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# Adults With Type 2 Diabetes Mellitus Exhibit a Greater Exercise-Induced Increase in Arterial Stiffness and Vessel Hemodynamics

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1　**Adults with Type 2 Diabetes Exhibit a Greater Exercise-Induced Increase in Arterial**

2　**Stiffness and Vessel Hemodynamics**

3　Running title: Post-exercise arterial stiffness in diabetes

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30  **ABSTRACT**

31  Individuals with type 2 diabetes mellitus (T2DM) have a greater blood pressure (BP) response to

32  acute maximal exercise compared to those without T2DM; however, whether they exhibit a

33  different arterial stiffness (AS) response to maximal exercise has yet to be explored. Adults with

34  (n=66) and without T2DM (n=61) underwent an 'arterial stress test': at rest and immediately

35  post-exercise, carotid-femoral pulse wave velocity (cfPWV), the gold-standard measure of AS,

36  brachial BP, heart rate (HR) and other hemodynamic measurements were assessed. Linear

37  regression models were used to evaluate between-group differences at rest, and the response to

38  exercise (post-exercise value), adjusting for covariates including BP and HR when relevant, and

39  the corresponding baseline value of each parameter. All participants (mean±SD: age 59.3±10.6

40  years; BMI 31.2±3.9 kg/m$^2$) had hypertension (mean BP 130±14/80±9 mmHg). At rest,

41  participants with T2DM had significantly higher cfPWV (10.3±2.7 vs. 9.1±1.9 m/s), HR (69±11

42  vs. 66±10 beats/min), and lower DBP (79±9 vs. 83±9 mmHg), but SBP (129±15 vs. 131±13

43  mmHg) was similar. In response to exercise, participants with T2DM showed greater increases

44  in cfPWV (1.6, 95%CI 0.4, 2.9 m/s), and SBP (9, 95% CI 1, 17 mmHg) than participants without

45  T2DM. A greater proportion of participants with T2DM had a hypertensive response to exercise

46  compared to participants without T2DM (n=23, 35% vs. n=11, 18%) (P=0.033). By

47  incorporating exercise as a vascular stressor, we provide evidence of a greater increase in AS in

48  individuals with T2DM, independently of resting AS, and the BP post-exercise.

49

50  **Keywords:** arterial stiffness, hypertension, type 2 diabetes mellitus, exercise, blood pressure,

51  exercise testing

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) increases arterial stiffness through pathological changes in the vasculature, including reduced nitric oxide bioavailability, increased oxidative stress and inflammation, as well as structural changes within the arterial wall[1]. As a result, for many individuals with T2DM, their vascular "age" surpasses their chronological age[2]. Furthermore, during maximal exercise, individuals with T2DM are more likely to experience an exaggerated blood pressure (BP) response[3]; this is defined as a rise in systolic BP (SBP) exceeding 210 mmHg in men and 190 mmHg in women, and is associated with higher cardiovascular disease (CVD) risk and mortality[4]. The physiological changes underlying this altered response have not been fully elucidated, but underlying vascular abnormalities are thought to play a pivotal role[5]. However, whether individuals with T2DM have a different arterial stiffness response to exercise, independent of the resting value, has yet to be explored. In this context, increased demands associated with acute exercise might exaggerate vascular abnormalities present in these individuals.

The 'gold standard' metric for assessing arterial stiffness non-invasively is carotid-femoral pulse wave velocity (cfPWV), a measure of the speed of the pressure pulse wave in the central elastic arteries[6]. Higher values of cfPWV indicate greater arterial stiffness, which is associated with a greater risk of CVD events and mortality[7, 8].

With increased metabolic demands during acute exercise, the vascular system plays an important role in the redistribution of blood flow to ensure adequate perfusion of the exercising muscle[9]. This leads to a transient increase in mean arterial pressure, sympathetic activity, and vascular tone, as well as central arterial stiffness[9]. During the recovery period, arterial stiffness has been shown to decrease to a level at, or below resting values[9]. While the initial increase in

75   arterial stiffness is recognized as a normal adaptation to acute exercise, the extent of the increase

76   in arterial stiffness and recovery trajectory may reflect the ability of the arteries to respond to

77   increased demands.

78       In the present study, we aimed to examine the acute response of arterial stiffness and

79   hemodynamic parameters to maximal exercise in adults with and without T2DM. We

80   hypothesized that individuals with T2DM would have a higher arterial stiffness in response to

81   exercise, independently of the resting values and BP.

82 **METHODS**

83     The data that support the findings of this study are available from the corresponding author

84 upon reasonable request.

85 **Ethical Approval**

86     The study was approved by the ethics review board of McGill University Faculty of

87 Medicine. Written informed consent was obtained from all participants.

88 **Study Cohort**

89     Participants were recruited through McGill-affiliated clinics for the SMARTER trial, a one-

90 year randomized controlled trial examining the impact of step count prescriptions on arterial

91 health[10]. All participants of the trial were overweight or obese (body mass index 25-40 kg/m$^2$),

92 had T2DM and/or hypertension, and did not have any gait abnormalities preventing exercise.

93 Hypertension and T2DM were diagnosed by the referring physician following Canadian

94 guidelines[11, 12]. The analyses herein were conducted in hypertensive participants with and

95 without T2DM who underwent the 'arterial stress test' at the baseline evaluation.

