10 Cardiovascular flexibility in middle-aged overweight South Asians *vs.* white Caucasians: response to short-term caloric restriction

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ABSTRACT

Background. South Asians have a higher risk of developing cardiovascular disease than white Caucasians. The underlying cause is unknown, but might be related to higher cardiac susceptibility to metabolic disorders. Short-term caloric restriction can be used as a metabolic stress test to study cardiac flexibility. We assessed whether metabolic and functional cardiovascular flexibility to caloric restriction differs between South Asians and white Caucasians.

Methods. Cardiovascular function and myocardial triglycerides were assessed using a 1.5T-MRI/S-scanner in 12 middle-aged overweight male South Asians and 12 matched white Caucasians before and after an 8-day very low calorie diet (VLCD).

Results. At baseline South Asians were more insulin resistant than Caucasians. Cardiac dimensions were smaller, despite correction for body surface area, and PWV in the distal aorta was higher in South Asians. Systolic and diastolic function, myocardial triglycerides and pericardial fat did not differ significantly between groups. After the VLCD body weight reduced on average with 4.0±0.2 kg. Myocardial triglycerides increased in both ethnicities with 69±18%, and diastolic function decreased although this was not significant in South Asians. However, pericardial fat and PWV in the proximal and total aorta were reduced in Caucasians only.

Conclusions. Myocardial triglyceride stores in middle-aged overweight and insulin resistant South Asians are as flexible and amenable to therapeutic intervention by caloric restriction as age-, sex- and BMI-matched but less insulin resistant white Caucasians. However, paracardial fat volume and PWV showed a differential effect in response to an 8-day VLCD in favour of Caucasians.

INTRODUCTION

People of South Asian descent are at an increased risk of developing cardiovascular disease compared to white Caucasians. The age-standardized mortality rate from cardiovascular disease is approximately 50% higher for South Asians.[1-3] Furthermore, cardiovascular disease in South Asians is more aggressive and has higher mortality rates at younger ages.[1;2;4] The mean age of first acute myocardial infarction is around five years earlier than in Caucasians.[5]

Traditional risk factors, such as smoking, hypertension and cholesterol levels, do not seem to account for the excess risk for cardiovascular disease in South Asians.[3] Major contributing factors to the high prevalence of cardiovascular disease in South Asians are insulin resistance and type 2 diabetes, also highly prevalent in this group. Mortality risk of cardiovascular disease associated with diabetes is higher in South Asians compared to Caucasians,[3] which might suggest that South Asians have a higher cardiac susceptibility to metabolic disorders. Since South Asians represent one fifth of the world's population, the increased risk for cardiovascular disease and type 2 diabetes in this ethnicity poses a major burden on the health care system. Therefore, we aimed to gain more insight in the underlying cause of the increased susceptibility of South Asians to develop cardiovascular disease compared to white Caucasians, and, more specifically, in the interrelationship between metabolic disorders and cardiac function.

We have shown previously that short-term caloric restriction can be used as a metabolic stress test to induce a short-term physiological increase of plasma free fatty acid (FFA) levels, which enables us to study the flexibility of myocardial triglyceride (TG) content and cardiac function, as assessed by magnetic resonance (MR) techniques.[6-9] Surprisingly, so far no studies have been published on the effect of caloric restriction on cardiovascular function in South Asians.

Given the high risk of cardiovascular disease in South Asians, we hypothesize that cardiovascular function in middle-aged overweight South Asians is impaired compared to Caucasians. Furthermore, we hypothesize that the metabolic and functional cardiovascular flexibility in response to caloric restriction is compromised in people of South Asian descent. Therefore, we subjected middle-aged, overweight South Asians and age-, sex- and BMI-matched white Caucasians to an 8-day very low calorie diet (VLCD) and studied cardiac function and myocardial TG content using MR techniques. In addition, we studied aortic pulse wave velocity (PWV), a cardiovascular risk indicator.

