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

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Abstract *Background and aims:* 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 (CR) can be used as a metabolic stress test to study cardiac flexibility. We assessed whether metabolic and functional cardiovascular flexibility to CR differs between South Asians and white Caucasians.
Methods and results: 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). At baseline South Asians were more insulin resistant than Caucasians. Cardiac dimensions were smaller, despite correction for body surface area, and pulse wave velocity (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 by 4.0 ± 0.2 kg. Myocardial triglycerides increased in both ethnicities by 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.
Conclusion: Myocardial triglyceride stores in middle-aged overweight and insulin resistant South Asians are as flexible and amenable to therapeutic intervention by CR 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 favor of Caucasians.
Clinical Trial Registration: NTR 2473 (URL: http://www.trialregister.nl/trialreg/admin/rctsearch.asp?Term=2473).

Abbreviations: A, atrial contraction; BSA, body surface area; CR, caloric restriction; CVD, cardiovascular disease; E, early filling phase; EDM, end-diastolic mass; EDV, end-diastolic volume; EF, ejection fraction; EPFR, early peak filling rate; ESV, end-systolic volume; FFA, free fatty acid; IR, insulin resistance; MR, magnetic resonance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; OGTT, oral glucose tolerance test; PWV, pulse wave velocity; SV, stroke volume; T2D, type 2 diabetes; TG, triglyceride; VLCD, very low calorie diet.

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Introduction

People of South Asian descent are at an increased risk of developing cardiovascular disease (CVD) compared to white Caucasians (hereafter referred to as Caucasians). The age-standardized mortality rate from CVD is approximately 50% higher for South Asians [1–3]. Furthermore, CVD 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 CVD in South Asians [3]. Major contributing factors to the high prevalence of CVD in South Asians are insulin resistance (IR) and type 2 diabetes (T2D), also highly prevalent in this group. Mortality risk of CVD 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 CVD and T2D 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 CVD compared to Caucasians, and, more specifically, in the interrelationship between metabolic disorders and cardiac function.

We have shown previously that short-term caloric restriction (CR) can be used as a metabolic stress test to induce a short-term physiological increase in 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 CR on cardiovascular function in South Asians.

Given the high risk of CVD 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 CR is compromised in people of South Asians 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 Asians origin (n = 12) or Dutch white Caucasians origin (n = 12), aged 40–50 year, with a BMI between 25 and 30 kg/m [2], waist circumference of >90 cm (South Asians) or >94 cm (Caucasians), and a positive family history for T2D (at least 1 (grand) parent and 1 other family member with T2D). 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 T2D. Other exclusion criteria were: CVD, 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 overnight fast, separated by an 8-day VLCD. The VLCD consisted of three sachets of Modifast® (Nutrition & Santé Benelux, Netherlands) per day (~450 kcal/day; ~50 g protein, 50–60 g carbohydrates, ~7 g lipids and ~15 g dietary fibers). 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 MR-scanner (Gyroscan ACS-NT15; Philips Medical Systems, 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 myocardial 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 SPIR. Contours were drawn around both