96 **Exercise Testing**

97     All participants underwent a maximal exercise test to exhaustion on a treadmill following a

98 modified Bruce protocol[13]. Peak oxygen consumption (VO$_{2\text{ peak}}$) was obtained using a metabolic

99 cart (Medisoft's Ergocard, Sorinne, Belgium). To ensure all participants had achieved

100 exhaustion, participants who did not attain age-based cutoffs for the respiratory exchange ratio

101 (RER) were excluded (aged 20-49: RER$\geq$1.10; aged 50-64: RER$\geq$1.05; aged $\geq$65: RER$\geq$1.00)[14].

102 Peak heart rate (HR) was obtained using the 3-lead electrocardiogram (ECG) connected to the

103 metabolic cart but was not used as a criterion to establish maximal effort due to the influence of

104 β-blockers on the HR response to exercise.

**Arterial Stiffness and Hemodynamics**

All measurements were performed in the morning to avoid circadian rhythm variations[15, 16]. Participants fasted for 12 hours prior to the assessment, and abstained from caffeine, alcohol, and smoking. Participants were offered a small healthy snack after the blood draw and prior to the 'arterial stress test' to prevent hypoglycemia and because a fasted state could have prevented participants from exerting themselves fully. Participants avoided exercise for 24 hours prior to the assessment. All usual medications, except anti-hyperglycemic agents, were taken the morning of assessment.

Brachial BP was measured using an automated oscillometric BP monitor (BpTRU, Medical Devices Ltd, BC, Canada) in a seated position at rest[12], as well as in a supine position at rest and after exercise (at 3, 5, 10, 15 and 20 minutes), following the cfPWV measurement. MAP was calculated as: brachial diastolic BP (DBP) + 1/3(brachial SBP-DBP)[17]. Due to the impact of body position on BP, brachial BP was assessed in the supine position in order to calibrate the central hemodynamic measures obtained in a supine position. Standing measurements of brachial BP were obtained manually using the auscultatory method immediately before and after exercise (0 minutes). This measure was used to evaluate whether participants experienced a hypertensive response to exercise, which was defined as a brachial SBP >210 mmHg in men and >190 mmHg in women[4].

Arterial stiffness, central BP, and augmentation index (AIx) were measured using applanation tonometry (SphygmoCor, AtCor Medical, Sydney, Australia) in a supine position before and immediately after exercise following a standardized protocol in a controlled environment at the Vascular Health Unit at the McGill University Health Centre. Baseline measurements were obtained after a 10-minute rest period. Following exercise completion,

128    participants returned to a supine position for the measurement of cfPWV (at 3, 5, 10, 15, and 20

129    minutes) and carotid-radial PWV (crPWV), central BP and AIx (at 5, 10, 15, and 20 minutes).

130    As per SphygmoCor recommendations, the radial pressure waveforms were calibrated using

131    brachial SBP and DBP. As calibration with MAP and DBP has been increasingly suggested[18], we

132    also performed this analysis. HR was acquired at the same time as the cfPWV measurement

133    using the built-in 3-lead ECG. To account for the influence of HR on wave reflection, AIx was

134    corrected for a HR of 75 beats/ minute (AIx75). Path length was estimated using the subtraction

135    method, whereby the distance between the carotid artery site and the sternal notch was subtracted

136    from the distance between the sternal notch and the femoral artery site[6]. At rest, measurements

137    were repeated until two PWV measurements were within 0.5 m/s, and two augmentation

138    pressures were within 4%. PWA measurements with an operator index <80 and PWV

139    measurements with a pulse transit time standard deviation >13% or HR difference >5 beats/min

140    between sites were deemed poor quality and not considered. Due to time restrictions post-

141    exercise, only one good quality measurement was collected. Non-invasively recorded central

142    waveforms (derived from the radial artery) have been validated against invasively recorded

143    central waveforms at rest, as well as during and after cycling exercise[19]. Furthermore, good test-

144    retest reproducibility has been demonstrated for cfPWV, central BP and AIx acquired during and

145    after exercise[20, 21].

146        We also evaluated the BP-independent changes in arterial stiffness by calculating an index of

147    stiffness that is considered equivalent to the intrinsic stiffness index $\beta_0$, where $\beta_0$ is the exponent

148    of the pressure ($P$)-diameter ($D$) relationship within the vessel[22]:

149
$$P = P_{\text{ref}} e^{\beta_0 \left( \frac{D}{D_{\text{ref}}} - 1 \right)}.$$

150    $P_{ref}$ is a reference pressure and $D_{ref}$ is the diameter of the artery at the reference pressure. Using

151    cfPWV, the corresponding brachial DBP ($P_d$), and estimated blood mass density ($\rho$=1.050 kg/L),

152    and $P_{ref}$=100 mmHg, aortic stiffness index $\beta_0$ was determined[23] as

153
$$\beta_0 = \frac{\text{cfPWV}^2 \cdot 2\rho}{P_d} - \ln\left(\frac{P_d}{P_{ref}}\right).$$

154    The left ventricular ejection duration was derived from the central pressure waveform and

155    calculated as the time from the foot of the waveform to the incisura.

156    The timing of the measurements is summarized in Figure 1. Due to a short time window post-

157    exercise, we prioritized the measurement of brachial BP and cfPWV at the 3-minute time point.

