Postprandial vascular dysfunction is associated with raised blood pressure and adverse left ventricular remodelling in adolescent adiposity

Hauser: Mesenteric vasoreactivity and CV risk in teenagers

Jakob A. Hauser, MBBS[1, 2]; Vivek Muthurangu, MD(Res)[1]; Naveed Sattar, MD, PhD[3]; Andrew M. Taylor, MD(Res)[1]; Alexander Jones, PhD[4]

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

[2]Department of Paediatrics and Adolescent Medicine, Division of Paediatric Cardiology, Medical University of Vienna, Austria

[3]Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK

[4]Department of Paediatrics, University of Oxford, UK

Address for correspondence:

Jakob A. Hauser

Centre for 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

Word count: 5,814

Abstract

Background: Left ventricular (LV) hypertrophy (LVH) is a major risk factor for cardiovascular disease, including heart failure. Although linked to obesity and hypertension, its aetiology is multifactorial. Blunted postprandial sympathetic regulation of gut blood flow has been observed in overweight animals and suggested as a promotor of hypertension and LVH. We hypothesized that blunted postprandial superior mesenteric blood flow responses would be more common in overweight humans and associated with increased blood pressure (BP) and LVH.

Methods: LV dimensions and haemodynamic responses to a standardised high-calorie liquid meal were measured in healthy adolescents (N=82; 39 overweight/obese) by magnetic resonance imaging. Covariates such as body mass index (BMI), BP, Tanner score, and an index of insulin resistance were included in multiple regression models to examine the independent associations of mesenteric flow response with BP status and LVH.

Results: Food ingestion increased cardiac output (mean Δ 0.45 [SD 0.62] $L.min^{-1}$; $P=3.8x10^{-8}$) and superior mesenteric artery flow (mean Δ 0.76 [SD 0.35] $L.min^{-1}$; $P=4.2x10^{-31}$). A blunted mesenteric flow response was associated with increased LV mass (B=-12.7 $g.m^{-2.7}$ per $L.min^{-1}.m^{-0.92}$; $P=6x10^{-5}$), and concentric LVH (log likelihood -9.9; $P=0.001$), independently of known determinants of LVH, including BMI. It was also associated with elevated systolic BP (B=-18.0 mmHg per $L.min^{-1}.m^{-0.92}$; $P=0.001$) but this link did not explain the association with LV mass.

Conclusion: Postprandial mesenteric vascular dysfunction is associated with LVH and hypertension, independently of common risk factors for those conditions. These findings highlight a new, independent marker of cardiovascular risk in the young.

Key words: Hypertrophy, Magnetic Resonance Imaging (MRI), Vascular Disease, Obesity, High Blood Pressure.

Clinical summary

We found that individuals with a blunted gut blood flow response to high calorie food ingestion tended to be overweight, and were more likely to be hypertensive and have left ventricular hypertrophy. These are known, major risk factors for the development of cardiovascular disease. The present study could not determine why they were linked to abnormal postprandial vascular responses, but the associations did not depend on a range of factors known to drive their development, such as adiposity or insulin resistance. This raises the possibility of a previously unrecognised mechanism underlying the development of hypertension and left ventricular hypertrophy in young people. Exploration of this could yield new diagnostic tools and even, perhaps, lead to interventions in the earliest stages of cardiovascular disease. For example, vascular responses to a high fat, high sugar meal could be used to identify increased cardiovascular risk in young people before other, more established risk factors, are diagnosed, allowing for earlier preventative measures. Interestingly, blunted vasoreactivity was associated with increased left ventricular mass independently of systolic blood pressure. Thus, a simple mechanism for the association, acting through increased blood pressure and, therefore, left ventricular strain, is unlikely. Other possibilities, such as deranged neurohumoral signalling, could be responsible and deserve further investigation.

Introduction

Obesity causes adverse cardiac remodelling in adults.[1] Changes in left ventricular (LV) mass (LVM) and geometry develop as this process advances. LV hypertrophy (LVH) is the eventual result and is a major risk factor for cardiovascular disease (CVD), including diastolic and systolic heart failure, atrial fibrillation, myocardial infarction and stroke.[2, 3] Indeed childhood obesity has been identified as a strong risk factor for developing heart failure, in particular, in adulthood.[4] LVH may develop before other risk factors – such as hypertension – are diagnosed, highlighting its importance as an independent marker of early cardiovascular risk.[5] In children, increased LVM has been independently linked to adiposity before other potential contributing factors such as hypertension or hyperinsulinemia were seen, indicating that the process starts earlier in life than previously thought.[6-8] The increasing global prevalence of childhood obesity necessitates early identification of such pathology and a better understanding of its underlying mechanisms in order to improve prevention of heart failure and other CVD.[9]

The link between childhood obesity and LVH remains poorly understood.[6, 8] Animal experiments have revealed a new potential mechanism to explain the association.[10, 11] A lipid-rich diet and obesity were both linked to disordered arterial control in the splanchnic vascular bed in rats.[11] Reflex vasodilation in this vascular bed is the typical response to food ingestion, but blunting of this reflex was found in obese rats [12] and was associated with hypertension and increased LVM.[11] Despite a widespread preference for high-calorie diets in Western countries and the observation that most people spend the greater proportion of their day in a postprandial state,[13] this link has not been demonstrated in humans before. Limited conventional techniques may have prevented such investigation. We developed a novel magnetic resonance imaging (MRI) approach to comprehensively characterise global and

regional cardiovascular responses to food ingestion.[12] Using this method, we sought to determine whether abnormal postprandial vascular function is linked to increased blood pressure (BP) and adverse LV remodelling in adolescents with varying degrees of adiposity.

