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Impact of cardiac magnetic resonance on endothelial function in type 2 diabetic patients

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ABSTRACT

Objectives Recent studies have shown that cardiac magnetic resonance (CMR) scanning is associated with cellular DNA damage. The aim of the present study was to assess the impact of CMR scanning on endothelial function in Chinese men with type 2 diabetes. **Methods** A randomized, single-blind, parallel-group study was conducted in 60 Chinese men with type 2 diabetes treated with or without CMR (CMR and sham CMR group), and the changes of endothelial function before and after CMR were compared. High-resolution ultrasound was used to measure flow-mediated endothelium-dilation (FMD) of the brachial artery. **Results** The FMD in CMR group at Day 1 after CMR was 3.60%, which was significantly lower than that (3.85%) in sham CMR group ($p < 0.001$). The levels of C-reactive protein (CRP), thiobarbituric acid-reactive substances (TBARS), tumor necrosis factor alpha (TNF-α) and interleukin-6(IL-6) in CMR group were significantly higher than those in sham CMR group at Day 1 ($p < 0.001$). But these characteristics did not differ between two groups at baseline, Day 2 and Day 3 ($p > 0.05$). Linear correlation and multiple regression analyses showed that CRP, TBARS, TNF-α and IL-6 were associated with FMD in the CMR group ($p < 0.01$). **Conclusions** The present data showed that CMR scanning can reversibly suppress endothelial function, probably through the increased production of oxygen-derived free radicals and inflammatory reactions in Chinese men with type 2 diabetes, indicating that CMR should be used with caution in order to avoid unnecessary damage to the endothelium. **Clinical Trial Registration** URL: https://register.clinicaltrials.gov/, Unique Identifier: NCT02001753.

Magnetic resonance (MR) imaging is an established clinical diagnostic tool with the number of systems installed world-wide approaching 4000 [1]. By using a static and a gradient magnetic field in combination with a radiofrequency field, MR provides excellent contrast among different tissues of the body including the brain, musculoskeletal system, and heart. Although long-term effects on human health from exposure to strong static magnetic fields seem unlikely [2], acute effects such as vertigo, nausea, change in blood pressure, reversible arrhythmia [3], and neurobehavioural effects have been documented from occupational exposure to 1.5 T [4].

Cardiac magnetic resonance (CMR) is a noninvasive tool that provides high-resolution, three-dimensional images of the heart; CMR requires some of the strongest and fastest switching electromagnetic gradients available in MR, exposing patients to the highest administered energy levels accepted by the controlling authorities [5]. Studies focusing on the experimental teratogenic [6–10] or carcinogenic [11–13] effects of MR have revealed conflicting results. Since CMR is emerging as one of the fastest growing new fields of broad MR application [14], it is of particular concern that a recent *in vitro* study with CMR sequences has reported CMR-induced DNA damage in white blood cells up to 24 h after exposure to 1.5 T CMR [5]. Moreover, one in vivo study showed that contrast CMR scanning in daily clinical routine is associated with increased lymphocyte DNA damage [15]. However, to date, no data are available on the relationship between CMR and endothelial

Abbreviation: BMI, Body mass index; CMR, cardiac magnetic resonance; CRP, C-reactive protein; FMD, flow-mediated vasodilation; FBG, fasting blood glucose; GTN, glyceryl trinitrate; HDL-C, high-density lipoprotein cholesterol; HbA1c, haemoglobinA1c; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; MR, magnetic resonance; 2h-BG, postprandial 2 h glucose; TC, total cholesterol; TG, triglyceride; TBARS, thiobarbituric acid reactive substances; TNF-α, tumor necrosis factor-alpha; UAER, urinary albumin excretion rate; WHO, World Health Organization.

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dysfunction, especially in diabetic conditions. Therefore, the aim of the present study was to assess the impact of routine CMR scanning on endothelial function in Chinese men with type 2 diabetes.

1. Subjects and methods

1.1. Subjects

From Dec. 2013 to Feb. 2014, the newly diagnosed Chinese type 2 diabetic men, who had been referred to our hospital for diabetic evaluation, were identified as potentially eligible subjects (540 cases). The type 2 diabetes was diagnosed according to the World Health Organization (WHO) 1999 criteria. Of them, a total of 60 eligible Chinese type 2 diabetic men, aged 40–65 years old (mean 54 ± 7 years old), were included in this study. Patients with clinical angiopathy including micro- and macroangiopathy as well as hypertension were excluded from this study. Microangiopathy included nephropathy [urinary albumin excretion rate (UAER) > 20 μg/min], retinopathy (at least one microaneurysm or hemorrhage or exudates in either eye), and neuropathy (pain in the extremities, paresthesias, absent tendon reflexes, and/or absent vibration sensation); and macroangiopathy included coronary artery disease (myocardial infarction, ischemia electrocardiogram changes, and angina), cerebrovascular disease (transient ischemic attack or stroke), and peripheral vascular disease (the abolition of one or more peripheral arterial pulses, and/or intermittent claudication, and/or a past history of revascularization of the lower limbs). The recruited patients were all required to have an office blood pressure (BP) < 140/90 mm Hg, which was measured by a trained nurse. After at least a 5-min rest, two successive readings were taken from the right arm using a mercury manometer with a 12-cm by 33.5-cm cuff. During the same period, 28 healthy men (all from the medical staff in our hospital), who had had a normal glucose tolerance, were selected as control subjects. Subjects who were obese [body mass index (BMI) > 30 kg/m^2], or smokers, or had malignant neoplasms, renal or liver diseases, or endocrinological diseases other than diabetes were excluded from the study. In addition, no patients were taking any drugs, such as oestrogen supplements, thyroxine, diuretics, diabetic medications, antihypertensive and hypolipidaemic drugs. All subjects enrolled in the study gave their informed consent. The study protocol was in agreement with the guidelines of the ethics committee at our hospital.

