Comprehensive MRI assessment of the cardiovascular responses to food ingestion in Fontan physiology

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Jakob A. Hauser[1, 2]; Alexander Jones[1, 3]; Bejal Pandya[4]; Andrew M. Taylor[1, 5]; Vivek Muthurangu[1]

[1]Centre for Translational Cardiovascular Imaging, University College London, London, UK

[2]Department of Pediatrics and Adolescent Medicine, Division of Pediatric Cardiology, Medical University of Vienna, Vienna, Austria

[3]Department of Pediatrics, University of Oxford, Oxford, UK

[4]Barts Heart Centre, London, UK

[5]Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Address for correspondence:

Jakob Hauser

Centre for Translational Cardiovascular Imaging

University College London

30, Guilford Street

London. WC1N 1EH

United Kingdom

jakob.hauser@ucl.ac.uk

Tel: +44 20 7813 8106

Fax: +44 20 7813 8263

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Author contribution:

J.A.H.: Study design and conduct of the experiment, participant recruitment, data analysis, draft of manuscript;

A.J.: Study design, development of statistical plan, critical review and approval of manuscript;

B.P.: Participant recruitment, data acquisition, critical review and approval of manuscript;

A.M.T.: Study design, acquisition of funds, imaging infrastructure, critical review and approval of manuscript;

V.M.: Study design, imaging methodology and infrastructure, drafting and approval of manuscript.

Abstract

In univentricular (Fontan) physiology, peripheral and splanchnic vascular tone may be raised to counteract reduced cardiac output (CO) and elevated central venous pressure, and thus maintain vital organ perfusion. This could negatively affect the normal cardiovascular response to food ingestion, where mesenteric vasodilation and a concurrent rise in CO are central. We sought to elucidate this using rapid cardiovascular MRI. Thirty fasting subjects (50% controls; 40% female) ingested a standardized meal. Responses over ~50 minutes in mean arterial pressure (MAP), CO and blood flow in all major aortic branches were measured and regional vascular impedance (Z_0) calculated. Differences from baseline and between groups were assessed by repeated-measures mixed models. Compared to the control group, Fontan patients had greater fasting Z_0 of the legs and kidneys, resulting in greater systemic Z_0 and similar MAP. They further had similar blood flow to the digestive organs at baseline, despite larger variation in mesenteric resistance. Postprandially, blood flow to the legs decreased in the control group but not in patients. Increases in CO and superior mesenteric blood flow were similar in both groups but the celiac response was blunted in patients. No significant differences in MAP responses were observed. In conclusion, alterations in vascular tone to counteract adverse hemodynamics and raised hepatic afterload may blunt vasoreactivity in the legs and the celiac axis in Fontan physiology. Further study is needed to determine whether blunted celiac or mesenteric vasoreactivity is linked to deteriorating hemodynamics and poor prognosis in Fontan patients.

New and Noteworthy

Novel data on cardiovascular physiology in response to a meal in Fontan patients are presented. Using a previously validated dynamic MRI protocol, we demonstrated that the usual increase in cardiac output and the dilation of the superior mesenteric artery are preserved in clinically well Fontan patients. By contrast, vasoconstriction of the legs may have prevented redistribution of blood flow from this region in response to the meal. This may also affect responses to other types of stress. Celiac vasodilation was also absent in Fontan patients. This may be due to abnormal hepatic circulation. The proposed protocol may be used to study Fontan complications secondary to abnormal regional hemodynamics.

Introduction

The total cavo-pulmonary connection (TCPC), in which the venae cavae are attached directly to the pulmonary arteries (PA), is the standard approach for the palliation of univentricular congenital heart disease. Although the TCPC (or Fontan circulation) ensures normal oxygen saturation, it comes at significant hemodynamic cost.(4) Firstly, the systemic and pulmonary vascular beds are added in series and both contribute to the non-pulsatile component of systemic vascular impedance (Z_0). This increases afterload and may partly explain the lower cardiac output (CO) usually seen in these patients.(4, 23) Secondly, in the absence of a sub-pulmonary ventricle, increased central venous pressure (CVP) becomes the main driving force for pulmonary blood flow. However, as mean arterial pressure (MAP) is usually normal in these patients, elevated CVP results in reduced organ perfusion pressure. Consequently, vasoconstriction of the limbs and the splanchnic vascular bed has been suggested as a possible compensatory mechanism to ensure perfusion of vital organs in Fontan physiology.(13, 29)

