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Functional and metabolic imaging of the cardiovascular system in young healthy South Asians and white Caucasians unveils early differences

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ABSTRACT

Background. South Asians have a higher risk of developing cardiovascular disease than white Caucasians. Since the mortality risk of cardiovascular disease associated with type 2 diabetes is higher in South Asians, the excess cardiovascular disease risk in this group might be due to inherent ethnicity-associated structural cardiac diseases and/or a higher cardiac susceptibility to metabolic disorders. Therefore, this study assessed whether cardiac dimensions and cardiovascular function differ between young South Asians and white Caucasians and whether there is a differential response to a high fat diet.

Methods. Cardiac dimensions and cardiovascular function were assessed using a 1.5T-MRI-scanner in 12 young, healthy South Asian and 12 matched white Caucasian men. Both groups were subjected to a 5-day high fat high calorie diet (HFHCD) to study cardiac response to metabolic stress.

Results. At baseline South Asians had lower left ventricular mass (p<0.001) and end-diastolic volume (p<0.001), indexed for body surface area, than Caucasians. Furthermore, differences in cardiac function profile were observed. E acceleration peak (p=0.010) and E deceleration peak (p=0.005) were lower in South Asians. Additionally, South Asians had lower acceleration (p=0.001) and deceleration peak flows (p<0.001) over the aorta. A 5-day HFHCD did not increase these differences. Finally, pulse wave velocity at baseline was higher in South Asians (p=0.022), which normalized after the diet.

Conclusions. Young, healthy South Asians have smaller cardiac dimensions and a different cardiovascular function profile than white Caucasians. A 5-day HFHCD did not increase these differences, suggesting these findings cannot be explained by a different metabolic response to dietary fat.
Cardiovascular function in young South Asians

INTRODUCTION

People of South Asian descent, originating from the Indian subcontinent, represent one fifth of the world’s population. South Asians are at an increased risk of developing cardiovascular disease compared to white Caucasians. The age-standardized mortality rate from cardiovascular disease is around 50% higher for South Asians than for white Caucasians. Furthermore, the mean age of first acute myocardial infarction is approximately five years earlier in South Asians than in Caucasians. Moreover, cardiovascular disease in this population is more aggressive and has higher mortality rates at younger ages.

The differences in cardiovascular disease prevalence and severity between both ethnicities cannot be explained by traditional risk factors, such as smoking, hypertension and cholesterol levels. Since insulin resistance and type 2 diabetes mellitus are highly prevalent in South Asians and the mortality risk of cardiovascular disease associated with type 2 diabetes is higher in this ethnicity compared to Caucasians, the increased cardiovascular disease risk might be related to inherent ethnicity-associated structural cardiac features and/or a higher susceptibility to detrimental metabolic changes as reflected by ectopic fat deposition in organs such as the heart, liver and skeletal muscle.

Little is known about differences in cardiovascular function between South Asians and Caucasians at a relatively young age. In a previous study, in which cardiac function was assessed with echocardiography, middle-aged South Asians had attenuated longitudinal left ventricular (LV) function, higher LV filling pressure and a greater degree of concentric remodelling compared to Caucasians. Whether these findings are related to the increased cardiovascular disease risk, however, remains to be determined.

The aim of the present study was to assess whether differences in cardiac dimensions, cardiovascular function, and myocardial triglyceride (TG) content are present between young, healthy South Asians and matched Caucasians using Magnetic Resonance (MR) Imaging (MRI) and Spectroscopic (MRS) techniques. In addition, we measured abdominal fat distribution and hepatic TG content. We hypothesized that possible differences in cardiovascular function between South Asians and Caucasians can be attributed to a higher cardiac susceptibility to metabolic disorders in South Asians. In a previous study, short-term high fat feeding decreased diastolic function. If the differences in cardiovascular function and dimensions in South Asians can indeed be attributed to a higher susceptibility to metabolic stress, a high fat high calorie diet (HFHCD) may have more profound effects on cardiovascular function in this ethnicity than in white Caucasians. Therefore, we subjected the participants to a 5-day HFHCD.
METHODS

Subjects
Twelve Dutch South Asian and twelve Dutch Caucasian healthy men matched for age (19-25 years) and BMI (<25 kg/m²), with a positive family history for type 2 diabetes were enrolled. Exclusion criteria were: any significant chronic disease (including type 2 diabetes), use of medication known to influence glucose and/or lipid metabolism, smoking, recent weight change and general contraindications to MR-scanning. Subjects were recruited via advertisements in newspapers. The study was approved by the local ethics committee and performed in accordance with the principles of the revised Declaration of Helsinki. Written informed consent was obtained from all subjects.