Subjects and methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

Healthy adolescents, aged 13-19 years, were recruited via newspaper advertisements and through an obesity clinic between September 2014 and May 2016. Participants were instructed to eat a standardized meal (margarita pizza) on the evening prior to attendance then fast overnight and consume nothing but water until after the experiment. They were also asked to abstain from tobacco, alcohol, recreational drugs, caffeine and formal exercise for the preceding 24 hours. Exclusion criteria were: Chronic diseases requiring hospital management; endocrine or congenital obesity; known or possible pregnancy; MRI-incompatible metal implants; regular use of medication, and known dairy allergy. The study complies with the Declaration of Helsinki and was approved by National Research Ethics Service London – Queen Square. Informed consent was obtained from all participants or their parents, as applicable.

Study protocol

Study visits took place at 9:30am. Prior to the meal challenge, a fasting blood sample was collected. Height and weight were recorded using calibrated devices and standard protocols. Baseline BP was assessed after participants had been lying quietly for 15 minutes (IQR 12-17

minutes) and before any interventions or blood tests. BP measurements obtained successfully in this quiescent period were averaged (mean 2.5 measurements; range 1-6). BP was measured every 5 minutes in the non-dominant arm in supine position with each study participant's arms by their side, using an oscillometric device (Datex Ohmeda, General Electric, Boston, MA, USA). Participants underwent a meal challenge under continuous haemodynamic MRI and BP assessment, as described before.[12] In brief, LV volumes, aortic blood flow and superior mesenteric artery (SMA) flow were measured under fasting conditions. Participants were then asked to sit up on the scanning table and drink a high-fat, high-carbohydrate liquid meal, consisting of 300 ml of double (heavy) cream and 89 g of maltose syrup (fat 142 g, glucose equivalent 75 g, protein 5.1 g, energy 1,635 kcal, total volume ~350 ml). The timing of meal ingestion was recorded and the meal was typically consumed within 2 minutes (IQR 1-3 minutes). Flow measurements were repeated for at least 40 minutes.

Imaging protocol and post processing

All imaging was performed on a 1.5 T MRI system (Avanto, Siemens, Berlin, Germany) using 2 spine coils and 1 body matrix coil, comprising 12 coil elements in total. A vectorcardiogram was used for cardiac gating and heart rate (HR) monitoring. Imaging planes for blood flow measurements were planned by steady-state free precession (SSFP) single-shot imaging of the aorta and by multi plane reformatting of 3D-SSFP data for the SMA.[12] This took approximately 8-10 minutes. Planning was repeated after meal ingestion due to patient movement and displacement of abdominal contents by the meal. Aortic blood flow was measured above the coronary sinuses using cardiac-gated spiral phase-contrast MRI within a single breath hold.[14] SMA blood flow was measured by high spatial resolution (0.78 mm^2) RR-interval averaged golden-angle spiral phase-contrast imaging within a single breath hold

(Figure 1).[15] LV volume and mass were acquired from a stack of short axis cine images encompassing the heart from the apex to the atria using real time radial SSFP *k-t* SENSE during free breathing.[16] The average interval between bouts of MRI data acquisition was 7 minutes. The last imaging cycle started approximately 50 minutes after ingestion of the meal, resulting in a postprandial scanning time of ~1 hour. Total scanning time was ~90 minutes.

Images were processed offline using custom plugins for OsiriX v6.5.2 (Pixmeo, Bernex, Switzerland). LV myocardial volume was obtained by manual contouring and subtraction of the endocardial from the epicardial volume. Papillary muscles were included in the myocardial volume. LVM was calculated by multiplying myocardial volume by a density estimate of 1.05 $g.mL^{-1}$. Aortic flow measures from spiral triggered phase-contrast MRI were obtained by semi-automated, frame-wise segmentation of the magnitude and phase images. Mean SMA flow over a cardiac cycle was measured from a single phase-contrast image after defining the region of interest on the magnitude image (Figure 1).

Data standardization and allometric scaling

Body mass index (BMI) was calculated from weight and height and converted to age- and sex-specific z-scores using published data.[17] Overweight was defined as a BMI z-score ≥1.04 (85^{th} centile) and obesity as a BMI z-score of ≥1.64 (95^{th} centile), according to current guidelines.[18] Blood flow and stroke volume (SV) were indexed to height [m] raised to powers of 0.92 and 1.45, respectively (such variables are indicated by an "i" suffix, e.g. SVi).[19, 20] LVM was indexed to height [m] to the power of 2.7. These adjustments correct for the influence of skeletal size with minimal confounding by obesity and are preferred over adjustment for body surface area in this context.[7, 21] To address limitations of reference MRI data in children, we generated normal values within our study population using an established

technique.[7] First, LVMi was adjusted for age and sex by linear regression. LVH was defined as an adjusted LVMi above the 95th centile in a subpopulation with a normal BMI distribution (N=55, BMI z-score mean 0.17, SD 0.94, range -1.96 to 1.87). This centile and its 95% confidence interval were found by a bootstrap method. LVM to LV end-diastolic volume ratio (LVM:EDV) was calculated and an upper limit for this measure was defined using the same approach. Eccentric hypertrophy was defined as LVMi >95th centile and concentric hypertrophy was defined as LVM:EDV >95th centile and LVMi >95th centile.[7] In accordance with recent guidelines, elevated systolic BP (eSBP) was defined as systolic BP (SBP) >120 mmHg but <130 mmHg, and diastolic BP <80 mmHg. Hypertension was defined as systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg.[22]