158    From 5 minutes onwards, all parameters were measured, in the same order for all participants.

159    **Blood Collection**

160    Fasting venous blood samples were obtained for the quantification of glucose and insulin

161    levels following standard laboratory methods. In participants not taking insulin, fasting glucose

162    and insulin values were used to compute the Homeostatic Model Assessment-Insulin Resistance

163    (HOMA-IR).

164    **Analysis**

165    Demographic factors and resting parameters were compared between groups using the

166    Student's T-test or Mann-Whitney test, as appropriate. Categorical variables were assessed using

167    the chi-square test for independence. Linear regression models were used to evaluate between-

168    group differences in hemodynamic parameters post-exercise. In evaluating the response to

169    exercise, models were consistently adjusted for the baseline parameter, age, sex, as well as

170    waist:hip ratio and angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor

171    blocker (ARB) use to account for group differences in these variables. ACEis/ARBs are known

172    to influence the cardiovascular response to exercise. We further evaluated models with and

173    without statin use due to group differences, but it should be noted that statin use was strongly

174    correlated with T2DM status, given that clinical guidelines recommend statin therapy in patients

175    with T2DM. Further, all measurements were adjusted for HR at the time of measurement.

176        To correct for the BP dependence of cfPWV, brachial DBP at the time of the measure was

177    included as a covariate in our statistical models. DBP was chosen given that the SphygmoCor

178    system uses the diastolic foot of the proximal and distal waveforms for the estimation of transit

179    time, and therefore, provides a velocity measure that is dependent on DBP. However, we also

180    assessed differences adjusting for mean arterial pressure (MAP) since we acknowledge that the

181    brachial BP differs from central BP, and this difference may be amplified during exercise[24].

182    Lastly, we also evaluated two separate models, where 1) both SBP and DBP were included, and

183    2) SBP replaced DBP.

184        To evaluate the impact of T2DM on overall vascular function after physical stress, area under

185    the curve (AUC) values were calculated for vessel hemodynamic parameters measured at

186    baseline, 3, 5, 10, 15, and 20 minutes. In order to compare the AUC irrespective of the baseline

187    value, a 'baseline AUC' was determined using the pre-exercise value and subtracted from the

188    total AUC (Figure S1). Differences in the AUC were assessed using linear regression, adjusting

189    for age, sex, waist:hip ratio, and ACEi/ARB use.

190        Mean differences between groups were computed with 95% confidence intervals (CIs). SAS

191    V9.3 was used.

**RESULTS**

Overall, 266 participants completed the exercise test. We excluded 1) participants with T2DM who did not have hypertension (n=30), 2) participants who did not meet criteria for exhaustion (n=80), and 3) participants who were missing the 3-minute post-exercise arterial stiffness measures (n=26) (Figure 2). We further identified two participants with T2DM who were significant outliers when we evaluated the post-exercise cfPWV, and whose inclusion likely exaggerated between-group differences (Table S1). Excluded participants who did not reach exhaustion during the exercise test exercised for a shorter duration, and had a lower $VO_{2peak}$ and peak HR, but were otherwise comparable to those who were included in the final analysis (Table S2). Our main analyses compared participants with (n=66) and without T2DM (n=61).

In our main analysis, participants with T2DM had a greater waist:hip ratio, but body mass index was similar. A comparable proportion of participants with and without T2DM were treated for hypertension; however, a greater proportion with T2DM were taking ACEi/ARBs, in accordance with clinical practice guidelines (Table 1)[12]. There were differences in the lipid profile, and statins were taken by 79% of participants with T2DM versus 33% without T2DM. Fasting glucose and HOMA-IR levels were higher in those with T2DM, who had a mean hemoglobin A1c of 7.9±1.3%.

At rest, participants with T2DM had higher cfPWV and aortic stiffness $\beta_0$, and lower central and brachial DBP, but no significant differences in SBP or other hemodynamic measures were noted (Table 1).

*Response to Exercise*

Unadjusted values of all parameters post-exercise are presented in the online supplement (Table S3). In adjusted analyses, no differences were observed between subjects with and

215 without T2DM for the duration of exercise, exercise capacity ($VO_{2peak}$), or maximal HR (Table

216 2). A higher proportion of participants with T2DM had a hypertensive response to exercise

217 compared to participants without T2DM [n=23 (35%) vs. n=11 (18%); difference 17% (95% CI

218 2, 32 %)]. However, the peak exercise BP (0 minutes) was not significantly different between

219 groups in adjusted analyses. Table 2 also presents the arterial stiffness and hemodynamic

220 parameters according to their first available measurement post-exercise (3 or 5 minutes) to

221 demonstrate the initial response to exercise. Immediately after exercise (at 3 minutes), we

222 observed significantly greater brachial SBP by 8.9 mmHg (95% CI 0.9, 16.9 mmHg) in

223 participants with T2DM, but no differences in DBP or peak HR.

224     Interestingly, participants with T2DM had a greater increase in cfPWV and aortic stiffness $\beta_0$,

225 as well as pulse pressure. The differences in cfPWV persisted in models adjusting for brachial

226 DBP at the time of measurement (Table 2), MAP, and both SBP and DBP (Table S4). The

227 increase in cfPWV was not significant when adjusting for only brachial SBP post-exercise

228 (Table S4). In addition, it is noteworthy that the elevated SBP at 3 minutes post-exercise in

229 T2DM was no longer significant when additionally adjusting for the corresponding post-exercise

230 cfPWV [6.1 (95% CI -2.1, 14.2 mmHg)]. A significant between-group difference in aortic

231 stiffness $\beta_0$ remained when SBP was included (7.70, 95% CI 0.05, 15.34). Univariate, partially

232 adjusted, and fully adjusted models for aortic stiffness $\beta_0$ are presented in Table S5.

