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Tissue oxygen saturation assessment of microvascular perfusion in adults with fontan palliation and comparator groups using vascular optical spectrophotometry – a pilot study

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3 **Tissue Oxygen Saturation Assessment of Microvascular Perfusion in Adults with**
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5 **Fontan Palliation and Comparator Groups using Vascular Optical Spectrophotometry**
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7 **– A Pilot Study**
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ABSTRACT (250 Words)

Objective: The Fontan operation greatly improves survival for single ventricle congenital heart disease patients but creates a physiology that leads to long-term multi-organ dysfunction. A non-invasive screening tool that can identify impending decline is sought. The objective of this pilot study was to assess the microcirculation in Fontan-palliated patients by measuring tissue oxygen saturation (StO₂) in superficial and deeper tissues.

Approach: Three patient cohorts were studied: Fontan group (n=8) and two patient control groups, liver disease group (n=8) and tetralogy of Fallot group (n=9). 22 healthy controls were also examined. Superficial and deeper StO₂ was measured at the forearm, thenar eminence, index and ring fingers of both arms using the LEA O2C spectrophotometry device.

Main Findings: Superficial StO₂ was reduced in Fontan patients compared to healthy controls (p=0.002) and tetralogy patients (p=0.016), but not compared to the liver group (p=0.313). Deeper StO₂ was similar between groups (p=0.112). The gap between deeper and superficial StO₂ was raised in Fontan patients compared to healthy controls (p=0.001) and tetralogy patients (p=0.037), but not compared to the liver group (p=0.504). There was no clinically relevant difference in StO₂ between the left and right arms, and the variation in StO₂ according to measurement site was similar between the four groups.

Significance: Vascular optical spectrophotometry is a feasible non-invasive measure of micro-circulatory function that can easily be performed in the clinic setting and may have utility in patients with Fontan circulations. Further, we provide important normal range data in the healthy control population which can be used to design future studies.

INTRODUCTION

The most complex and rare forms of congenital heart disease (CHD) are those conditions that are characterised by the presence of only one functional ventricle. Tricuspid atresia, double inlet left ventricle and hypoplastic left heart are some examples, which together occur in around 16 per 100 000 children and 2 per 100 000 adults in the UK.¹ The prognosis of these conditions was dismal until the development of the Fontan palliation, a staged surgical repair that provides pulmonary blood flow through passive venous return directly from the vena cavae and reserves the single functional ventricle to support the systemic circulation (see Figure 1).² In the UK around 200 Fontan operations are performed per year.³ Although a relatively small number, these patients are of increasing concern because of their high healthcare utilisation and also the predicament they present with late onset multi-organ morbidity that creates difficulties for extended palliation through heart transplant.⁴⁻⁶ Documented complications include plastic bronchitis, protein losing enteropathy, liver disease including cirrhosis, portal hypertension, hypervascular nodules and hepatocellular carcinoma, chronic venous insufficiency and renal disease.^{7,8} It is not fully known why this morbidity occurs; lack of pulsatility in the venous circulation and arterial vasoconstriction with elevated systemic vascular resistance occurring in response to relatively fixed cardiac output are both hypothesised to underlie these problems.^{5,6,9} Fontan patients also demonstrate endothelial dysfunction, which may contribute to vasoconstriction as well as the pro-coagulant phenotype observed in this cohort.¹⁰⁻¹³ Measures of endothelial dysfunction have been correlated with measures of functional health status in this group and thus may have prognostic value.¹³ The features of Fontan physiology failure are heterogeneous and difficult to predict. A clinical measurement that would allow monitoring of the progression of Fontan physiology failure and allow identification of impending decompensation would be of significant clinical benefit.