Laboratory analysis

Blood samples were obtained using standard techniques, following at least 20 minutes of rest in the supine position. Samples were immediately centrifuged and stored at -80°C before batch analysis. Fasting glucose was measured using a Vitros 5600 Clinical Chemistry analyser (Ortho Clinical Diagnostics, Raritan, NJ, USA) and fasting insulin was determined using a chemiluminescent immunoassay (Immulite 2500, Siemens Diagnostics, Berlin, Germany).

Statistics

All statistics were performed using Stata SE v14.2 (StataCorp, College Station, TX, USA). To account for variations of synchronization between measures, BP and MRI data were linearly interpolated at 10-minute intervals, starting from the beginning of meal ingestion, and truncated at 50 minutes. Postprandial SMA flow response (ΔSMA) was calculated by area-under-the-curve (AUC) analysis using the trapezoidal rule on non-interpolated measures.

Each AUC was divided by the time difference between meal ingestion and the last measure, yielding a time-weighted mean to control for individual variations in experiment duration. ΔSMA was calculated by subtracting resting values from these means. Responses recorded for less than 40 minutes were excluded in the final model (n=7). Haemodynamic responses to the meal are presented initially both unindexed and indexed for a power of height to show that the findings do not depend on this adjustment. Changes in physiological data over time and the effect of sex and BMI z-score were assessed using repeated measures mixed models. These models account for the correlated nature of repeated measures over time. Marginal mean estimates were then calculated from these models at three values of BMI z-score representing the normal range (-2, 0, and +2) to illustrate the time-varying, continuous associations found in these models. The coefficients of these models for each time point after baseline represent the time-dependent change from baseline and their *P*-values represent the significance of that change. These *P*-values are reported to illustrate the significance of postprandial responses. Multiple linear regression was used to assess the effects of ΔSMA on LVM, independently of known determinants of LVM, i.e. sex, pubertal stage (self-assessed Tanner score),[23] BMI, age, resting SBP, SV and homeostatic model assessment of insulin resistance (HOMA-IR = [fasting glucose * fasting insulin] / 22.5). A similar model was used to assess the effects of ΔSMA on SBP accounting for the same potential confounders, except resting HR was included as an independent variable and BP was not. Logistic regression was used to determine the risk of LVH and eSBP on the basis of ΔSMA. These models were repeated with the inclusion of other potential determinants, as for LVM, to test for independent effects. Right-skewed data were log-transformed prior to parametric testing and group means were back-transformed to geometric means for presentation in natural units. Goodness-of-fit tests were carried out for linear and logistic models to ensure that our models did not contravene model assumptions. Comparison between normal weight and

overweight/obese groups was done using student *t*-tests. In order to determine intra- and interobserver variability, SMA flow data of 16 randomly selected cases were re-segmented by the original examiner and a second investigator, and intraclass correlation coefficients were calculated with 95%-confidence intervals (CI). Univariate associations were assessed by Pearson correlation. $P<0.05$ was considered statistically significant.

Results

Study population and cardiometabolic parameters at rest

Eighty-two participants were enrolled (36 female; median age 16 [IQR 14-18] years). Data from two participants who vomited during the MRI scan were excluded from longitudinal analyses. The remaining 80 completed the protocol without side-effects. Thirty participants were obese and a further 9 were overweight. At baseline, overweight/obese participants had significantly higher indexed cardiac output (COi), HOMA-IR, SBP, LVM and LVMi and lower indexed SMA flow (SMAi) than normal weight comparators (Table 1). They were also more likely to have LVH and eccentric hypertrophy, but not concentric hypertrophy, and they were more likely to have hypertension. Linear associations of BMI z-score with COi (r=0.39; $P=0.0003$), SVi (r=0.48; $P<0.0001$), SBP (r=0.30; $P=0.009$) and SMAi (r=–0.23; $P=0.04$), supported these findings. BMI z-score did not correlate with diastolic or mean BP, or HR.

Postprandial haemodynamics and associations with adiposity

Both unindexed and indexed mean CO increased significantly within 10 minutes of meal ingestion, plateaued at 40 minutes (time-weighted mean unindexed ΔCO 0.45 [SD 0.62] $L.min^{-1}$; $P=3.8x10^{-8}$) and did not fall significantly before the end of the experiment. The magnitude of this increase did not differ significantly by BMI z-score but baseline COi did ($P<0.001$; Figure 2).

Unindexed and indexed SMA flow increased too (time-weighted mean unindexed ΔSMA flow 0.76 [SD 0.35] $L.min^{-1}$; $P=4.2x10^{-31}$) and by more, on average, than CO did (mean difference in responses 0.31 $L.min^{-1}$; $P=5x10^{-5}$), suggesting that, in addition to the CO rise, some flow redistribution from other regions occurred to support increased flow demand in the mesenteric vascular bed. The magnitude of this response was blunted by increased adiposity ($P<0.05$ at 10 minutes and $P<0.01$ at 20, 30 and 50 minutes for the continuous interaction of time and BMI z-score; Figure 2). Both ΔSMA (B=-0.07 $L.min^{-1}$; $P=0.003$) and ΔSMAi (Figure 2) were blunted in those with greater BMI z-score.

