger artery pathophysiology are likely to be relevant to blood pressure control, including central blood pressure and blood pressure variability. Based on these findings trials of treatments, whether lifestyle or pharmacological, will then be possible to start to establish how an altered CAVI in early life might be targeted to reduce risk of cardiovascular disease.

ACKNOWLEDGEMENTS AND DISCLOSURES

PL is supported by the British Heart Foundation (FS/06/024 and FS/11/65/28865), the National Institute for Health Research Oxford Biomedical Research Centre and Oxford British Heart Foundation Centre for Research Excellence. He has also previously received an unrestricted research grant and speaker honoraria from Fukuda Denshi who manufacture the VaSera.

REFERENCES

1. Group SR, Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC, Jr., Fine LJ, Cutler JA, Cushman WC, Cheung AK and Ambrosius WT. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015;373:2103-16.
2. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A and Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957-67.
3. Hypertension in adults: diagnosis and management *NICE guideline*. 2011;CG127.
4. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R and Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903-13.
5. Williamson W, Foster C, Reid H, Kelly P, Lewandowski AJ, Boardman H, Roberts N, McCartney D, Huckstep O, Newton J, Dawes H, Gerry S and Leeson P. Will Exercise Advice Be Sufficient for Treatment of Young Adults With Prehypertension and Hypertension? A Systematic Review and Meta-Analysis. *Hypertension*. 2016;68:78-87.
6. Lovibond K, Jowett S, Barton P, Caulfield M, Heneghan C, Hobbs FD, Hodgkinson J, Mant J, Martin U, Williams B, Wonderling D and McManus RJ. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study. *Lancet*. 2011;378:1219-30.
7. Davis EF, Lewandowski AJ, Aye C, Williamson W, Boardman H, Huang RC, Mori TA, Newnham J, Beilin LJ and Leeson P. Clinical cardiovascular risk during young adulthood in offspring of hypertensive pregnancies: insights from a 20-year prospective follow-up birth cohort. *BMJ Open*. 2015;5:e008136.
8. Johnson HM, Thorpe CT, Bartels CM, Schumacher JR, Palta M, Pandhi N, Sheehy AM and Smith MA. Antihypertensive medication initiation among young adults with regular primary care use. *Journal of general internal medicine*. 2014;29:723-31.
9. Williamson W, Boardman H, Lewandowski AJ and Leeson P. Time to rethink physical activity advice and blood pressure: A role for occupation-based interventions? *European journal of preventive cardiology*. 2016;23:1051-3.
10. Boivin A, Luo ZC, Audibert F, Masse B, Lefebvre F, Tessier R and Nuyt AM. Pregnancy complications among women born preterm. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2012;184:1777-84.
11. Davis EF, Newton L, Lewandowski AJ, Lazdam M, Kelly BA, Kyriakou T and Leeson P. Pre-eclampsia and offspring cardiovascular health: mechanistic insights from experimental studies. *Clinical science*. 2012;123:53-72.
12. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM and Authors/Task Force M. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European heart journal*. 2016;37:2315-81.
13. Boardman H, Birse K, Davis EF, Whitworth P, Aggarwal V, Lewandowski AJ and Leeson P. Comprehensive multi-modality assessment of regional and global arterial structure and function in adults born preterm. *Hypertension research : official journal of the Japanese Society of Hypertension*. 2016;39:39-45.
14. Boardman H, Birse K, Davis EF, Whitworth P, Aggarwal V, Lewandowski AJ and Leeson P. Comprehensive multi-modality assessment of regional and global arterial structure and function in

adults born preterm. *Hypertension research : official journal of the Japanese Society of Hypertension*. 2015.

15. Petersen SE, Matthews PM, Bamberg F, Bluemke DA, Francis JM, Friedrich MG, Leeson P, Nagel E, Plein S, Rademakers FE, Young AA, Garratt S, Peakman T, Sellors J, Collins R and Neubauer S. Imaging in population science: cardiovascular magnetic resonance in 100,000 participants of UK Biobank - rationale, challenges and approaches. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance*. 2013;15:46.