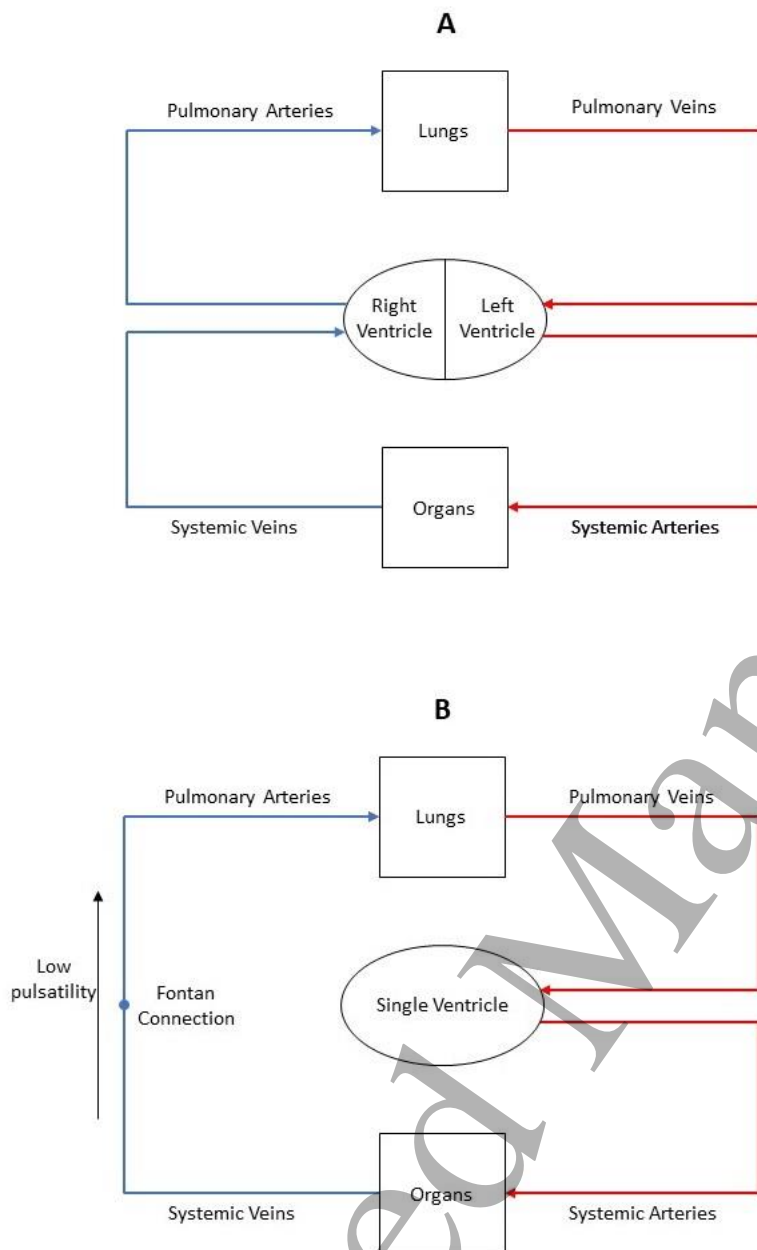


Figure 1. A) normal biventricular circulation and B) Fontan circulation

Microvascular dysfunction has been demonstrated and suggested as a biomarker in a range of conditions such as coronary artery disease, heart failure, systemic sclerosis and diabetes.^{14,15} The microcirculation can be assessed non-invasively by measurement of tissue oxygen saturation (StO_2), which is the oxygen saturation of haemoglobin within a tissue bed. This reflects the balance between oxygen delivery and consumption in the assessed tissue.¹⁶ The LEA O2C device uses micro-light guided spectrophotometry to

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3 simultaneously measure StO₂ at depths estimated at ~2 mm, with capability to assess skin
4 microcirculation e.g. venular plexus and ~6 mm in deeper tissues.¹⁷ The measurement is
5 derived from blood vessels smaller than 100µm in diameter, which includes arterioles,
6 capillaries, and venules.¹⁸ It does not require the vessel to be pulsatile to work and it can
7 measure oxygen saturation accurately at low levels unlike pulse oximetry. Previous studies
8 have demonstrated the prognostic value of StO₂ measurements in situations of
9 cardiovascular dysfunction. A prospective study¹⁹ recruited stable chronic heart failure
10 patients and measured their superficial StO₂ (1 mm depth) using the O2C device. After 6
11 months, they found that patients who experienced adverse outcomes had lower baseline
12 StO₂ measurements compared to those who remained stable (44.8% vs 62.9%, p = 0.015).
13 A meta-analysis²⁰ reported that in sepsis patients, StO₂ is significantly lower in non-survivors
14 compared to survivors (74.5% vs 81.7%, p = 0.020).
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28 The aim of this pilot study was to assess the microcirculation in Fontan patients and
29 compare their findings with relevant patient groups. A group with tetralogy of Fallot was
30 compared; these patients have also undergone childhood cardiac surgical repair and
31 experience ventricular dysfunction in later life like Fontan patients²¹ but have a biventricular
32 circulation, more aligned to a conventional heart failure phenotype. A group with isolated
33 liver disease and no primary cardiac pathology was compared; Fontan patients universally
34 exhibit advanced liver disease and it is not clear how this influences other organ systems
35 and their decline.²² A healthy cohort was also studied.
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METHODS