SBP also rose in response to the meal (time-weighted mean Δ 1.96 mmHg; $P=7x10^{-5}$) and was significantly greater than baseline from 10 minutes onwards ($P<0.05$ at 10 minutes, $P<0.01$ at 30 minutes, and $P<0.001$ at 20, 40 and 50 minutes; Figure 2). Baseline SBP was associated with increased BMI z-score ($P=0.006$) but the magnitude of the postprandial response was not.

Associations of mesenteric vascular function with SBP and LV remodelling

Blunted ΔSMAi was associated with increased resting SBP (Table 2, Model 1; Figure 3). Addition of BMI (Model 2) and resting HR (Model 3) did not explain this association. Moreover, blunted ΔSMAi was associated with a significantly increased risk of hypertension (log likelihood: -20.3; odds ratio: 0.01 [95% CI: $7x10^{-4}$, 0.89], $P=0.045$; $R^2=0.11$), but not eSBP, a prehypertensive category in children ($P=0.33$).

Blunted ΔSMAi was associated with increased risks of LVH (log likelihood: -5.4; odds ratio: 0.005 [95% CI: $1x10^{-3}$, 0.219], $P=0.003$; $R^2=0.15$) and concentric hypertrophy (log likelihood: -9.9; odds ratio: 5x10-5 [95% CI: 4x10-8, 0.061], $P=0.001$; $R^2=0.31$), but not

eccentric hypertrophy (P=0.48). This was supported by an inverse linear association of ΔSMAi with LVMi (Table 2, Model 1; Figure 3). A similar association was found between the unindexed variables. Addition of BMI (Model 2) and of resting SBP (Model 3) to the multiple regression did not fully explain the association. In further modelling, all associations remained significant after addition of age, Tanner score, and HOMA-IR (Supplemental File: Table 1). Associations with LVMi were also independent of resting SVi and postprandial SBP response (time-weighted mean Δ).

Reliability analysis

Mesenteric blood flow measurements showed very good intra- and interobserver agreement, with intraclass correlation coefficients of 0.95 [95% CI: 0.86, 0.98] and 0.91 [95% CI: 0.76, 0.97], respectively.

Discussion

Given that LVH is a major risk factor for cardiovascular morbidity and mortality and that it appears early in the disease process, understanding factors that drive its emergence in young people is vital for the development of effective cardiovascular disease prevention. Abnormal (blunted) ΔSMA after ingestion of a high-calorie liquid meal was associated with concentric LVH, increased LV mass, higher resting BP, and hypertension in adolescents. These findings were independent of factors known to influence LV mass (age, sex, pubertal status, BMI, insulin resistance, SV and BP). Perhaps most importantly, the associations were not influenced by variation in progression through puberty and therefore are unlikely to be explained by altered sex hormone levels, which are known to influence LV mass.

Although our study cannot elucidate any mechanism causally linking postprandial vascular dysfunction in the gut with LVH, we found some supporting evidence in adolescents for a mechanism already detailed in rodents. Under fasting conditions, blood supply to the gut is centrally inhibited by sympathetic vasomotor outflow from the rostroventrolateral medulla.[10] Food ingestion normally suppresses the activity of these efferents via vagal feedback to the brainstem, increasing blood flow in the gut.[10, 24] Obesity and fatty diet in rodents have been shown to blunt this reflex, reducing vasodilatory responses.[10, 24] The authors suggested that increased afterload caused by raised splanchnic vascular resistance in this context could promote development of hypertension and LVH. We found that adolescent obesity was similarly associated with blunting of normal postprandial vasodilatory responses. Interestingly, blunted ΔSMA was associated with raised LVM independently of resting BP or postprandial BP responses, suggesting that the explanation for this association is probably more complex than previously suggested.[10, 24] For example, disordered neurohumoral signalling that affects both vascular function in the gut and cardiomyocyte growth could mediate this association. Our study was not designed to investigate such possibilities. The partial independence of our findings from the degree of adiposity is consistent with the observation that postprandial vascular dysfunction in high-fat fed rodents normalises with low-fat diet irrespective of weight loss and suggests a role for abnormal diet in the pathogenesis of postprandial vascular dysfunction.[24] The high-calorie meal used in this experiment was designed to replicate the worst excesses of a modern diet. Further study will be needed to determine how altering diet composition affects the postprandial response.

We generated and tested our primary hypothesis based on animal experiments[10, 11] and found that dysregulated vascular responses to high-calorie food ingestion were linked to known major cardiovascular risk factors. Secondary analyses have been carried out to address

possible explanations of these associations and generate new hypotheses. These showed that our findings were robust to adjustment for a range of possible confounders and support the need for further study to determine underlying pathophysiological mechanisms. Nevertheless, there are potentially important clinical implications. We found that vascular dysregulation was more common in overweight/obese individuals. This supports existing advice to reduce high-calorie food intake in adolescents and is evidence for a potential new pathway linking obesity and LVH in young people. Notably, high BMI in a cohort of Swedish adolescents has been shown to be a particularly strong risk for future heart failure, with hazard ratios approaching 10 for those with a BMI above 35.[4] Further investigation of the mechanism behind the findings of the present study could, therefore, yield new opportunities for prevention of the cardiac and vascular consequences of poor diet and obesity in the young.