METHODS

Study population

Eligible participants were men of Dutch South Asian origin (n=12) or Dutch white Caucasian origin (n=12), aged 40-50 year, with BMI between 25 and 30 kg/m^2, waist circumference >90 cm (South Asians) or >94 cm (Caucasians), and a positive family history for type 2 diabetes (at least 1 (grand)parent and 1 other family member with type 2 diabetes). Subjects were recruited between October 2010 and May 2012 via local advertisements, and underwent a medical screening including a physical examination, blood chemistry tests and an oral glucose tolerance test (OGTT) to exclude type 2 diabetes. Other exclusion criteria were: cardiovascular disease, any significant chronic disease, use of medication known to influence glucose and/or lipid metabolism, smoking, recent weight change, and general contraindications to MR scanning. The study was approved by the local ethics committee and performed in accordance with the principles of the revised Declaration of Helsinki. Subjects gave written informed consent prior to participation.

Study design

In this prospective, non-randomized clinical intervention study, participants were studied on 2 study days after a 10-hour fast, separated by an 8-day VLCD. The VLCD consisted of three sachets of Modifast® (Nutrition & Santé Benelux, Breda, The Netherlands) per day (~450 kcal/day; ~50 g protein, 50-60 g carbohydrates, ~7 g lipids and ~15 g dietary fibres). MR studies were performed shortly before the start and at the end of the 8th day of the diet. Subjects were instructed not to alter life style habits. Anthropometric measurements were performed according to WHO recommendations. Body fat was assessed by bioelectrical impedance analysis (Bodystat® 1500). Blood pressure was measured with a vital function monitor (Philips Sure Signs VS3). A 75-gram 2-hour OGTT was performed on the screening day. Total areas under the curve (AUC) for glucose and insulin were determined using the linear trapezoidal rule. The Matsuda index was used as a measure for insulin sensitivity.[10]

MR protocol

Measurements were performed using a 1.5-Tesla whole-body MR-scanner (Gyroscan ACS-NT15; Philips Medical Systems, The Netherlands) in postprandial state (four hours after last meal).

Myocardial triglyceride content

MR spectroscopy (^{1}H-MRS) was used to quantify myocardial TG content as described before.[11] In summary, an 8-mL voxel was placed in the interventricular septum on four-chamber and short-axis images at end-systole. Electrocardiographic triggering (for myo-

cardial spectra) and respiratory pencil beam navigator were used during acquisition.[11] Acquisitions were performed with and without water suppression, with myocardial TG expressed as percentage of the unsuppressed water signal.

Pericardial fat quantification

As described before,[12] to quantify the pericardial fat volume, the heart was imaged using electrocardiographically-gated breath-holds with a multi shot turbo spin echo sequence in a four-chamber view orientation. Water was suppressed using Spectral Inversion Recovery (SPIR). Contours were drawn around both pericardial fat layers surrounding the ventricles and atria using MASS® software (Medis, Leiden, The Netherlands) (**Figure 1**). The number of pixels were converted to square centimetres and multiplied by the slice thickness to obtain volume.

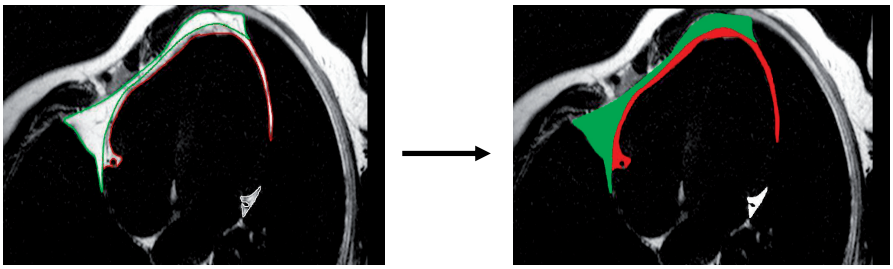

Figure 1. Quantification of the pericardial fat layer. This figure shows the quantification of the pericardial fat layer, which can be divided in an epicardial (red) and paracardial (green) fat layer.

Left ventricular dimensions and function

Data were analysed blinded for ethnicity and study occasion. As previously described, the entire heart was imaged in short-axis orientation, using electrocardiographically-gated breath-hold cine steady-state free-precession sequences.[13] Left ventricular (LV) epicardial and endocardial contours were manually drawn in the end-systolic and end-diastolic phases of the short-axis images, using validated MASS® software. LV end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), stroke volume (SV) and end-diastolic mass (EDM) were calculated.