Two to three days before the beginning of the study, advice on a standard, well-balanced, controlled diet was given to all the eligible subjects. Diabetic patients were then scheduled to undertake a 4-day randomized, single-blind, parallel-group trial of investigations with or without CMR scanning. The patients were divided randomly into two groups, 30 cases in each group (the CMR group and sham CMR group). In the CMR group, CMR scanning for evaluation of left ventricular mass was performed at 8–10 AM; in the sham CMR group, all subjects remained in the supine position in the same MR machine scanner at 8–10 AM and the patients were not subjected to the pulse sequences of a typical examination. Our previous studies showed that oxidative stress and inflammation as well as blood glucose are associated with endothelial dysfunction [16–19], therefore, the examinations of vascular function, blood glucose, oxidative stress, and inflammation were performed at 1 day (baseline) before and at 1 day (Day 1), 2 days (Day 2), 3 days (Day 3) after the CMR procedure for the CMR group or the sham CMR procedure for the without CMR group. Only a one-time examination was performed for the healthy controls at baseline.

2. Methods

2.1. CMR scanning

The CMR imaging was performed on a 1.5-T Magnetom Avanto scanner (Siemens, Erlangen, Germany) for the CMR group. Serial contiguous short-axis cines were acquired from the vertical long axis and horizontal long axis of the left ventricle [electrocardiogram gated, steady-state free precession imaging (true fast imaging with steady-state precession), with the short-axis imaging parameters being a repetition time of 2.5 ms, echo time of 1.1 ms, flip angle of 60°, and slice thickness of 6 mm]. Regarding the procedure for the sham CMR group, the patients only stayed in the scanner for the same length of time as subjects in the CMR group.

2.2. Brachial artery ultrasonography

Brachial artery ultrasonography was performed noninvasively, as previously described by us [16,17]. High resolution ultrasonography was used to measure arterial diameter changes in response to reactive hyperemia (with increased flow producing an endothelium-dependent stimulus to vasodilation; flow-mediated vasodilation, FMD) and to glyceryl trinitrate (GTN, an endothelium-independent vasodilator; GTN-induced dilation; 128XP/10 with a 7.0 MHz linear array transducer: Acuson, Mountain View, CA, USA). The intra- and interobserver variability in our laboratory for repeated measurements of artery diameter are 0.09 ± 0.10 and 0.08 ± 0.13 mm, respectively. The coefficients of variation for the FMD measurements over time are 6.8–8.2%.

2.3. Laboratory methods

Venous blood was collected after a 12-h fast at baseline for all individuals and at Day 1, Day 2 and Day 3 after the CMR or sham CMR procedure for diabetic patients. Measurements of serum lipids, serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride and high-density lipoprotein cholesterol (HDL-C) were measured enzymatically. Creatinine was measured enzymatically. Blood glucose including fasting blood glucose (FBG) and postprandial 2-h glucose (2-h BG) was measured by a glucose oxidase procedure. HaemoglobinA1c (HbA1c) was measured by high-performance liquid chromatography. The C-reactive protein (CRP) concentration was measured by using the CRP (Latex) ultrasensitive assay. Nitrite and nitrate, stable metabolites of NO, were measured using methods reported by Xiang et al. [18]. The plasma lipid peroxide content was determined using thiobarbituric acid reactive substances (TBARS) as markers [18,19]. Briefly, 2.0 mL of trichloroacetic acid-thiobarbituric acid-HCl reagent was added to 1.0 mL of sample and vortexed. To minimize peroxidation during the assay procedure, butylated hydroxytoluene was added to the thiobarbituric acid reagent mixture. The results were expressed as malondialdehyde equivalent content (nmol MDA/mL plasma). Interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) were measured using high-sensitivity commercial ELISA kits. The urinary albumin excretion rate (UAER) was measured by a radioimmunoassay. The intra-assay coefficients of variation for these assays were 1–2% (TC, HDL-C, blood glucose, and CRP), 2–3% (LDL-C and nitrite/nitrate), 2–4% (UAER and TBARS), 5.3%–6.9% (TNF-α and IL-6).

3. Statistical methods

As expected from our previous study [19], the standard deviation (SD) for FMD was about 0.75, and the expected absolute error