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**Exercise-induced vasodilation is not impaired following radial artery
catheterization in coronary artery disease patients**

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Running Head. Exercise vasodilation post catheterization damage in CAD

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1 **Abstract**

2 Diagnosis and treatment for coronary artery disease (CAD) often involves
3 angiography and/or percutaneous coronary intervention. However, the radial artery
4 catheterization required during both procedures may result in acute artery
5 dysfunction/damage. Whilst exercise-based rehabilitation is recommended for CAD
6 patients following catheterization, it is not known if there is a period when exercise
7 may be detrimental due to catheter-induced damage. Animal studies have
8 demonstrated exercise-induced paradoxical vasoconstriction post-catheterization.
9 This study aimed to examine arterial responses to acute exercise following
10 catheterization. Thirty-three CAD patients (65.8 ± 7.3 yr, 31.5 ± 6.3 kg.m⁻², 82%♂)
11 undergoing transradial catheterization were assessed pre- and 1 week post-
12 catheterization. Radial artery (RA) diameter and shear rate were assessed during
13 handgrip exercise (HE), in both the catheterized (CATH) and control (CON) arms.
14 Endothelial function was also assessed via simultaneous bilateral radial flow
15 mediated dilation (FMD) at both time-points. We found that the increase in RA
16 diameter and shear stress in response to HE ($P < 0.0001$) was maintained post-
17 catheterization in both the CATH and CON arms, whereas FMD following
18 catheterization was impaired in the CATH [$6.5 \pm 3.3\%$ to $4.7 \pm 3.5\%$ ($P = 0.005$)] but not
19 in the CON [$6.2 \pm 2.6\%$ to $6.4 \pm 3.5\%$ ($P = 0.797$)] limb. Whilst endothelial dysfunction,
20 assessed by FMD, was apparent 1 week post-catheterization, the ability of the RA to
21 dilate in response to exercise was not impaired. The impact of catheterization and
22 consequent endothelial denudation on vascular dys/function in humans may
23 therefore be stimulus specific and a highly level of redundancy appears to exist that
24 preserves exercise-mediated vasodilator responses.

25 **Key words:** acute exercise, arterial function, catheterization-induced damage,

26 coronary artery disease

27

28 **New & Noteworthy**

29 Despite depressed flow-mediated endothelium-dependent dilation following
30 catheterization-induced damage, radial artery responses to handgrip exercise were
31 preserved. This suggests that arterial responses to catheterization may be stimulus
32 specific and that redundant mechanisms may compensate for vasodilator impairment
33 during exercise. This has implications for exercise-based rehabilitation after
34 catheterization.

35

36 **Introduction**

37 Cardiovascular disease (CVD) is the leading cause of mortality worldwide (24), with
38 coronary artery disease (CAD) the primary cause of CVD death (23). Catheterization
39 procedures such as percutaneous transluminal coronary angiography (PTCA) and/or
40 percutaneous coronary intervention (PCI; angioplasty), are routinely used in the
41 diagnosis and treatment of CAD (14, 15, 26). However, such procedures are likely to
42 mechanically damage endothelial cells (19), leading to artery dysfunction. Indeed,
43 previous studies have reported endothelial dysfunction in both catheterized coronary
44 (13, 28) and peripheral arteries(7, 20) following PTCA and/or PCI.

45

46 Whilst exercise training is generally recommended for CAD patients (22),
47 catheterization-induced arterial damage may transiently elevate the risk of cardiac
48 events when the stimulus of exercise is superimposed. Indeed, previous animal
49 studies have demonstrated that catheterization results in 'paradoxical'
50 vasoconstriction of damaged arteries in response to exercise (4). If such responses
51 are apparent in humans, there may be a basis to suggest delaying cardiac
52 rehabilitation, post-catheterization. Although assessment of flow-mediated dilation
53 (FMD) post-catheterization may provide useful information about arterial recovery,
54 and therefore the safest to begin exercise rehabilitation post-catheterization, there is
55 currently no data on the response of human arteries to exercise stimuli following
56 catheterization-induced endothelial damage. Given the complex mechanisms by
57 which exercise regulates blood flow (12), the vascular response of damaged arteries
58 at rest or in response to FMD may be different from the arterial response to exercise.
59 The aim of this study was to examine conduit arterial responses to acute exercise

60 pre- and post-catheterization in humans. We assessed vascular function using both
61 flow-mediated dilation (FMD) and handgrip exercise (HE), pre- and post-
62 catheterization. Additional vascular parameters, such as blood velocity, blood flow,
63 shear rate (mean, anterograde and retrograde), as well as blood pressure, handgrip
64 strength and rating of perceived exertion (RPE), were secondary outcomes. We
65 hypothesized that vascular function, assessed via FMD and the response to HE,
66 would be impaired 1 week following PTCA and/or PCI in the catheterized arm, but
67 not in the contralateral control artery.