Study design
The study consisted of 2 occasions separated by a 5-day HFHCD. The HFHCD consisted of the subject’s regular diet, supplemented with 375 mL of cream per day (=1275 kcal/day, 94% fat), yielding to around 3775 kcal/day and 54% of fat. Subjects underwent MRI/MRS shortly before the start of the HFHCD and at the end of the 5th day of the diet. Participants were instructed not to alter lifestyle habits. Anthropometric measurements and blood samples were obtained on both occasions after a 10-hour overnight fast.

MR protocol
All measurements were performed on a 1.5-Tesla MR-scanner (Gyroscan ACS-NT15; Philips Medical Systems, The Netherlands) in supine position, and were made in post-prandial state (four hours after the last meal).

Left ventricular dimensions and function
Data were analysed blinded for ethnicity and study occasion.

The heart was imaged in short-axis orientation, using electrocardiographically gated breath-hold cine steady-state free-precession sequences as previously described. Imaging parameters were: repetition time (TR) 3.4ms, echo time (TE) 1.7ms, flip angle (FA) 35°, field of view (FOV) 400×320mm, and slice thickness 10mm, no slice gap was used. Epicardial and endocardial left ventricular (LV) contours were manually drawn in the end-systolic and end-diastolic phases of the short-axis data, using validated MASS® software (Medis, Leiden, The Netherlands). LV end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), stroke volume (SV) and end-diastolic mass (EDM) were assessed. We divided LVEDM by LVEDV to obtain the LVEDM/LVEDV ratio (also known as concentricity). Volumes and mass were indexed (I) for body surface area (BSA).

We calculated LV end systolic wall stress (LVESWS) with the formula 0.133*systolic blood pressure*(3xESV/wall volume)+1).
For assessment of LV diastolic function, transmitral flow was measured, using electrocardiographically gated gradient echo sequence with a velocity sensitivity of 100 cm/sec (TR 9.1ms, TE 1.0ms, FA 20º, slice thickness 8mm, FOV 350mm², matrix 256x256 pixels). Flow velocities in early diastole (E) and at atrial contraction (A) were measured.

**Figure 1. Panel A: Mitral valve flow curve. Panel B and C: Aortic flow curve.**

Panel A shows an example of the flow through the mitral valve, representing diastolic cardiac function. The black line represents a South Asian subject, the dotted line a Caucasian subject. These curves suggest that cardiac relaxation is prolonged in South Asians.

Panel B shows how aortic flow parameters are assessed. * is the AO peak flow rate. Acceleration duration is the time between the beginning of the flow curve and the peak flow rate. The deceleration duration is the time between the peak flow rate and the end of the deceleration period. The acceleration peak is the peak slope (dy/dx) of the acceleration phase, the deceleration peak the peak slope (dy/dx) of the deceleration phase.

Panel C shows an example of flow velocity curve through the ascending aorta. The black line represents a typical curve of a South Asian subject, the dotted line of a Caucasian subject: the cardiac contraction is somewhat prolonged in South Asians.
and their peak flow ratio was calculated (E/A ratio) using FLOW® software (Medis, Leiden, The Netherlands). Furthermore the peak deceleration gradient of E, the E/A peak ratio and LV filling pressures E/Ea were determined.\textsuperscript{15,16} Heart rate was monitored and stored during the transmitral flow measurements.

