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Impact of sympathetic nervous system activity on post-exercise flow-mediated dilatation in humans

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Key points

- Previous studies indicate a transient reduction in arterial function following large muscle group exercise, but the mechanisms involved are unknown.
- Sympathetic nervous system activation may contribute to such reductions through direct effects in the artery wall, or because of decreases in arterial shear stress.
- Administration of prazosin (an α_1-adrenoreceptor blocker) abolished the transient reduction in vascular function observed under placebo conditions following exercise. This effect could not be explained by drug-induced changes in arterial shear stress.
- These results suggest that sympathetic vasoconstriction directly competes with endothelium-dependent dilator activity to influence post-exercise vascular function.
- These findings have implications for understanding the stimuli responsible for exercise-induced adaptations in arterial function and health in humans.

Abstract   Transient reduction in vascular function following systemic large muscle group exercise has previously been reported in humans. The mechanisms responsible are currently unknown. We hypothesised that sympathetic nervous system activation, induced by cycle ergometer exercise, would contribute to post-exercise reductions in flow-mediated dilatation (FMD). Ten healthy male subjects (28 ± 5 years) undertook two 30 min sessions of cycle exercise at 75% HR_{max}. Prior to exercise, individuals ingested either a placebo or an α_1-adrenoreceptor blocker (prazosin; 0.05 mg kg^{-1}). Central haemodynamics, brachial artery shear rate (SR) and blood flow profiles were assessed throughout each exercise bout and in response to brachial artery FMD, measured prior to, immediately after and 60 min after exercise. Cycle exercise increased both mean and antegrade SR ($P < 0.001$) with retrograde SR also elevated under both conditions ($P < 0.001$). Pre-exercise FMD was similar on both occasions, and was significantly reduced (27%) immediately following exercise in the placebo condition (*t*-test, $P = 0.03$). In contrast, FMD increased (37%) immediately following exercise in the prazosin condition (*t*-test, $P = 0.004$, interaction effect $P = 0.01$). Post-exercise FMD remained different between conditions after correction for baseline diameters preceding cuff deflation and also post-deflation SR. No differences in FMD or other variables were evident 60 min following recovery. Our results indicate that sympathetic vasoconstriction competes with endothelium-dependent dilator activity to determine post-exercise arterial function. These findings have implications for understanding the chronic impacts of interventions, such as exercise training, which affect both sympathetic activity and arterial shear stress.

Abbreviations　BF, blood flow; CO, cardiac output; FMD, flow-mediated dilatation; HR, heart rate; LBNP, lower body negative pressure; MAP, mean arterial pressure; MSNA, muscle sympathetic nerve activity; SNS, sympathetic nervous system; SR, shear rate; SR_{AUC}, shear rate area under curve; SV, stroke volume; TPRi, total peripheral resistance index.

Introduction

Flow-mediated dilatation (FMD) is a widely used method of assessment of vascular function that provides a surrogate index for arterial health (Takase *et al.* 1998; Gocke *et al.* 2003; Thijssen *et al.* 2011). While the chronic effect of exercise training on FMD has been documented in a wide range of individuals (Maiorana *et al.* 2001; Green *et al.* 2004; Watts *et al.* 2004; Tinken *et al.* 2008, 2010; Birk *et al.* 2012), the impact of acute exercise on FMD responses is less clear (Dawson *et al.* 2013). The acute FMD response to large muscle mass exercise has therefore been a focus for recent studies, with a number of these documenting a transient reduction in FMD (Goel *et al.* 2007; Dawson *et al.* 2008; Jones *et al.* 2010; Johnson *et al.* 2012*b*; Birk *et al.* 2013), which may be intensity-dependent (Johnson *et al.* 2012*b*; Birk *et al.* 2013). In addition, studies focusing on the impact of cycle ergometer exercise have demonstrated reductions in FMD in the upper limb vasculature (Jones *et al.* 2010; Johnson *et al.* 2012*b*; Birk *et al.* 2013), which return to baseline levels approximatetly 1 h following the exercise bout, invoking the concept of 'hormesis' (Padilla *et al.* 2011*a*). The mechanisms responsible for this apparent reduction in FMD immediately following exercise are currently unknown, but may include oxidative stress, changes in blood pressure, arterial shear rate (SR) (in particular retrograde SR; Dawson *et al.* 2013), and/or sympathetic nervous system (SNS) activation.