68

69

70 **Materials and methods**

71 ***Participants and Ethical Approval***

72 Thirty-three patients undergoing prospective transradial cardiac catheterization
73 (PTCA and/or PCI) for known or suspected CAD were recruited from Liverpool Heart
74 and Chest Hospital (LHCH). Patients gave written informed consent. Patients were
75 excluded if they had a recent acute coronary syndrome or transradial cardiac
76 catheterization within the last 3 months. This study conformed to the Declaration of
77 Helsinki, and ethical approval was obtained from the Liverpool East NHS Research
78 Ethics Committee (REC 13/NW/0088).

79

80 ***Study design***

81 Vascular function measurements were assessed prior to, and 1 week post-
82 catheterization (PTCA and/or PCI). Both experimental visits were completed in a
83 quiet room, between 0800 and 1100 hrs and patients were fasted (including caffeine

84 and alcohol) and asked to abstain from exercise and cigarettes for 12 hours before
85 each visit (37). Diabetic patients had a standardised breakfast (porridge or plain
86 toast), which was the same on both occasions. The pre-assessment was undertaken
87 on the day of the prospective catheterization, before the intervention (~1-4 hours).
88 Experimental visits included two tests (bilateral radial artery FMD and bilateral HE),
89 undertaken in both the catheterized (CATH) and the contralateral (CON) arm.

90

91 ***Transradial Cardiac Catheterization***

92 PTCA and/or PCI was performed predominantly via the right radial artery (RA) (9%
93 via left radial artery). Local anaesthesia was achieved with 2% lignocaine (Antigen
94 Pharmaceuticals, Ireland). The RA was punctured with a 21-gauge needle through
95 which a 0.0118" platinum-tipped nitinol guide wire was introduced. Then, a 5F (4
96 patients), 6F (28 patients) or 7F (1 patient) hydrophilic sheath introducer (sheath
97 length 16 cm) was inserted (PreludeEase, MeritMedical, UK). A weight-adjusted
98 dose of heparin and routine use of vasodilator cocktail (nitroglycerine, verapamil, or
99 diltiazem) was introduced into the central circulation during the procedure, as
100 required. All introducer sheaths were removed at the end of the procedure and
101 haemostasis was achieved in the catheterization laboratory through a compression
102 device (MedPlus, UK). The patients were mobilized immediately but remained in the
103 hospital until the compression device was removed (after ~4 hours).

104

105 ***Experimental procedures***

106 Maximal voluntary contraction (MVC) of both arms was measured, during both visits,
107 using a dynamometer (Takei 5420 Grip-D Digital Hand Grip Dynamometer, Japan).
108 Patients then rested in the supine position for >10 min to ensure that all

109 hemodynamic variables stabilised. Blood pressure (BP) and heart rate (HR) were
110 measured using an automated sphygmomanometer (GE Pro 300V2, Dinamap,
111 Tampa, FL, USA), after the resting period. Two 12-MHz multi-frequency linear array
112 probes, attached to two high-resolution ultrasound machines (T3000 or Terason u-
113 smart 3300; Teratech, Burlington, MA, USA) were used to image the RA (10-15 cm
114 proximal from the scaphoid bone in the wrist), for both tests. Once optimal images
115 were obtained, the probes were held stable and the ultrasound parameters were set
116 to optimize the longitudinal, B-mode image of the lumen–arterial wall interface.
117 Continuous Doppler velocity assessments were obtained using the ultrasounds
118 (insonation angle $< 60^\circ$). The same ultrasounds and sonographers were used
119 between the visits, and within participants.

120

121 ***Bilateral radial artery FMD***

122 Both arms were extended $\sim 45^\circ$ from the torso, and two inflation/deflation pneumatic
123 cuffs (D.E. Hokanson, Bellevue, WA) were placed proximal to the wrists (~ 1 cm
124 proximal from the scaphoid bone) to provide a stimulus for ischemia. The RA in both
125 wrists (10-15 cm proximal from the scaphoid bone in the wrist) was scanned for 1
126 minute to obtain baseline parameters. Then, the forearm cuffs were inflated
127 (≥ 220 mmHg) for 5min. Diameter and velocity recordings resumed 30s prior to cuff
128 deflation and continued for 3min thereafter, in accordance with guidelines (36, 37).