As a measurement of more subtle changes in systolic function of the heart, aortic flow curves were acquired, using electrocardiographically gated gradient echo sequence with a velocity sensitivity of 150 cm/sec (TR 5.0ms, TE 1.0ms, FA 20°, slice thickness 8mm, FOV 300mm\(^2\), matrix 128x128 pixels). Flow velocities in the ascending aorta at the level of the pulmonary trunk were measured and calculated using FLOW® software (Medis, Leiden, The Netherlands). The peak slope of the acceleration (aortic (AO) acceleration peak) and deceleration (AO deceleration peak) of the aortic flow curve were calculated. Furthermore, AO duration, AO peak filling rate and AO deceleration duration were determined (Figure 1B).

**Pulse Wave Velocity**

Aortic PWV was determined for the evaluation of aortic stiffness, using a previously described protocol.\textsuperscript{17} In short, a scout view of the aorta was performed. Next, a velocity encoded image perpendicular to the ascending aorta at the level of the pulmonary trunk, and at the level of the aortic bifurcation was assessed. This resulted in through-plane flow measurements of the ascending and descending aorta. Scan parameters were: TR 5.0ms, TE 1.0ms, flip angle 20°, FOV 300mm, 128x128 acquisition matrix, slice thickness 8mm, with maximal number of phases reconstructed ensuring high (6-10ms) effective temporal resolution. True temporal resolution is defined as 2 times TR = 10ms. PWV was calculated using the formula: \(\frac{\Delta x}{\Delta t}\), where \(\Delta x\) describes the aortic path length between two measurement sites and \(\Delta t\) describes the transit time between the arrival of the PWV at three respective sites. The distance between the measurement sites was manually determined by drawing a poly-line in the centre of the aorta as defined in a double-oblique parasagittal aortic scout view, using the software package MASS®. Data were analysed using MASS\textsuperscript{®} and FLOW® (Medis, Leiden, The Netherlands).

**Myocardial and liver triglyceride content**

MR spectroscopy (\(\text{\textsuperscript{1}H-MRS}\)) was used to quantify myocardial and hepatic TG content. Details on \(\text{\textsuperscript{1}H-MRS}\) acquisition and post processing were published before.\textsuperscript{18,19} In short, myocardial and hepatic \(\text{\textsuperscript{1}H-MR}\) single voxel MR spectroscopic data were acquired using a point resolved spectroscopy sequence. For the heart an 8-mL voxel was positioned in the interventricular septum on four-chamber and short-axis images in end-systole, avoiding contamination from epicardial fat. Electrocardiographically triggering (only for myocardial spectra) and respiratory pencil beam navigator were used during acquisition.\textsuperscript{18} For the liver, voxel sites were matched at both study occasions, avoiding
blood vessels and bile ducts. Main acquisition parameters for water suppressed spectra were: TE 26ms, TR 3000ms, 1,024 data points, spectral bandwidth 1,000-Hz, 128 averages. Acquisitions were performed with and without (TE 10000ms, 4 averages) water suppression, with myocardial TG expressed as percentage of the unsuppressed water signal. Hepatic ¹H-MRS was performed using the same acquisition parameters, except for 64 averages for the suppressed spectrum. Java-based MR user interface software (jMRUI v2.2, Leuven, Belgium) was used for fitting of the spectra.¹⁹ The TG content was calculated as the amplitude of the (TG signal/amplitude of water signal)*100.

**Visceral and subcutaneous fat**

Abdominal visceral and subcutaneous fat volumes were imaged using a turbo spin echo imaging sequence.²⁰ During one breath-hold, three consecutive transversal slices of 10mm thickness were scanned at level of L5 (TR 168ms, TE 11ms, FA 90°). Volumes of visceral and subcutaneous fat depots were quantified using MASS® software (Medis, Leiden, The Netherlands). Visceral and subcutaneous fat areas of each individual slice were multiplied by the slice thickness to acquire a volume and the volumes of all three slices were summed.

**Assays**

Serum concentrations of glucose, total cholesterol, HDL and triglycerides were measured on a Modular P800 analyser (Roche, Netherlands), and serum insulin levels on an Immulite 2500 (Siemens, The Netherlands). HbA₁c was measured on an HPLC system (Kordia, The Netherlands). Plasma free fatty acids (FFAs) concentrations were measured by a commercial kit (Wako Chemicals, Germany).