Study Population

Healthy controls were recruited from the Newcastle University campus and the Freeman Hospital by advertisement. Patients were identified from departmental databases and approached at routine clinic appointments. Four groups of adult subjects (>18 years) were included in this study: healthy controls, patients with Fontan circulation (Fontan group), patients with repaired tetralogy of Fallot (Tetralogy group), and patients with isolated liver disease (Liver group) (Figure 2A).

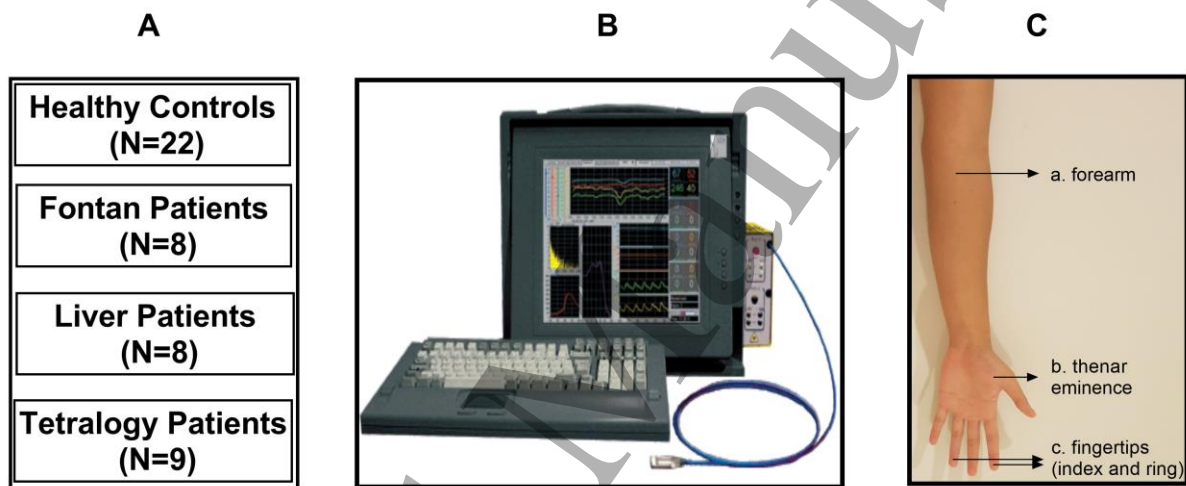


Figure 2. A) The four diagnostic groups included in this study. B) The LEA O2C device. C) Locations of StO_2 measurement on the arm.

Ethical Approval

Ethical approval for patients was granted by the Proportionate Review Sub-Committee of the Health and Social Care Research Ethics Committee B (HSC REC B) (Ref:17/NI/0247). For the study of healthy subjects, ethical approval was granted by Faculty of Medical Sciences Research Ethics Committee, Newcastle University (Ref:1474/3891). All subjects gave written informed consent for inclusion in the study.

Study Protocol

Measurements were conducted at the Microvascular Facility within the Northern Medical Physics and Clinical Engineering department at the Freeman hospital, Newcastle Hospitals NHS Foundation Trust. Room conditions were controlled for all subjects, including thermostatically controlled ambient temperature (23.5°C). Subjects were asked to refrain from consuming coffee or smoking on the day of their appointment. After 30 minutes of acclimatisation StO₂ measurements were carried out.

Tissue Oxygen Saturation (StO₂) Measurements

The LEA O2C device (LEA Medizintechnik GmbH) (Figure 2B) was used to measure superficial and deep StO₂ levels in this study using a LF2 optical probe. The probe was calibrated in ambient room lighting before each subject's measurements. StO₂ was measured in superficial and deeper tissue at the forearm (2 cm distal to the antecubital fossa), thenar eminence, index fingertip, and ring fingertip in both arms (Figure 2C). After the probe was placed on the skin, a 15 second period was allowed for measurements to stabilise before they were recorded. Three sets of measurements were recorded at each site, and an average of the readings was used for further analysis.