129

130 ***Bilateral HE***

131 Following the FMD test described above, patients performed an incremental
132 handgrip exercise (HE) protocol, while in the seated position. Participants completed
133 3 min of HE at each of 5, 10 and 15% pre-determined MVC, with 1-min rest between

134 these bouts. An metronome (Korg MA30 Metronome 2006, Japan), was used to
135 keep constant pace for the handgrip exercise HE (30 contractions per min). Diameter
136 and velocity recordings were obtained from the RA, before the HE, and three times
137 during the 1-min rest at the end of each HE intensity (at 5% MVC, 10% MVC and
138 15% MVC). Rating of perceived exertion (RPE) on a 1-10 scale (1: no effort to 10:
139 maximal effort) was taken at the end of each HE bout.

140

141 ***Data analysis***

142 Custom-designed edge-detection and wall-tracking software was used to analyse
143 both the FMD and HE, in order to minimise the investigator bias (36, 40). Blood flow
144 was calculated as the product of synchronized diameter (CSA) and velocity data, at
145 30Hz. Shear rate (SR) (an estimate of shear stress without viscosity) was calculated
146 as four times mean velocity/diameter. FMD was reported as the percentage
147 difference in diameter from baseline to peak, following cuff release (36). Other
148 parameters measured during FMD, such as SRAUC (shear rate area under the
149 curve) and time to peak dilation, were calculated from the point of cuff release to the
150 point of maximal post-deflation diameter.

151

152 For HE, changes in diameter, velocity, blood flow AUC (mean, anterograde, and
153 retrograde), and SRAUC (mean, anterograde and retrograde) were calculated as
154 averages (usually a 1-minute recording), before, and during the 1-min rest between
155 the incremental HE bouts. For further analysis of HE parameters, baseline values
156 taken before HE (Pre-Ex) and the peak value achieved (Peak-Ex) during HE (either
157 at 5%, 10% or 15% MVC) were compared.

158 **Statistics**

159 All analyses were performed using IBM SPSS statistics for Windows, version 25.0
160 (Armonk, NY: IBM Corp.). For FMD, allometric scaling was performed to control for
161 differences in baseline diameter (2) and then a mixed-linear model (arm*time),
162 controlling for baseline diameter, was undertaken. For HE, a mixed-linear model
163 (arm*time*exercise) was used. A mixed-linear model was also used to analyze the
164 differences in MVC, and RPE, between arms and/or pre-post catheterization. Paired
165 *t*-test were used to assess BP and HR changes pre- to post-catheterization. Pairwise
166 comparisons were performed, using the Fisher's least significant difference (LSD),
167 when significant main or interaction effects were detected. Data are presented as
168 mean±SD and alpha significance was set at $P \leq 0.05$.

169

170

171 **Results**

172 Patient characteristics and medications, prior to catheterization, are shown in Table
173 1. The majority of the patients were taking at least one of the following: aspirin, beta-
174 blocker, angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor
175 blocker (ARB), nitrate or a statin. All 33 patients had successful transradial
176 catheterization; 20 patients had PTCA and 13 patients PCI (1 x no stent, 9 x 1 stent,
177 2 x 2 stents, 1 x 3 stents). Four patients were referred for coronary artery bypass
178 graft (CABG) following the diagnostic PTCA. These patients were stable, and their
179 CABG was scheduled more than 1 week following diagnostic PTCA, therefore
180 patients were allowed to attend the follow-up visit 1 week post-catheterization. FMD
181 was performed on all 33 patients, while 29 patients completed the HE protocol (2x
182 equipment failure, 1x avoid exercise due to dizziness following FMD, 1x previous

183 injury to their hand). Arterial patency was not recorded immediately after
184 catheterization, but none of the 33 patients we assessed 1 week post-catheterization
185 using Doppler ultrasound had any apparent radial occlusion.

186

187 ***Impact of catheterization on HE response***

188 There was a main effect of HE on RA diameter, with RA diameter increasing in
189 response to HE (main effect of exercise, $P < 0.001$). This exercise-induced
190 vasodilation was similar in both arms and remained unchanged pre- and post-
191 catheterization (time*arm*exercise interaction ($P = 0.725$)). A significant finding
192 (time*arm interaction, $P < 0.001$) suggested that the diameter of the catheterized RA
193 was higher 1 week post-catheterization, compared with pre-catheterization
194 ($P < 0.001$), whereas RA diameter was unchanged in the control RA ($P = 0.086$) (Table
195 2). There was no difference in percentage change in RA diameter in response to HE,
196 pre- vs post-catheterization, in either arm (Figure 1A).