**Statistical analysis**

Data are presented as mean ± SEM or median (interquartile range (IQR)). A mixed model was applied to assess mean differences before and after the intervention within and between groups, and to assess differences in diet effect. Nonparametric tests (Wilcoxon signed-rank test within group, Mann-Whitney between groups) were performed when appropriate. Significance level was set at p < 0.05. Statistical analyses were performed using SPSS for Windows version 20.0 (IBM, USA).

**RESULTS**

**Clinical and metabolic characteristics**

Mean age was 22.1 ± 0.4 years. BSA was lower in South Asians. As expected, BMI did not differ between groups (South Asians: 20.9 ± 0.6 kg/m² vs. Caucasians: 22.2 ± 0.6
kg/m² (p=0.11)), but South Asians were shorter and weighed less. After the HFHCD a very small increase in BMI and weight to a similar extent in both groups was observed. Waist circumference did not differ between groups. Blood pressure and heart rate were comparable between groups and did not change after the HFHCD (Table 1).

HbA₁c was higher in South Asians. Fasting glucose, insulin levels and HOMA-B, a measure for pancreas function, were comparable at baseline, but were significantly higher in South Asians after the diet. FFAs were comparable between groups and no diet effect was found. LDL-cholesterol was slightly higher in South Asians, whereas other lipid levels did not differ significantly (Table 1).

### Table 1. Clinical and metabolic characteristics

|                      | white Caucasians | South Asians |            |            |
|----------------------|-----------------|--------------|------------|------------|
|                      | before HFHCD    | after HFHCD   | before HFHCD | after HFHCD |
| **Clinical characteristics** |                 |              |            |            |
| age (years)          | 22.1 ± 0.6      | 22.2 ± 0.7   | 22.1 ± 0.6 | 22.2 ± 0.7 |
| height (m)           | 1.84 ± 0.01     | 1.74 ± 0.02**| 1.74 ± 0.02** | 1.84 ± 0.01 |
| weight (kg)          | 75.1 ± 1.8      | 75.6 ± 1.8   | 63.2 ± 2.3**| 63.7 ± 2.3**|
| BSA (m²)             | 1.97 ± 0.02     | 1.98 ± 0.02  | 1.76 ± 0.04**| 1.76 ± 0.04**|
| BMI (kg/m²)          | 22.2 ± 0.6      | 22.4 ± 0.6   | 20.9 ± 0.6 | 21.0 ± 0.6**|
| waist (cm)           | 81 ± 2          | 82 ± 2       | 79 ± 2     | 80 ± 3     |
| systolic BP (mmHg)   | 135 ± 3         | 133 ± 3      | 129 ± 3   | 129 ± 3    |
| diastolic BP (mmHg)  | 79 ± 3          | 80 ± 2       | 76.8 ± 2.3| 76 ± 2     |
| heart rate (bpm)     | 65 ± 2          | 64 ± 2       | 61 ± 2    | 66 ± 3     |
|                      |                 |              |            |            |
| **Metabolic characteristics** |                 |              |            |            |
| HbA₁c (%)            | 5.02 ± 0.06     | 5.24 ± 0.05* |            |            |
| HbA₁c (mmol/mol)     | 31.2 ± 0.5      | 33.8 ± 0.6*  |            |            |
| glucose (mmol/L)     | 5.09 ± 0.09     | 5.22 ± 0.07  | 5.26 ± 0.09| 5.53 ± 0.08**|
| insulin (pmol/L)     | 16 (24)         | 30 (37)      | 30 (26)   | 52 (31)**  |
| HOMA-B%              | 52 ± 11         | 55 ± 10      | 65 ± 14   | 90 ± 11**  |
| free fatty acids (mmol/L) | 0.46 ± 0.05 | 0.43 ± 0.04  | 0.51 ± 0.04| 0.54 ± 0.05|
| triglycerides (mmol/L) | 0.79 (0.26) | 0.75 (0.67)  | 1.01 (0.65)| 1.12 (0.77)|
| total cholesterol (mmol/L) | 3.10 (1.80) | 4.34 (2.21)  |            |            |
| HDL-cholesterol (mmol/L) | 1.05 (0.35) | 1.02 (0.38)  |            |            |
| LDL-cholesterol (mmol/L) | 1.84 (0.91) | 2.77 (1.69)* |            |            |
| total cholesterol/HDL ratio | 3.00 (0.80) | 4.05 (2.48)  |            |            |

