

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/m²) 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

52 INTRODUCTION

53 Type 2 diabetes mellitus (T2DM) increases arterial stiffness through pathological changes in
54 the vasculature, including reduced nitric oxide bioavailability, increased oxidative stress and
55 inflammation, as well as structural changes within the arterial wall¹. As a result, for many
56 individuals with T2DM, their vascular “age” surpasses their chronological age². Furthermore,
57 during maximal exercise, individuals with T2DM are more likely to experience an exaggerated
58 blood pressure (BP) response³; this is defined as a rise in systolic BP (SBP) exceeding 210
59 mmHg in men and 190 mmHg in women, and is associated with higher cardiovascular disease
60 (CVD) risk and mortality⁴. The physiological changes underlying this altered response have not
61 been fully elucidated, but underlying vascular abnormalities are thought to play a pivotal role⁵.
62 However, whether individuals with T2DM have a different arterial stiffness response to exercise,
63 independent of the resting value, has yet to be explored. In this context, increased demands
64 associated with acute exercise might exaggerate vascular abnormalities present in these
65 individuals.

66 The ‘gold standard’ metric for assessing arterial stiffness non-invasively is carotid-femoral
67 pulse wave velocity (cfPWV), a measure of the speed of the pressure pulse wave in the central
68 elastic arteries⁶. Higher values of cfPWV indicate greater arterial stiffness, which is associated
69 with a greater risk of CVD events and mortality^{7, 8}.

70 With increased metabolic demands during acute exercise, the vascular system plays an
71 important role in the redistribution of blood flow to ensure adequate perfusion of the exercising
72 muscle⁹. This leads to a transient increase in mean arterial pressure, sympathetic activity, and
73 vascular tone, as well as central arterial stiffness⁹. During the recovery period, arterial stiffness
74 has been shown to decrease to a level at, or below resting values⁹. 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 health¹⁰. All participants of the trial were overweight or obese (body mass index 25-40 kg/m²),
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 protocol¹³. Peak oxygen consumption ($\text{VO}_{2\text{ peak}}$) 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: $\text{RER} \geq 1.10$; aged 50-64: $\text{RER} \geq 1.05$; aged ≥ 65 : $\text{RER} \geq 1.00$)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.

105 **Arterial Stiffness and Hemodynamics**

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

113 Brachial BP was measured using an automated oscillometric BP monitor (BpTRU, Medical
114 Devices Ltd, BC, Canada) in a seated position at rest¹², as well as in a supine position at rest and
115 after exercise (at 3, 5, 10, 15 and 20 minutes), following the cfPWV measurement. MAP was
116 calculated as: $\text{brachial diastolic BP (DBP)} + 1/3(\text{brachial SBP-DBP})^{17}$. Due to the impact of
117 body position on BP, brachial BP was assessed in the supine position in order to calibrate the
118 central hemodynamic measures obtained in a supine position. Standing measurements of brachial
119 BP were obtained manually using the auscultatory method immediately before and after exercise
120 (0 minutes). This measure was used to evaluate whether participants experienced a hypertensive
121 response to exercise, which was defined as a brachial SBP >210 mmHg in men and >190 mmHg
122 in women⁴.

123 Arterial stiffness, central BP, and augmentation index (AIx) were measured using
124 applanation tonometry (SphygmoCor, AtCor Medical, Sydney, Australia) in a supine position
125 before and immediately after exercise following a standardized protocol in a controlled
126 environment at the Vascular Health Unit at the McGill University Health Centre. Baseline
127 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 suggested¹⁸, 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 site⁶. 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 exercise¹⁹. 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 β_0 , where β_0 is the exponent
148 of the pressure (P)-diameter (D) relationship within the vessel²²:

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 $P_{\text{ref}}=100$ mmHg, aortic stiffness index β_0 was determined²³ as

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

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 exercise²⁴.
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.

192 **RESULTS**

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

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

209 At rest, participants with T2DM had higher cfPWV and aortic stiffness β_0 , and lower central
210 and brachial DBP, but no significant differences in SBP or other hemodynamic measures were
211 noted (Table 1).

212 *Response to Exercise*

213 Unadjusted values of all parameters post-exercise are presented in the online supplement
214 (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 β_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 β_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 β_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 β_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 β_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.