233     No significant differences in central BP, crPWV, AIx75, or left ventricular ejection duration

234 were observed. Calibration of central BP with brachial MAP and DBP instead of SBP and DBP

235 did not change the results (Table S6).

236     Participants with T2DM exhibited a greater AUC for cfPWV, aortic stiffness $\beta_0$, and brachial

237 SBP and DBP than participants without T2DM (Table 3). There were no differences between

238    subjects with and without T2DM beyond 3 minutes for brachial SBP (Figure 3). While the

239    overall AUC was different between groups for brachial DBP, there were no differences at 3

240    minutes, or at other points during the recovery. cfPWV and aortic stiffness $\beta_0$ were both

241    significantly different at 3, 5, 10 and 20 minutes in unadjusted analyses, and only at 3 and 10

242    minutes in adjusted analyses, accounting for the pre-exercise value, age, sex, waist:hip ratio,

243    ACEi/ARB use, and DBP (cfPWV only) and HR at the time of measurement. Between-group

244    differences for all parameters during recovery (5, 10, 15 and 20 minutes) are presented in Table

245    S7.

**DISCUSSION**

By incorporating exercise as a vascular stressor, we provide evidence of a greater increase in cfPWV and aortic stiffness $\beta_0$ in individuals with T2DM, independently of resting arterial stiffness, and the brachial BP post-exercise. In a fully adjusted model, we observed a difference in cfPWV of 1.6 m/s between individuals with and without T2DM. A meta-analysis of 17 longitudinal studies (n=15,877 individuals) showed that a 1 m/s increase in resting aortic stiffness corresponds to a 14%, 15%, and 15% increased risk of CVD events, CVD mortality and all-cause mortality, respectively, adjusting for traditional CVD risk factors[7]. This robust association was confirmed in a more recent large individual participant meta-analysis in 17,635 individuals[8]. While the clinical significance of differences in cfPWV post-exercise has not been established, the magnitude of the difference in cfPWV observed in our study is not trivial.

Calculating the AUC allowed us to generate a single variable that summarizes multiple longitudinal measurements, capturing the combined response and recovery of each parameter to maximal stress. Our results, indicating significant differences in the AUC for cfPWV and aortic stiffness $\beta_0$, support an overall difference in the response of arterial stiffness to exercise between individuals with and without T2DM. The AUC for brachial SBP was also higher in individuals with T2DM but this was mainly driven by differences between groups immediately post-exercise, given that both groups followed a similar trajectory afterwards, i.e., from 5 to 20 minutes post-exercise.

In subjects with T2DM, we observed a greater increase in brachial SBP at 3 minutes post-exercise, which is in line with findings by Scott and colleagues demonstrating an excessive rise in brachial SBP in response to maximal treadmill exercise in adults with T2DM compared to healthy controls[3]. While they also observed a significantly greater increase in central SBP

269   immediately post-exercise (<3 minutes), we only observed a trend for an increase, likely because

270   central BP in our study was captured 5 minutes post-exercise, at which point values had returned

271   to baseline.

272     To our knowledge, no prior studies have evaluated the arterial stiffness response

273   immediately post-maximal exercise in adults with T2DM. A study of a hypertensive population

274   demonstrated elevated cfPWV 40 minutes and 1 hour after maximal cycling exercise compared

275   with baseline levels[25]. This increase post-exercise was not observed in normotensive controls;

276   however, this analysis did not compare the post-exercise cfPWV between groups. Instead, we

277   have demonstrated an elevated cfPWV response in individuals with T2DM and hypertension

278   compared to subjects with hypertension alone. Climie and colleagues compared the arterial

279   stiffness and hemodynamic response to a short bout of light-moderate cycling exercise between

280   individuals with T2DM and healthy controls[26]. They measured cfPWV while still on the cycle

281   ergometer, enabling more immediate cfPWV measurements. They observed a significantly

282   higher cfPWV post-exercise in individuals with T2DM (unadjusted); however, this analysis did

283   not account for differences in resting cfPWV or other covariates, as this was not the main interest

284   of this paper.

285     The relationship between arterial stiffness and BP is bi-directional and complex[27]. Arterial

286   stiffening increases the amplitude of the forward traveling pressure waves, as well as the speed

287   of propagation of both the forward and backward waves[6]. Consequently, the reflected waves

288   return earlier during the cardiac cycle and become superimposed on the systolic part of the

289   forward wave, leading to elevated central SBP and a widened pulse pressure[6]. Interestingly,

290   during light-moderate cycling exercise, the elevation in central SBP is mainly due to an increase

291   in the amplitude of the forward travelling wave, rather than reflected waves[28]. Therefore, arterial

292 stiffness and forward wave amplitude both contribute to the BP change observed during exercise.

293 Conversely, given the exponential relationship between artery diameter and pressure, there is a

294 clear acute relationship between the arterial BP and stiffness, represented by the tangent slope[23].

