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IMPACT OF CATHETER INSERTION USING THE RADIAL APPROACH ON VASODILATION IN HUMANS

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ABSTRACT

The aim of this study was to determine the impact of catheter sheath insertion, a model of endothelium disruption in humans, on the conventional flow-mediated dilation (FMD) response *in vivo*. Seventeen subjects undergoing transradial catheterization were recruited and assessed prior to, the day after, and 3-4 months post-catheterization. The catheter sheath's external diameter was 2.7mm and the average pre-procedure internal radial artery diameter was 2.8mm, indicating a high likelihood of endothelial denudation as a consequence of sheath placement. Radial artery flow-mediated and endothelium-derived nitric oxide (NO)-dependent function (FMD) was assessed within the region of sheath placement (sheath site) and also above the sheath (catheter site). Glyceryl trinitrate (GTN) endothelium-independent NO-mediated function was also assessed distally. Measurements were made in both arms at all time points; the non-catheterized arm provided an internal control. Neither sheath ($4.5 \pm 0.9\%$) nor catheter ($4.4 \pm 0.9\%$) insertion abolished FMD, although both significantly decreased FMD from pre-intervention levels (9.0 ± 0.8 sheath segment; 8.4 ± 0.8 catheter segment; $P < 0.05$). The impact of sheath and catheter placement on FMD was no longer evident after ~3 months recovery (8.0 ± 1.5 and $8.1 \pm 1.7\%$, sheath and catheter, respectively). GTN responses also decreased from 14.8 ± 1.7 to $7.9 \pm 1.0\%$ ($P < 0.05$) as a result of sheath placement, but values returned to baseline at ~3 months ($13.0 \pm 1.8\%$). These data suggest that the presence of an intact, functional endothelial layer and consequent NO release may not be obligatory for some component of the FMD response. This raises the possibility of an endothelium-independent contribution to the flow-induced vasodilation in humans.

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INTRODUCTION

In recent years, flow mediated dilatation (FMD) has become a popular technique in cardiovascular medicine and clinical physiology, as evidence has accrued that depressed FMD is an independent prognostic index of incident and recurrent cardiovascular events which adds predictive value to established risk factor approaches [1-5]. The physiological rationale for the use of FMD, and a proposed reason for its prognostic relevance, is that it reflects endothelium- and nitric oxide (NO)-dependent vascular function.

When Celermajer, Deanfield and colleagues introduced the now conventional and widely adopted FMD approach in the *Lancet* in 1992 [6], no direct evidence was available that brachial and femoral dilation, subsequent to the release of cuff induced ischaemia, were endothelium- or NO-dependent in humans. The approach was therefore based on evidence available at the time that the endothelium released a labile vasodilator substance [7, 8], that increased luminal flow induced vasodilation in human conduit arteries [9-12] and, crucially, that FMD in animals was dependent upon the presence of an intact endothelial lining. In these latter studies, insertion of a catheter and balloon inflation was used to denude the endothelial layer, which abolished FMD. Very few studies of this nature have been undertaken in humans to examine FMD after endothelial damage [13-15]. Whilst previous studies have reported a depression in the vasodilator function of the radial artery after it has been catheterized [13, 14], the methods used to assess arterial vasodilator function were limited. In particular, discreet time measurements were used to assess the peak diameter and as such the 'true' peak is likely to be missed. Furthermore, these studies did not assess the stimulus the artery received during the FMD test (shear rate area under the curve; SR_{AUC}). This has previously been demonstrated to be an important determinant of the FMD response, and should be reported in order to elucidate whether the any changes in FMD are due to alterations in the artery's ability to dilate as opposed to a reduction in the stimulus [16]. In addition the time-course of recovery from endothelial damage remains largely unknown.