246 **DISCUSSION**

247 By incorporating exercise as a vascular stressor, we provide evidence of a greater increase in
248 cfPWV and aortic stiffness β_0 in individuals with T2DM, independently of resting arterial
249 stiffness, and the brachial BP post-exercise. In a fully adjusted model, we observed a difference
250 in cfPWV of 1.6 m/s between individuals with and without T2DM. A meta-analysis of 17
251 longitudinal studies (n=15,877 individuals) showed that a 1 m/s increase in resting aortic
252 stiffness corresponds to a 14%, 15%, and 15% increased risk of CVD events, CVD mortality and
253 all-cause mortality, respectively, adjusting for traditional CVD risk factors⁷. This robust
254 association was confirmed in a more recent large individual participant meta-analysis in 17,635
255 individuals⁸. While the clinical significance of differences in cfPWV post-exercise has not been
256 established, the magnitude of the difference in cfPWV observed in our study is not trivial.

257 Calculating the AUC allowed us to generate a single variable that summarizes multiple
258 longitudinal measurements, capturing the combined response and recovery of each parameter to
259 maximal stress. Our results, indicating significant differences in the AUC for cfPWV and aortic
260 stiffness β_0 , support an overall difference in the response of arterial stiffness to exercise between
261 individuals with and without T2DM. The AUC for brachial SBP was also higher in individuals
262 with T2DM but this was mainly driven by differences between groups immediately post-
263 exercise, given that both groups followed a similar trajectory afterwards, i.e., from 5 to 20
264 minutes post-exercise.

265 In subjects with T2DM, we observed a greater increase in brachial SBP at 3 minutes post-
266 exercise, which is in line with findings by Scott and colleagues demonstrating an excessive rise
267 in brachial SBP in response to maximal treadmill exercise in adults with T2DM compared to
268 healthy controls³. 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 levels²⁵. 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 controls²⁶. 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 complex²⁷. 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 waves⁶. 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 pressure⁶. 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 waves²⁸. 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 slope²³.
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 proposed²³. Most commonly, arterial stiffness is statistically adjusted for BP at the time of
299 measurement. Adjusting for the MAP is often recommended⁶; however, adjusting for the DBP
300 may be more relevant as this represents the pressure in the artery when the transit time is
301 calculated²⁹. 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 β_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 β , may show a residual acute BP dependence²³. They provide a modified
309 formula that theoretically removes the acute BP dependence, yielding CAVI₀. Our inclusion of
310 cfPWV versus heart-to-ankle PWV in the case of CAVI₀ provides an estimate of the intrinsic
311 stiffness β_0 in the central elastic arteries. In our study, statistical correction of cfPWV for DBP,
312 and the aortic stiffness β_0 yielded comparable results. Similar to cfPWV, a significant aortic
313 stiffness β_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

315 intrinsic arterial stiffness dependence on DBP (as corrected for through calculation of aortic
316 stiffness β_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 collagen¹.
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 wall¹. 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-exercise¹. Additionally, excess
337 sympathetic activity in individuals with T2DM may potentiate greater exercise-induced

338 vasoconstriction¹. 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 stiffness³¹.

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 trial¹⁰, 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 we have included brachial DBP in our models. However, DBP is relatively stable,
352 with little difference between peripheral and central values⁶. Pulse pressure amplification
353 increases during exercise in healthy individuals²⁴; however, a follow-up study by the same group
354 demonstrated that the degree of amplification is reduced in older patients with
355 hypercholesterolemia³². 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

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384

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391

392 **CONFLICTS OF INTEREST/DISCLOSURE**

393 None.

394

395 **SUPPLEMENTAL MATERIALS**

396 Online Figure S1

397 Online Data Tables S1-S7

398 **REFERENCES**

- 399 1. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease:
400 Pathophysiology, clinical consequences, and medical therapy: Part i. *Eur Heart J.* 2013;34:2436-
401 2443
- 402 2. Stone JA, Fitchett D, Grover S, Lewanczuk R, Lin P. Vascular protection in people with
403 diabetes. *Can J Diabetes.* 2013;37 Suppl 1:S100-104
- 404 3. Scott JA, Coombes JS, Prins JB, Leano RL, Marwick TH, Sharman JE. Patients with type
405 2 diabetes have exaggerated brachial and central exercise blood pressure: Relation to left
406 ventricular relative wall thickness. *Am J Hypertens.* 2008;21:715-721
- 407 4. Schultz MG, Otahal P, Cleland VJ, Blizzard L, Marwick TH, Sharman JE. Exercise-
408 induced hypertension, cardiovascular events, and mortality in patients undergoing exercise stress
409 testing: A systematic review and meta-analysis. *Am J Hypertens.* 2013;26:357-366
- 410 5. Schultz MG, Sharman JE. Exercise hypertension. *Pulse (Basel).* 2014;1:161-176
- 411 6. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR,
412 Heffernan KS, Lakatta EG, McEniery CM, Mitchell GF, Najjar SS, Nichols WW, Urbina EM,
413 Weber T, American Heart Association Council on H. Recommendations for improving and
414 standardizing vascular research on arterial stiffness: A scientific statement from the american
415 heart association. *Hypertension.* 2015;66:698-722
- 416 7. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and
417 all-cause mortality with arterial stiffness: A systematic review and meta-analysis. *J Am Coll*
418 *Cardiol.* 2010;55:1318-1327
- 419 8. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie
420 P, Cameron J, Chen CH, Cruickshank JK, et al. Aortic pulse wave velocity improves