295 Therefore, the intrinsic stiffness of the artery will depend on BP. This bi-directional relationship

296 complicates the assessment of arterial stiffness independently of BP; however, different

297 mechanisms for evaluating the BP-independent response of arterial stiffness have been

298 proposed[23]. Most commonly, arterial stiffness is statistically adjusted for BP at the time of

299 measurement. Adjusting for the MAP is often recommended[6]; however, adjusting for the DBP

300 may be more relevant as this represents the pressure in the artery when the transit time is

301 calculated[29]. We have performed analyses adjusting for brachial DBP as well as for MAP.

302 Hermeling and colleagues have demonstrated that PWV changes dramatically over the cardiac

303 cycle, reporting a mean difference of 2.4 m/s between the diastolic and systolic phase (range 0.8-

304 4.4 m/s)[30]. In our study we have calculated transit time using the foot of the arterial pressure

305 waveform, and therefore, elected to adjust analyses for the brachial DBP. Similarly, aortic

306 stiffness $\beta_0$ is derived by inputting the DBP. Spronck and colleagues demonstrated that cardio-

307 ankle vascular index (CAVI), which has been proposed to be a pressure-independent estimate of

308 the intrinsic stiffness $\beta$, may show a residual acute BP dependence[23]. They provide a modified

309 formula that theoretically removes the acute BP dependence, yielding $CAVI_0$. Our inclusion of

310 cfPWV versus heart-to-ankle PWV in the case of $CAVI_0$ provides an estimate of the intrinsic

311 stiffness $\beta_0$ in the central elastic arteries. In our study, statistical correction of cfPWV for DBP,

312 and the aortic stiffness $\beta_0$ yielded comparable results. Similar to cfPWV, a significant aortic

313 stiffness $\beta_0$ difference remained when adjusting for SBP. This observation strengthens our

314 finding that the observed difference in arterial stiffness between groups is independent of the

14

315    intrinsic arterial stiffness dependence on DBP (as corrected for through calculation of aortic

316    stiffness $\beta_0$), as well as independently of SBP. We also observed an elevated cfPWV response in

317    models adjusting for MAP. A significant association between brachial SBP immediately post-

318    exercise and the corresponding post-exercise cfPWV was also noted. Specifically, the elevated

319    SBP response post-exercise in T2DM was no longer significant when adjusting for the

320    corresponding post-exercise cfPWV. On the other hand, the higher cfPWV response in T2DM

321    was independent of brachial SBP and DBP post-exercise. Taken together, these findings indicate

322    that arterial stiffness may mediate the exaggerated SBP increase.

323       Participants with T2DM had elevated arterial stiffness at rest, which is likely a function of

324    structural changes of the arteries. High levels of circulating glucose lead to the development of

325    advanced glycation end products, whereby glucose forms cross-links with collagen proteins

326    within the arteries, and therefore, may alter the important balance between elastin and collagen[1].

327    Hyperglycemia causes the activation of protein kinase C, which leads to the generation of

328    reactive oxygen species, and inflammation, further altering the structural and functional integrity

329    of vascular wall[1]. When assessing post-exercise values of cfPWV, we have adjusted for resting

330    values of cfPWV. Furthermore, we have demonstrated that the increase in arterial stiffness after

331    acute exercise occurs independently of BP at the time of measurement, suggesting that these

332    changes are due to changes in intrinsic properties of the arterial wall. As structural changes in

333    such time frame (minutes) are unlikely, we attribute differences in response to exercise mainly to

334    functional changes. For example, individuals with T2DM have endothelial dysfunction; higher

335    levels of endothelin-1 and reduced nitric oxide bioavailability may cause an impaired

336    vasodilatory response and increased arterial stiffness post-exercise[1]. Additionally, excess

337    sympathetic activity in individuals with T2DM may potentiate greater exercise-induced

338    vasoconstriction[1]. It is noteworthy that vasoconstriction does not always lead to a functional

339    increase in stiffness; for example, in healthy subjects, vasoconstriction may shift pressure load

340    bearing towards elastin, offloading the stiff collagen. However, in individuals with T2DM who

341    have impaired arterial function, vasoconstriction presumably leads to increased functional

342    stiffness[31].

343        The sample size of our study is relatively small; however, we demonstrated conclusive

344    between-group differences in our main outcome, while adjusting for relevant covariates. This

345    study constituted a secondary analysis of our SMARTER trial[10], and thus we did not carry out

346    power calculations *a priori*. Due to time constraints post-exercise, we could only obtain single

347    measurements at each time point and were only able to measure select indices of arterial stiffness

348    (i.e., cfPWV) at the 3-minute time point. Thus, we were not able to capture differences in central

349    hemodynamic parameters earlier, as these measurements were only obtained after 5 minutes

350    post-exercise. To this end, because we did not have central DBP measures immediately after

351    exercise wwe have included brachial DBP in our models. However, DBP is relatively stable,

352    with little difference between peripheral and central values[6]. Pulse pressure amplification

353    increases during exercise in healthy individuals[24]; however, a follow-up study by the same group

354    demonstrated that the degree of amplification is reduced in older patients with

355    hypercholesterolemia[32]. Moreover, the pulse pressure amplification is likely driven more by an

356    increase in SBP. We examined central and peripheral BP at 5 minutes; although on average

357    brachial SBP was 15 mmHg greater than central SBP, there was only a 2 mmHg average

358    difference for DBP (data not shown). Therefore, while brachial DBP seems to closely estimate

359    the central DBP, we still included analyses adjusting for MAP (mainly driven by DBP)[17].