The relevance of determining the degree to which FMD responses are endothelium-dependent is heightened by a recent debate over the extent to which FMD represents an endothelium-dependent and NO-mediated response [18, 19]. NO blockers have been infused during flow mediated dilation in humans, with differing effects. Joannides et al. [20] demonstrated that L-NMMA infusion converted flow mediated vasodilatation to constriction in the radial artery in healthy young humans, whilst Doshi reported abolition of FMD with L-NMMA [21]. Somewhat in contrast, Mullen et al. [22] Lieberman et al. [23] and Koojiman et al. [24] all also observed decreased FMD in the presence of L-NMMA, but FMD was not abolished by NO blockade in these studies. In addition, eNOS knockout mice exhibit preserved FMD responses [25]. These studies suggest that compensatory mechanisms may play a role in the FMD response if the endothelial release of NO is dysfunction or absent and/or that NO is not obligatory for a dilator response to ischaemia. They also raise the question of to what extent FMD responses are dependent upon the presence of an intact and functional endothelium, *per se*.

The principal aim of the present study was to use a model of endothelium-disruption in humans to determine the impact on FMD acutely. We also examined the impact of sheath versus catheter placement, the impact of sheath placement on endothelium-independent glyceryl trinitrate (GTN) responses and the time-course of recovery of FMD and GTN responses. We hypothesized that catheter sheath insertion would diminish or abolish the endothelium-dependent and -independent function within, but not above, the catheter sheath site.

MATERIAL AND METHODS

The study conformed to the standards set by the Declaration of Helsinki and ethical approval was obtained from the Liverpool Local Regional Ethics Committee.

Patients

Seventeen subjects (16 men, 1 woman) were recruited from the list of patients requiring radial artery catheterization for coronary angiography or coronary angioplasty. All patients provided informed written consent. The following were excluded: patients who had previously undergone coronary artery bypass surgery or coronary intervention via the radial route or had myocardial infarction during the previous 3 months, valvular heart disease, a left ventricular ejection fraction <40%, chronic obstructive lung disease, or renal or hepatic dysfunction.

Study Design

Patients were tested on three occasions: the day of the transradial procedure (immediately before the catheterization "Pre"), the day after catheterization ("Post") and ~3 months after catheterization ("Recov"). Volunteers were requested to abstain from alcohol or caffeinated beverages and cigarettes (if they were smokers) for 12 hours prior to each testing session. Assessments were taken in a quiet, temperature controlled room. Patients rested in the supine position for approximately 20 minutes to ensure that all hemodynamic variables had stabilized. The radial artery was assessed with the arm extended and supported at an angle of approximately 80° from the torso. A rapid inflation/deflation pneumatic cuff was positioned on the imaged arm around the wrist. A standard catheter sheath was then used to mark the length of the catheter on the surface of the arm, from the scaphoid process. Care was taken to image the same section of the artery during repeat measurements. We assessed both arms to determine whether changes as a consequence of catheterization were specific, or more generalized, throughout the vascular system. On each occasion endothelial dependent function (FMD) was assessed over a distal section of the radial artery (FMD Sheath), within the zone containing the sheath, and over a proximal section (FMD Catheter) which lay above the sheathed region. A minimum of 20 minutes was observed between repeated FMD assessments in the same arm. The order in which the arms were tested was randomized for FMD and GTN. The Endothelium-independent function was assessed as the vascular response to a sublingual dose of glyceryl trinitrate (GTN) with the scans taken in the distal section of the radial artery after the FMD assessments. A minimum of 30 minutes was given between repeat doses of glyceryl trinitrate.

Radial artery access and procedural details

In this study we recruited patients undergoing treatment for coronary artery disease. These patients have their coronary arteries either imaged (angiography) or have the narrow arteries widened (angioplasty). In order to gain access to the coronary circulation a catheter is placed into a peripheral artery, in this case the radial artery, and the catheter is guided up to the heart. Introducer sheaths are used to gain the access to the radial artery and to keep the artery open in order to facilitate the exchange of the guiding coronary catheter to the heart.