In normal subjects, the ingestion of food acutely triggers a number of changes in vascular tone and cardiac function. Using rapid MRI, we have previously demonstrated a substantial postprandial drop in mesenteric resistance and a compensatory increase in CO.(6, 7) Other changes in regional vascular function have also been described.(1, 12, 21, 26) We hypothesized that in Fontan patients this response could be attenuated due to limited ability to increase CO,(5) or by overriding regional vasoconstriction. The inability of conventional techniques to measure regional blood flow reliably, non-invasively and rapidly may have partly prevented experiments resolving this question in the past.

We tested our hypothesis using a previously validated, dynamic MRI protocol,(6, 7) and characterized the cardiovascular responses to food intake in Fontan *versus* in normal physiology.

Materials and methods

Participants

Thirty participants (40% female), aged 16+ years, were enrolled between November 2016 and March 2018. Fontan patients were recruited from a cardiac outpatient clinic (n=15). Local hospital staff volunteered as healthy controls (n=15). Participants were instructed to fast overnight and to abstain from tobacco, alcohol, recreational drugs, caffeine and formal exercise for the preceding 24 hours. The consumption of water was allowed during the fasting period. Exclusion criteria were: Chronic diseases requiring hospital management (in control subjects); hepatic or renal comorbidity; history of arrhythmia; known or possible pregnancy and MRI-incompatible implants; residual aortic coarctation, and/or significant vessel lesions or kinking in the regions of interest. The study was approved by the National Research Ethics Service London and performed under its license (reference 16/LO/1649). Informed consent was obtained from all participants. The study complies with the Declaration of Helsinki.

Study protocol

In all subjects, the study started at 9:30 am. Oxygen saturation was measured by pulse-oximetry in patients. Height and weight were measured using calibrated devices in order to calculate body mass index (BMI = weight [kg] / height $[m]^2$) and body surface area (BSA = 0.007184 × weight $[kg]^{0.425}$ × height $[m]^{0.725}$). Participants then underwent the meal challenge under continuous hemodynamic MRI-assessment, as detailed previously.(6, 7) Briefly, all subjects first underwent baseline scanning (as detailed in the imaging section below) and BP measurement in the non-dominant arm using an oscillometric device. Subjects were then asked to sit up on the scanning table and drink a high-calorie liquid meal, consisting of 170 ml of double (heavy) cream and 45 g of maltose syrup (fat 81 g, glucose equivalent 43 g, energy 925 kcal, total fluid volume ~200 ml). Subjects were asked to consume this meal in 1-2 minutes. We have previously shown in volunteers that this type of meal evokes a

cardiovascular response, unlike a sham meal (water).(7) After the meal, flow data and BP were recorded intermittently. BP was measured every 5 minutes. MRI data were acquired in cycles of ~7 minutes with the first cycle starting approximately 7-10 minutes after ingestion of the meal. The last imaging cycle was started approximately 50 minutes after ingestion of the meal, resulting in a postprandial scanning time of ~1 hour. Total scanning time was ~90 minutes.

Imaging protocol and post processing

All imaging was performed on a 1.5 T MRI system (Avanto, Siemens, Germany) using 2 spine coils, 2 body matrix coils and 1 neck coil. A vectorcardiogram was used for cardiac gating and heart rate (HR) monitoring.

Aortic blood flow was measured just above the sinotubular junction and proximal to the iliac bifurcation using a breath hold cardiac-gated spiral phase contrast MRI (PCMR) sequence (SENSE, factor of 3; resolution 1.56 x 1.56 mm / 32.0 ms, breath hold ~5 s).(27). The imaging planes were planned using steady-state free precession (SSFP) single-shot imaging of the aorta.