197

198 There was a significant increase in mean, antegrade and retrograde shear rate in
199 response to HE ($P < 0.001$), but there were no differences in these responses
200 between arms ($P = 0.138$, $P = 0.098$, and $P = 0.133$ respectively), or pre- to post-
201 catheterization ($P = 0.121$, $P = 0.148$, and $P = 0.172$ respectively) (Figure 2B and Table
202 3). Similarly, blood velocity, total mean blood flow, antegrade blood flow and
203 retrograde blood flow followed the same pattern, with significant increases in
204 response to exercise ($P < 0.001$), but no differences pre- to post-catheterization
205 ($P = 0.274$, $P = 0.275$, $P = 0.286$ and $P = 0.614$ respectively) or between arms ($P = 0.102$,
206 $P = 0.157$, $P = 0.107$ and $P = 0.064$ respectively) (Table 3).

207 ***Impact of catheterization on FMD***

208 There was a significant impact of catheterization on FMD (time*arm interaction),
209 when controlling for baseline diameter (P=0.034), and without baseline diameter
210 normalization (P=0.011). There was a significant reduction in FMD in the
211 catheterized RA [6.5±3.3% to 4.7±3.5% (P=0.005)], with no change in the non-
212 catheterized RA [6.2±2.6% to 6.4±3.5% (P=0.797)] following catheterization (Figure
213 2).

214

215 As with the HE data, baseline artery diameter during the FMD test significantly
216 differed after catheterization (significant time*arm interaction for P=0.046). When
217 pairwise comparisons were performed, an increase in baseline diameter 1 week
218 post-catheterization was observed in the catheterized RA, compared to pre-
219 catheterization (P=0.009). There was no change in the control RA (P=0.785).
220 Baseline RA diameter was not different between arms before the catheterization
221 (P=0.707) but was significantly higher in the catheterized RA compared to the control
222 arm 1 week post-catheterization (P=0.016). There was no change in peak diameter,
223 time to peak diameter or shear rate under the curve (SRAUC) (Table 3).

224

225 ***Impact of catheterization on systemic haemodynamic measurements, MVC,***
226 ***and RPE***

227 There was no change in BP or HR pre- to post-catheterization (Table 4). MVC was
228 higher in the catheterized arm compared with the control arm (P=0.024), during both
229 visits. MVC was unchanged following catheterization (P=0.265; Table 4). RPE was
230 increased with incremental HE (main effect P<0.001), but there was no effect of

231 catheterization (P=0.588). When pairwise comparisons were examined, RPE at 5%
232 MVC was lower than 10% MVC (P=0.001) and 15% MVC (P<0.001), but there was
233 no difference between the RPE at 10% and 15% MVC (P=0.177) (Table 4).

234

235

236 **Discussion**

237 This study aimed to examine the impact of catheterization on radial artery function in
238 CAD patients. We assessed two vascular responses: a) a shear stress mediated
239 assessment of endothelium-dependent dilation (FMD), which is largely mediated by
240 nitric-oxide, and b) the response to handgrip exercise (HE) which represents a
241 mechanistically complex but ecologically valid measure of vascular function. To our
242 knowledge, this is the first study in humans to examine radial artery responses to
243 exercise following catheterization. We observed that vasodilator responses to
244 exercise were relatively preserved 1 week following catheterization, whereas there
245 was evidence for impairment in FMD responses post-catheterization. These data
246 suggest that the impact of catheterization on functional arterial responses may be
247 stimulus specific.

248

249 Our observation that RA dilation in response to exercise was not impaired 1 week
250 post-catheterization contrasts with some previous studies in animals, which have
251 reported a paradoxical vasoconstriction in response to exercise following endothelial
252 denudation (4, 30). In addition, two studies in patients performing supine bicycle
253 exercise during a follow-up PTCA reported an exercise-induced constriction in the
254 treated vessels, at 6 months post-PCI with 1st generation (38) and at 16 months with

255 2nd generation drug-eluting stents (DES) (31). However, this impairment may indicate
256 the presence of long-term complications of stenting, such as in-stent restenosis (29),
257 rather than the effects of catheterization-induced damage *per se*. In addition, there
258 were no baseline assessments in either study and it is therefore possible that
259 impairment was the result of advanced atherosclerotic disease (9) apparent prior to
260 catheterization. In any event, the paradoxical constriction of catheterized arteries in
261 response to exercise reported in these studies may contribute to exercise-induced
262 myocardial ischemia post-catheterization (4). Indeed, endothelial damage following
263 catheterization has been proposed as a factor to take into account when considering
264 the optimal time to begin exercise rehabilitation (39).

265

266 In the present study, we assessed the short-term impact of catheterization on arterial
267 responses to exercise, by evaluating the responses of the RA before and 1 week
268 post-procedure, alongside a contralateral internal control. This experimental design
269 suggests that our result, indicating preserved arterial response to exercise, is robust.
270 Radial arteries are comparable in size and histopathology to coronaries (3). Whilst
271 our results cannot be directly extrapolated to other arterial beds, they nonetheless
272 suggest that conduit arteries can retain their ability to dilate in response to exercise
273 following catheterization. This may have implications for recommendations pertaining
274 to safe timing of the uptake of cardiac rehabilitation. Two large-scale studies
275 conducted to determine the incidence of cardiac events induced by exercise in
276 patients who underwent PCI, concluded that performing exercise a few days post-
277 PCI is safe (10, 33).