The radial artery was approached with the arm extended and supported with the wrist in mild hyperextension. Local anesthesia was achieved with 2% lignocaine after disinfection at the puncture site. The radial artery was punctured with a 21 gauge arterial needle through which a 0.118 inch platinum-tipped nitinol guidewire was introduced. Following this, the needle was withdrawn and a small skin incision was made. A 6 F introducer sheath (13 cm in length, external diameter 2.7 mm, Cook Medical Inc. Bloomington, IN, U.S.A) with a dilator tip length of 2.5 cm was inserted. A weight-adjusted dose of heparin was introduced into the central circulation following the introduction of the first catheter. All introducer sheaths were removed at the end of the procedure and haemostasis achieved in the catheterization laboratory by a compression device. The patients were mobilized immediately and the compression device was removed after two to four hours.

Experimental Procedures

Ultrasound assessment of conduit artery function

Heart rate (HR) and mean arterial pressure (MAP) were determined from an automated sphygmomanometer (Dinamap; GE Pro 300V2, Tampa, Florida) on the contralateral arm. A 12 MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (T3000, Terason, Burlington, MA) was used to assess radial artery function.

Flow mediated dilatation (FMD) (endothelium-dependent NO-mediated function): Baseline scans assessing resting vessel diameter and flow were recorded in the final minute of the initial rest period. The occluding cuff was then inflated to >200 mmHg for 5 minutes. Diameter and flow recordings resumed 30 sec prior to cuff deflation and continued for 5 minutes thereafter. Blood pressure and heart rate were recorded during the resting period and once the cuff had been released.

Glyceryl trinitrate (GTN) dilatation (endothelial-independent NO-mediated function): Vessel diameter was recorded 1-min before, and continuously for 10-min after, sublingual administration of GTN (400 μ g). Blood pressure and heart rate were recorded during the rest period and 5 minutes after the GTN had been administered.

Data Analysis

Post-test analysis was carried out using custom-designed edge detection and wall tracking software [26, 27]. Our previous detailed analysis of power requirements using this software indicates that, at an alpha level of 0.05, 7 subjects are required to ensure 90 power to detect a 2% change in FMD [27]. FMD or GTN were calculated as the percentage rise from preceding baseline diameters. The time to peak (TTP) diameter (in seconds) was calculated from the point of cuff deflation to the time of peak post-deflation diameter. Post-deflation shear rate data, derived from simultaneously acquired velocity and diameter measures at 30 Hz, was exported to a spreadsheet and the area under the shear rate curve (SR_{AUC}) calculated for data up to the point of maximal post-deflation diameter (FMD) using the Riemann sum technique for each individual. SR_{AUC} represents the stimulus for FMD [17].

Statistics

The responses were assessed using a 2-way repeated measures ANOVA. Where significant interaction was observed, a 1-way ANOVA was carried out on each arm separately to identify differences. Results are expressed as means \pm SE. A P value <0.05 was considered significant.

RESULTS

The clinical characteristics of the patients are described in Table 1. The majority of the patients were on aspirin, clopidogrel, a statin, an ACE inhibitor, and a beta blocker. Efforts were made to avoid changes to the patients' drug regimes throughout the study. In any event, the within-subjects design, with contemporaneous contralateral limb measures at each time point, controlled for any drug effects.

Seventeen subjects completed the pre and post scans for the FMD Sheath site and 11 subjects completed all three testing points. For the FMD Catheter site (proximal) data, 13 subjects completed the pre and post scans, and 9 subjects completed all three testing sessions. For the GTN protocol 15 subjects were tested pre and post catheterization, and 11 completed all three testing protocols. The average age of the subjects was 64 ± 10 years, mean blood pressure was 95 ± 15 mmHg and heart rate was 59 ± 7 bpm and the baseline clinical characteristics are shown in Table 1.

There was no significant difference in resting radial artery diameter between arms at the Sheath site (distal) prior to catheterization, but diameter was significantly larger ($P < 0.05$) in the Catheter (proximal) section of the catheterized arm compared to the Control (non-catheterized) arm (Table 2). This may relate to the fact that the catheterized arm was typically the dominant right arm. There was no significant difference in SR_{AUC} or TTP between arms or across time.