Blood flow was also measured in the common carotid and vertebral, the celiac, the superior mesenteric (SMA) and the renal arteries. In order to rapidly acquire high enough spatial resolution data, a breath hold RR-interval averaged spiral PCMR technique was used (resolution 0.78 x 0.78 mm, breath hold ~6 s).(28) Good intra- and interobserver agreement has been demonstrated for this technique previously.(6) In this previously validated approach, data are combined over ~5 R-R intervals to yield a single “time-averaged” image that can be used to calculate mean flow through a vessel. For these vessels, the imaging planes were planned using multi plane reformatting of cardiac gated 3D-SSFP images of the abdominal vasculature.(7) Imaging planes were re-planned after ingestion of the meal due to patient movement and shifting of the of abdominal organs by the filled stomach.

Images were processed offline using custom plugins for OsiriX v9.0 (Pixmeo, Switzerland). Aortic blood flow data from spiral triggered PCMR acquisitions were obtained by semi-automated, frame-wise segmentation of the magnitude and phase images. Blood flow from RR-interval averaged imaging data was derived from the mean volume flow across one cardiac cycle within the region of interest defined on the respective magnitude image.

Statistics

All statistical analyses were performed using Stata SE v14.2 (StataCorp, USA). Continuous data were represented as medians (IQR), or as mean ± SD if normally distributed. Group comparisons in such data were done by Mann-Whitney-U-test or by Student *t*-test, as appropriate. Reported CO, regional blood flow and stroke volume (SV) were all indexed for BSA. In this study, we used the non-pulsatile (at 0Hz) component of vascular input impedance (Z_0) rather than resistance, as in the Fontan population, systemic pressure-flow relationships also included pulmonary vascular resistance (PVR). Nevertheless, calculation of Z_0 is similar to calculation of resistance.(18) Global vascular impedance index was calculated MAP divided by indexed CO. Regional vascular Z_0 was obtained by dividing MAP by indexed regional blood flow. In regions supplied by more than one artery (e.g., the head), Z_0 was calculated from the sum of all flow data measured in the supplying vessels. This assumes that MAP in major vessels was the same as brachial MAP, which is in keeping with previous invasive studies that compared MAP in the aorta with MAP in the radial, brachial and femoral arteries.(14) To account for asynchrony between data acquisition, BP and flow data were linearly interpolated at 10-minute intervals, starting from the beginning of meal ingestion, and truncated at 50 minutes. Changes in hemodynamic measures over time and the effect of Fontan physiology, sex and BMI were examined using repeated measures mixed models. These models account for the correlated nature of repeated measures over time. Their coefficients for each time point after baseline reflect the time-dependent

change from baseline. Their *P*-values represent the significance of that change and are reported to illustrate the significance of postprandial responses.

Results

Study population and resting (fasting) physiology

In the patient group, 12 (80%) had undergone total cavo-pulmonary connection with an extracardiac conduit, with the remainder having received the classic (atriopulmonary) Fontan procedure. Oxygen saturation level was 94% (93, 95) in the Fontan group.

At baseline, there was no statistically significant difference in MAP between groups. However, Fontan patients had significantly higher systemic Z_0. Although SV was significantly lower in Fontan subjects, their resting HR was significantly higher, resulting in only a trend towards lower CO compared to controls (Table 1).

Fontan patients had significantly greater baseline regional Z_0 in the kidneys (~1.3x) and legs (~1.7x), compared to controls. This resulted in a significantly lower proportion of blood flow distribution to the legs, but no statistically significant difference in renal perfusion (Table 1). In all other territories, relative blood flow and vascular Z_0 showed no statistically significant difference between groups. Three patients took diuretics and/or angiotensin converting enzyme inhibitors. Adjustment for such therapy had no significant impact on the regression analysis.

Postprandial global hemodynamic responses

All subjects completed the protocol without adverse events. Following ingestion of the meal, systemic Z_0 dropped significantly after 20 minutes with no statistically significant difference between groups. In both groups, systemic Z_0 started to normalize after 50 minutes with no significant difference

compared to baseline. Correspondingly, there was a rise in CO with a peak observed at 40 minutes. This response was not statistically different between groups and attributable to an increment in HR in both. SV and MAP did not change significantly in either group after ingestion of meal (Figure 1).