16. Staff AC, Redman CW, Williams D, Leeson P, Moe K, Thilaganathan B, Magnus P, Steegers EA, Tsigas EZ, Ness RB, Myatt L, Poston L, Roberts JM and Global Pregnancy Collaboration. Pregnancy and Long-Term Maternal Cardiovascular Health: Progress Through Harmonization of Research Cohorts and Biobanks. *Hypertension*. 2016;67:251-60.

17. Lewandowski AJ and Leeson P. Preeclampsia, prematurity and cardiovascular health in adult life. *Early Hum Dev*. 2014;90:725-9.

18. Augustine D, Lewandowski AJ, Lazdam M, Rai A, Francis J, Myerson S, Noble A, Becher H, Neubauer S, Petersen SE and Leeson P. Global and regional left ventricular myocardial deformation measures by magnetic resonance feature tracking in healthy volunteers: comparison with tagging and relevance of gender. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance*. 2013;15:8.

19. Harrison S, Petrovic G, Chevassut A, Brook L, Higgins N, Kenworthy Y, Selwood M, Snelgar T, Arnold L, Boardman H, Heneghan C, Leeson P, Redman C and Granne I. Oxfordshire Women and Their Children's Health (OxWATCH): protocol for a prospective cohort feasibility study. *BMJ open*. 2015;5:e009282.

20. Leeson CP, Robinson M, Francis JM, Robson MD, Channon KM, Neubauer S and Wiesmann F. Cardiovascular magnetic resonance imaging for non-invasive assessment of vascular function: validation against ultrasound. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance*. 2006;8:381-7.

21. Wiesmann F, Petersen SE, Leeson PM, Francis JM, Robson MD, Wang Q, Choudhury R, Channon KM and Neubauer S. Global impairment of brachial, carotid, and aortic vascular function in young smokers: direct quantification by high-resolution magnetic resonance imaging. *Journal of the American College of Cardiology*. 2004;44:2056-64.

22. Rider OJ, Lewandowski A, Nethononda R, Petersen SE, Francis JM, Pitcher A, Holloway CJ, Dass S, Banerjee R, Byrne JP, Leeson P and Neubauer S. Gender-specific differences in left ventricular remodelling in obesity: insights from cardiovascular magnetic resonance imaging. *European heart journal*. 2013;34:292-9.

23. Nethononda RM, Lewandowski AJ, Stewart R, Kylinterias I, Whitworth P, Francis J, Leeson P, Watkins H, Neubauer S and Rider OJ. Gender specific patterns of age-related decline in aortic stiffness: a cardiovascular magnetic resonance study including normal ranges. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance*. 2015;17:20.

24. Lewandowski AJ, Lazdam M, Davis E, Kylintireas I, Diesch J, Francis J, Neubauer S, Singhal A, Lucas A, Kelly B and Leeson P. Short-term exposure to exogenous lipids in premature infants and long-term changes in aortic and cardiac function. *Arterioscler Thromb Vasc Biol*. 2011;31:2125-35.

25. Reference Values for Arterial Stiffness C. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *European heart journal*. 2010;31:2338-50.

26. Kelly RP, Millasseau SC, Ritter JM and Chowienczyk PJ. Vasoactive drugs influence aortic augmentation index independently of pulse-wave velocity in healthy men. *Hypertension*. 2001;37:1429-33.

27. Shirai K, Hiruta N, Song M, Kurosu T, Suzuki J, Tomaru T, Miyashita Y, Saiki A, Takahashi M, Suzuki K and Takata M. Cardio-ankle vascular index (CAVI) as a novel indicator of arterial stiffness: theory, evidence and perspectives. *Journal of atherosclerosis and thrombosis*. 2011;18:924-38.