Blunted postprandial mesenteric blood flow responses were associated with concentric LVH, but not other patterns of LVH. Although the relationship between patterns of LVH and underlying pathology is not fully understood,[25] concentric LVH in animal models arises largely as a compensatory mechanism to normalise LV wall stress in response to pressure overload. This would be consistent with our finding that blunted ΔSMA was related to increased resting BP and hypertension. However, relationships of blunted ΔSMA with LVMi and concentric LVH were not fully explained by resting BP status. Therefore, the mechanism of concentric LVH development in this context may not be simply due to increased LV afterload. Irrespective of the mechanism, abnormal mesenteric vascular function is an independent biomarker for a phenotype prone to LVH and, possibly therefore, to cardiovascular disease.

This study had several strengths. We used a standardised, validated MRI food challenge protocol of high-fat, high-sugar food.[12] Diets high in fat and sugar are now common in the modern era, particularly in the obese, and have been implicated in LVH development.[26] We controlled for time of day, caffeine, exercise and other potential confounders. Cardiovascular measures were standardised using allometric scaling approaches that have been shown to minimise the confounding effect of obesity. Each participant ate a standard meal and then fasted for a similar duration. Acquisition of SMA flow data using conventional cardiac-gated cine phase-contrast MRI typically requires long imaging times (~8 minutes) and respiratory navigation, due to the high spatial resolution needed for this small vessel. Such conventional flow acquisition is poorly suited for generating accurate, repeated measures of the postprandial flow response, in a time-efficient manner. We used RR-interval averaged imaging to overcome this problem and allow rapid data acquisition at high spatial resolution. Very good reliability has been demonstrated for this method.

Limitations

Accurate definition of LVH on the basis of MRI measures in childhood is challenging. No published paediatric reference ranges are adjusted for a power of height and existing references are based on small populations. This and widespread variations in imaging and image segmentation techniques mean that current published MRI LVM normal values in adolescents are not a reliable reference. To address this issue, and recognising that our sample of normal adolescents is larger than many such reference populations, we defined a normal range for LVM in our population and adjusted for age and sex in order to minimise their influence on the normal distribution. Because our study cohort was partly recruited from an obesity clinic, this normal range was defined in a subpopulation with a normally distributed BMI range.[7]

The nature of the associations shown and their direction, if causal, remain unknown. Longitudinal studies will be required to confirm whether obesity is a cause of postprandial vascular dysfunction, or *vice-versa*, and if the latter is a cause of LVH. However, we have demonstrated that LVH emerges to a significant degree even in otherwise healthy adolescent populations. Therefore, the timeframe for such follow-up studies is achievable. If confirmed, mechanistic studies are required to determine how postprandial vascular function might lead to LVH in humans. Our findings support those of mechanistic studies in animals, demonstrating the need for further human studies.

Conclusion

We showed that abnormal splanchnic vascular responses to high-calorie food ingestion could be observed in otherwise healthy teenagers. Such a response was linked to greater adiposity and was found to be strongly associated with LVH, increased LV mass, raised resting BP and hypertension, independently of known determinants of LVH. This is the first evidence of a new, independent marker of cardiovascular risk in the young.

Acknowledgements

We thank Wendy Norman, Rod Jones, Steven Kimberley, and the NIHR BRC at Great Ormond Street Hospital for able assistance with the study as well as Dave Miller of Cargill Starches & Sweeteners for kind donation of food-grade maltose syrup.

This report also incorporates independent research from the National Institute for Health Research Biomedical Research Centre Funding Scheme at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London. The views expressed in this

publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health.

Sources of Funding: Alexander Jones is supported by a British Heart Foundation Intermediate Clinical Research Fellowship (FS/18/22/33479). Jakob Hauser is funded as part of the Framework Package-7 project MD-PAEDIGREE of the European Commission (contract no. 600932).

Conflict of Interest: none.

References

1. Wade KH, Chiesa ST, Hughes AD, Chaturvedi N, Charakida M, Rapala A, Muthurangu V, Khan T, Finer N, Sattar N et al. Assessing the causal role of body mass index on cardiovascular health in young adults: Mendelian randomization and recall-by-genotype analyses. *Circulation*. 2018;138:2187-2201.

2. Hoang K, Zhao Y, Gardin JM, Carnethon M, Mukamal K, Yanez D and Wong ND. LV Mass as a Predictor of CVD Events in Older Adults With and Without Metabolic Syndrome and Diabetes. *JACC Cardiovasc Imaging*. 2015;8:1007-1015.

3. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL and Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol*. 2008;52:2148-55.

4. Rosengren A, Aberg M, Robertson J, Waern M, Schaufelberger M, Kuhn G, Aberg D, Schioler L and Toren K. Body weight in adolescence and long-term risk of early heart failure in adulthood among men in Sweden. *Eur Heart J*. 2017;38:1926-1933.

5. de Simone G, Devereux RB, Roman MJ, Schlussel Y, Alderman MH and Laragh JH. Echocardiographic left ventricular mass and electrolyte intake predict arterial hypertension. *Ann Intern Med*. 1991;114:202-9.