Furthermore, an electrocardiographically-gated gradient-echo sequence with velocity encoding (100 cm/sec) was performed to measure transmitral blood, for the determination of LV diastolic function. Analysis was performed by using FLOW® software (Medis, Leiden, The Netherlands). The early filling phase (E) and the atrial contraction (A) were analysed and their peak flow ratio was calculated (E/A ratio). Additionally, the peak deceleration gradient of E and LV filling pressures (E/Ea) were assessed.[14;15] Heart rate was monitored and stored during the transmitral flow measurements.

Pulse Wave Velocity

To evaluate the aortic stiffness, aortic PWV was determined, using a previously described protocol.[16] Shortly, a scout view of the aorta was performed. Subsequently, a velocity encoded image perpendicular to the ascending aorta at the level of the pulmonary trunk, at the level of the aorta crossing the diaphragm and at the level of the aortic bifurcation was assessed (**Figure 2**). This resulted in through-plane flow measurements of the ascending and descending aorta. PWV was calculated using the formula: $\Delta x/\Delta t$, where Δx is the aortic path length between two measurement sites and Δt is the time delay between the arrivals of the foot of the pulse wave at the respective measurements site. The distance between the measurement sites was determined manually using MASS®. Data were analysed using MASS® and FLOW®.

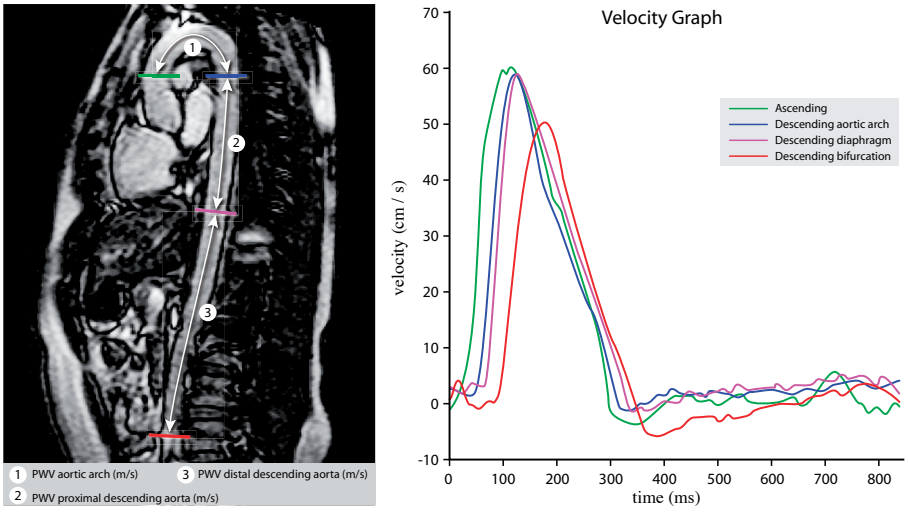

Figure 2. Aortic PWV determination with MRI. The left panel shows a double-oblique parasagittal image of the aorta. The coloured lines represent the acquisition planes for velocity-encoded MRI which are positioned perpendicular to the aorta. 1 is the path length of the aortic arch, 2 of the proximal descending aorta and 3 of the distal descending aorta, determined along the centreline of the aorta. The right panel shows the velocity-time curves for the four different measurement sites in the aorta.

Assays

Serum concentrations of glucose, total cholesterol, HDL and TG were measured on a Modular P800 analyser (Roche, The Netherlands), serum insulin levels on an Immulite 2500 (Siemens, The Netherlands), HbA_{1c} on an HPLC system (Kordia, The Netherlands), and plasma FFAs by a commercial kit (Wako Chemicals, Germany).

Statistical analysis

Data are presented as mean±SEM or median (interquartile range (IQR)). A mixed effects model was applied to assess mean differences within and between groups, and to determine differences in diet effect. Groups and intervention were modelled as fixed effects and the subject specific deviances from the group mean were modelled as random effects. Nonparametric tests were performed when appropriate (related-samples Wilcoxon Signed Rank Test (within group), independent-samples Mann-Whitney U Test (between-group)). Significance level was set at $p<0.05$ (two-sided). Statistical analyses were performed using SPSS for Windows version 20.0 (IBM, USA).