There was a significant increase in baseline diameter (Table 2) post-procedure in the catheterized arm ($16 \pm 5\%$) in the sheath section only ($P < 0.05$). There was no significant change in baseline diameter in the Control arm at either the Catheter or Sheath sites. The recovery (15 ± 1 week) resting baseline diameters were not significantly different from pre-procedure in either the catheterized or non-catheterized Control arm.

There was no significant difference in FMD or GTN between arms pre-catheterization (Fig 1). There was a significant reduction in FMD at both the Sheath ($P < 0.01$) and Catheter sites ($P < 0.01$) in the catheterized arm (Fig 1), but FMD was not completely abolished at either site. Similarly, there was a significant decrease ($P < 0.05$), but not abolition, of the artery response to GTN post-procedure in the Sheath segment of the catheterized arm. These decreases had returned towards pre-procedure values by 3-4 months after the catheterization (Fig 2). In contrast there was no change in FMD or GTN across any of the time-points in the Control arm (Fig 1). One patient had an occluded artery post-procedure that remained occluded at the three-month recovery period.

There was no change in mean arterial blood pressure (MAP) across time (Table 3). There was a decrease in MAP with administration of GTN which was significant for both arms at the pre and post testing sessions ($P < 0.01$).

DISCUSSION

The aim of this study was to determine the impact of radial artery sheath and catheter placement on vascular function *in vivo*. There are several novel findings. This is the only study, to our knowledge, which has assessed both distal and proximal sections of the radial artery in order to determine whether function was affected within the region of the catheter sheath alone or whether catheterization has more generalized effects on vasodilator function. Importantly, continuous measurement of artery diameter and flow allowed us to record the 'true' peak in vasodilation in addition to the SR_{AUC} , which represents the stimulus the artery receives during the FMD test. We also repeated measures ~3 months post catheterization to determine whether arterial function recovered and we included within-subjects control measures on the contralateral non-catheterized limb. Our findings indicate that endothelium-dependent function is decreased acutely as a result of catheterization, both within and above the site of sheath, whilst no changes in arterial function were observed in the non-catheterized Control arm at any time point. This is similar to Heiss et al. [15] who also reported a reduction in brachial as well as radial artery function post catheterization. The lack of a significant change in the SR_{AUC} , an estimate of the vasodilatory stimulus, supports the notion that the reduction in the FMD was due to an impaired ability of the artery to dilate. Impairment in FMD function was not complete however, as substantial dilation occurred despite sheath and catheter placement. Responses largely resolved following ~3 months recovery.

The external diameter of the catheter sheaths used in this study was 2.7 mm and mean pre-procedure internal radial artery diameter above the insertion site was 2.8 mm (range 2.2-3.5 mm). Whilst we cannot say for certain the artery was denuded, given the fragile nature of the endothelial monolayer it is highly likely that placement of the sheath disrupted and/or denuded the endothelial layer, in a similar manner to the induction of endothelial denudation by balloon inflation in animal models [28, 29]. The suggestion that we induced endothelial disruption or denudation is supported by the finding that baseline arterial diameter in the sheathed radial segment was larger following the procedure (mean 3.2 mm). Studies of the impact of catheterization and subsequent denudation on radial arterial function are scant. Burstein et al. reported that transradial catheterization impaired FMD immediately post procedure. Recently, Heiss et al. [15] also observed a reduction in FMD in the radial artery 6 hours post catheterization. In contrast to our findings, values recovered after 12 hours in non-smokers. Heiss and colleagues did not assess GTN function, so there were unable to determine whether smooth muscle function was affected. In contrast, Sanmartin and colleagues reported no change in post-ischemic radial artery dilation immediately after the procedure, although this was probably due to an initial impairment in function [14]. Interestingly, despite a significant reduction in FMD in this study, there was still some vasodilation in response to the hyperemic challenge. This suggests that placement of a large sheath and consequent disruption or denudation of the endothelial layer decreases, but does not abolish, FMD. This is in agreement with some previous studies which have blocked NO function and found only partial reductions in FMD [22-24]. Likewise, eNOS knockout mice have been shown to have preserved FMD