421 cardiovascular event prediction: An individual participant meta-analysis of prospective
422 observational data from 17,635 subjects. *J Am Coll Cardiol.* 2014;63:636-646

423 9. Mutter AF, Cooke AB, Saleh O, Gomez YH, Daskalopoulou SS. A systematic review on
424 the effect of acute aerobic exercise on arterial stiffness reveals a differential response in the
425 upper and lower arterial segments. *Hypertens Res.* 2017;40:146-172

426 10. Dasgupta K, Rosenberg E, Joseph L, Cooke AB, Trudeau L, Bacon SL, Chan D,
427 Sherman M, Rabasa-Lhoret R, Daskalopoulou SS. Physician step prescription and monitoring to
428 improve arterial health (smarter): A randomized controlled trial in patients with type 2 diabetes
429 and hypertension. *Diabetes Obes Metab.* 2017;19:695-704

430 11. Punthakee Z, Goldenberg R, Katz P. Definition, classification and diagnosis of diabetes,
431 prediabetes and metabolic syndrome. *Can J Diabetes.* 2018;42 Suppl 1:S10-s15

432 12. Nerenberg KA, Zarnke KB, Leung AA, Dasgupta K, Butalia S, McBrien K, Harris KC,
433 Nakhla M, Cloutier L, Gelfer M, et al. Hypertension canada's 2018 guidelines for diagnosis, risk
434 assessment, prevention, and treatment of hypertension in adults and children. *Canadian Journal*
435 *of Cardiology.* 2018;34:506-525

436 13. Bruce RA. Exercise testing of patients with coronary heart disease. Principles and normal
437 standards for evaluation. *Annals of clinical research.* 1971;3:323-332

438 14. Edvardsen E, Hem E, Anderssen SA. End criteria for reaching maximal oxygen uptake
439 must be strict and adjusted to sex and age: A cross-sectional study. *PLoS One.* 2014;9:e85276

440 15. Papaioannou TG, Karatzis EN, Papamichael CM, Karatzi KN, Zakopoulos NA, Lekakis
441 JP, Mavrikakis M, Stefanadis C. Circadian variation of arterial pressure wave reflections.
442 *American Journal of Hypertension.* 2006;19:259-263

- 443 16. Kollias GE, Stamatelopoulos KS, Papaioannou TG, Zakopoulos NA, Alevizaki M,
444 Alexopoulos GP, Kontoyannis DA, Karga H, Koroboki E, Lekakis JP, Papamichael CM. Diurnal
445 variation of endothelial function and arterial stiffness in hypertension. *J Hum Hypertens*.
446 2009;23:597-604
- 447 17. Salvi P. *Pulse waves*. Italy: Springer-Verlag; 2012.
- 448 18. Papaioannou TG, Karageorgopoulou TD, Sergentanis TN, Protogerou AD, Psaltopoulou
449 T, Sharman JE, Weber T, Blacher J, Daskalopoulou SS, Wassertheurer S, et al. Accuracy of
450 commercial devices and methods for noninvasive estimation of aortic systolic blood pressure a
451 systematic review and meta-analysis of invasive validation studies. *J Hypertens*. 2016;34:1237-
452 1248
- 453 19. Sharman JE, Lim R, Qasem AM, Coombes JS, Burgess MI, Franco J, Garrahy P,
454 Wilkinson IB, Marwick TH. Validation of a generalized transfer function to noninvasively derive
455 central blood pressure during exercise. *Hypertension*. 2006;47:1203-1208
- 456 20. Keith LJ, Rattigan S, Keske MA, Jose M, Sharman JE. Exercise aortic stiffness:
457 Reproducibility and relation to end-organ damage in men. *J Hum Hypertens*. 2013;27:516-522
- 458 21. Holland DJ, Sacre JW, McFarlane SJ, Coombes JS, Sharman JE. Pulse wave analysis is a
459 reproducible technique for measuring central blood pressure during hemodynamic perturbations
460 induced by exercise. *Am J Hypertens*. 2008;21:1100-1106
- 461 22. Hayashi K, Handa H, Nagasawa S, Okumura A, Moritake K. Stiffness and elastic
462 behavior of human intracranial and extracranial arteries. *J Biomech*. 1980;13:175-184
- 463 23. Spronck B, Avolio AP, Tan I, Butlin M, Reesink KD, Delhaas T. Arterial stiffness index
464 beta and cardio-ankle vascular index inherently depend on blood pressure but can be readily
465 corrected. *J Hypertens*. 2017;35:98-104