RESULTS

Clinical and metabolic characteristics

Baseline Mean age was 44.6±0.8 year. Body surface area (BSA) was significantly lower in South Asians compared to Caucasians. However, BMI (28.3±0.3 kg/m^2), waist and hip circumference and percentage of fat mass were comparable between groups. The same was true for blood pressure and heart rate. Both ethnicities had similar fasting glucose levels, but insulin levels (both fasting and during OGTT) were higher and Matsuda index was lower in South Asians. Fasting FFAs, TGs and cholesterol levels did not significantly differ between groups (**Table 1**).

Effect of VLCD Anthropometric measurements were significantly reduced after the diet in both groups. The mean reduction in body weight for both groups was 4.0±0.2 kg, of which approximately 50% was fat mass. BMI decreased on average with 1.28±0.07 kg/m^2. Systolic and diastolic blood pressure were reduced in both ethnicities. The heart rate was not affected. In both groups, fasting glucose, insulin, TG and total cholesterol levels decreased significantly, while FFAs increased in response to the VLCD (**Table 1**).

Myocardial TG content

Baseline No differences in myocardial TG content were found between both groups at baseline (**Table 2, Figure 3**).

Effect of VLCD Myocardial TG content increased in both ethnicities, although in Caucasians this did not reach significance ($p=0.067$). The percentage of myocardial TG increase, however, was comparable between groups (69±18%, $p=0.868$) (**Table 2, Figure 3 and 4**).

Pericardial fat distribution

Baseline There were no differences in pericardial, epicardial or paracardial fat volumes between groups at baseline (**Table 2, Figure 3**).

Table 1. Clinical and metabolic characteristics.

	white Caucasians		South Asians	
	before VLCD	after VLCD	before VLCD	after VLCD
Clinical characteristics				
age (years)	44.3 ± 1.1		44.9 ± 0.9	
height (m)	1.81 ± 0.02		1.75 ± 0.01**	
weight (kg)	92.6 ± 2.5	88.2 ± 2.5††	86.7 ± 1.4	83.2 ± 1.6††‡
BSA (m^2)	2.14 ± 0.04	2.09 ± 0.04††	2.02 ± 0.02*	1.99 ± 0.02††*‡
BMI (kg/m^2)	28.1 ± 0.5	26.8 ± 0.5††	28.4 ± 0.4	27.3 ± 0.4††
waist (cm)	103 ± 2	100 ± 2††	99 ± 2	97 ± 1††
hip (cm)	102 ± 1	100 ± 1	99 ± 2	97 ± 1†
WHR	1.01 ± 0.01	0.99 ± 0.01†	1.02 ± 0.01	1.01 ± 0.01
fat mass (%)	23.1 ± 0.6	21.8 ± 0.6††	23.8 ± 0.6	23.0 ± 0.6††
systolic BP (mmHg)	130 ± 3	118 ± 2††	136 ± 3	124 ± 3††
diastolic BP (mmHg)	85 ± 3	77 ± 3††	90 ± 4	85 ± 3††
heart rate (bpm)	64 ± 3	61 ± 2	70 ± 3	65 ± 3
Metabolic characteristics				
free fatty acids (mmol/L)	0.53 ± 0.03	1.36 ± 0.13†	0.58 ± 0.04	0.85 ± 0.06†*‡
triglycerides (mmol/L)	1.29 (2.48)	0.89 (0.18) †	1.78 (2.91)	0.91 (0.25)†
total cholesterol (mmol/L)	5.56 ± 0.24	4.72 ± 0.33†	5.74 ± 0.28	5.13 ± 0.26†
HDL-cholesterol (mmol/L)	1.09 ± 0.08	0.99 ± 0.06	1.00 ± 0.07	0.95 ± 0.05
LDL-cholesterol (mmol/L)	3.54 ± 0.28	3.42 ± 0.37	3.58 ± 0.25	3.77 ± 0.24
total cholesterol/HDL ratio	5.57 ± 0.59	5.02 ± 0.54	6.05 ± 0.48	5.49 ± 0.35
HbA_{1c} (mmol/mol, %)	33.0 (6), 5.20 (0.5)		36.5 (1)*, 5.45 (0.1) *	
glucose (mmol/L)	5.33 ± 0.20	4.45 ± 0.22††	5.30 ± 0.11	4.51 ± 0.14††
insulin (mU/L)	6.0 (3.0)	1.7 (3.7)††	8.5 (2.5)**	2.3 (4.7)††
Oral glucose tolerance test				
2 hour insulin (mU/L)	31 (29)		77 (76)*	
glucose AUC (mmol/L * h)	959 ± 32		1027 ± 58	
insulin AUC (mU/L * h)	4477 ± 586		8790 ± 711**	
Matsuda index	7.1 ± 1.3		3.9 ± 0.6*	