Postprandial changes in regional blood flow and vascular impedance

Superior mesenteric vascular Z_0 decreased significantly within 10 minutes and further decreased until the end of the experiment in both groups (Figure 2). This was associated with a similar increase in SMA blood flow in both groups (Figure 3). It should be noted that the increase in SMA blood flow was greater than the increase in CO, indicating that blood flow was redistributed from other compartments.

In the celiac artery, there was a decrease in regional Z_0 at 10 minutes in the control group associated with an increase in blood flow (Figure 2). This response was not seen in the Fontan group. After 40 minutes, celiac blood flow was lower than baseline in both groups (Figure 3).

Hemodynamic responses in the lower limbs differed significantly between groups. In the Fontan group, lower limb Z_0 had decreased significantly from 10 minutes onwards (Figure 2). As a result, blood flow was significantly higher than baseline by 50 minutes (Figure 3). By contrast, lower limb Z_0 increased initially in the control group, leading to a transient drop in blood flow (Figures 2 and 3). In this group, lower limb Z_0 and blood flow returned to baseline levels by the end of the experiment.

There was also a small but significant decrease in renal Z_0 and an increase in renal blood flow in both groups after meal ingestion (Figures 2 and 3). In the cranial vessels, no significant change in Z_0 or blood flow was seen.

Discussion

In this study, we used a previously validated protocol(6, 7) to investigate the postprandial cardiovascular response in Fontan patients compared to a control group. The main findings were that Fontan patients had (i) increased baseline systemic, renal and lower limb Z_0, and (ii) similar global hemodynamic responses, but blunted celiac and lower limb vascular responses to food ingestion.

At baseline, systemic Z_0 in patients was greater than in the control group. This was expected as in Fontan physiology, Z_0 includes PVR, as well as systemic vascular resistance (SVR) due to their addition in series. This is in contrast to normal subjects in whom $Z_0 \approx$ SVR (assuming low RAP). As systemic Z_0 is one of the primary components of cardiac afterload, these data partly explain the reduced SV seen in Fontan patients. Although reduced SV was partially compensated for by an increase in HR, there was a trend for lower CO in Fontan patients.

Our data suggest that this may be compensated for by regional increases in vascular resistance, in keeping with previous research.(13, 29) However, our findings must be interpreted in the context of the fact that we measured regional vascular impedance (Z_0), rather than vascular resistance. Similar to global systemic Z_0, regional Z_0 also includes a component of PVR in the Fontan circulation. It can be shown that in Fontan patients, regional Z_0 approximates to regional vascular resistance scaled by [(SVR+PVR)/SVR]. Using our data, this ratio could also be estimated as $Z_{0\ (Fontan)}/Z_{0\ (Control)}$ (i.e. $35.2/30.3 \approx 1.16$). Normalization of regional Fontan Z_0 measures for this factor may allow for more meaningful comparison with corresponding measures from normal subjects (Table 2). This shows that after normalization, lower limb Z_0 remains elevated in Fontan patients, supporting vasoconstriction of the legs. This is in keeping with previous research and may reflect a mechanism to prioritize blood flow to more important vascular beds.(13) Other authors found links between diminished muscle mass of the legs and poor perfusion of the extremities, possibly as a consequence of physical inactivity.(29)

While the direction of the causal link between muscle mass and limb perfusion, if any, has yet to be fully determined, it is possible that poorer vascularity of the legs due to sarcopenia, possibly caused by lack of exercise, explained the poor perfusion of the lower extremity in our population.

Similar to the legs, the raised Z_0 we found in the renal compartment could be explained by vasoconstriction secondary to neurohumoral activation, as seen in other states with low CO, such as heart failure.(29) However, the normalized renal Z_0 (Table 2) was only slightly higher in Fontan patients, suggesting that this finding may also be partly explained by raised CVP in this group. By contrast, our data suggest vasodilation of the celiac axis in Fontan patients. This may be due to a decrease in hepatic arterial resistance, which has been described as a possible mechanism to counteract hepatic congestion in the Fontan circulation.(3, 8, 10) Dynamic regulation of regional vascular resistance is a central element of postprandial physiology.(6, 7) Therefore, we tested vasoreactivity in Fontan patients with a meal.