Data are presented as mean ± SEM or median (IQR). BSA, body surface area; BMI, body mass index; BP, blood pressure. † p<0.05, †† p<0.05 within groups. * p<0.05, ** p<0.005 between groups. § p<0.05, §§ p<0.005 diet effect between groups.
Left ventricular dimensions and function

At baseline all cardiac left ventricular dimensions indexed for BSA, i.e. EDVI, ESVI, SVI, CI and EDMI, were lower in South Asians than in Caucasians (Table 2). EF did not differ between groups at baseline. In addition, LVESWS and LVEDM/LVEDV were comparable (Table 2).

Table 2. Cardiac dimensions and parameters of cardiovascular function assessed with MRI before and after a 5-day HFHCD.

| Cardiac dimensions and basic function | white Caucasians | South Asians |
|--------------------------------------|------------------|--------------|
|                                      | before HFHCD     | after HFHCD   | before HFHCD | after HFHCD |
| LVEDMI (g/m²)                        | 62.2 ± 1.2       | 62.0 ± 1.5   | 50.7 ± 1.4** | 50.0 ± 1.3**|
| EDVI (mL/m²)                         | 102.2 ± 3.0      | 102.7 ± 2.8  | 83.3 ± 3.4** | 81.5 ± 2.9**|
| ESVI (mL/m²)                         | 42.8 ± 2.1       | 42.3 ± 2.4   | 33.9 ± 2.0** | 33.1 ± 1.7**|
| SVI (mL/m²)                          | 59.4 ± 2.2       | 60.4 ± 1.3   | 49.3 ± 2.1** | 48.3 ± 1.7**|
| CI (mL/min/m²)                       | 3.8 ± 0.3*10¹   | 3.8 ± 0.2*10³| 3.0 ± 0.1*10³**| 3.2 ± 0.2*10³*|
| EF (%)                               | 58.2 ± 1.5       | 59.1 ± 1.4   | 59.4 ± 1.4   | 59.4 ± 1.1  |
| LVESWS (kN/m²)                       | 56.3 ± 1.4       | 55.4 ± 2.1   | 53.0 ± 1.8   | 52.4 ± 1.2  |
| LVEDM/EDV (g/mL)                     | 0.61 ± 0.02      | 0.61 ± 0.02  | 0.62 ± 0.02  | 0.62 ± 0.02|

Systolic cardiac function

| AO peak filling rate (mL/s)          | 538 ± 17         | 549 ± 18     | 404 ± 17**   | 429 ± 14**  |
| AO acceleration peak (mL/s²*10⁻³)   | 13.1 ± 0.5       | 13.6 ± 0.7   | 10.6 ± 0.4** | 12.6 ± 0.5*|
| AO acceleration duration (ms)       | 101 ± 3          | 99 ± 4       | 91 ± 2*      | 88 ± 3*     |
| AO deceleration peak (mL/s²*10⁻³)   | -5.9 ± 0.3       | -5.9 ± 0.4   | -3.7 ± 0.2** | -3.9 ± 0.2**|
| AO deceleration duration (ms)       | 227 ± 6          | 231 ± 4      | 252 ± 4**    | 240 ± 5†    |
| AO duration (ms)                    | 328 ± 6          | 330 ± 5      | 343 ± 5      | 328 ± 6†    |

