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Endothelial Function In Tanzanian Children With Sickle Cell Disease: Baseline Results From The Vascular Function Intervention Trial (VFIT)

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Abstract

Introduction

Endothelial function is impaired in adults with sickle cell anaemia (SCA), but limited data exists in children. Endothelial damage occurs from chronic inflammation, oxidant damage, immune cell activation and ischemia-reperfusion injury. In addition, availability of nitric oxide (NO) as the major vasodilator may be reduced as a result of scavenging by plasma haemoglobin and reduced arginine substrate for endothelial nitric oxide synthase.

Methods

Tanzanian children (N=119) with SCA (HbSS) aged 8-11.9 years enrolled in the Vascular Function Intervention Trial (ISRCTN74331412/NCT01718054) underwent baseline assessment of endothelium-dependent and -independent vasodilatation. All children were determined clinically well at assessment, hydroxyurea naive, on no long-term medication and not receiving chronic blood transfusions. Blood pressure and vasomotion were assessed after 10 minutes recumbent rest in a temperature controlled room between 08-13:00 hrs. An identical protocol as published in children (Donald & Charakida *et al.* Eur Heart J; 2010: 31; 1502-10) was used. In brief, brachial arterial endothelium dependent dilatation was

assessed by 1 of 3 trained technicians using ultrasound imaging (Ultrasonix SonixTouch with a 12Mz probe & stereotactic holder) to assess flow-mediated dilatation (FMD) in response to reactive hyperaemia induced after release of transient blood pressure cuff occlusion (5 min, 200 mmHg, Hokanson, USA) using an automated air regulator (Logan Research, UK). Automated B-mode image edge detection was used to measure maximum change in arterial diameter (Brachial Tools) expressed as a percentage of resting baseline diameter (FMD_{max}). Endothelium-independent responses to 2.5µg sub-lingual glyceryl-trinitrate (GTN) were also assessed. All recordings were over-read by an experienced researcher in the UK. Venepuncture for full blood count, clinical chemistry and amino acids was conducted after FMD assessment.

Results

Patient characteristics are described in Table 1. Mean brachial artery diameter at baseline was 2.61mm (95% CI 2.55 – 2.67mm). Mean FMD_{max} was 7.70% (95% CI 7.09 – 8.32%). Endothelium-independent vasodilation (GTN_{max}) was 4.15% (95% CI 3.83 – 4.47%). The FMD_{max} response was on greater than the GTN_{max} response (Figure 1). No effect of room or skin temperature on FMD_{max} or GTN_{max} was observed. There was a strong inverse association between baseline artery diameter and FMD_{max} (-3.46, $P<0.001$) (Figure 2). The time to peak brachial artery diameter in response to hyperaemia was positively skewed (median 55s (IQR: 43-79s)) and was not associated with FMD_{max}. The only patient characteristic associated with FMD_{max} was age with a non-significant inverse correlation (-0.52, P=0.06) but was reduced when adjusting for baseline diameter. Baseline heart rate was positively associated with FMD_{max} and GTN_{max} (P=0.01 & 0.025).