28. Shirai K, Utino J, Otsuka K and Takata M. A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). *Journal of atherosclerosis and thrombosis*. 2006;13:101-7.
29. Shore AC and Tooke JE. Microvascular function in human essential hypertension. *Journal of hypertension*. 1994;12:717-28.
30. Yu GZ, Aye CY, Lewandowski AJ, Davis EF, Khoo CP, Newton L, Yang CT, Al Haj Zen A, Simpson LJ, O'Brien K, Cook DA, Granne I, Kyriakou T, Channon KM, Watt SM and Leeson P. Association of Maternal Antiangiogenic Profile at Birth With Early Postnatal Loss of Microvascular Density in Offspring of Hypertensive Pregnancies. *Hypertension*. 2016;68:749-59.
31. Huckstep O, Lewandowski AJ and Leeson P. Invited Commentary: Hypertension During Pregnancy and Offspring Microvascular Structure-Insights From the Retinal Microcirculation. *American journal of epidemiology*. 2016.
32. Antoniadou C, Mussa S, Shirodaria C, Lee J, Diesch J, Taggart DP, Channon KM and Leeson P. Relation of preoperative radial artery flow-mediated dilatation to nitric oxide bioavailability in radial artery grafts used in off-pump coronary artery bypass grafting. *The American journal of cardiology*. 2009;103:216-20.
33. Lazdam M, de la Horra A, Diesch J, Kenworthy Y, Davis E, Lewandowski AJ, Szmigielski C, Shore A, Mackillop L, Kharbanda R, Alp N, Redman C, Kelly B and Leeson P. Unique blood pressure characteristics in mother and offspring after early onset preeclampsia. *Hypertension*. 2012;60:1338-45.
34. Lewandowski AJ, Pitcher A, Banerjee R and Leeson P. Arterial stiffness: using simple surrogate measures to make sense of a biologically complex phenomenon. *Hypertension research : official journal of the Japanese Society of Hypertension*. 2012;35:155-6.
35. Lazdam M, Lewandowski AJ, Kyliantreas I, Cunningham C, Diesch J, Francis J, Trevitt C, Neubauer S, Singhal A and Leeson P. Impaired endothelial responses in apparently healthy young people associated with subclinical variation in blood pressure and cardiovascular phenotype. *Am J Hypertens*. 2012;25:46-53.
36. Leeson P. Pediatric Prevention of Atherosclerosis: Targeting Early Variation in Vascular Biology. *Pediatrics*. 2007;119:1204-1206.
37. Kelly BA, Lewandowski AJ, Worton SA, Davis EF, Lazdam M, Francis J, Neubauer S, Lucas A, Singhal A and Leeson P. Antenatal glucocorticoid exposure and long-term alterations in aortic function and glucose metabolism. *Pediatrics*. 2012;129:e1282-90.
38. Lewandowski AJ, Davis EF, Yu G, Digby JE, Boardman H, Whitworth P, Singhal A, Lucas A, McCormick K, Shore AC and Leeson P. Elevated blood pressure in preterm-born offspring associates with a distinct antiangiogenic state and microvascular abnormalities in adult life. *Hypertension*. 2015;65:607-614.
39. Vishram JK, Dahlof B, Devereux RB, Ibsen H, Kjeldsen SE, Lindholm LH, Mancia G, Okin PM, Rothwell PM, Wachtell K and Olsen MH. Blood pressure variability predicts cardiovascular events independently of traditional cardiovascular risk factors and target organ damage: a LIFE substudy. *Journal of hypertension*. 2015;33:2422-30.
40. Boardman H, Lewandowski AJ, Lazdam M, Kenworthy Y, Whitworth P, Zwager CL, Francis JM, Aye CYL, Williamson W, Neubauer S and Leeson P. Aortic stiffness and blood pressure variability in young people: A multi-modality investigation of central and peripheral vasculature. *Journal of hypertension*. 2016;(in press).
41. Lee JM, Shirodaria C, Jackson CE, Robson MD, Antoniadou C, Francis JM, Wiesmann F, Channon KM, Neubauer S and Choudhury RP. Multi-modal magnetic resonance imaging quantifies atherosclerosis and vascular dysfunction in patients with type 2 diabetes mellitus. *Diabetes and Vascular Disease Research*. 2007;4:44-48.