Statistical Analysis

Normality of data was assessed using the Shapiro-Wilk test. Normal data is presented as mean with standard deviation and non-normal data as median with inter-quartile range. Categorical data is presented as absolute number and percentage. To compare superficial and deeper StO₂ between right and left arms, measurements at all four sites were averaged for each arm and compared within groups using the paired Student t-test for normal data and the Wilcoxon matched pair signed rank test for non normal data. To compare superficial and deeper StO₂ and the difference between the two according to diagnostic group, an average of superficial and deeper measurements from all sites on both arms was made and the difference calculated. Diagnostic groups were compared using one-way ANOVA where data

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3 was normally distributed, and Kruskal-Wallis test where data was not-normally distributed. If
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5 a significant difference was observed, appropriate post-hoc testing was conducted using
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7 Tukey's test for normal data and Dunn's test for non-normal data, both of which account for
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9 multiple comparisons. A p-value of <0.05 was considered statistically significant. Prism 7 by
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11 GraphPad was used to conduct all statistical analyses in this study.
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RESULTS

Study population

47 subjects completed the study protocol; 22 in the healthy control group, 8 in the Fontan group, 9 in the tetralogy group, and 8 in the liver group (Figure 2A). Demographic information is presented in Table 1.

| | Controls (n=22) | Fontan (n=8) | Tetralogy (n=9) | Liver (n=8) | p |
|---------------------------|-------------------------------|------------------|-------------------------------|-------------------------|-------|
| Female n(%) | 12 (54.5) | 3 (37.5) | 5 (55.6) | 8 (100) | |
| Age (years) | 27.9 (22.4-40.8) [†] | 34.5 (23.1-45.8) | 39.9 (37.5-58.4) [†] | 52.0 (39.2-64.7) | 0.001 |
| BMI (kg/m ²) | 25.6 (23.1-27.2) [†] | 22.7 (21.3-24.1) | 27.0 (24.6-29.5) | 27.5 (23.6-31.4) | 0.012 |
| SBP (mmHg) | 122 (106-138) | 113 (103-123) | 116 (110-147) [†] | 123 (110-136) | 0.630 |
| DBP (mmHg) | 77 (66-89) | 74 (69-78) | 73 (61-85) | 74 (62-86) | 0.706 |
| Heart Rate (bpm) | 69 (59-79) | 73 (65-81) | 70 (57-82) | 76 (65-86) | 0.399 |
| Pulse Oximetry (%) | 99 (98-99) [†] | 95 (90-99) | 98 (97-99) [†] | 99 (97-99) [†] | 0.004 |
| Relevant surgery* n(%) | 0 (0) | 5 (62.5) | 1 (11.1) | 0 (0) | |

Table 1. Subject Demographics [^{*}Blalock-Taussig Shunt or coarctation repair, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, bpm: beats per minute]

[†]Non-normal data.

Comparison of tissue StO₂ in right and left arms

CHD patients have often had previous operations that affect blood flow to the aortic arch and upper limbs, e.g Blalock-Taussig shunt or repair of coarctation of the aorta (Table 1). We therefore asked if there would be differences in the StO₂ measurements in the left compared with the right arm. There was no overall difference between StO₂ measurements in each arm in the patients known to have had such operations and in the overall cohort (Table 2). A difference in superficial StO₂ between right and left arms (67.7% vs 68.8%, p=0.031) was

observed in the healthy control group, but this was not felt to be of clinical significance, and not seen in the patient groups (Table 2). It is unclear whether this difference is due to the effects of hand dominance, as there were insufficient individuals that were left-handed to evaluate this; nevertheless this observed difference was small and not clinically significant.