We have previously published studies pertaining to the impact of distinct patterns of blood flow and SR on FMD responses (Thijssen *et al.* 2009*b*, 2014; Tinken *et al.* 2009; Carter *et al.* 2013). Retrograde SR has been linked to a pro-atherogenic phenotype (Chappell *et al.* 1998; Ziegler *et al.* 1998; Hastings *et al.* 2007; Laughlin *et al.* 2008; Conway *et al.* 2010) and reductions in arterial diameter (Carter *et al.* 2013) and FMD (Thijssen *et al.* 2009*b*; Tinken *et al.* 2009; Schreuder *et al.* 2014). Exercise that predominently activates the lower limbs, for example cycle ergometry, increases retrograde SR in the brachial artery (Green *et al.* 2002, 2005; Thijssen *et al.* 2009*a*; Padilla *et al.* 2011*b*), particularly during the initial phase of exercise. It was recently suggested that this may be linked to increased vasoconstrictor outflow (Padilla *et al.* 2010; Simmons *et al.* 2011). However, the systemic impact of elevations in retrograde SR mediated by SNS activation during lower limb exercise has not been directly studied.

SNS activation, independent of exercise, has also been linked to a reduction in FMD (Ghiadoni *et al.* 2000; Hijmering *et al.* 2002; Lind *et al.* 2002; Spieker *et al.* 2002; Dyson *et al.* 2006). Hijmering *et al.*(2002) utilised lower body negative pressure (LBNP: −20 mmHg) to increase sympathetic outflow and demonstrated an acute reduction in FMD that was abolished by intra-arterial infusion of phentolamine. While other studies could not replicate LBNP-induced reductions in FMD (Dyson *et al.* 2006), reduced FMD responses have been observed following mental stress (Ghiadoni *et al.* 2000; Spieker *et al.* 2002) and cold pressor tests (Lind *et al.* 2002; Dyson *et al.* 2006). We recently demonstrated that LBNP of −35 mmHg reduced brachial artery FMD (Thijssen *et al.* 2014) and that this response was mitigated when the increase in retrograde SR induced by LBNP was abolished by the simultaneous application of a heating stimulus. We concluded that SNS activation induced by LBNP may cause a reduction in FMD which is, at least partly, due to changes in arterial SR patterns. This experiment was performed in resting subjects.

The impact of exercise-mediated SNS activation on brachial artery FMD remains unclear, as does the extent to which any such impact can be attributed to changes in arterial (especially retrograde) SR. We therefore hypothesised that SNS activation as a result of cycle exercise would contribute to reductions in post-exercise FMD, an effect mediated by changes in brachial artery SR.

Methods

Ethical approval

All study procedures were approved by the University of British Columbia (Okanagen) institutional ethics committee and adhered to the Declaration of Helsinki. All participants provided written, informed consent before participating in the study.

Participants

Ten healthy, recreationally active male subjects (age: 28 ± 5 years, height: 1.91 ± 0.40 m, weight: 80.1 ± 14.7 kg) volunteered for the study. Subjects were normotensive (systolic blood pressure < 130 mmHg and diastolic blood pressure < 85 mmHg), medication free and non-smokers, with no previous history of cardiovascular disease(s).

Experimental design

Participants were required to report to our laboratory on two occasions. All participants arrived in a fasted state (>6 h) (Thijssen *et al.* 2011), having avoided strenuous exercise, alcohol and caffeine for a minimum of 8 h prior to testing. Time of day of testing sessions was kept consistent for each participant with a minimum of 48 h and maximum of 7 days between sessions. Ninety minutes before commencing the experimental protocol participants orally ingested a capsule containing either an α_1-adrenoreceptor blocker (prazosin; 0.05 mg kg^{-1} body mass) or a placebo (empty capsule) and were instructed to lie down. This dosage of prazosin provides ~80% alpha blockade and has previously been utilised in research studies similar in nature (Jones *et al.* 2011; Lewis *et al.* 2013, 2014). Following 90 min of rest, individuals were placed on a semi-supine bike (Lode Ergometer, Lode, Groningen, Netherlands) and their arm was extended and secured ~80 deg from the torso. An initial assessment of brachial artery endothelial function, using the flow-mediated dilatation technique (Thijssen *et al.* 2011), was then conducted. Each subject then completed 30 min of cycle exercise at 75% of maximum heart rate (mean workloads were 161 ± 16 W in the placebo condition and 140 ± 20 W in the prazosin condition). During every 5 min period of exercise, a 1 min measurement of brachial artery SR and blood flow was recorded, whilst blood pressure parameters were recorded continuously (Finometer Pro, Finapres Medical Systems, Amsterdam, Netherlands). Previous data from our laboratory indicate that the coefficient of variation associated with repeated Finometer measures collected at rest is ~5% (Lewis *et al.* 2015) and others have validated model flow approaches during exercise (Sugawara *et al.* 2003). Post-exercise FMD was then measured immediately after and 60 min after exercise cessation. The order of the conditions, i.e. prazosin *vs.* placebo, was randomised.