6. Brady TM. The Role of Obesity in the Development of Left Ventricular Hypertrophy Among Children and Adolescents. *Curr Hypertens Rep*. 2016;18:3.

7. Jing L, Binkley CM, Suever JD, Umasankar N, Haggerty CM, Rich J, Wehner GJ, Hamlet SM, Powell DK, Radulescu A et al. Cardiac remodeling and dysfunction in childhood obesity: a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson*. 2016;18:28.

8. Stewart MH, Lavie CJ, Shah S, Englert J, Gilliland Y, Qamruddin S, Dinshaw H, Cash M, Ventura H and Milani R. Prognostic Implications of Left Ventricular Hypertrophy. *Prog Cardiovasc Dis*. 2018;61:446-455.

9. de Onis M, Blossner M and Borghi E. Global prevalence and trends of overweight and obesity among preschool children. *Am J Clin Nutr*. 2010;92:1257-64.

10. Sartor DM. Sympathoinhibitory signals from the gut and obesity-related hypertension. *Clin Auton Res*. 2013;23:33-9.

11. How JM, Pumpa TJ and Sartor DM. Renal sympathoinhibitory and regional vasodilator responses to cholecystokinin are altered in obesity-related hypertension. *Exp Physiol*. 2013;98:655-64.

12. Hauser JA, Muthurangu V, Steeden JA, Taylor AM and Jones A. Comprehensive assessment of the global and regional vascular responses to food ingestion in humans using novel rapid MRI. *Am J Physiol Regul Integr Comp Physiol*. 2016;310:R541-5.

13. Sharrett AR, Heiss G, Chambless LE, Boerwinkle E, Coady SA, Folsom AR and Patsch W. Metabolic and lifestyle determinants of postprandial lipemia differ from those of fasting triglycerides: The Atherosclerosis Risk In Communities (ARIC) study. *Arterioscler Thromb Va c Biol*. 2001;21:275-81.

14. Steeden JA, Atkinson D, Hansen MS, Taylor AM and Muthurangu V. Rapid flow assessment of congenital heart disease with high-spatiotemporal-resolution gated spiral phase-contrast MR imaging. *Radiology*. 2011;260:79-87.

15. Steeden JA and Muthurangu V. Investigating the limitations of single breath-hold renal artery blood flow measurements using spiral phase contrast MR with R-R interval averaging. *J Magn Reson Imaging*. 2015;41:1143-9.

16. Muthurangu V, Lurz P, Critchely JD, Deanfield JE, Taylor AM and Hansen MS. Real-time assessment of right and left ventricular volumes and function in patients with congenital heart disease by using high spatiotemporal resolution radial k-t SENSE. *Radiology*. 2008;248:782-91.

17. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C and Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ*. 2007;85:660-7.

18. Barlow SE and Expert C. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. 2007;120 Suppl 4:S164-92.

19. de Simone G, Devereux RB, Daniels SR, Mureddu G, Roman MJ, Kimball TR, Greco R, Witt S and Contaldo F. Stroke volume and cardiac output in normotensive children and adults. Assessment of relations with body size and impact of overweight. *Circulation*. 1997;95:1837-43.

20. de Simone G, Devereux RB, Daniels SR, Koren MJ, Meyer RA and Laragh JH. Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. *J Am Coll Cardiol*. 1995;25:1056-62.

21. Armstrong AC, Gidding S, Gjesdal O, Wu C, Bluemke DA and Lima JA. LV mass assessed by echocardiography and CMR, cardiovascular outcomes, and medical practice. *JACC Cardiovasc Imaging*. 2012;5:837-48.

22. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics*. 2017;140.

23. Carel JC and Leger J. Clinical practice. Precocious puberty. *N Engl J Med*. 2008;358:2366-77.

24. Sfrantzis KD, How JM and Sartor DM. Implications of diet modification on sympathoinhibitory mechanisms and hypertension in obesity. *Auton Neurosci*. 2015;189:25-30.

25. Drazner MH. The progression of hypertensive heart disease. *Circulation*. 2011;123:327-34.

26. Sharma N, Okere IC, Duda MK, Chess DJ, O'Shea KM and Stanley WC. Potential impact of carbohydrate and fat intake on pathological left ventricular hypertrophy. *Cardiovasc Res*. 2007;73:257-68.