| | Superficial Tissue StO ₂ (%) | | | Deeper Tissue StO ₂ (%) | | |
|--------------|---|----------------------------------|-------|------------------------------------|----------------------------------|-------|
| | Right | Left | p | Right | Left | p |
| All Subjects | 67.3 (58.9-68.8) [†] | 66.8 (60.5-71.2) [†] | 0.101 | 83.4 (80.3-86.3) [†] | 82.7 (80.3-85.0) [†] | 0.057 |
| Controls | 67.7 (64.6-69.3) [†] | 68.8 (65.9-71.9) [†] | 0.031 | 82.9 (78.6-87.2) | 83.0 (81.0-85.1) [†] | 0.238 |
| Fontan | 56.8 (54.7-58.9) | 58.1 (54.1-62.0) | 0.369 | 80.9 (78.1-83.8) | 80.5 (78.2-82.7) | 0.436 |
| Liver | 67.3 (58.9-68.9) [†] | 63.3 (55.0-71.7) | 0.461 | 83.9 (80.9-86.9) | 83.5 (79.4-87.6) | 0.507 |
| Tetralogy | 68.7 (64.5-70.9) [†] | 65.4 (52.6-78.2) | 0.496 | 85.3 (82.2-87.2) [†] | 82.1 (80.2-86.7) [†] | 0.359 |

Table 2. Comparison of Tissue StO₂ in Right and Left Arms. [†]Non-normal data

Variation in superficial and deep tissue StO₂ according to probe location

Because Fontan patients have higher systemic vascular resistance and reduced cardiac output, microvascular function might be expected to deteriorate with increasing distance from the heart. The variation in StO₂ from forearm to thenar eminence (approximate distance 25cm) and from thenar eminence to fingers (average of index and ring, approximated distance 14cm) was plotted (Figure 3A and 3B). Variation in StO₂ according to measurement site follows a similar trend in all groups.

