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Association of Exercise Intolerance in Type 2 Diabetes With Skeletal Muscle Blood Flow Reserve

Julian W. Sacre, PhD,*† Christine L. Jellis, MD, PhD,‡ Brian A. Haluska, PhD,‡ Carly Jenkins, PhD,‡ Jeff S. Coombes, PhD,* Thomas H. Marwick, MD, PhD,‡§ Michelle A. Keske, PhD§

ABSTRACT

OBJECTIVES This study sought to investigate the association of exercise intolerance in type 2 diabetes (T2DM) with skeletal muscle capillary blood flow (CBF) reserve.

BACKGROUND Exercise intolerance in T2DM strongly predicts adverse prognosis, but associations with muscle blood flow independent of cardiac dysfunction are undefined.

METHODS In 134 T2DM patients without cardiovascular disease, left ventricular function and contrast-enhanced ultrasound of the quadriceps (for CBF; i.e., product of capillary blood volume and velocity) were assessed at rest and immediately following treadmill exercise for peak oxygen uptake ($V_{O_{2peak}}$). Left ventricular systolic and diastolic functional reserve indexes were derived from changes in systolic and early diastolic color tissue Doppler velocities. Cardiac index reserve and its constituents (stroke volume and chronotropic indexes) and left ventricular filling pressure (ratio of early diastolic mitral inflow and annular velocities) were also measured.

RESULTS $V_{O_{2peak}}$ correlated with muscle CBF reserve ($\beta = 0.16$, $p = 0.005$) independent of cardiac index reserve and clinical covariates. This was explained by higher muscle capillary blood velocity reserve ($\beta = 0.18$, $p = 0.002$), rather than blood volume reserve ($p > 0.10$) in patients with higher $V_{O_{2peak}}$. A concurrent association of $V_{O_{2peak}}$ with cardiac index reserve ($\beta = 0.20$, $p < 0.001$) appeared to reflect chronotropic index ($\beta = 0.15$, $p = 0.012$) rather than stroke volume index reserve ($p > 0.10$), although the systolic functional reserve index was also identified as an independent correlate ($\beta = 0.16$, $p = 0.028$). No associations of $V_{O_{2peak}}$ with diastolic functional reserve were identified ($p > 0.10$).

CONCLUSIONS $V_{O_{2peak}}$ is associated with muscle CBF reserve in T2DM, independent of parallel associations with cardiac functional reserve. This is consistent with a multifactorial basis for exercise intolerance in T2DM.
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Exercise intolerance is now widely recognized in type 2 diabetes mellitus (T2DM) per se—that is, independent of cardiovascular disease or other comorbidities such as obesity (1–4). However, despite strong predictive power for cardiovascular and all-cause mortality (5,6), the determinants of exercise capacity in T2DM remain incompletely understood. Subclinical cardiovascular dysfunction secondary to the abnormal metabolic milieu may be central to a multifactorial etiology (1,3,4,7); however, the relative contributions of cardiac versus peripheral vascular abnormalities remain difficult to discern. Exercise intolerance as a consequence of peripheral vascular dysfunction in T2DM may reflect compromised arterial blood flow during exercise secondary to impaired endothelium-dependent vasodilation (8).

From the *School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane, Australia; †Baker IDI Heart and Diabetes Institute, Melbourne, Australia; ‡School of Medicine, University of Queensland, Brisbane, Australia; and the §Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia. This work was supported in part by a Centre of Clinical Research Excellence award from the National Health and Medical Research Council, Canberra, Australia. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Sherif Nagueh, MD, served as Guest Editor for this paper.

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ABBREVIATIONS AND ACRONYMS

BP = blood pressure

CBF = capillary blood flow

ECG = electrocardiography

E/Em = ratio of early diastolic mitral inflow and septal annular velocities

Em = early diastolic tissue velocity

HbA_{1c} = glycosylated hemoglobin

LV = left ventricular

MAP = mean arterial pressure

Sm = systolic tissue velocity

SVI = stroke volume index

T2DM = type 2 diabetes mellitus

Vo_{2peak} = peak exercise oxygen uptake

However, blood flow reserve at the muscle capillary level (i.e., site of oxygen/substrate exchange) relies on microvascular function as well as on upstream hyperemia. Indeed, blunting of muscle capillary blood flow (CBF) during forearm contractions is described in T2DM patients with microvascular complications (9) and unites with slowed or reduced flow reserve during submaximal exercise (7,10). These observations certainly argue for important roles for peripheral vascular sequelae; however, associations with maximal exercise capacity in T2DM—particularly relative to left ventricular (LV) dysfunction—are unknown.