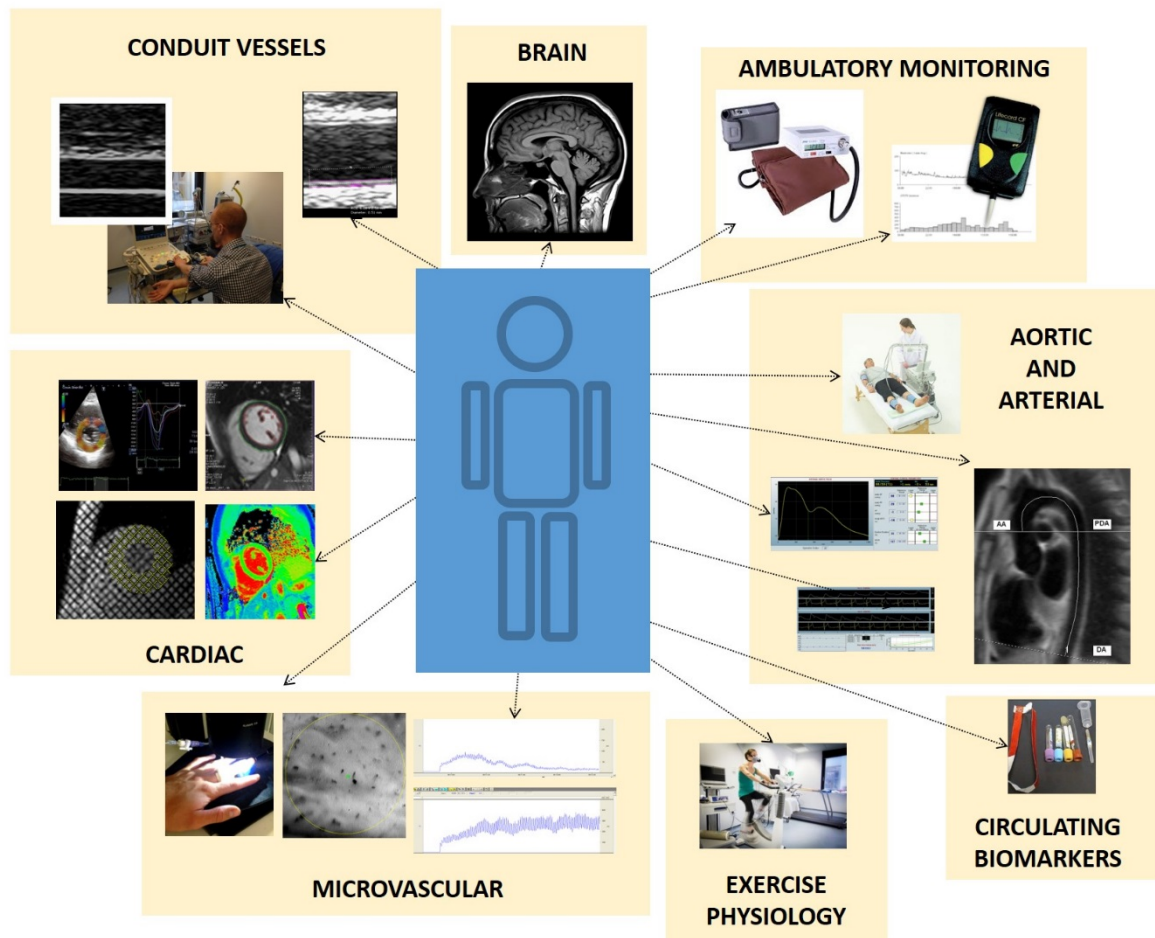


Figure 1: Figure to demonstrate the breadth of measures that can be measured within single study visits in young people. These deep phenotyping studies allow for evaluation of the cardiovascular system from heart to capillary, while also including assessment of the cerebrovasculature and brain structure alongside imaging adiposity, liver and other organs. CAVI provides a measure of global arterial function within this multi-modality approach that is complementary to other measures such as cardiovascular magnetic resonance, ultrasound, tonometry and microscopy.

