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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Abstract

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

Key words: acute exercise, arterial function, catheterization-induced damage, coronary artery disease

New & Noteworthy

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

Introduction

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

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

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

Materials and methods

Participants and Ethical Approval

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

Study design

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

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

Transradial Cardiac Catheterization

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

Experimental procedures

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

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

Bilateral radial artery FMD

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

Bilateral HE

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

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

Data analysis

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

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

Statistics

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

Results

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

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

Impact of catheterization on HE response

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

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

Impact of catheterization on FMD

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

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

Impact of catheterization on systemic haemodynamic measurements, MVC, and RPE

There was no change in BP or HR pre- to post-catheterization (Table 4). MVC was higher in the catheterized arm compared with the control arm (P=0.024), during both visits. MVC was unchanged following catheterization (P=0.265; Table 4). RPE was 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

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

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

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

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

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

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

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

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

Acknowledgements

We would like to thank Rafaella Rodighiero and James Shelley for their help during the data collection, as well as the staff at the Liverpool Heart and Chest Hospital for their support during the patient recruitment and data collection.

Grants

Prof. Green is funded by the National Health and Medical Research Council of Australia Principal Research Fellowship (1080914).

Disclosures

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

Author contribution

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

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546

Tables

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

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

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.

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

563 **Figures**

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

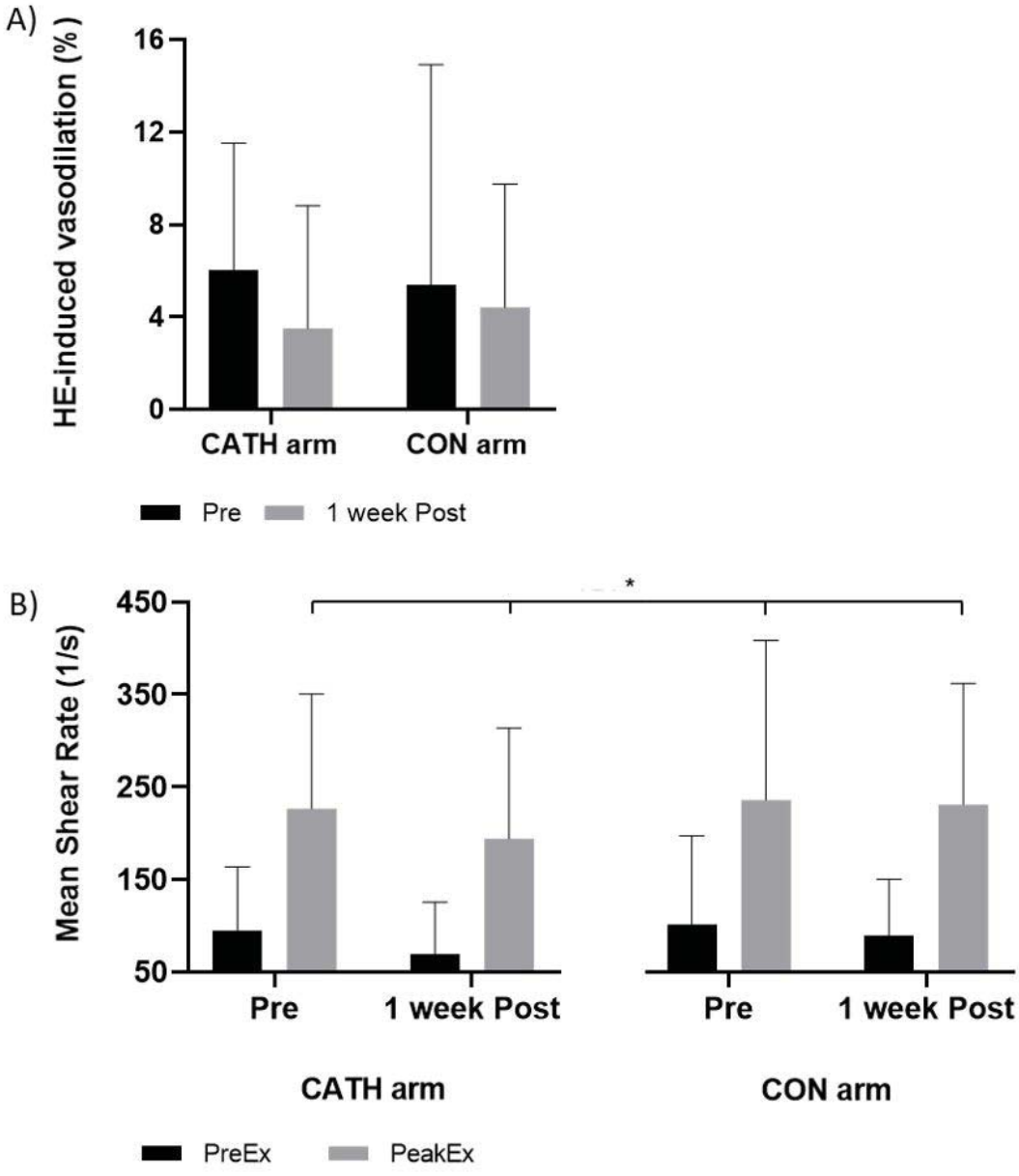
565 Percentage change in RA diameter following HE (A), in the catheterized RA (CATH
566 arm) and contralateral control RA (CON arm), pre- and 1 week post-catheterization.
567 Mean shear rate (B), prior to exercise (PreEx) and at peak (PeakEx), in the CATH
568 arm and CON arm, pre- and 1 week post-catheterization. Results are presented as
569 mean ± 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 ± 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).