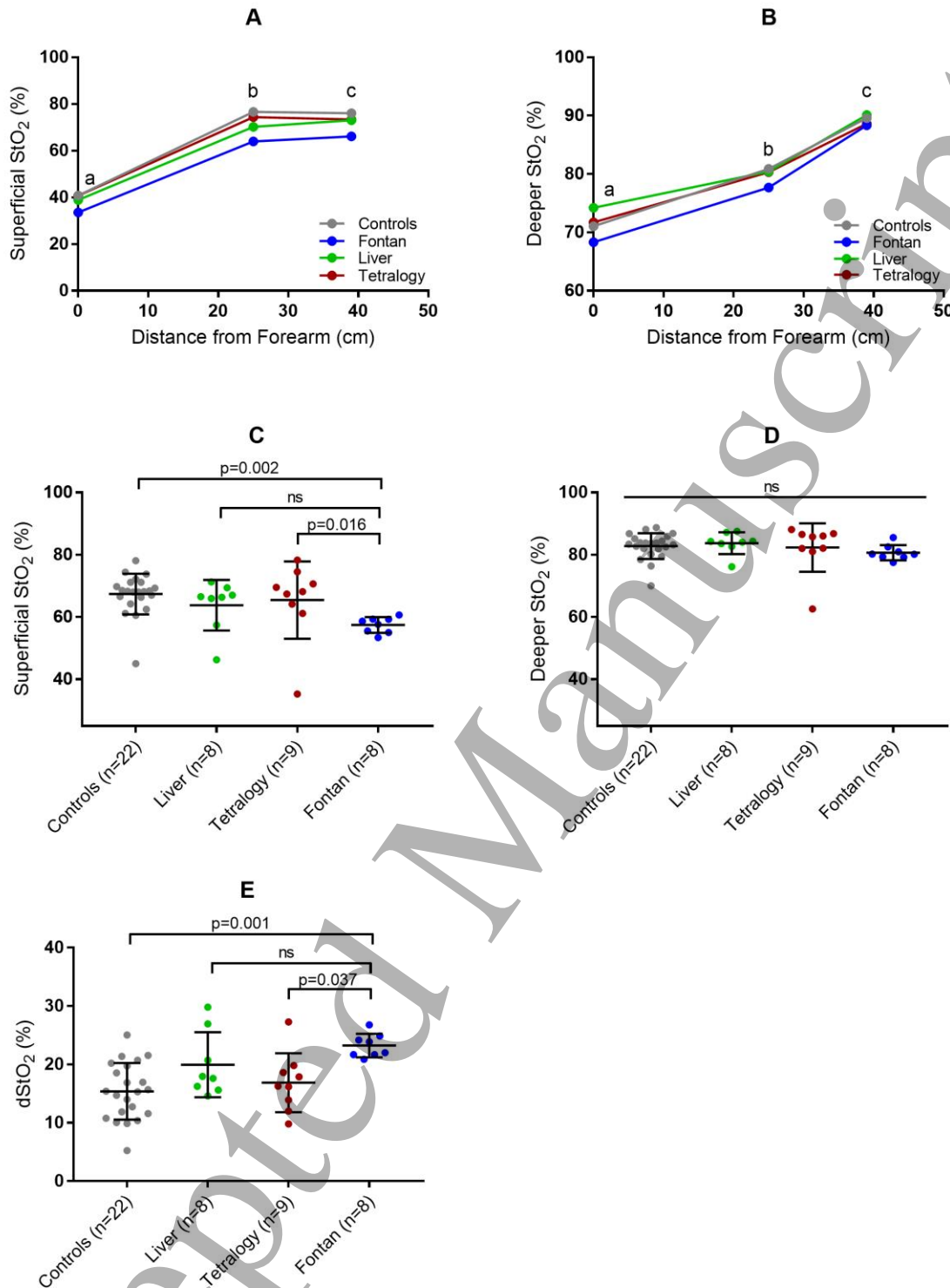


Figure 3. A) and B) - variation in superficial and deeper StO₂ according to distance from forearm, respectively. Labels a, b, and c represent location of probe as shown in figure 2C. C) and D) - superficial and deeper StO₂ according to diagnostic group, respectively. E) - dStO₂ according to diagnostic group. Error bars represent mean and standard deviation.

Absolute and differential StO₂ values.

We next asked if there were differences in the StO₂ levels between different patient groups. Whilst there was no overall difference between deeper StO₂ levels ($p=0.112$; Figure 3C), a significant difference was observed between superficial StO₂ levels ($p=0.002$). Fontan patients had significantly lower superficial StO₂ measurements compared to healthy controls (57.4% vs 67.4%, $p=0.002$) and tetralogy patients (57.4% vs 65.5%, $p=0.016$), but not compared to the liver group (57.4% vs 63.8%, $p=0.313$) (Figure 3D).

Deeper tissue StO₂ was consistently higher than superficial StO₂ in the whole cohort (82.5% vs 64.7%, $p<0.001$). In view of this we next asked if the difference between absolute superficial and absolute deep StO₂ measurements (dStO₂) varied in the four subject groups. An overall difference in dStO₂ was observed between groups ($p=0.001$), with Fontan patients having significantly greater dStO₂ values compared to healthy controls (23.2% vs 15.4%, $p=0.001$) and tetralogy patients (23.2% vs 16.9%, $p=0.037$), but again not liver patients (23.2% vs 20.0%, $p=0.504$) (Figure 3E).

DISCUSSION

This pilot study demonstrates that CHD patients with Fontan circulation have reduced superficial StO_2 , with increased $dStO_2$ compared to healthy controls and patients with repaired tetralogy of Fallot. Although a difference in StO_2 between arms was seen in the healthy volunteers, this was not seen in any patient group. There was also no difference seen in the pattern of StO_2 variation according to location along the arm amongst the four groups. The abundance of low-resistance arteriovenous anastomoses in glabrous skin of human palms²³ may explain the observation of elevated StO_2 in fingertips and thenar eminence compared to the forearm (Figures 3A and 3B). Additionally, we define a normal range for StO_2 measurements in healthy individuals which can be used to inform the design of future studies. In healthy controls, tissue StO_2 at the thenar eminence has proven most robust in terms of variability and this alongside our results should be considered in designing future clinical studies.²⁴

A limitation of this study is its size and the heterogeneity of the patients within each group, particularly with respect to their stage of disease progression. Demographic differences existed between the groups in our study, specifically in age and BMI (Table 1). However, other studies have shown that these factors do not influence tissue StO_2 at rest. Rosenberry, et al²⁵ reported no difference in resting StO_2 measurements between young (18–35 year old) and older (65–80 year old) subjects, and Soares, et al²⁶ reported no difference in measurements between lean (BMI 18-25 kg/m^2) and obese (BMI >30 kg/m^2) individuals. Nevertheless, the low superficial StO_2 and increased $dStO_2$ seem to be robust findings that indicate possible microvascular dysfunction in the Fontan group. It is possible that the failure to produce a difference in stO_2 between arms in the patient groups may indicate a general circulatory issue or in a fully powered study may disappear. Conversely, whilst our current study did not suggest any clinical features that might associate with the reduced superficial StO_2 observed in the Fontan group, these may appear in a full study.