responses [25]. In these studies it was assumed that some compensatory mechanisms, including the release of other endothelium-dependent vasodilators such as prostaglandins [25] may come into play if the endothelial release of NO is impaired or absent. However, our data raise the possibility that there may be a non endothelium-dependent vasodilation in response to increased blood flow and shear stress in humans. Future studies will be required to elucidate the contribution of both the endothelium-dependent and independent vasodilators to the conventionally used FMD technique.

In addition to the assessment of endothelial-dependent function, we measured endothelial-independent NO mediated responses to glyceryl trinitrate (GTN). As a NO donor, GTN provides a measure of the smooth muscle component of the vascular NO-dilator system. It is possible that insertion of the relatively large sheath into the radial artery results in disruption of the smooth muscle layer of the vessel wall. Decreased GTN responses in the catheterized, but not the non-catheterized, arm supports the contention that sheath related impacts may not be limited to the intima and is in agreement with the previous literature [13, 14]. As with the FMD data, it is notable that sheath placement did not completely abolish GTN mediated vasodilation, suggesting that some smooth muscle cell function remains intact despite the placement of the sheath, and that sheath placement impairs but does not eradicate smooth muscle responsiveness to a NO donor. These observations have implications for the use of nitrovasodilators in the clinical setting soon after percutaneous interventions are carried out. It is possible that the mechanical stretch induced by the sheath insertion played a role in the depressed vascular function as diameter is an important determinant of the dilator response magnitude, at least when large differences exist in the resting diameter. In the present study, artery diameter increased modestly as a result of artery catheterisation (0.4mm). Our previous data suggests that this magnitude of change in resting diameter is unlikely to fully explain the change in FMD observed in the present study, with an expected FMD of 10% in healthy subjects for a radial artery of 2.8 mm and 8% for a radial artery of 3.2 mm [30].

In addition to measuring endothelial function within the region of the catheter sheath, we also examined endothelium-dependent function in the proximal section of the artery, which was exposed to the catheter but not the catheter sheath. As with the distal section of the artery, we observed a reduction in FMD in the section of the artery only exposed to the catheter. From these data we can suggest that the impact of catheterization extends beyond the site of sheath placement. This is in agreement with Heiss et al. [15], who reported a reduction in brachial artery function 6 hours post radial artery cannulation, although this depression recovered after 12 hours in non-smokers and remained depressed in smokers. It is feasible that the catheter itself may damage the endothelium as it is advanced. However, we cannot rule out the possibility that the catheter is associated with localized inflammation or irritation as a mechanism for reduced function in the catheterized arm [31]. Reduced function above the sheath site raises questions about injury to the rest of the arterial tree through which the catheter passes, including perhaps the coronary arteries. Since FMD in the contralateral arm was not depressed, a global impact of catheterization, mediated via inflammation or oxidative stress, seems unlikely.

It is interesting to note that both endothelial and smooth muscle responses return to near baseline levels following a 3 month recovery period. This is in contrast to Burstein et al. who previously reported that the impairment in FMD following transradial catheterization was still evident 6 weeks after surgery [13]. Our findings that vascular function had recovered ~3 months post procedure suggests that this period may be the minimum required for arterial function to normalize after catheterization and sheath insertion.

Limitations

This is the first study of its type to use automated edge detection and wall tracking software to derive operator independent measures of arterial diameter and FMD. The study of two sites within and above the catheter sheath site along the radial artery also provides novel information, as does the repeated measurement following a recovery period. However, the present study also has some limitations. There were a relatively small number of subjects in each group and we could not get all patients back for the 3 month recovery period. This limitation is somewhat mitigated by our within subjects design and analysis. We did not control for age, pre-existing vascular disease, history of smoking or drug treatment. However, the use of contralateral arm as an internal control helped to negate this limitation.