Figures

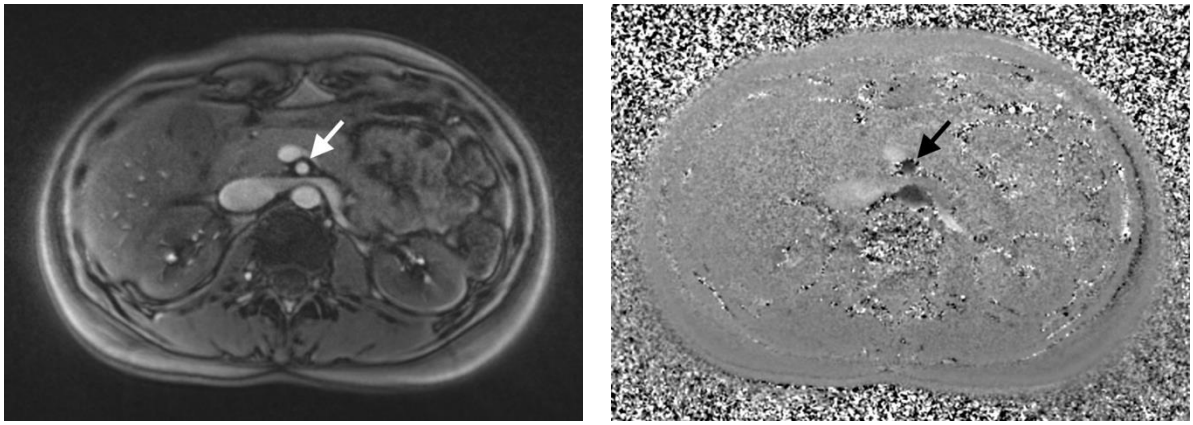

Figure 1. RR-interval averaged golden-angle spiral phase-contrast MRI of the superior mesenteric artery (arrow). This technique acquires data over ~5 RR intervals to yield a single “time-averaged” image that can be used to calculate mean flow through a vessel (resolution 0.78 x 0.78 mm, breath hold ~6 seconds).

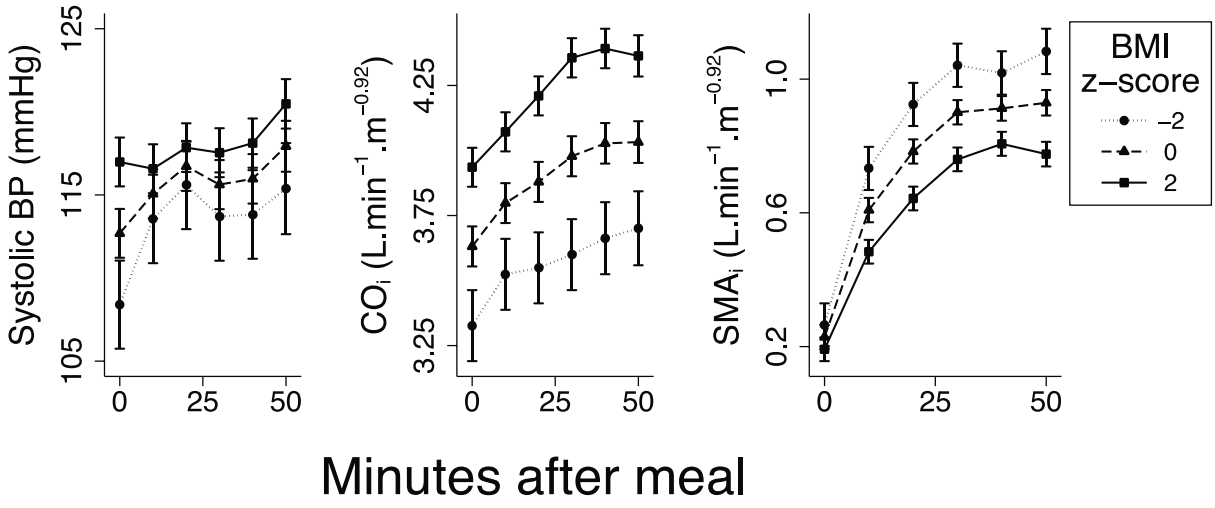

Figure 2. Marginal mean (±SE) postprandial systolic blood pressure (BP), indexed cardiac output (COi) and indexed superior mesenteric artery (SMAi) flow responses in relation to adiposity. Systolic BP and COi were significantly greater than baseline from 10 minutes onwards but the magnitudes of these responses were not associated with BMI z-score. SMAi also rose significantly and the magnitude of this response was blunted by increased adiposity (see Results section for comparisons of individual time points with baseline values). BMI = body mass index.

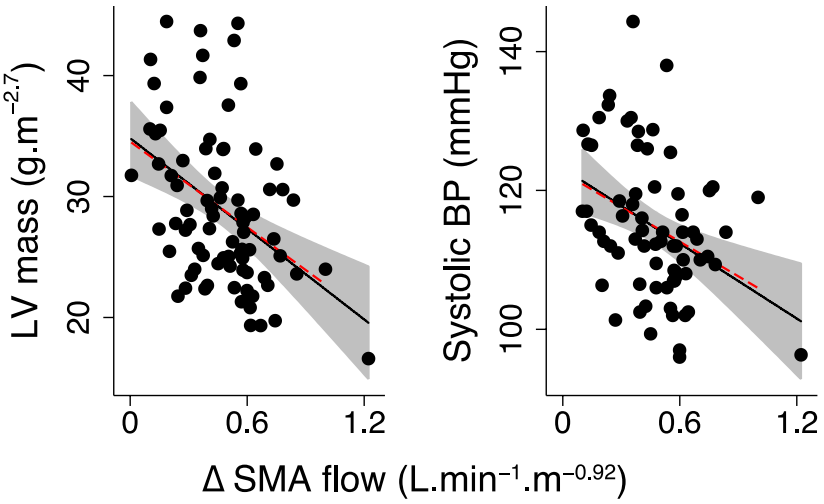

Figure 3. Inverse relationships of postprandial superior mesenteric artery flow response (ΔSMAi) with left ventricular (LV) mass index and resting systolic blood pressure (BP). Graphs show the unadjusted models (r=-0.43, *P*=0.0001 for LV mass, and r=-0.32, *P*=0.006 for systolic BP). The associations were robust to adjustment for a range of potential confounders (Table 2 & Supplemental File: Table 1) and to exclusion of the rightmost point on the graphs. Solid lines show linear regressions, dashed lines show effect of removing rightmost point, and 95% CIs are shown as grey bands.