Diastolic cardiac function

| E peak filling rate (mL/s)           | 570 ± 20         | 571 ± 13     | 431 ± 18**   | 447 ± 14**  |
| E acceleration peak (mL/s²*10⁻³)    | 7.5 ± 0.5        | 7.3 ± 0.4    | 5.9 ± 0.3**  | 6.4 ± 0.3   |
| E deceleration peak (mL/s²*10⁻³)    | -5.0 ± 0.3       | -4.9 ± 0.4   | -3.8 ± 0.2*  | -4.1 ± 0.2  |
| A peak filling rate (mL/s)           | 262 ± 10         | 266 ± 13     | 201 ± 9**    | 205 ± 10**  |
| A acceleration peak (mL/s²*10⁻³)    | 4.4 ± 0.3        | 4.8 ± 0.4    | 3.3 ± 0.2*   | 3.7 ± 0.3*  |
| A deceleration peak (mL/s²*10⁻³)    | -4.6 ± 0.3       | -4.7 ± 0.3   | -3.7 ± 0.3*  | -4.2 ± 0.5  |
| E/A-peak ratio                       | 2.2 ± 0.1        | 2.2 ± 0.1    | 2.2 ± 0.1    | 2.2 ± 0.1   |
| E/Ea                                 | 8.8 ± 1.0        | 8.6 ± 0.6    | 11.0 ± 1.3   | 10.4 ± 1.1  |

Pulse wave velocity

PWV total aorta (m/s) 4.3 ± 0.1 4.4 ± 0.1 4.7 ± 0.1* 4.4 ± 0.1†

Data are mean ± SEM. HFHCD, high fat high calorie diet; LV, left ventricular; EDM, end diastolic mass; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; CI, cardiac index; EF, ejection fraction; ESWS, end-systolic wall stress. I, indexed for body surface area; AO, Aortic; E, early diastolic wave; A, atrial diastolic wave; E/Ea, estimated left ventricular filling pressure; PWV, pulse wave velocity. † p<0.05 within groups. * p<0.05, ** p<0.005 between groups. § p<0.05 diet effect between groups.
Flow velocities through the ascending aorta were measured. Typical aortic flow curves of a South Asian versus a Caucasian subject are depicted in Figure 1C. The acceleration peak and duration were significantly lower in South Asians. Furthermore, the aortic peak flow rate, deceleration peak and duration were significantly lower in South Asians. After the HFHCD the acceleration peak and deceleration duration over the aorta significantly changed in South Asians, but not in Caucasians (Table 2).

Several parameters of diastolic cardiac function differed at baseline between both groups: E peak filling rate, E acceleration peak and E deceleration peak were significantly lower in South Asians as compared with Caucasians. In addition, the A peak filling rate, the A acceleration peak and A deceleration peak were significantly lower in South Asians (Table 2). E/A ratio and the estimated filling pressure E/Ea were the same in both groups and did not change after the HFHCD. Examples of mitral valve flow curves of a South Asian versus a Caucasian subject are depicted in Figure 1A.

**Pulse Wave Velocity**

The aortic PWV was significantly higher in South Asians than in Caucasians at baseline, 4.7±0.1 m/s vs. 4.3±0.1 m/s, p=0.022. After the HFHCD, PWV decreased significantly only in South Asians, and was no longer different from Caucasians.

**Fat distribution**

Although South Asians tended to have more visceral and subcutaneous adipose tissue, differences were not significant between groups (Table 3). Also, the visceral/subcutaneous fat ratio did not differ between groups. Furthermore, no diet effect was observed. Additionally, there was no significant difference between groups in hepatic and myocardial TG content at baseline (Table 3). After the HFHCD hepatic TG content increased in both groups, whereas myocardial TG content did not change.

|                           | white Caucasians | South Asians |
|---------------------------|------------------|--------------|
|                           | before HFHCD | after HFHCD | before HFHCD | after HFHCD |
| Visceral fat (mL)         | 104 ± 14       | 111 ± 12    | 120 ± 19     | 125 ± 18    |
| Subcutaneous fat (mL)     | 348 ± 54       | 363 ± 59    | 442 ± 61     | 432 ± 54    |
| Visceral / subcutaneous ratio | 0.33 ± 0.04   | 0.36 ± 0.05 | 0.28 ± 0.03  | 0.29 ± 0.03 |
| Total fat (mL)            | 453 ± 65       | 474 ± 70    | 563 ± 76     | 558 ± 71    |
| Myocardial TG content (%) | 0.34 ± 0.06   | 0.32 ± 0.03 | 0.33 ± 0.04  | 0.34 ± 0.08 |
| Hepatic TG content (%)    | 1.7 ± 0.4      | 4.5 ± 0.8** | 1.3 ± 0.4    | 3.0 ± 0.5** |