Conclusions

In conclusion, transradial catheterization results in reversible depression in NO-mediated endothelial and smooth muscle function in the catheterized arm. This effect is evident in the region of the sheath and also above the site of the catheter sheath, suggesting that both sheath and catheter insertion impact upon the vasculature, possibly via a localized inflammatory or irritant response. Although FMD responses were impaired by sheath placement, they were not abolished, suggesting that some endothelium-independent vasodilator mechanisms may contribute to the vasodilation response to an FMD test in humans. This hypothesis will require further investigation. From a clinical perspective, it is possible that optimizing the function and size of the artery prior to its cannulation may improve the outcome and recovery of the artery. To this end, exercise training has been shown to improve arterial function and induce outward remodeling [32-36], both of which might limit the impact of transradial catheterization and improve the health and recovery of the artery post-procedure.

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FIGURE LEGENDS

Figure 1. Changes in FMD (%) within the area of the sheath (Sheath Site, n=17) and above the area of the sheath (Catheter Site, n=13) and changes in GTN (%) within the area of the sheath (n=15) in the catheterized and non-catheterized (Control) arms pre and post-procedure. Data is presented as mean \pm SE. *, significantly different from pre P<0.05

Figure 2.

Changes in FMD (%) within the area of the sheath (Sheath Site, n=11) and above the area of the sheath (Catheter Site, n=9) and changes in GTN (%) within the area of the sheath (n=11) in the catheterized arm pre, post and ~3months (Recov) post-procedure. Data is presented as mean \pm SE. *, significantly different from pre P<0.05

TABLE 1. Clinical characteristics of the study patients (n=17).

Male	16 (94%)
PCI	17 (100%)
Current smoker	3 (18%)
Ex-smoker	11(65%)
Diabetes Mellitus	3 (18%)
Hyperlipidemia on medication	17 (100%)
Hypertension on medication	13 (77%)
Values are number of patients (percentages)	

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TABLE 2. Baseline diameter and time to peak pre-procedure (pre), the day following the procedure (post) and ~3months post-procedure (Recov) in the catheterized (Sheath or Catheter Site) and non-catheterized (Control) arms.

		Baseline Diameter (mm)			Time to Peak (s)			SR _{AUC} (s ⁻¹ 10 ³)		
		Pre	Post	Recov	Pre	Post	Recov	Pre	Post	Recov
FMD	Sheath	2.8 ± 0.1	3.2 ± 0.1*	2.7 ± 0.2	95 ± 10	87 ± 11	77 ± 1	30.0 ± 2.9	20.7 ± 3.8	25.3 ± 3.6
	Control	2.6 ± 0.1	2.8 ± 0.1	2.9 ± 0.2	78 ± 9	79 ± 8	83 ± 14	23.5 ± 3.3	26.6 ± 1.9	32.6 ± 6.6
FMD	Sheath Site	3.1 ± 0.1	3.4 ± 0.1	2.8 ± 0.2	73 ± 9	105 ± 11	63 ± 15	20.7 ± 3.5	23.7 ± 3.8	27.5 ± 6.5
	Control	2.8 ± 0.2#	2.8 ± 0.1	2.8 ± 0.2	110 ± 14	90 ± 8	71 ± 13	31.7 ± 6.2	28.3 ± 3.8	24.0 ± 3.9
GTN	Sheath	2.8 ± 0.1	3.2 ± 0.1	2.6 ± 0.2	308 ± 23	263 ± 31	333 ± 30			
	Control	3.0 ± 0.2	2.9 ± 0.1	3.2 ± 0.2	351 ± 30	297 ± 28	276 ± 40			

Endothelium dependent flow mediated dilator function (FMD) was assessed in the distal section of the artery exposed to the catheter sheath (Sheath Site, n=17 for pre and post and 11 for Recov) and the proximal section of the artery, above the sheath (Catheter Site, n=13 for Pre and Post and 9 for Recov). Endothelial-independent function (GTN) was assessed in the distal section (n=15 for Pre and Post and 11 for Recov) of the artery within the site of the catheter sheath. *significantly different from pre P<0.05; # significantly different from Cath. Data is presented as mean ± SE.