Globally, we found no significant differences in the hemodynamic response to food ingestion, with a similar increase in CO and decrease in systemic Z_0 observed in both groups. By contrast, regional responses differed significantly. In the control group, there was an early increase in lower limb Z_0 and an associated fall in lower limb blood flow, with a slow recovery back to baseline. This suggests redistribution of blood flow from the legs to the gut, as described previously.(26) Conversely, in Fontan patients, lower limb Z_0 fell in response to the meal, leading to a modest but steady increase in lower limb blood flow.

We believe that this aligns with previous reports showing a biphasic vascular response of the legs in humans.(25, 26) In the normal population, early postprandial vasoconstriction of the limbs is driven by increased sympathetic activity, whereas late vasodilation has been linked to humoral responses,

such as insulin secretion.(15, 16, 25) In the present experiment, Fontan patients already showed signs of vasoconstriction of the legs at baseline and therefore, may have been unable to increase sympathetic vasoconstriction any further. Blunted responsiveness to vasoconstrictive signaling could have unmasked the effect of humoral vasodilators released in response to a meal. Several studies have shown that gut-released hormones are potent peripheral vasodilators and, without a counteracting increase in sympathetic tone, cause a significant drop in vascular resistance, even in non-digestive territories.(9, 19) This appears to be one of the causes of postprandial hypotension in patients with autonomic dysfunction.(15, 16, 22) It is possible that a similar mechanism explains our findings and could increase the risk of postprandial hypotension in this population, especially as they age.(11) This may be particularly true in more realistic situations where subjects are not in supine position.

Further evidence of an abnormal vascular response to food ingestion was seen in the celiac axis, where Fontan patients did not show the early postprandial fall in celiac Z_0 (and the associated increase in blood flow) seen in the control group. As noted previously, our data suggest that the celiac vascular bed may already be vasodilated in Fontan patients at baseline. This may explain the lack of a further decrease in celiac Z_0 in this group. It has been shown previously that fasting celiac resistance predicts future protein losing enteropathy (PLE).(2) Future research could address whether abnormal celiac vasoreactivity provides additional prognostic information compared to resting celiac Z_0 alone.

Interestingly, we found that mesenteric vascular responses were preserved in our Fontan population, contrasting previous ultrasound-based studies showing greater vascular resistance under fasting conditions.(17, 24) This finding could be explained by the relatively well-compensated clinical condition and young age of our population, compared to previous experiments, which focused on patients with PLE. Furthermore, previous studies typically assessed fasting physiology only, and were limited by their use of Doppler-sonography which does not provide reliable or absolute measures of

blood flow or vascular resistance. Nevertheless, decreased mesenteric blood flow has been proposed as a key mechanism causing PLE, one of the most serious long-term complications of the Fontan palliation.(20, 23) Such derangement has been suggested to promote leakage of chyle into the intestinal lumen via reduced perfusion of the intestinal mucosal layer. While the abnormalities in blood flow demonstrated by our experiment may not be clinically relevant, our findings could help generate new hypotheses for future research and perhaps support the development of new markers for clinical practice. Further longitudinal studies of larger populations of Fontan patients are needed to determine whether abnormal mesenteric vascular resistances and/or vasoreactivity may be linked to long-term complications, such as PLE, in a subset of patients.