Data are mean ± SEM. HFHCD, high fat high calorie diet; TG, triglyceride. **p<0.005 within groups.
DISCUSSION

This study shows that young, healthy South Asians have smaller cardiac dimensions compared to age- and BMI-matched white Caucasians, even after correction for BSA. Furthermore, diastolic cardiac function in South Asians is different. In addition, although the EF, a gross parameter of systolic function, was comparable between both groups, more subtle parameters of systolic function were different. A 5-day HFHCD did not increase these differences. Finally, South Asians had a higher aortic PWV on baseline.

Cardiac dimensions

Little is known about differences in cardiac dimensions and cardiovascular function at a young age between South Asians and Caucasians. Previous studies showed smaller left heart volumes, i.e. LVEDV, LVESV, and LV mass in South Asians, which is in line with our results. However, these studies were performed in older subjects (mean age ~50yr) using echocardiography, while in the current study young adults (mean age ~22yr) were included and MRI was used. One might suggest that the smaller cardiac dimensions observed in South Asians are a consequence of their overall smaller body size. However, adjustment for different parameters of body size such as BMI, BSA and lean body mass did not attenuate the observed differences in the present and other studies.

Left ventricular function

Besides smaller cardiac dimensions, we found a different diastolic and systolic functional profile between both ethnicities. Although the traditional parameters of diastolic function (E/A) and systolic function (EF) did not differ between both groups, more sensitive parameters were significantly different. E and A peak filling rate, and E and A acceleration peak were lower and E and A deceleration peak were higher in South Asians, suggesting that cardiac relaxation is prolonged in South Asians compared to Caucasians (Figure 1A). The E/Ea ratio, an estimation of LV filling pressure, was the same for both ethnicities, which is expected in two groups with comparable blood pressures. In concordance with the present study, Chahal et al. also found that E/A ratio did not differ between South Asians and Caucasians. However, in contrast to the present study, they did find a higher E/Ea ratio in South Asians. This discrepancy could be due to differences in age of subjects and/or to different methods of cardiac assessment between the studies. In this study we assessed flow through the aorta ascendens at the level of the pulmonary trunk. This showed a flow profile difference between groups. The difference is similar to what we observed in the diastolic flow profile as described above: the cardiac contraction is somewhat prolonged in South Asians (Figure 1C).

LVESWS, which is considered to be an important determinant of cardiac function and myocardial oxygen demand, did not differ between South Asians and Caucasians.
This finding indicates that no pressure overload was present in either of the groups, which is compatible with the normal LV mass in both groups. Additionally, LVEDM/EDV, a measure for concentricity, was the same between both groups, suggesting there was no difference in LV concentric remodelling either.

**Effect of HFHC diet**

With respect to the increased risk of cardiovascular disease, an important notion is that insulin resistance and type 2 diabetes are also highly prevalent in South Asians. Moreover, South Asians develop type 2 diabetes at a younger age and lower BMI compared to Caucasians, suggesting South Asians are metabolically at a higher risk. The increased risk of cardiovascular disease might be related to the metabolic changes that occur with insulin resistance. Therefore, we hypothesized that alterations in energy metabolism between South Asians and Caucasians, including differential fat distribution, might be responsible for the higher risk of cardiovascular disease in South Asians. In this study, South Asians were already more insulin resistant at baseline compared to Caucasians, as reflected by a comparable glucose but higher insulin curve and area under the curve measured by an OGTT (data not shown). Since people with insulin resistance are known to have abnormal cardiac relaxation, the prolonged cardiac relaxation observed in South Asians in this study might be due to their underlying insulin resistance.

To test whether possible differences in cardiovascular function between South Asians and Caucasians can be attributed to alterations in energy metabolism the effect of a 5-day HFHCD, inducing fat overload, on cardiovascular function was assessed. Previous studies showed that short-term dietary interventions can induce changes in cardiac function. A short-term HFHCD, consisting of 800 mL cream per day, in 15 Caucasian healthy males (age 25.0±6.6yr), already decreased diastolic function after 3 days. Therefore, we expected that if metabolic variations were the cause of differences in cardiovascular function, these differences would become more pronounced after a HFHCD.