278

279 Our exercise outcomes are informed by the fact that we also collected FMD data,
280 relating to endothelial function. In contrast to the exercise-mediated dilation, FMD
281 was impaired in the catheterized arm 1 week post-catheterization. There was no
282 change in the contralateral arm, suggesting that the impact of catheterization was
283 localised and not systemic. Our FMD findings are consistent with previous studies in
284 humans, which have indicated an immediate (within 24h) reduction in FMD in the
285 catheterized artery, but not in the contralateral artery, following transradial
286 catheterization (5-8, 20, 41). Although a recent study observed impaired endothelial
287 function 1 week post-procedure (lower FMD in the catheterized arm compared to the
288 control arm) (19), this study did not measure change in function pre- to post-
289 procedure. Consequently, our FMD findings are the first to report direct data on local
290 endothelial impairment 1 week following PTCA and/or PCI. FMD evaluates
291 endothelium-dependent dilation, which is largely nitric oxide (NO)-mediated (11). It is
292 therefore likely that PTCA and/or PCI impair NO-production in the catheterized
293 vessels. Reduced NO-production has been associated with proliferation and
294 migration of VSMC, as well as the activation of platelet cascades, increasing the risk
295 for restenosis and thrombosis (17). Interestingly, some observations indicate
296 impaired FMD in non-catheterized vessels following PCI (16, 21, 27), suggesting that
297 the endothelial dysfunction induced by catheterization may also reflect systemic
298 arterial dysfunction, potentially due to elevated oxidative stress, inflammation and
299 platelet aggregation induced by invasive procedures. Importantly, here we have
300 shown that effects remained localized to the catheterized vessels.

301

302 Regulation of blood flow during exercise is complex, involving a number of
303 mechanisms and vasoactive compounds, with multiple interactions and redundancy

304 (34, 35). Our finding that catheterization impaired FMD, but not HE responses,
305 suggests that vascular responses to exercise are preserved by redundant pathways
306 other than those purely related to NO-mediated function. In support of this notion,
307 Padilla *et al.* 2006 (25) demonstrated impaired FMD, but preserved responses to
308 handgrip exercise, in healthy subjects following a high-fat meal. Our findings
309 regarding stimulus specific vascular changes highlight the importance of applying
310 multiple techniques to evaluate arterial function. Indeed, previous experiments have
311 indicated that different periods of cuff inflation induce arterial dilation via distinct
312 pathways in humans (11). Routinely assessing vascular responses to exercise could
313 provide an ecologically valid assessment to complement FMD measures in future
314 studies, particularly as it is the most relevant test to provide insights regarding
315 exercise-based rehabilitation in CAD patients following catheterization.

316

317 Previous studies of the brachial artery have indicated that, as is the case for FMD
318 responses, HE mediated arterial dilation is shear stress mediated (1, 18, 32). For
319 example, McPhee and Pyke (2018) (18) suggested that handgrip exercise resulted in
320 similar vasodilation induced by reactive hyperaemia (FMD) and sustained shear
321 (HE). In contrast, there are other studies suggesting that vasodilation in response to
322 reactive and active hyperaemia may be driven by distinct mechanisms (25). If it can
323 be assumed that HE-mediated dilation of the *radial* artery is shear stress mediated,
324 then our finding that catheterization does not impact HE responses, despite
325 impacting radial FMD, would suggest that the stimulus specificity relates to the
326 nature of the shear stress stimulus. Our approach utilising post-catheterization
327 responses may provide future insight into the sensitivity of different arteries to stimuli
328 that induce distinct shear stress profiles.

329

330 In addition to functional impacts, we have also shown that structural changes may
331 occur after catheterization. There was an increase in RA diameter in the catheterized
332 arm, but not in the contralateral arm, 1 week post-catheterization. This was observed
333 prior to both FMD and HE. Previous studies have reported similar findings of
334 elevated RA diameter in the catheterized arm 24h post-catheterization (6-8, 41).
335 Collectively, our findings suggest that such structural modifications remained
336 apparent 1 week post-catheterization and therefore should be consider as a
337 consequence of catheterization and not just an immediate reaction of the artery to
338 the procedure. The time-course of structural adaptation or remodelling following
339 catheterization is an important question that might be addressed in future studies.