Limitations

An important point to note is that the observed increase in SMA blood flow was greater than explained by the increase in CO and the decrease in leg perfusion alone. This suggests redistribution of blood flow from vascular beds not assessed in our protocol, such as the arms, the inferior mesenteric artery, as well as bronchial arteries and aorto-pulmonary collaterals in Fontan patients. Future research should include these regions to assess their role in the Fontan circulation. All subjects underwent MRI in supine position. This could have influenced cardiac loading conditions. As this study was non-invasive in design, central venous (Fontan) pressure was not measured and therefore, vascular resistance *per se* not assessed. However, we found no literature suggesting that CVP, pulmonary arterial pressure or pulmonary capillary wedge pressure would change following ingestion of a meal. Therefore, Z_0 was assessed as an estimate of vascular function in this group. Furthermore, we do not believe that the brief time (1-2 minutes) that the subjects sat up to ingest the meal affected our results as imaging was resumed ~7-10 minutes after ingestion. We believe that by this time, the acute effects of the brief period of sitting should have mostly subsided. The formula used to calculate Z_0 relied on the assumption that MAP is constant throughout the examined body compartments. While efforts were

undertaken to rule out any vascular abnormalities that could have caused regional variations in MAP (e.g., kinking or stenosis), such lesions could, in theory, have confounded our findings if undetected. While abnormal vascular tone was demonstrated for some compartments, our study may have been underpowered to detect weaker signals in others.

Conclusion

In Fontan patients, alterations in vascular tone to counteract adverse hemodynamics may blunt vasoreactivity of the legs and the celiac axis, compared to normal subjects. Further longitudinal study is needed to determine whether abnormal regulation of mesenteric or celiac vasoreactivity is associated with poor Fontan function or prognosis in a subset of patients.

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Table 1. Baseline (fasting) physiology and population data.

	Control (n=15)	Fontan (n=15)	*P*-value
Age (years)	32.1 (29.1, 38.6)	27.6 (21.8, 34.6)	.059
Female	7 (46.7%)	5 (33.3%)	.456
BSA (m^2)	1.76 (1.64, 1.96)	1.79 (1.68, 1.93)	.885
CO ($L.min^{-1}.m^{-2}$)	2.8 (SD: 0.4)	2.6 (SD: 0.6)	.067
Heart rate ($beats.m^{-1}$)	62.8 (56.2, 67.6)	73.3 (64.7, 80.5)	.007
SV ($mL.min^{-1}.m^{-2}$)	44.1 (40.1, 51.4)	35.7 (28.3, 41.3)	.008
MAP (mmHg)	85 (SD: 6)	86 (SD: 7)	.695
Systemic Z_0 ($WU.m^2$)	30.3 ± 4.5	35.2 ± 10.1	.048
Distribution of blood flow (relative to CO) at baseline			
Head (%)	19.2 (18.1, 24.7)	21.4 (15.8, 27.7)	1.000
Legs (%)	23.1 (19.7, 25.7)	16.2 (9.9, 19.2)	.029
Celiac (%)	13.9 (9.7, 20.6)	17.0 (16.2, 17.7)	.662
SMA (%)	5.2 (4.5, 7.5)	5.4 (1.9, 10.0)	.694
Kidneys (%)	19.7 (17.5, 24.5)	17.5 (11.7, 23.7)	.206
Vascular impedance (Z_0) by compartment			
Head ($WU.m^2$)	145 (125, 168)	154 (108, 251)	.432
Legs ($WU.m^2$)	130 (110, 147)	223 (148, 363)	$8x10^{-4}$
Celiac ($WU.m^2$)	224 (143, 358)	177 (167, 212)	.836
SMA ($WU.m^2$)	549 (433, 737)	658 (324, 1,607)	.576
Kidneys ($WU.m^2$)	154 (138, 178)	195 (168, 216)	.008

MAP was divided by indexed blood flow, measured by MRI, to obtain vascular impedance (Z_0). Data are presented as mean (SD) and were compared by *t*-test if normally distributed, or presented as median (IQR) and compared by Mann-Whitney-U test otherwise (except X^2 for sex). BSA = body surface

area; CO = cardiac output; MAP = mean arterial pressure; SMA= superior mesenteric artery; SV = stroke volume; WU = Wood unit.

Table 2. Normalized Fontan vascular impedance versus control subjects.