- 466 24. Sharman JE, McEniery CM, Campbell RI, Coombes JS, Wilkinson IB, Cockcroft JR. The
467 effect of exercise on large artery haemodynamics in healthy young men. *Eur J Clin Invest*.
468 2005;35:738-744
- 469 25. Attina TM, Drummond ID, Malatino LS, Maxwell SR, Webb DJ. Phosphodiesterase type
470 5 inhibition improves arterial stiffness after exercise but not exercise capacity in hypertensive
471 men. *Am J Hypertens*. 2013;26:342-350
- 472 26. Climie RE, Srikanth V, Keith LJ, Davies JE, Sharman JE. Exercise excess pressure and
473 exercise-induced albuminuria in patients with type 2 diabetes mellitus. *Am J Physiol Heart Circ*
474 *Physiol*. 2015;308:H1136-1142
- 475 27. Mitchell GF. Arterial stiffness and hypertension: Chicken or egg? *Hypertension*.
476 2014;64:210-214
- 477 28. Schultz MG, Davies JE, Roberts-Thomson P, Black JA, Hughes AD, Sharman JE.
478 Exercise central (aortic) blood pressure is predominantly driven by forward traveling waves, not
479 wave reflection. *Hypertension*. 2013;62:175-182
- 480 29. Spronck B, Delhaas T, Butlin M, Reesink KD, Avolio AP. Options for dealing with
481 pressure dependence of pulse wave velocity as a measure of arterial stiffness: An update of
482 cardio-ankle vascular index (cavi) and cavi0. *Pulse (Basel)*. 2018;5:106-114
- 483 30. Hermeling E, Vermeersch SJ, Rietzschel ER, de Buyzere ML, Gillebert TC, van de Laar
484 RJ, Ferreira I, Hoeks AP, van Bortel LM, Reneman RS, Segers P, Reesink KD. The change in
485 arterial stiffness over the cardiac cycle rather than diastolic stiffness is independently associated
486 with left ventricular mass index in healthy middle-aged individuals. *J Hypertens*. 2012;30:396-
487 402

- 488 31. Lacolley P, Regnault V, Segers P, Laurent S. Vascular smooth muscle cells and arterial
489 stiffening: Relevance in development, aging, and disease. *Physiol Rev.* 2017;97:1555-1617
- 490 32. Sharman JE, McEniery CM, Dhakam ZR, Coombes JS, Wilkinson IB, Cockcroft JR.
491 Pulse pressure amplification during exercise is significantly reduced with age and
492 hypercholesterolemia. *J Hypertens.* 2007;25:1249-1254
- 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 parameters to acute maximal exercise in individuals with hypertension and with and without type 2 diabetes mellitus (T2DM)
- 497
- We provide evidence of a greater increase in carotid-femoral pulse wave velocity, the ‘gold standard’ measure of central arterial stiffness, in individuals with T2DM in response to acute maximal exercise, independently of resting arterial stiffness and the blood pressure (BP) post-exercise
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- A significantly higher post-exercise response of aortic stiffness β_0 , a novel BP independent measure of arterial stiffness, was observed in individuals with T2DM versus without T2DM
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506 **What is relevant?**

- Our study confirmed an exaggerated BP response in individuals with T2DM, which has been previously associated with higher cardiovascular disease risk and mortality
 - Our findings demonstrating a greater arterial stiffness response in individuals with T2DM help unravel the physiological mechanisms of the elevated BP response to exercise observed in this population
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512 **Summary**

- By incorporating acute maximal exercise as a vascular stressor, we provide evidence of a greater increase in arterial stiffness post-exercise in individuals with hypertension and T2DM compared to individuals with hypertension alone
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- 514
- 515

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, VO₂, 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 β_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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539 TABLES

540 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 β_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

554 **Table 2. Between-group differences in arterial stiffness and hemodynamics in initial**
 555 **response to exercise each parameter (3 or 5 minutes)**

Variable	Without T2DM	With T2DM	Mean difference
	(n=61)	(n=66)	(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 β_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 β_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.

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

Area Under the Curve	Without T2DM	With T2DM	Mean difference
Variable	(n=61)	(n=66)	(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 β_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)
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569

570 All analyses were adjusted for age, sex, waist:hip ratio, and ACEi/ARB use. Adjusted means
571 (95% CI) are presented.

572

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