360    Following guidelines, measurements of arterial stiffness and hemodynamics were performed in a

361     supine position pre- and post-exercise; however, we were not able to control for the possible

362     postural influence of lying down after treadmill exercise on vessel hemodynamics. Since we

363     aimed to provoke maximal changes in arterial stiffness and hemodynamics, a graded treadmill

364     test was selected over supine cycling exercise. Lastly, since all participants included in our

365     analysis were hypertensive, the results of this study may not be generalizable to younger, lower-

366     risk individuals with T2DM.

367

368     **PERSPECTIVES**

369         Our study has demonstrated that evaluating the exercise-induced response of arterial stiffness

370     provides additional information by capturing the effect of T2DM on the ability of the arteries to

371     respond to increased demands during exercise. Central arterial stiffness directly influences BP

372     and likely contributes to the exaggerated BP response in participants with T2DM. Increased

373     central arterial stiffness has a number of clinical consequences; it imposes a greater load on the

374     left ventricle, decreases coronary perfusion, and exposes the microcirculation and end-organs to

375     increased pulsatile pressure. Given that we do not spend our lives at rest, and physical stress

376     commonly occurs during daily activities, this altered arterial stiffness response to strenuous

377     exercise may contribute to the increased risk for CVD events in these individuals. The 'arterial

378     stress test' may serve as a useful model for evaluating vascular impairment and CVD risk in

379     individuals with T2DM. Future studies are needed to confirm the clinical utility of this model.

380

391

392 **CONFLICTS OF INTEREST/DISCLOSURE**

393 None.

394

395 **SUPPLEMENTAL MATERIALS**

396 Online Figure S1

397 Online Data Tables S1-S7

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493

494    **NOVELTY AND SIGNIFICANCE**

495    **What is new?**

496    - Our study is the first to examine the acute response of arterial stiffness and hemodynamic

497      parameters to acute maximal exercise in individuals with hypertension and with and

498      without type 2 diabetes mellitus (T2DM)

499    - We provide evidence of a greater increase in carotid-femoral pulse wave velocity, the

500      'gold standard' measure of central arterial stiffness, in individuals with T2DM in

501      response to acute maximal exercise, independently of resting arterial stiffness and the

502      blood pressure (BP) post-exercise

503    - A significantly higher post-exercise response of aortic stiffness $\beta_0$, a novel BP

504      independent measure of arterial stiffness, was observed in individuals with T2DM versus

505      without T2DM

506    **What is relevant?**

507    - Our study confirmed an exaggerated BP response in individuals with T2DM, which has

508      been previously associated with higher cardiovascular disease risk and mortality

509    - Our findings demonstrating a greater arterial stiffness response in individuals with T2DM

510      help unravel the physiological mechanisms of the elevated BP response to exercise

511      observed in this population

512    **Summary**

513    - By incorporating acute maximal exercise as a vascular stressor, we provide evidence of a

514      greater increase in arterial stiffness post-exercise in individuals with hypertension and

515      T2DM compared to individuals with hypertension alone

516 **FIGURE LEGENDS**

517

518 **Figure 1.** Timing of procedures included in the 'arterial stress test' protocol.

519 AIx75, augmentation index corrected for a HR of 75 beats/minute; BP, blood pressure; cfPWV,

520 carotid-femoral pulse wave velocity; crPWV, carotid-radial pulse wave velocity; HR, heart rate;

521 RER, respiratory exchange ratio, $VO_2$, oxygen consumption.

522

523 **Figure 2.** Participant flowchart outlining the number of participants excluded from the final

524 analysis.

525 cfPWV, carotid-femoral pulse wave velocity; RER, respiratory exchange ratio; T2DM, type 2

526 diabetes mellitus.

527

528 **Figure 3.** Trajectory of unadjusted A) cfPWV, B) aortic stiffness $\beta_0$, C) systolic blood pressure

529 and D) diastolic blood pressure changes from rest to post-exercise at 3, 5, 10, 15, and 20 minutes.

530 Error bars represent 95% confidence intervals. Linear regression models were used. *Indicates a

531 significant between-group difference in unadjusted analyses, and ^ indicates a significant

532 difference in adjusted analyses (described in Table 2).

533 cfPWV, carotid-femoral pulse wave velocity; T2DM, type 2 diabetes mellitus.

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**TABLES**

**Table 1: Baseline characteristics**

| Variable | Without T2DM (n=61) | With T2DM (n=66) | P- value |
|---|---|---|---|
| **Demographic factors** | | | |
| Age (years) | 59.0±10.4 | 59.6±10.9 | 0.749 |
| Women, no (%) | 35 (57.4) | 28 (42.4) | 0.092 |
| Body mass index (kg/m$^2$) | 31.7±3.9 | 30.7±3.8 | 0.132 |
| Waist circumference (cm) | 101.7±9.5 | 103.4±10.1 | 0.353 |
| Hip circumference (cm) | 111.8±8.9 | 107.2±7.7 | **0.002** |
| Waist:hip ratio | 0.91±0.07 | 0.96±0.07 | **<0.001** |
| **Smoking history, no (%)** | | | |
| Past Smoker | 21 (34.4) | 23 (35.4) | 0.910 |
| Current Smoker | 2 (3.3) | 5 (7.6) | 0.269 |
| **Type 2 Diabetes** | | | |
| Duration (years) | | 10.5±7.5 | |
| **Medications, no (%)** | | | |
| Anti-hypertensive agents | 58 (95.1) | 65 (98.5) | 0.273 |
| ACEi or ARBs | 39 (63.9) | 62 (93.9) | **<0.001** |
| Calcium channel blockers | 18 (29.5) | 14 (21.2) | 0.282 |
| Diuretics | 29 (47.5) | 28 (42.4) | 0.562 |
| Beta-blockers | 18 (29.5) | 15 (22.7) | 0.384 |
| Statins | 20 (32.8) | 52 (78.8) | **<0.001** |