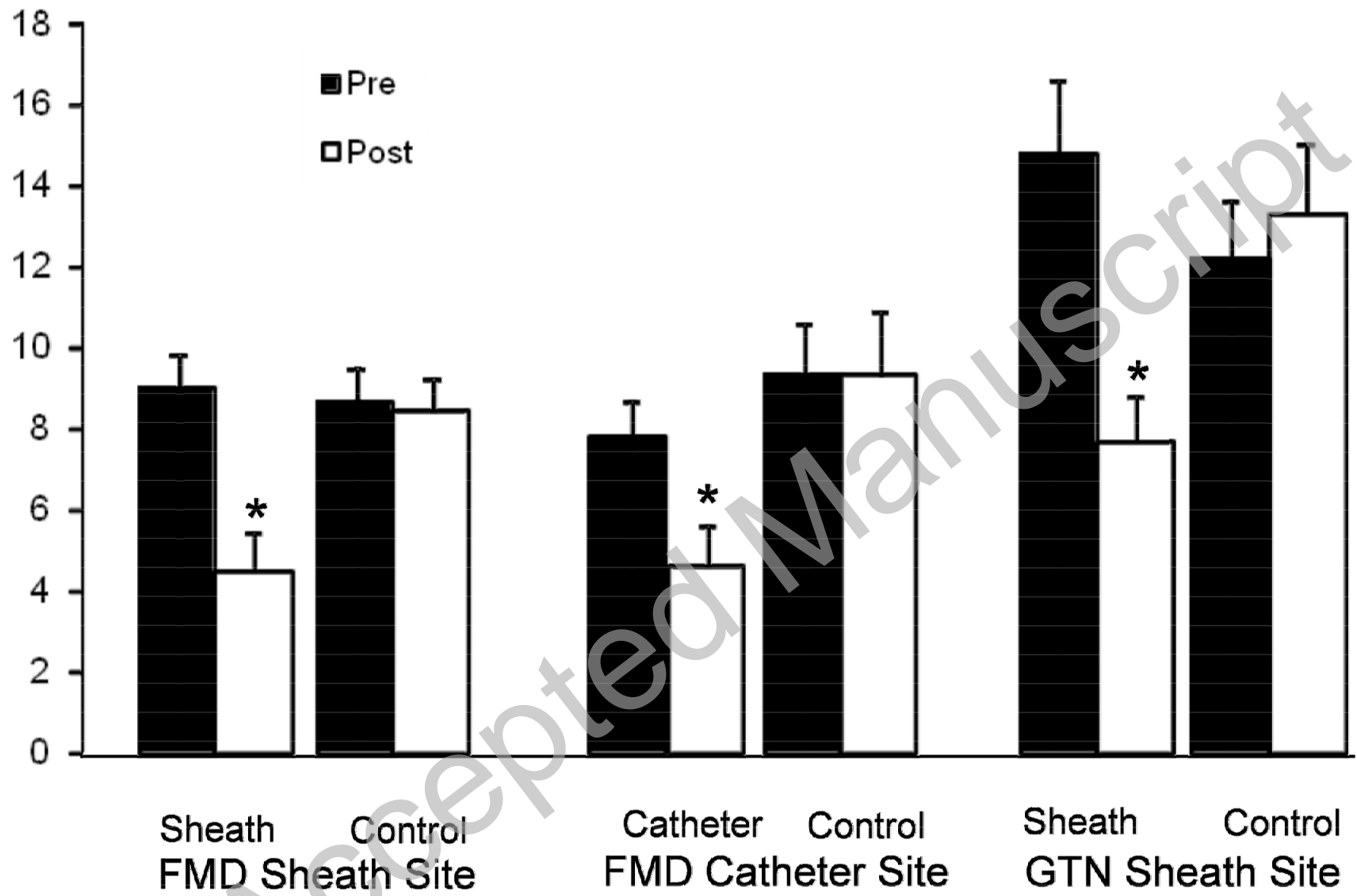
TABLE 3. Mean arterial pressure (MAP) during baseline measurements and post-cuff release or post glyceryl trinitrate (GTN) administration pre-procedure (pre), the day following the procedure (post) and ~3months post-procedure (Recov) in the catheterized (cath) and non-catheterized (Control) arms.