579


A)
HE-induced vasodilation (%)
16
12
8
4
0
CATH arm
CON arm
Pre
1 week Post
B)
Mean Shear Rate (1/s)
450
350
250
150
50
*
Pre
1 week Post
Pre
1 week Post
CATH arm
CON arm
PreEx
PeakEx

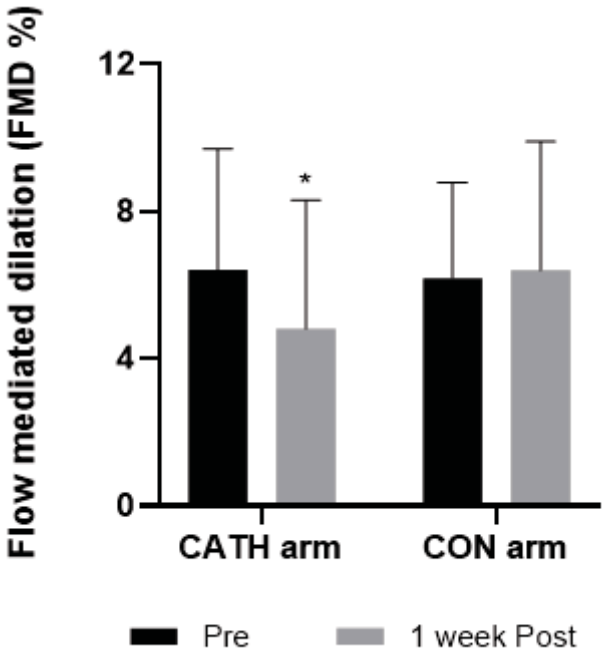

Flow mediated dilation (FMD %)
12
8
4
0
*
CATH arm
CON arm
Pre
1 week Post

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

Clinical Characteristic		**Mean ± SD or n (%)**
Age (years)		65.8 ± 7.3
Sex (males)		27 (81.8)
BMI (m/kg^2)		31.5 ± 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	
Diameter (mm)	**Pre**	**1 week Post**	**Pre**	**1 week Post**
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	-15.1.2±20.5
PeakEx	-4.8±7.2*	-3.5±3.6*	-7.1±13.1*	-3.7±5.7*

Results are presented as mean ± 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 dimeter, 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} 10^3)	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.