340

341 This study had a number of limitations. We did not control for age, gender, pre-
342 existing disease (diabetes, hypertension, peripheral artery disease), history of
343 smoking or medication use (including potential changes pre- to post-intervention).
344 However, our patient population are typical of those attending for interventions and
345 our repeated measures study design and contralateral within-subjects control artery
346 somewhat mitigates these limitations. In addition, we were not able to control for
347 different introducer catheter size, or compression time, which were both clinically
348 determined, as indicated. These may have affected arterial patency and possibly
349 vascular outcomes. In our study, 6F introducers were mostly used (28 out of 33
350 patients), with 5F and 7F introducers used in 4 and 1 patient, respectively. However,
351 we performed a supplementary mix-model liner regression, for FMD and HE

352 responses, with catheter size as a covariate and this did not affect the study
353 outcomes or interpretation.

354

355 In conclusion, this study provides important information regarding arterial function
356 following catheterization in humans. Our data showed that, although catheterization
357 induced localised impairment in flow mediated dilation, the ability of the RA to dilate
358 in response to exercise following catheterization-induced damage was largely
359 unaffected. This highlights that vascular responses to catheterization may be
360 stimulus specific. Since arterial responses to exercise were relatively preserved
361 following catheterization, it may be safe to undertake exercise-based rehabilitation
362 soon after catheterization procedures, although this should be confirmed in other
363 cohorts and in larger samples.

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368

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372

373 **Disclosures**

374 No conflicts of interest, financial or otherwise, are declared by the authors

375

376 **Author contribution**

377 **D.G. and E.D.** designed research; **A.T. and E.D.** conducted research; **A.T.** drafted
378 manuscript; **M.C., D.G., J.M. and E.D.** edited and revised the manuscript and **E.D.**
379 and **M.C.** approved final version of manuscript.

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546

547 **Tables**

548 **Table 1.** Characteristics of the study population (n=33).

549

550 **Table 2.** Vascular responses to handgrip exercise (HE). Vascular parameters, at rest,
551 prior to HE (PreEx) and the peak value to HE (PeakEx), in the catheterized radial
552 artery (CATH) and the contralateral control RA (CON), before the catheterization (Pre)
553 and at 1 week post-catheterization.

554

555 **Table 3.** Baseline diameter, peak diameter, time to peak and SRAUC associated
556 with the FMD tests before the procedure (Pre) and at 1 week post-catheterization, in
557 the catheterized (CATH) arm and the contralateral (CON) arm.

558

559 **Table 4.** Resting hemodynamic measurements, MVC in the catheterized arm
560 (CATH) and control arm (CON), and RPE during HE, pre- and 1 week post-
561 catheterization.

562

563 **Figures**564 **Figure 1. Vascular responses to handgrip exercise (HE).**

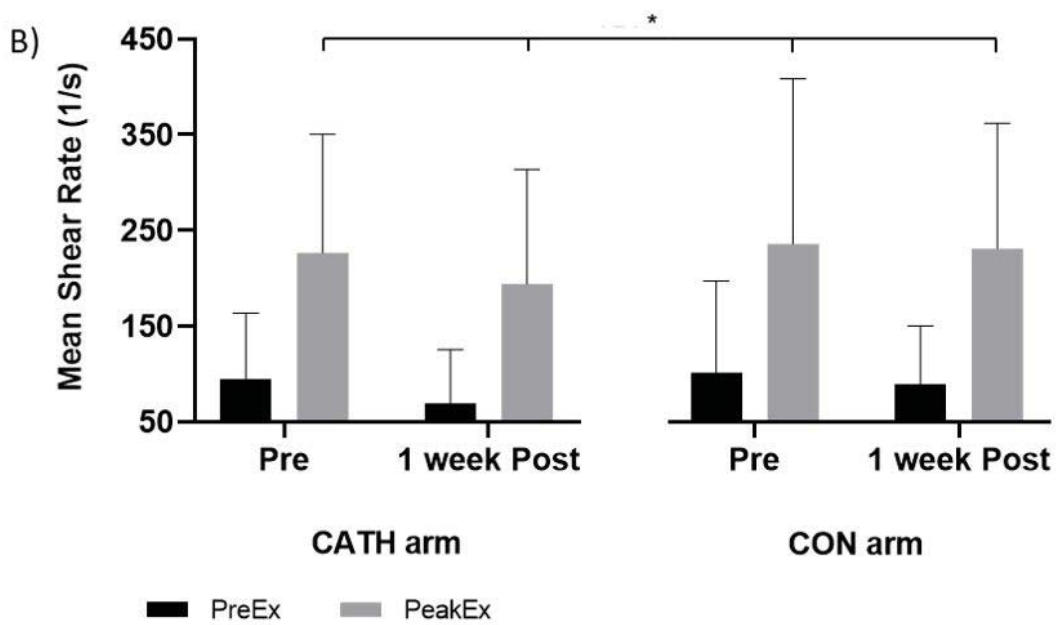
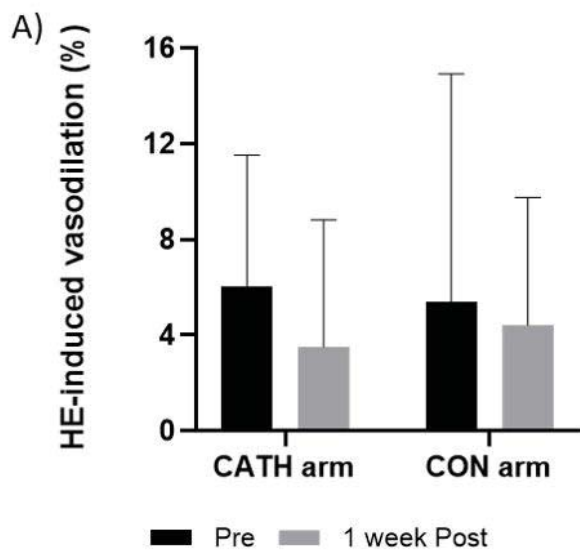
565 Percentage change in RA diameter following HE (A), in the catheterized RA (CATH
566 arm) and contralateral control RA (CON arm), pre- and 1 week post-catheterization.
567 Mean shear rate (B), prior to exercise (PreEx) and at peak (PeakEx), in the CATH
568 arm and CON arm, pre- and 1 week post-catheterization. Results are presented as
569 mean \pm SD n=29 (24 males). *Significantly different from PreEx, main effect of
570 exercise intensity (P<0.05).