However, although both insulin levels and HOMA-B% increased significantly only in South Asians, indicating they became even more insulin resistant, cardiovascular function did not deteriorate after the diet. Therefore, we did not find support for our hypothesis. It might be that the observed differences in cardiovascular function are innate and that these findings are simply representative of differing normal reference values in these two ethnic groups. Whether these findings are related to increased cardiovascular disease risk in South Asians is unclear.

After the HFHCD hepatic TG content significantly increased in both groups, indicating good dietary compliance of the volunteers. In contrast to accumulation of hepatic TG content, myocardial TGs did not increase after the diet in both groups. A possible explanation is that the liver acts as a buffer for excessive postprandial flux of FFAs and
TGs resulting in no net change in myocardial TG content. This is in line with results of the above mentioned study in Caucasian males who received a 3-day HFHCD.\textsuperscript{13} However, in contrast to other studies, which observed higher hepatic TG in (young) healthy South Asians compared to Caucasians,\textsuperscript{26,27} in the present study no differences were found between groups before and after the diet. Surprisingly, we did not find a significant difference in abdominal fat distribution between groups either, although South Asians tended to have more visceral and subcutaneous fat mass. Other studies did find significantly more abdominal fat mass in South Asians compared to Caucasians,\textsuperscript{27-29} though not all studies reached significance.\textsuperscript{30} These differences in (ectopic) fat distribution might be attributed to the relatively young age and low BMI of subjects in the present study compared to other studies. Possibly, the differences in body fat distribution become stronger with increasing age. Other explanations might be that we included only males, or that the group sizes were too small to reach significance.

**Vascular function**

PWV is a surrogate marker for arterial stiffness and is a powerful independent predictor of cardiovascular events.\textsuperscript{31} The aortic PWV in this study was significantly higher in South Asians at baseline, indicating a stiffer aorta. Previous studies in older subjects also reported a higher PWV in South Asians than in Caucasians.\textsuperscript{32,33} After the HFHCD the PWV decreased significantly in South Asians, but not in Caucasians. This difference in diet effect might be explained by the significant increase in insulin levels after the diet occurring only in South Asians. Insulin is known to acutely act as a vasodilator via stimulation of the vasculature to produce endothelial-derived vasodilator nitric oxide.\textsuperscript{34,35} In contrast, long-term increased insulin levels, as present in insulin resistance and type 2 diabetes, can contribute to increased arterial wall thickness by direct and indirect trophic effects on smooth muscle cells.\textsuperscript{36}

The strength of this study is that this is the first time that the response to a HFHCD on cardiovascular function was assessed in South Asians. Furthermore, cardiovascular function was extensively analysed. A possible limitation of this study is the small sample size, which might limit generalization potential. In addition, a 5-day HFHCD might not necessarily be of sufficient duration to already observe differences in cardiovascular function. However, previous studies showed that short-term dietary interventions can induce changes in cardiac function in young, healthy people.\textsuperscript{13,25}

In conclusion, already at a young age, South Asians have smaller cardiac dimensions and different diastolic and systolic cardiac function profiles as compared to white Caucasians. To our knowledge, these differences in cardiac dimensions and function between healthy, lean South Asians and Caucasians of young age have not been described before.
Additionally, South Asians have higher aortic PWV, indicating increased arterial stiffness. Reduced insulin sensitivity and increased LDL-cholesterol might be causally related to the different cardiac function profiles in South Asians.\textsuperscript{24,37} Whether these differences contribute to the higher incidence of cardiovascular disease in South Asians, however, remains to be determined. A 5-day HFHCD did not increase the observed functional cardiovascular differences between both groups, despite distinct metabolic effects of the diet. This might suggest that these findings cannot be explained by a different metabolic response to short-term dietary fat consumption between both ethnicities at young age. It is possible, however, that a longer HF-diet is needed to induce changes.
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