Table 1

Patient characteristics

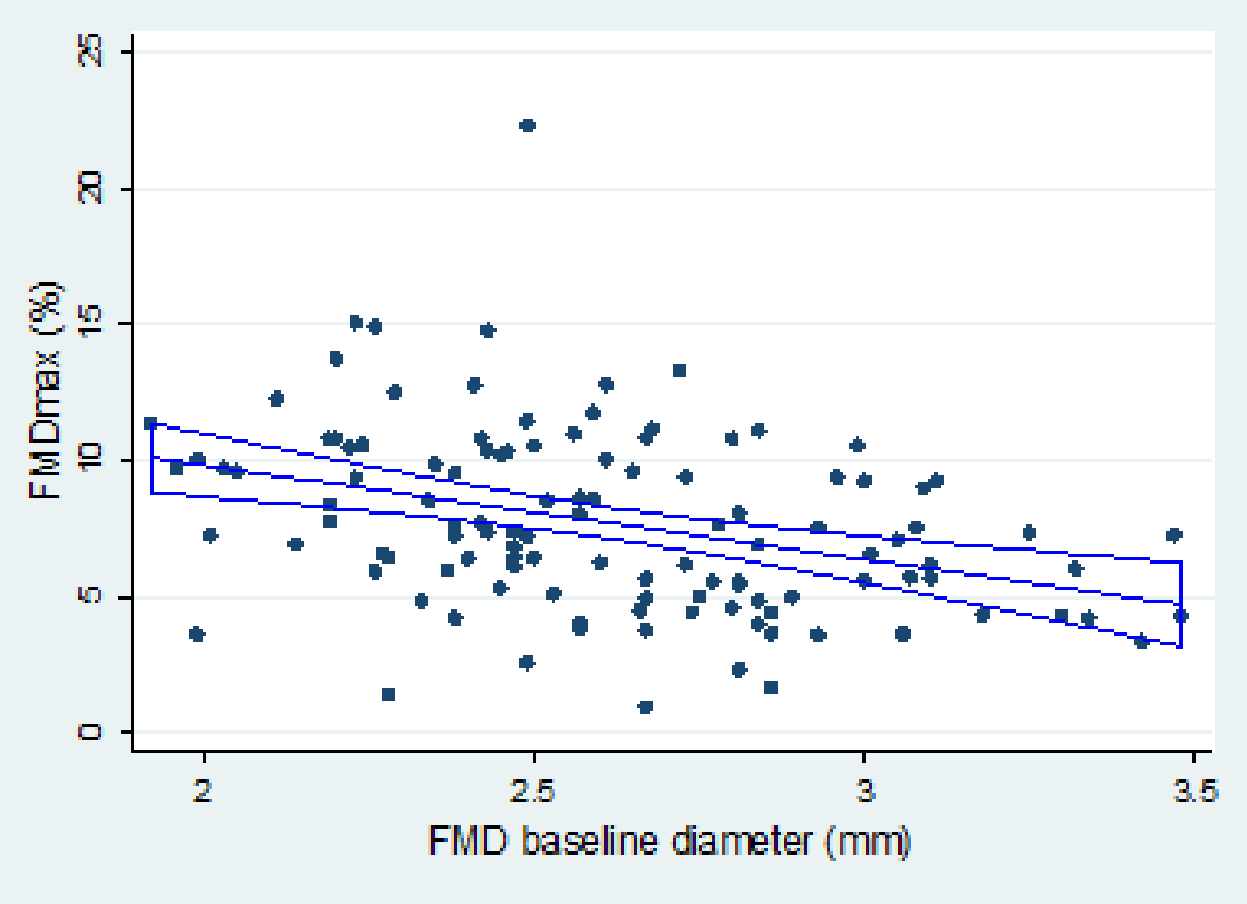
Subjects N=119	**Mean (SD) unless otherwise stated**
Age [years]	10.3 (1.1)
Males (%)	71 (60%)
Systolic BP (supine) [mmHg]	103.9 (6.9)
Diastolic BP (supine) [mmHg]	60.1 (6.4)
Hemoglobin oxygen saturation [%]	99.0 (1.3)
Body Mass Index z-score	-1.71 (0.88)
Height-for-age z-score	-2.09 (-1.01)
Hemoglobin [g/dl]	7.5 (1.1)
Reticulocyte No [x10x6] (N=30)*	0.299 (0.120)
Reticulocyte % (N=30)*	10.8 (5.2)
Lactate dehydrogenase [IU]	599 (150)

Subjects N=119	Mean (SD) unless otherwise stated
Bilirubin – unconjugated [umol/L] median (IQ range)	24.4 [17.0 -36.7]

** subset when automated reticulocyte count data was available (Sysmex XTi).*

Figure 1 **Endothelium-dependent (FMD_{max}) and endothelium-independent (GTN_{max}) vasodilatation**

Figure 2 **Correlation between FMD_{max} with baseline brachial artery diameter**



Discussion

We have characterised peripheral vascular function in a large cohort of children with SCA. Mean FMD_{max} was slightly lower than that observed in predominantly Caucasian non-SCA British children of similar age (8.1% [SD3.4]) (Donald & Charakida *et al.* Eur Heart J 2010: 31; 1502-10), but higher than reported in 21 older French children with SCA (5.6 +/- 0.2) (Montalembert *et al.* Haematol 2007: 92; 1709-10) which might reflect deterioration of endothelial function with age. There was no apparent association between FMD_{max} and hemolytic markers or with nutritional status at baseline. Recruitment and assessment of appropriate local non-SCA controls for comparison is planned. Amino acid analyses are ongoing.

Disclosures:

No relevant conflicts of interest to declare.

Author notes

* Asterisk with author names denotes non-ASH members.