| | | | |
|---|---|---|---|
| Insulin | | 22 (33.3) | |
| Metformin | | 57 (86.4) | |
| Sulfonylureas | | 22 (33.3) | |
| **Laboratory Parameters** | | | |
| Fasting glucose (mmol/L)* | 5.5 [5.0-6.1] | 7.9 [6.5-8.8] | **<0.001** |
| Fasting insulin (pmol/L)* | 65.0 [44.1-92.9] | 55.8 [43.1-87.7] | 0.698 |
| Hemoglobin A1c (%) | | 7.6 [7.0-8,4] | |
| HOMA-IR | 2.7 [1.7-3.6] | 3.2 [2.3-4.6] | **0.043** |
| HDL (mmol/L) | 1.3±0.3 | 1.2±0.3 | **0.035** |
| LDL (mmol/L) | 3.0±1.0 | 2.1±0.6 | **<0.001** |
| Triglycerides (mmol/L) | 1.3 [1.0-2.0] | 1.5 [1.1-2.2] | 0.326 |
| Total cholesterol (mmol/L) | 5.1±1.2 | 4.1±0.8 | **<0.001** |
| **Arterial Stiffness and Hemodynamics (measured supine)** | | | |
| cfPWV (m/s) | 9.2±1.9 | 10.3±2.7 | **0.009** |
| Aortic stiffness $\beta_0$ | 15.1 [12.3-19.8] | 19.8 [15.0-25.8] | **0.003** |
| crPWV (m/s) | 8.6±1.1 | 8.9±1.3 | 0.184 |
| Brachial SBP (mmHg) | 131±13 | 129±15 | 0.630 |
| Brachial DBP (mmHg) | 82±9 | 78±9 | **0.030** |
| Brachial PP (mmHg) | 49±10 | 51±13 | 0.284 |
| Central SBP (mmHg) | 121±12 | 119±14 | 0.454 |
| Central DBP (mmHg) | 83±9 | 79±9 | **0.030** |
| Central PP (mmHg) | 38±10 | 40±13 | 0.421 |
| MAP (mmHg) | 99±10 | 97±10 | 0.120 |

| | | | |
|---|---|---|---|
| AIx75 (%) | 22.8±10.8 | 23.2±8.7 | 0.836 |
| Pulse Pressure Amplification | 1.3±0.2 | 1.3±0.2 | 0.991 |
| Resting HR (beats/minute) | 66.1±9.8 | 68.5±11.1 | 0.205 |
| Left ventricular ejection duration (ms) | 323.8±26.8 | 321.0±31.6 | 0.594 |
| **Blood Pressure (measured seated)** | | | |
| Brachial SBP (mmHg) | 125±12 | 125±16 | 0.983 |
| Brachial DBP (mmHg) | 79±9 | 76±11 | 0.079 |

541

542 Values expressed as mean±standard deviation, median [interquartile range], or number (%) as

543 appropriate.

544 *Not measured in participants with T2DM on insulin therapy (n=34).

545

546 ACEi, angiotensin-converting enzyme inhibitor; Aix75, augmentation index corrected for a heart

547 rate of 75 beats/minute; ARB, angiotensin receptor blocker; cfPWV, carotid-femoral pulse wave

548 velocity; crPWV, carotid-radial pulse wave velocity; DBP, diastolic blood pressure; HDL, high

549 density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; HR, heart rate;

550 LDL, low density lipoprotein; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic

551 blood pressure; T2DM, type 2 diabetes mellitus.

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553

**Table 2. Between-group differences in arterial stiffness and hemodynamics in initial**

**response to exercise each parameter (3 or 5 minutes)**

| Variable | Without T2DM (n=61) | With T2DM (n=66) | Mean difference (with-without T2DM) (95% CI) |
|---|---|---|---|
| **Immediately Post-Exercise** | | | |
| **Exercise time (minutes)** | 14.8 (14.3, 15.3) | 15.0 (14.5, 15.5) | 0.2 (-0.6, 1.0) |
| **VO$_{2peak}$ (mL/kg/min)** | 24.3 (23.1, 25.5) | 24.0 (22.9, 25.2) | -0.3 (-2.0, 1.5) |
| **Max HR (beats/min)** | 154.0 (148.8, 159.2) | 153.1 (148.2, 158.0) | -0.9 (-8.5, 6.7) |
| **Peak SBP (mmHg)** | 173.1 (166.2, 180.0) | 182.8 (176.3, 189.4) | 9.7 (-0.4, 19.8) |
| **Peak DBP (mmHg)** | 78.0 (74.1, 81.9) | 74.6 (70.8, 78.4) | -3.4 (-9.2, 2.4) |
| **3 minutes** | | | |
| **Brachial SBP (mmHg)** | 164.0 (158.6, 169.5) | 173.0 (167.8, 178.2) | **8.9 (0.9, 16.9)** |
| **Brachial DBP (mmHg)** | 82.7 (80.7, 84.8) | 84.1 (82.1, 86.1) | 1.4 (-1.7, 4.5) |
| **Brachial PP (mmHg)** | 81.4 (76.886.1) | 88.8 (84.4, 93.2) | **7.4 (0.6, 14.2)** |
| **cfPWV (m/s)** | 12.8 (12.0, 13.7) | 14.5 (13.7, 15.3) | **1.6 (0.4, 2.9)** |
| **Aortic stiffness $\beta_0$** | 35.0 (29.7, 40.2) | 43.6 (38.7, 48.6) | **8.7 (1.0, 16.4)** |
| **HR (beats/min)** | 98.3 (94.7, 101.8) | 98.6 (95.3, 102.0) | 0.4 (-4.8, 5.6) |