571

572 **Figure 2. Changes in flow mediated dilation (FMD %) in the catheterized radial**
573 **artery (CATH) and contralateral arm (CON), pre- and 1 week post-**
574 **catheterization.**

575 Results are presented as mean \pm SD n=33 (27 males). A mix-linear model
576 (arm*time) with Fisher's least significant difference post hoc for pairwise
577 comparisons was used. *Significantly different from Pre, main interaction effect of
578 time*arm (P<0.05).

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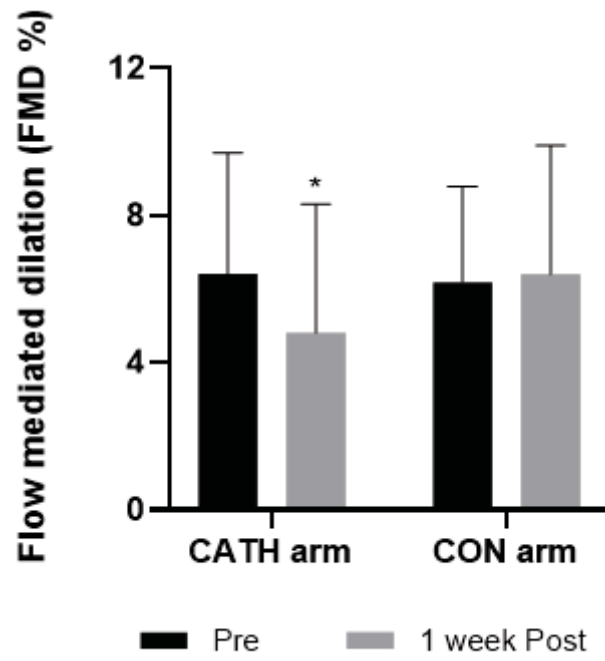


Table 1. Characteristics of the study population (n=33)

Clinical Characteristic		Mean \pm SD or n (%)
Age (years)		65.8 \pm 7.3
Sex (males)		27 (81.8)
BMI (m/kg²)		31.5 \pm 6.3
Risk Factors	Diabetes	9 (27.2)
	Hypertension	20 (60.6)
	Hypercholesterolemia	24 (72.5)
	Current smoker	3 (9.1)
	Ex-smoker	17 (51.5)
	Positive family history	20 (60.6)
Previous transradial catheterization (PTCA and/or PCI)		20 (60.6)
Previous CABG		0 (0)
Previous MI > 3 months		13 (39.4)
Medications	Aspirin	29 (87.8)
	Clopidogrel	2 (6)
	Beta-Blocker	20 (60.6)
	ACEI/ARB	22 (66.7)
	Nitrate	23 (69.7)
	Statin	26 (78.8)
	Calcium-Blocker	9 (27.3)
	Diuretics	7 (21.2)

BMI: body mass index, PTCA: percutaneous transluminal coronary angiography, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, MI:

myocardial infraction, ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Table 2. Vascular responses to handgrip exercise (HE). Vascular parameters, at rest, prior HE (PreEx) and the peak value to HE (PeakEx), in the catheterized radial artery (CATH) and the contralateral radial artery (CON), before the catheterization (Pre) and at 1 week post-catheterization.