Data are presented as mean ± SEM or median (IQR). VLCD, very low calorie diet. BSA, body surface area; BMI, body mass index; WHR, waist hip ratio; BP, blood pressure; AUC, total area under the curve. † $p<0.05$, †† $p<0.005$ within group *vs.* before diet. * $p<0.05$, ** $p<0.005$ *vs.* Caucasians. ‡ $p<0.05$, ‡‡ $p<0.005$ diet effect *vs.* Caucasians.

Table 2. Cardiac dimensions, parameters of cardiovascular function, pericardial fat distribution and myocardial triglyceride content assessed with MRI and MRS before and after an 8-day VLCD.

	white Caucasians		South Asians	
	before VLCD	after VLCD	before VLCD	after VLCD
Cardiac dimensions and basic function				
LVEDMI (g/m^2)	51 ± 2	48 ± 2††	52 ± 1	50 ± 1†
EDVI (mL/m^2)	87 ± 3	83 ± 2†	74 ± 3**	72 ± 3*
ESVI (mL/m^2)	34 ± 1	32 ± 1	29 ± 1*	27 ± 1*
SVI (mL/m^2)	53 ± 2	51 ± 2	46 ± 2*	45 ± 2*
CI ($mL/min/m^2$)	3.3 ± 0.1*10^3	3.1 ± 0.1*$10^{3\dagger}$	3.2 ± 0.2*10^{3}*	2.9 ± 0.1*$10^{3\dagger}$*
EF (%)	61 ± 2	62 ± 1	62 ± 1	63 ± 1
Diastolic cardiac function				
E peak filling rate (mL/s)	549 ± 28	477 ± 26††	493 ± 26	445 ± 22†
E acceleration peak (mL/s^2x10^{-3})	8.4 ± 0.6	7.0 ± 0.5††	7.5 ± 0.5	6.4 ± 0.3
E deceleration peak (mL/s^2x10^{-3})	-4.7 ± 0.3	-3.7 ± 0.2††	-4.9 ± 0.3	-4.1 ± 0.3†
E deceleration mean (mL/s^2x10^{-3})	-3.2 ± 0.2	-2.5 ± 0.2††	-3.4 ± 0.3	-2.8 ± 0.3†
A peak filling rate (mL/s)	392 ± 18	364 ± 20	365 ± 17	360 ± 10
E/A-peak ratio	1.43 ± 0.10	1.34 ± 0.09†	1.37 ± 0.08	1.24 ± 0.07
E/Ea	9.4 ± 0.7	8.3 ± 1.0	9.8 ± 0.8	7.2 ± 0.8†
Pulse wave velocity				
PWV aortic arch (m/s)	5.6 (0.9)	5.3 (1.1)	5.7 (1.3)	5.7 (0.9)
PWV proximal aorta (m/s)	6.7 (2.4)	5.2 (1.4)†	7.2 (3.7)	7.1 (2.6)**
PWV distal aorta (m/s)	5.0 (0.5)	4.9 (1.7)	5.5 (1.2)*	5.2 (1.0)
PWV total aorta (m/s)	5.5 (1.0)	5.2 (0.4)†	6.1 (0.9)	5.8 (0.9)*
Fat distribution				
Epicardial fat (mL)	3.1 (1.8)	3.6 (1.4)	3.3 (1.4)	3.0 (1.0)
Paracardial fat (mL)	4.8 (3.7)	3.7 (3.0)††	3.5 (2.1)	2.7 (2.6)‡
Pericardial fat (mL)	7.6 (4.0)	6.6 (3.5)†	6.7 (3.0)	6.0 (4.0)
Myocardial TG content (%)	0.56 ± 0.08	0.74 ± 0.08	0.59 ± 0.08	0.98 ± 0.13††

Data are mean ± SEM or median (IQR). VLCD, very low 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; E, early diastolic wave; A, atrial diastolic wave; E/Ea, estimated left ventricular filling pressure; PWV, pulse wave velocity; TG, triglyceride. † p<0.05, †† p<0.005 within group *vs.* before diet. * p<0.05, ** p<0.005 *vs.* Caucasians. ‡ p<0.05, ‡‡ p<0.005 diet effect *vs.* Caucasians.