| 5 minutes | | | |
|---|---|---|---|
| crPWV (m/s) | 8.7 (8.3, 9.0) | 8.9 (8.6, 9.2) | -0.3 (-0.2, 0.7) |
| Central SBP (mmHg) | 118.2 (115.0, 121.4) | 121.1 (118.0, 124.2) | 2.9 (-1.7, 7.7) |
| Central DBP (mmHg) | 79.6 (77.6, 81.6) | 81.2 (79.3, 83.1) | 1.6 (-1.4, 4.6) |
| Central PP (mmHg) | 38.6 (36.2, 41.0) | 40.0 (37.7, 42.2) | 1.36 (-2.1, 5.0) |
| AIx75 (%) | 26.0 (24.3, 27.7) | 24.4 (22.8, 26.0) | -1.6 (-4.1, 1.0) |
| Ejection duration (ms) | 302.6 (296.1, 309.1) | 304.8 (298.6, 311.0) | 2.2 (-7.3, 11.7) |

556

557  AIx75, augmentation index corrected for a heart rate of 75 beats/minute; cfPWV, carotid-femoral

558  pulse wave velocity; crPWV, carotid-radial pulse wave velocity; DBP, diastolic blood pressure;

559  PP, pulse pressure; SBP, systolic blood pressure; $VO_{2peak}$; peak oxygen consumption.

560  Adjusted means (95% CI) are presented.

561  Exercise time, $VO_{2peak}$, maximal HR, ejection duration, HR and AIx75 are adjusted for age, sex,

562  waist:hip ratio and ACEi/ARB use.

563  cfPWV and crPWV are adjusted for the pre-exercise value, age, sex, waist:hip ratio, ACEi/ARB

564  use, as well as HR and MAP at the time of measurement.

565  Aortic stiffness $\beta_0$ and BP is adjusted for for the pre-exercise value, age, sex, waist:hip ratio,

566  ACEi/ARB use, and HR at the time of measurement.

**Table 3: Between-group differences in the area under the curve for arterial stiffness and hemodynamics in response to exercise**

| Area Under the Curve Variable | Without T2DM (n=61) | With T2DM (n=66) | Mean difference (with-without T2DM) (95% CI) |
|---|---|---|---|
| Brachial SBP (mmHg·min) | -6.6 (-64.6, 51.4) | 79.9 (25.5, 134.3) | **86.5 (2.2, 170.7)** |
| Brachial DBP (mmHg·min) | -42.7 (-73.7, -11.7) | 9.4 (-19.7, 38,4) | **52.1 (7.1, 97.1)** |
| Brachial PP (mmHg·min) | 36.2 (-8.4, 80.7) | 70.5 (28.7, 112.4) | 34.4 (-30.4, 99.2) |
| cfPWV (m/s·min) | 20.7 (12.9, 28.6) | 36.3 (28.6, 44.0) | **15.5 (4.0, 27.1)** |
| Aortic stiffness $\beta_0$ | 105.3 (66.1, 144.5) | 175.6 (137.5, 213.6) | **70.2 (12.6, 127.8)** |
| crPWV (m/s·min) | -2.3 (-7.7, 3.1) | -0.7 (-6.0, 4.7) | 1.6 (-6.4, 9.7) |
| Central SBP (mmHg·min) | -134.1 (-184.4, -83.9) | -79.1 (-126.3, -31.8) | 55.1 (-18.4, 128.6) |
| Central DBP (mmHg·min) | -33.3 (-64.5, -2.2) | 0.7 (-28.6, 30.0) | 34.0 (-11.6, 79.6) |
| MAP (mmHg·min) | -63.3 (-97.6, -28.9) | -26.4 (-58.6, 5.9) | 36.9 (-13.3, 87.1) |
| Central PP (mmHg·min) | -100.8 (-135.7, -65.9) | -79.8 (-112.5, -47.0) | 21.0 (-30.0, 72.1) |

| | | | |
|---|---|---|---|
| AIx75 (%·min) | -9.0 (-31.3, 13.3) | -33.7 (-55.0, -12.3) | -24.7 (-57.5, 8.2) |

All analyses were adjusted for age, sex, waist:hip ratio, and ACEi/ARB use. Adjusted means (95% CI) are presented.

AIx75, augmentation index corrected for a heart rate of 75 beats/minute; BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; crPWV, carotid-radial pulse wave velocity; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; T2DM, type 2 diabetes mellitus.