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3 Superficial StO_2 and dStO_2 was significantly different in the Fontan group compared
4 to healthy controls and the tetralogy group, but not compared to the liver group (Fig. 3C and
5 3E respectively). This may indicate that liver dysfunction in Fontan patients contributes to the
6 observed peripheral microcirculatory disturbance. A previous study reported reduced resting
7 StO_2 values in the thenar eminence of liver cirrhosis patients compared to healthy controls
8 (75% vs 81%, $P=0.009$), with more pronounced reductions in late stage patients.²⁷ These
9 findings may be due to either the presence of atriovenous shunts in central vessels, or the
10 'splanchnic steal' phenomenon leading to extrasplanchnic peripheral vasoconstriction. This
11 is of interest, as Fontan patients often have advanced liver disease but preserved synthetic
12 function making early detection using conventional markers difficult. Alternatively, our
13 findings could be explained by a disturbance of vascular tone secondary to the unique
14 nature of the Fontan circulation. Several other studies have reported endothelial
15 dysfunction^{10,11,13,28,29} and sympathetic over-activation^{10,30} in Fontan patients, which may
16 combine to produce a pro-vasoconstrictor phenotype.³¹ The preload sensitivity and inability
17 of the Fontan circulation to easily increase overall cardiac output may be responsible for the
18 lower superficial StO_2 levels and the increased dStO_2 .

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37 The relationship between arterial saturation (SaO_2) and tissue StO_2 measurement
38 was not explored in this study. StO_2 represents the oxygen saturation of haemoglobin
39 globally in the microvascular bed of the assessed tissue, and is hence influenced by
40 systemic factors such as haemoglobin level and oxygen tension. Fontan patients may have
41 a varying degree of arterial desaturation, according to the presence of an atrial fenestration
42 and/or collateral circulation which is reflected in the reduced SaO_2 observed in our Fontan
43 cohort (table 1).

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Tissue StO_2 is a test that is simple to perform and could be carried out in a clinic
situation if differences were found in the Fontan circulation. The absence of differences in
 StO_2 measurements between groups according to position on the arm is important as it
makes the measurement relatively robust to differences in the site of measurement as
typically can happen within the clinic situation. A more detailed understanding of the

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3 relationship of StO_2 and $dStO_2$ with arterial and mixed venous saturations as well as
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5 haemoglobin in this population is needed. Understanding how $StO_2/dStO_2$ values may vary
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7 with defined exercise regimens may also be useful as one of the key features of the failing
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9 Fontan circulation is an inability to adapt cardiac output to activity. If shown to be useful,
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11 incorporation into a prospective longitudinal study may reveal its relationship with clinically
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13 relevant outcome measures.
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16 While the finding of reduced superficial StO_2 in the Fontan cohort indicates possible
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18 microvascular dysfunction, this was not observed in deeper tissue and hence must be
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20 interpreted with caution. Resting StO_2 is a static measurement that reflects the balance
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22 between demand and supply of oxygen in the assessed tissue and does not provide
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24 information on the responsiveness of microvessels to stimuli. Dynamic tests such as StO_2
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26 measurements in response to exercise or vascular occlusion-reperfusion would provide
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28 more information on microvascular responsiveness and hence function. The feasibility of
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30 such dynamic tests in these patient cohorts must be evaluated before incorporation into
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32 larger studies.
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34 35 36 37 **CONCLUSION**

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41 This pilot study indicates the possibility of microvascular dysfunction in the Fontan
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43 population but does not provide substantial evidence to overtly prove this. Vascular optical
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45 measurement of tissue StO_2 and $dStO_2$ has potential value as a practical measure of
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47 microcirculatory function in the Fontan circulation patient, and if feasible, dynamic
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49 measurements might be more informative in this regard. Further evaluation is needed to
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51 ascertain the physiological correlates of these measures, particularly relationship with
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53 arterial oxygen saturation, as well as clinical utility in a larger Fontan patient group.
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