	Control (n=15)	**Fontan (n=15)**
Head (WU.m^2)	145 (125, 168)	132 (93, 216)
Legs (WU.m^2)	130 (110, 147)	191 (127, 312)
Celiac (WU.m^2)	224 (143, 358)	152 (144, 183)
SMA (WU.m^2)	549 (433, 737)	566 (279, 1,384)
Kidneys (WU.m^2)	154 (138, 178)	168 (145, 186)

Fasting regional vascular resistance was approximated in Fontan patients by dividing MRI-measurements of Z_0 by 1.16. (obtained by $Z_{0\ (Fontan)}/Z_{0\ (Control)}$). This was done in order to normalize for pulmonary vascular resistance, which is part of Z_0 in Fontan patients. Data are presented as median (IQR). SMA = superior mesenteric artery; WU = Wood unit.

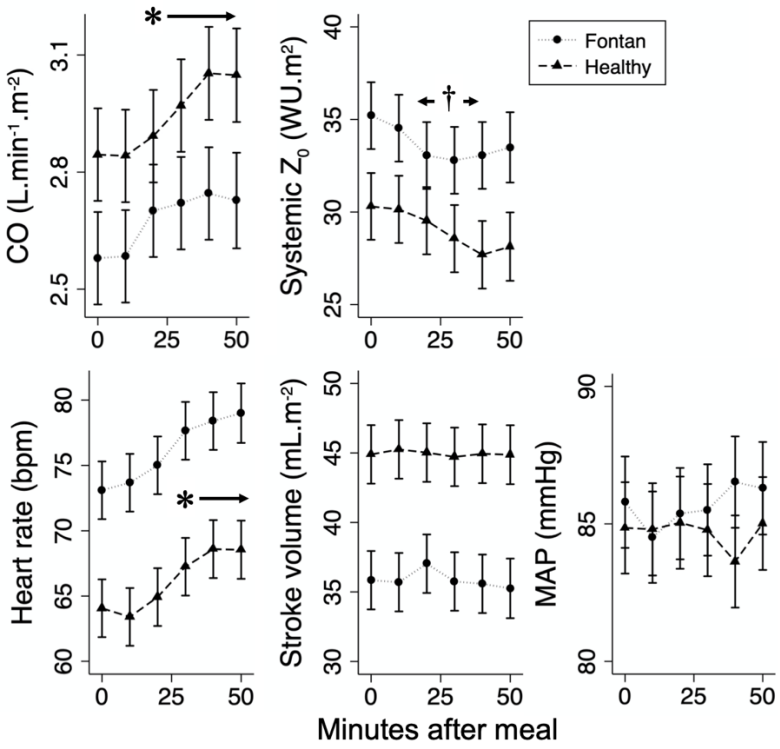

Figure 1. Global hemodynamic response (mean ± SE; repeated measures mixed model). Responses to a liquid meal were recorded by MRI in Fontan patients (n=15; 47% female; dotted plot) and healthy volunteers (n=15; 33% female; dashed plot) for 50 minutes. **P*<0.05 and †*P*≤0.001 for changes in overall response with respect to baseline. Adjustment for age, sex and body mass index had no significant effect on the response. CO = cardiac output; MAP = mean arterial pressure; WU = Wood unit; Z_0 = vascular impedance.