	CATH arm		CON arm	
	Pre	1 week Post	Pre	1 week Post
Diameter (mm)				
PreEx	2.7±0.5	2.9±0.4	2.8±0.5	2.7±0.5
PeakEx	2.9±0.5*	3.0±0.4*	2.9±0.6*	2.8±0.5*
Velocity (cm/s)				
PreEx	6.1±4.0	5.0±3.9	6.8±6.0	6.0±4.4
PeakEx	15.0±6.7*	13.9±7.7*	16.5±10.3*	15.8±8.8*
Total Blood Flow (ml/min)				
PreEx	20.5±15.2	20.2±15.8	25.0±28.0	21.7±22.0
PeakEx	54.7±25.4*	56.1±28.4*	67.7±46.6*	56.0±33.7*
Anterograde Blood Flow (ml/min)				
PreEx	23.5±14.9	22.7±15.3	28.5±27.1	25.7±21.1
PeakEx	54.9±24.6*	56.4±28.1*	68.1±46.2*	56.4±33.5*
Retrograde Blood Flow (ml/min)				
PreEx	-3.0±2.6	-2.4±1.8	-3.5±3.4	-4.0±5.5
PeakEx	-1.2±1.7*	-1.2±1.4*	-1.6±2.2*	-1.0±1.3*
Anterograde Shear rate (1/s)				
PreEx	108.1±67.3	79.5±56.5	115.0±91.1	104.7±58.4
PeakEx	227.4±122.8*	194.9±118.9*	238.2±171.0*	232.4±130.4*
Retrograde Shear Rate (1/s)				
PreEx	-13.2±13.2	-8.7±6.9	-13.3±13.8	-15.1±20.5
PeakEx	-4.8±7.2*	-3.5±3.6*	-7.1±13.1*	-3.7±5.7*

Results are presented as mean \pm SD, n=29 (24 males). A mix-linear model (arm*time*exercise) with Fisher's least significant difference post hoc for pairwise comparisons was used. *Significantly different from PreEx, main effect of exercise (P<0.05)

Table 3. Baseline diameter, peak diameter, time to peak and SRAUC associated with the FMD tests before the procedure (Pre) and at 1 week post-catheterization, in the catheterized (CATH) arm and the contralateral (CON) arm.

	CATH arm		CON arm	
	Pre	1 week Post	Pre	1 week Post
Baseline diameter (mm)	2.82±0.7	3.04±0.5*	2.85±0.5	2.73±0.5 [†]
Peak Diameter (mm)	3.00±0.7	3.18±0.5	3.03±0.5	3.01±0.6
Time to peak (s)	50.8±25.1	56.7±27.9	66.0±32.4	57.4±34.2
SRAUC (s⁻¹ 10³)	18.5±12.4	15.0±8.8	16.3±10.6	14.0±9.3

SRAUC: shear rate area under the curve. Results are presented as mean ± SD, n=33 (27 males). A mix-linear model (arm*time) with Fisher's least significant difference post hoc for pairwise comparisons was used. *Significantly different from Pre (P<0.05), [†]Significantly from CATH arm (P<0.05).

Table 4. Resting haemodynamic measurements, MVC in the catheterised arm (CATH) and control arm (CON), and RPE as reported during HE, pre and 1 week post-catheterization.

	Pre	1 week Post	P value
Haemodynamic measurements			
SBP (mmHg)	138±19	133±23	0.151
DBP (mmHg)	81±10	78±10	0.121
MAP (mmHg)	100±11	94±21	0.080
HR (beats per min)	62±12	61±11	0.428
MVC (Kg)			
CATH arm	32.6±9.7	33.7±9.7	0.297
CON arm	31.2±9.5	31.8±7.9	0.592
RPE (1-10) during incremental HE			
5% MVC	2.1±1.5 ^{†,‡}	1.7±1 ^{†,‡}	0.329
10% MVC	3.8±2 [*]	3.5±1.9 [*]	0.562
15% MVC	5.4±2.2 [*]	5.7±2.1 [*]	0.109

SBP: systolic blood pressure, DPB: diastolic blood pressure, MAP: mean blood pressure, HR: heart rate, MVC: maximal voluntary contraction, RPE: rate of perceived excursion (1: no effort to 10: maximal effort). Results are presented as mean ± SD, n=33 (27 males). A paired t-test was used to assess BP and HR. A mixed-linear model was used to analyze MVC and RPE, between arms and/or pre-post catheterization with Fisher's least significant difference post hoc for pairwise comparisons (P<0.05). ^{*}Significantly different from 5% MVC, [†]Significantly different from 10% MVC, [‡]Significantly different from 15% MVC.