In the current study of patients with T2DM without concurrent cardiovascular disease, we sought the association of skeletal muscle CBF reserve with exercise capacity (peak oxygen uptake [Vo_{2peak}]) independent of LV functional reserve and other potential covariates. Skeletal muscle CBF (contrast-enhanced ultrasound) (11) and LV function (echocardiography) were assessed at rest and immediately following maximal treadmill exercise.

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METHODS

PATIENT SELECTION. Patients with T2DM (n = 189), aged ≥40 years, and with no history of cardiovascular, psychiatric, or other severe illness, and with no symptomatic macrovascular or microvascular complications of T2DM, were recruited from the community. Patients were required to have an ejection fraction of ≥50%, no valvular disease, and no resting or inducible wall motion abnormalities indicative of ischemia, as previously described (12,13). The study was approved by the local human research ethics committee and all patients provided written informed consent.

Fasting blood glucose, glycosylated hemoglobin (HbA_{1c}), lipids, hemoglobin, creatinine, and a random urinary albumin-to-creatinine ratio (for microalbuminuria; i.e., ≥3.5 mg/mmol [female subjects] or ≥2.5 mg/mmol [male subjects]), were measured by standard hospital pathology laboratory protocols. Resting heart rate and blood pressure (BP) were recorded during supine rest.

STUDY PROTOCOL. Echocardiography for LV function and contrast-enhanced ultrasound for skeletal muscle CBF were performed sequentially at rest and then repeated immediately following maximal treadmill exercise testing according to the Bruce protocol. The imaging protocols were not performed simultaneously due to microbubble influence on Doppler-based echocardiographic measurements. In accordance with usual image acquisition times (14), post-exercise echocardiography was completed within 1 to 2 min after exercise (views for wall motion analysis were prioritized and completed first). Contrast-enhanced ultrasound was performed during the subsequent ~2.5 to 3.5 min (i.e., all imaging protocols completed by ~3.5 to 5.5 min post-exercise).

During treadmill exercise, an electrocardiogram (ECG) was recorded continuously and BP was measured during the final minute of each stage. Exercise capacity was measured by expired breath-by-breath gas analysis for Vo_{2peak} following 20-s interval data averaging (Vmax, SensorMedics, Yorba Linda, California). Patients with exercise-induced arrhythmias or abnormal exercise BP necessitating test termination (based on American College of Cardiology/American Heart Association exercise testing guidelines) (15), or with a peak respiratory quotient <1.0 (indicating submaximal effort), were excluded. The heart rate response to exercise (chronotropic index) was quantified by heart rate reserve (peak − resting heart rate) as a percentage of age-predicted heart rate reserve (12). Antihypertensive therapy was withheld for the preceding 24 h.

CONTRAST-ENHANCED ULTRASOUND. Contrast-enhanced ultrasound for skeletal muscle CBF was performed according to a protocol modified from Vincent et al. (11). Ultraharmonic images (Sonos 7500, Philips Medical Systems, Andover, Massachusetts) of the quadriceps (approximately one-third of the distance from the patella to inguinal fold) were acquired in cross section at centerline transmission and received frequencies of 1.3 and 3.6 MHz, respectively. Relevant settings were mechanical index = 1.0 (sufficient to destroy microbubbles in the ultrasound beam), gain = 1, and compression = 80%. Depth and focus were optimized for each study. Images were acquired intermittently during intravenous infusion of microbubbles (Definity, Lantheus Medical Imaging, North Billerica, Massachusetts) at ~0.15 ml/min (operator-controlled), using an internal ECG trigger timer to progressively increase the time between successive pulses (pulsing interval) from 1 to 40 RR intervals (~1 s to ≥25 s). Video intensity was derived from images at each pulsing interval in a region of interest encompassing the deep quadriceps (MCE software, University of Virginia, Charlottesville, Virginia). Because mean video intensity of images acquired at the lowest pulsing interval (i.e., 1 RR interval, which