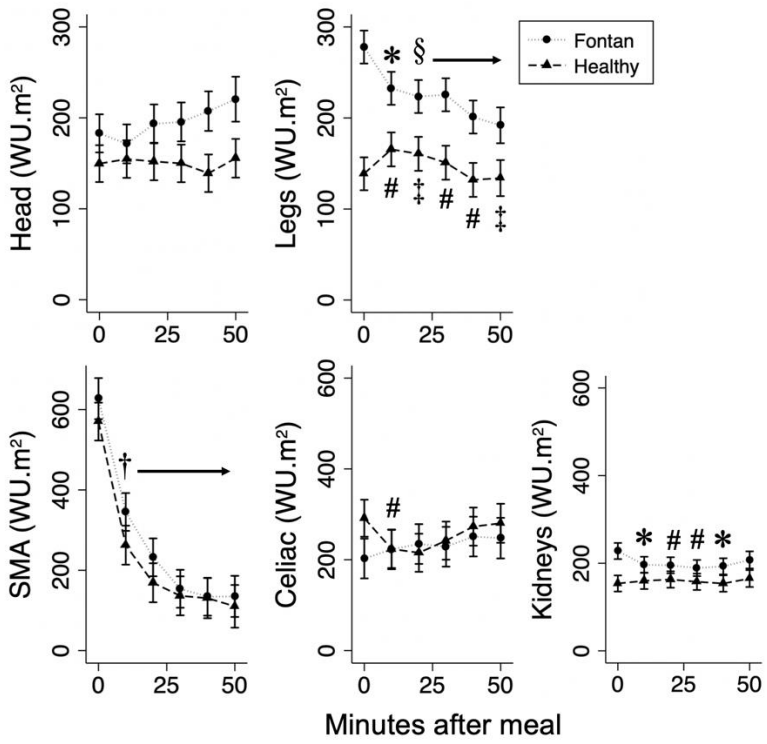

Figure 2. Changes in indexed regional vascular impedance (Z_0; mean ± SE; repeated measures mixed model). Responses to a liquid meal were recorded by MRI in Fontan patients (n=15; 47% female; dotted plot) and healthy volunteers (n=15; 33% female; dashed plot) for 50 minutes. Three outliers with excessive baseline SMA resistance were excluded in the Fontan group. *$P<0.05$, $^{\S}P\leq0.01$ and $^{\dagger}P<0.001$ for changes in overall response with respect to baseline; $^{\#}P<0.05$ and $^{\ddagger}P\leq0.01$ for differences in responses between groups. Adjustment for age, sex and body mass index had no significant effect on the response. SMA = superior mesenteric artery; WU = Wood units.

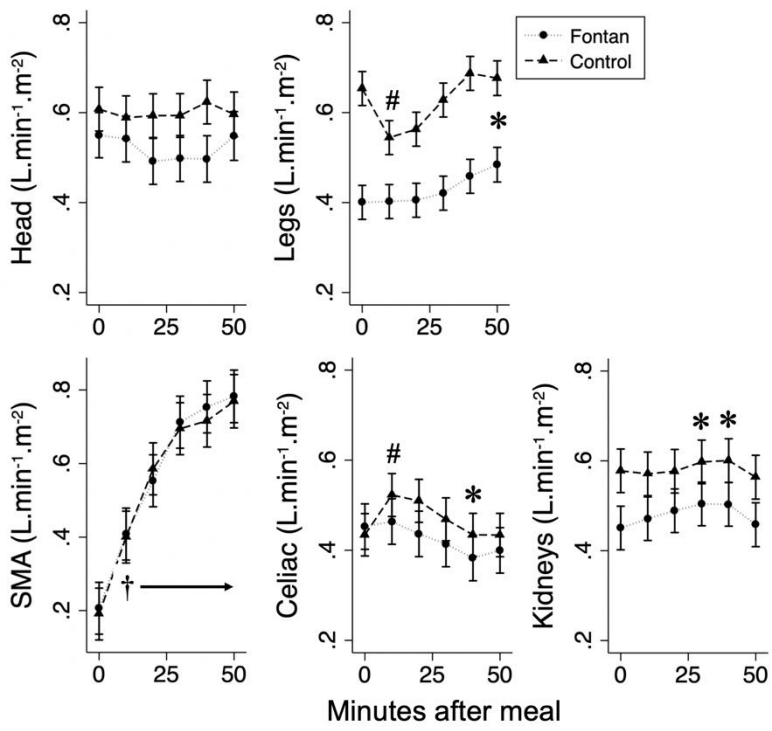

Figure 3. Regional indexed blood flow responses (mean ± SE; repeated measures mixed model). Responses to a liquid meal were recorded by MRI in Fontan patients (n=15; 47% female; dotted plot) and healthy volunteers (n=15; 33% female; dashed plot) for 50 minutes. **P*<0.05 and †*P*<0.001 for changes in overall response with respect to baseline; #*P*<0.05 for differences in responses between groups. Adjustment for age, sex and body mass index had no significant effect on the response. SMA = superior mesenteric artery.