Tables

Table 1. Mean (SD) cardiometabolic measures in normal weight and overweight/obese adolescents

	All	**Normal weight**	**Overweight / obese**	***P***
N	82	43	39	
Age (years)	16.2 (2.0)	16.1 (1.9)	16.3 (2.1)	0.814
Female	36 (43.9%)	20 (46.5%)	16 (41.0%)	0.617
BMI*	24.6 (7.5)	20.0 (2.4)	31.0 (6.6)	$7x10^{-17}$
BMI z-score	1.0 (1.6)	-0.2 (0.8)	2.5 (1.1)	$1x10^{-21}$
HOMA-IR*	1.44 (2.87)	0.92 (1.17)	2.18 (3.77)	0.003
LVH	11 (13.4%)	1 (2.3%)	10 (25.6%)	0.002
LV concentric hypertrophy	6 (7.3%)	1 (2.3%)	5 (12.8%)	0.068
LV eccentric hypertrophy	5 (6.1%)	0	5 (12.8%)	0.015
LV mass (g)	122.9 (36.9)	109.0 (30.8)	138.3 (37.4)	$5x10^{-3}$
LV mass ($g.m^{-2.7}$ height)	28.8 (6.5)	26.3 (4.8)	31.6 (7.1)	$2x10^{-3}$
Hypertension	7 (9.5%)	1 (2.6%)	6 (17.1%)	0.032
eSBP	12 (16.2%)	5 (12.8%)	7 (20.0%)	0.403
Pre-prandial, resting cardiovascular measures				
Systolic BP (mmHg)	114.6 (10.4)	111.7 (8.5)	117.7(11.5)	0.013
COi ($L.min^{-1}.m^{-0.92}$)	3.8 (0.7)	3.6 (0.7)	4.1 (0.5)	$5x10^{-3}$
HR (bpm)	68.1 (11.1)	68.3 (11.7)	67.8 (10.5)	0.839
SMAi ($L.min^{-1}.m^{-0.92}$)*	0.17 (0.12)	0.21 (0.13)	0.15 (0.12)	0.041
Post-prandial, time-weighted mean (AUC) cardiovascular responses				
∆Systolic BP (mmHg)	2.0 (4.0)	2.5 (3.5)	1.4 (4.5)	0.213

ΔCOi (L.min^{-1}.m$^{-0.92}$)	0.28 (0.38)	0.25 (0.35)	0.31 (0.42)	0.579
ΔHR (bpm)	5.0 (4.5)	5.5 (4.5)	4.4 (4.6)	0.160
ΔSMAi (L.min^{-1}.m$^{-0.92}$)	0.47 (0.22)	0.51 (0.23)	0.41 (0.18)	0.031

P-values are for comparisons with normal weight group by student *t*-test (except X^2 for sex and BP and LVH parameters). *Geometric mean. BMI = body mass index; BP = blood pressure; CO = cardiac output; eSBP = elevated systolic BP; HOMA-IR = homeostatic model assessment of insulin resistance; HR = heart rate; LV = left ventricle; LVH = LV hypertrophy; SMA = superior mesenteric artery.

Table 2. Associations of postprandial superior mesenteric artery blood flow response (ΔSMAi) with systolic blood pressure (SBP) and left ventricular (LV) mass.

	Resting SBP (mmHg)				LV Mass ($g.m^{-2.7}$ height)			
	B	**95% CI**	***P***	**R^2**	**B**	**95% CI**	***P***	**R^2**
Model 1								
ΔSMAi ($L.min^{-1}.m^{-0.92}$)	**-18.0**	**-28.5, -7.4**	**0.001**	**0.17**	**-12.7**	**-18.6, -6.8**	**$6x10^{-5}$**	**0.24**
Female	-3.8	-8.3, 0.8	0.10		-3.2	-5.8, -0.6	0.02	
Model 2								
ΔSMAi ($L.min^{-1}.m^{-0.92}$)	**-16.0**	**-26.8, -5.2**	**0.004**	**0.22**	**-8.7**	**-14.0, -3.4**	**0.002**	**0.45**
Female	-4.1	-8.6, 0.4	0.07		-3.1	-5.3, -0.9	0.007	
BMI	0.3	-0.0, 0.6	0.06		0.4	0.3, 0.6	$1x10^{-6}$	
Model 3								
ΔSMAi ($L.min^{-1}.m^{-0.92}$)	**-16.5**	**-27.7, -5.3**	**0.004**	**0.24**	**-7.8**	**-13.4, -2.1**	**0.008**	**0.56**
Female	-4.0	-8.5, 0.4	0.08		-3.9	-6.1, -1.6	0.001	
BMI	0.3	0.0, 0.6	0.04		0.5	0.4, 0.7	$2x10^{-8}$	
Resting heart rate (bpm)	0.1	-0.1, 0.3	0.26		-	-	-	
Resting SBP (mmHg)	-	-	-		0.0	-0.1, 0.2	0.54	

Multiple linear regression analysis to assess the independent influence of potential determinants of LV mass and resting SBP. Further models (Supplemental File: Table 1) showed that these associations were robust to adjustment for age, Tanner score, stroke volume and HOMA-IR (for LV mass). BMI = body mass index; HOMA-IR = homeostatic model assessment of insulin resistance.