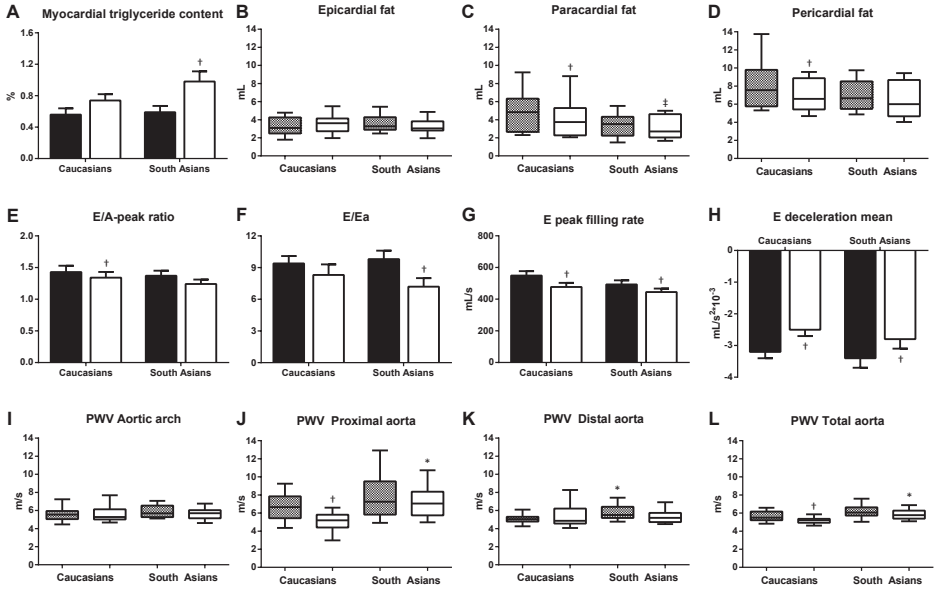

Figure 3. Overview of main results in middle-aged overweight South Asian and white Caucasian men before (dark bars) and after (open bars) an 8-day VLCD. A: Myocardial triglyceride content. B-D: pericardial fat. E-H: variables of diastolic cardiac function. I-L: pulse wave velocity (PWV). Data are expressed as mean ± SEM (A, E-H) or as median (IQR) in a box-whiskerplot (B-D, I-L). † p<0.05 within group *vs.* before diet. * p<0.05 *vs.* Caucasians. ‡ p<0.05 diet effect *vs.* Caucasians.

Effect of VLCD The pericardial and paracardial fat volumes decreased significantly in Caucasians in response to the VLCD (p=0.003 and p=0.050, respectively), whereas no significant changes occurred in South Asians (**Table 2, Figure 3**).

Left ventricular dimensions and function

Baseline Despite correction for BSA EDV, ESV and SV were significantly lower in South Asians. EF was on average 61±4%, and was comparable between ethnicities (p=0.808). There were no significant differences in diastolic cardiac function, as reflected in the E/A ratio (p=0.168) and the E/Ea ratio (p=0.088) (**Table 2, Figure 3**).

Effect of VLCD LV mass, indexed for BSA, decreased slightly in both groups after the diet. EDV reduced in Caucasians, however no significant change occurred in South Asians. The cardiac index reduced equally in both ethnicities. The E/A ratio reduced significantly in Caucasians, whereas no significant diet effect was observed in South Asians. In contrast, the VLCD did not induce significant changes in the E/Ea ratio in Caucasians, while in South Asians E/Ea decreased significantly. The early peak filling rate (EPFR) and early deceleration mean showed a significant decrease in both groups in response to the VLCD (**Table 2, Figure 3**).