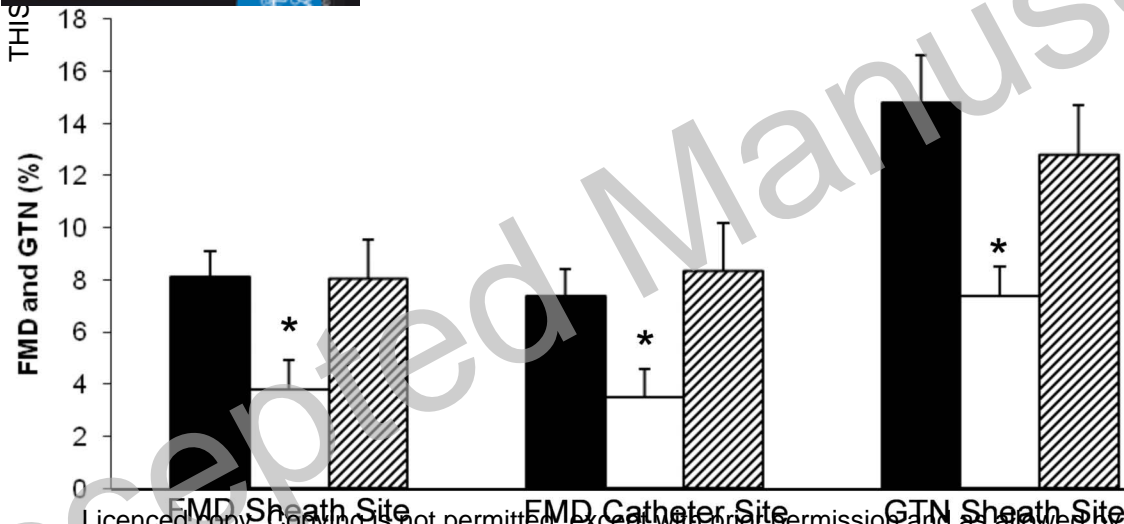
	MAP (mmHg)					
	FMD Sheath Site		FMD Catheter Site		GTN Sheath Site	
	Baseline FMD	During FMD	Baseline FMD	During FMD	Baseline GTN	During GTN
	Cath					
Pre	95 ± 4	94 ± 4	91 ± 4	94 ± 3	95 ± 3	87 ± 3*
Post	94 ± 3	92 ± 4	91 ± 3	90 ± 4	89 ± 3	85 ± 3*
Recov	96 ± 4	93 ± 5	88 ± 3	86 ± 2	88 ± 5	84 ± 5
	Control					
Pre	95 ± 4	95 ± 12	88 ± 3	91 ± 3	93 ± 3	86 ± 3*
Post	89 ± 4	88 ± 4	88 ± 5	87 ± 3	88 ± 3	83 ± 4*
Recov	95 ± 5	96 ± 5	93 ± 5	92 ± 6	89 ± 4	85 ± 4

Mean arterial pressure (FMD) was assessed in the contralateral arm. Measurements were taken during the baseline period and ~1 minute after cuff release or ~3min post GTN administration *significantly different from baseline P<0.05; # significantly different from Pre. Data is presented as mean ± SE.

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