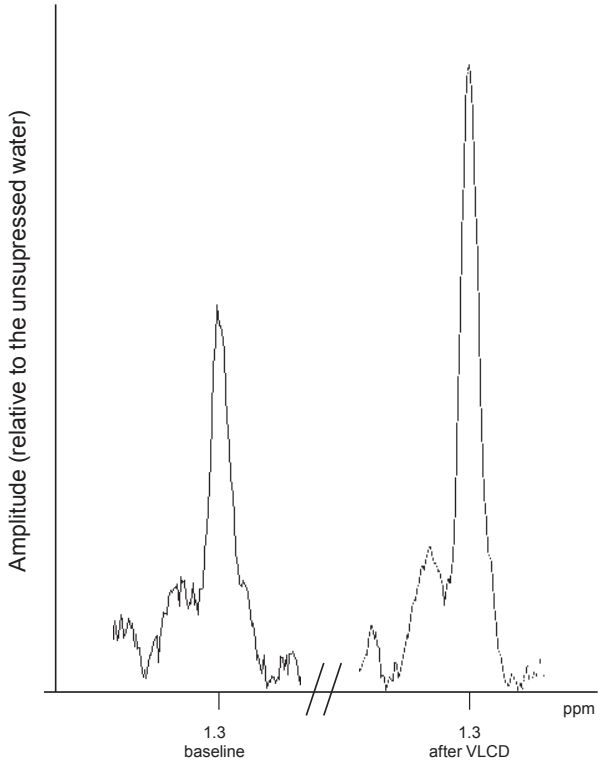

Figure 4. Myocardial spectra. Example of typical myocardial spectra of one subject before and after an 8-day VLCD.

Pulse wave velocity

Baseline PWV in the distal segment of the aorta was significantly higher in South Asians compared to Caucasians. Furthermore, PWV in the total aorta tended to be higher in South Asians, however this did not reach statistical significance (p=0.068) (**Table 2, Figure 3**).

Effect of VLCD After the VLCD, PWV in the proximal descending part of the aorta and PWV of the total aorta were significantly reduced in Caucasians. In contrast, no diet effect on PWV in any of the segments of the aorta was observed in South Asians (**Table 2, Figure 3**).

DISCUSSION

South Asians have a higher risk of developing cardiovascular disease than white Caucasians. Additionally, the risk of cardiac complications in subjects with insulin resistance

and type 2 diabetes is higher in this population, indicating they are metabolically more at risk. Previous studies in healthy subjects and obese patients with type 2 diabetes with and without cardiovascular disease of Caucasian descent demonstrated metabolic and functional flexibility of the heart in response to both short- and long-term caloric restriction. To date, however, it was unknown if caloric restriction in South Asians has comparable effects. This study showed that an 8-day VLCD increased myocardial TG content to a similar degree in middle-age overweight South Asians as compared to age-, sex- and BMI-matched but less insulin resistant Caucasians, indicating comparable flexibility of the heart. Paracardial fat volume and PWV, however, showed a differential effect in response to caloric restriction in favour of Caucasians.

Myocardial TG content

At baseline, South Asians were more insulin resistant, indicated by higher insulin levels (both in fasted condition and during OGTT) and lower Matsuda index (**Table 1**). Studies in animals and humans have demonstrated that increased myocardial TG content in insulin resistance is associated with impaired myocardial function.[17-19] Paradoxically, however, the increase in myocardial TG observed after a short-term VLCD is a sign of preserved metabolic flexibility of the heart. Given the high risk on cardiovascular disease and diabetes in South Asians, we hypothesized, therefore, that the flexibility of the heart to adjust myocardial TG content in response to caloric restriction was diminished in South Asians compared to Caucasians. Surprisingly, however, an 8-day VLCD increased myocardial TG similarly in both groups. Thus, South Asians showed a similar physiological flexibility of myocardial lipid metabolism as Caucasians.

Previous short-term VLCD studies have shown that the increase in myocardial TG is the net result of increased uptake of FFAs in cardiomyocytes in relation to oxidative FFA requirements. This increased uptake is due to an increased release of FFAs from the adipose tissue into the circulation, which is caused by increased lipolysis of TG in adipose tissue in response to caloric restriction.[7;9] Indeed, in the present study FFAs were significantly increased after the diet in both ethnicities, and waist fat was significantly reduced (data not shown), indicating increased lipolysis in the adipose tissue.

Pericardial fat

Pericardial fat, the layer of fat surrounding the heart, can be divided in an epicardial and paracardial layer. Both fat layers are metabolically different. Whereas epicardial fat has been shown to be a source of several inflammatory mediators, paracardial fat seems to have a greater importance in mechanical restriction, which exerts an unfavourable effect on the coronary vasculature.[20] In the present study, pericardial fat distribution was similar between groups at baseline. However, pericardial fat decreased significantly in Caucasians in response to the dietary intervention, mainly due to a reduction in the

paracardial fat layer, whereas in South Asians no significant diet effect was observed. Since the paracardial fat layer has been found to be a predictor of cardiovascular disease, the decrease in this specific fat compartment in Caucasians probably conveys reduced cardiovascular risk.[21]

Cardiac dimensions and function

Cardiac dimensions were smaller in South Asians compared to Caucasians, despite correction for BSA. This is in line with other studies, which showed smaller left heart volumes in middle-aged South Asians,[22;23] using echocardiography. In a recent study in healthy young adults, we showed that these smaller cardiac dimensions are already present at a young age.[24] No major effects of the diet on cardiac dimensions were observed.

Cardiac systolic function, reflected as the LV ejection fraction, was normal (~62%) and comparable in both groups. Systolic function was not affected by the diet, which is in line with previous VLCD studies.[7;9;25]

Diastolic cardiac function, reflected as the E/A ratio, decreased after the diet as expected from previous studies.[7;9;26] The reduction, however, was only significant in Caucasians. This difference in diet effect might be attributed to a decrease in filling pressure (E/Ea ratio) in South Asians. In addition, other parameters for diastolic function did decrease in both groups. The decrease in diastolic function can probably be explained by changes in elastic properties of the LV. In animal models, TG accumulation in cardiomyocytes is directly related to impaired cardiac function via complex mechanisms involving fatty acid derivatives.[17] An alternative explanation may be that changes in plasma FFAs, induced by caloric restriction, change the calcium homeostasis in the myocardium, thereby influencing LV diastolic function.[27]

Pulse wave velocity

The PWV is a powerful independent predictor of cardiovascular events.[28] In the present study, PWV in the distal aorta was significantly higher in South Asians compared to Caucasians at baseline, indicating a stiffer aorta. This is in line with other studies that showed a higher PWV in middle-aged South Asians compared to Caucasians.[29;30] In addition, we have shown recently that PWV is already higher in healthy young South Asians.[24] It is known that insulin resistance and diabetes compromise aortic elastic function. Although the precise underlying mechanisms remain unclear, it is known that long-term increased insulin levels can contribute to increased arterial wall thickness, and thereby to increased arterial stiffening, by direct and indirect trophic effects on smooth muscle cells.[31] In the present study, South Asians were more insulin resistant than Caucasian subjects – as reflected in higher insulin levels (both fasting and during OGTT) – which might explain the higher PWV observed in South Asians.

The PWV responded differentially to an 8-day VLCD, consisting of a reduction in proximal and total PWV in Caucasians, whereas no diet effect was observed in South Asians, suggesting that large arteries are less flexible in South Asians in response to caloric restriction. This might be due to the, probably long-term existing, higher insulin resistance observed in South Asians which may have induced irreversible changes in the arterial wall according to the aforementioned mechanism.

Strengths of this study are that this is the first time the response to a VLCD on cardiovascular function was assessed and the first time myocardial and pericardial TG content were measured in South Asians. We used an extreme intervention (8-day VLCD) to be able to detect differences between ethnicities. Furthermore, we matched on BMI in order to gain more insight in the pathophysiological mechanism behind the increased risk of South Asians to develop insulin resistance and type 2 diabetes at lower ranges of BMI than Caucasians. A possible limitation is the relatively small sample size, which might limit generalization potential. However, subjects were their own controls, which increases power to detect relevant differences.

In conclusion, this study proves that myocardial TG stores in middle-aged overweight and insulin resistant South Asians are as flexible and amenable to therapeutic intervention by caloric restriction as age-, sex- and BMI-matched but less insulin resistant Caucasians. However, paracardial fat volume and PWV showed a differential effect in response to an 8-day VLCD in favour of Caucasians.

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