Experimental measurements

Central haemodynamics. Changes in mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), stroke volume (SV) and total peripheral resistance index (TPRi) were continuously measured using a Finometer PRO (Finapres Medical Systems), with data exported into PowerLab (Labchart 7, AD Instruments, Sydney, Australia).

Assessment of brachial artery endothelial function. After extending the arm to an ~80 deg angle from the torso, a rapid inflation/deflation pneumatic cuff (D.E. Hokanson, Bellevue, Western Australia) was placed on the forearm, distal to the olecranon process. With the use of a 10–15 MHz multi-frequency-linear array probe attached to a high-resolution ultrasound machine (T3200; Terason, Burlington, MA, USA), a B-mode image of the brachial artery was obtained. Following optimal acquisition of an image and a 1 min baseline recording of artery diameter and velocity, the forearm cuffs were inflated to 220 mmHg for 5 min. Recordings of diameter and velocity continued until 30 s prior to cuff deflation and continued for 3 min thereafter, in accordance with previous studies (Woodman *et al.* 2001). This procedure was repeated immediately after and 60 min after cycle ergometer exercise.

Brachial artery diameter and blood flow/SR analysis. Brachial artery diameter and velocity were analysed using a custom-designed edge-detection and wall-tracking software, which is largely independent of investigator bias (Woodman *et al.* 2001), described in detail elsewhere (Black *et al.* 2008; Thijssen *et al.* 2011). Diameter measurements collected using this software are more reliable and observer-independent than manual methods and reduce observer error, while possessing an intra-observer coefficient of variation of 6.7% (Woodman *et al.* 2001). Continuous (30 Hz) diameter and velocity data were used to calculate blood flow (BF) (the product of lumen cross-sectional area and Doppler velocity). SR was calculated as 4 times mean blood velocity divided by vessel diameter. Finally, FMD was calculated in absolute (mm) and relative (%) terms as the increase from resting baseline diameter to peak diameter, as described elsewhere (Black *et al.* 2008; Thijssen *et al.* 2011).

Statistics

Statistical analysis was performed using SPSS 22.0 (SPSS, Chicago, IL, USA). All data are reported as mean ± SD unless otherwise stated and statistical significance was assumed at $P < 0.05$. A two-way repeated-measures ANOVA was used to compare mean SR and BF across 'time' (time points throughout and following exercise) and between 'conditions' (placebo and prazosin). Similar analysis was performed on each of the following variables: antegrade SR and BF, retrograde SR and BF, MAP, HR, SV, CO, TPRi, vascular conductance and brachial artery diameter. Additional two-way repeated-measures ANOVAs were completed for the assessment across time (pre, post and post 60) and condition (placebo and prazosin) for baseline brachial artery diameter, change in diameter during the FMD, FMD% and FMD SR area under curve (SR$_{AUC}$). *Post-hoc* analysis was performed using the least significant difference methods. Finally, we analysed the effects of time (pre, post and post60) and condition (placebo and prazosin) for FMD variables, on the change in logarithmically transformed diameter using a linear

Table 1. Baseline (pre-exercise) and post-exercise FMD, shear rate and blood flow, on each day

	Placebo			Prazosin			2-way ANOVA		
	Pre	Post	Post 60	Pre	Post	Post 60	Condition	Time	Time × Condition
Baseline diameter (mm)	4.43 ± 0.28	4.78 ± 0.66	4.41 ± 0.33	4.44 ± 0.28	4.57 ± 0.34	4.50 ± 0.26	0.55	0.04	0.11
Change in diameter during FMD (mm)	0.22 ± 0.07	0.15 ± 0.05	0.25 ± 0.07	0.21 ± 0.05	0.29 ± 0.08	0.26 ± 0.13	0.07	0.16	0.01
FMD (%)	5.09 ± 1.65	3.22 ± 1.13	5.78 ± 1.69	4.70 ± 1.18	6.32 ± 1.91	5.76 ± 2.82	0.06	0.11	0.01
FMD SR_{AUC} ($\times 10^3$ s^{-1})	15.87 ± 9.05	30.34 ± 9.30	17.71 ± 4.36	20.15 ± 8.36	37.42 ± 11.15	26.21 ± 8.12	0.01	<0.001	0.41
Corrected FMD (%)	2.10 ± 0.56	1.69 ± 0.62	2.47 ± 0.63	2.02 ± 0.48	2.56 ± 0.86	2.43 ± 1.13	0.19	0.10	<0.01

mixed model using baseline arterial diameter and SR_{AUC} as covariates (Atkinson *et al.* 2013). This approach accounts for any changes in FMD that may be related to baseline diameter or SR differences between conditions.

Results

There were no differences in pre-exercise measures of brachial artery diameter, SR, FMD% or SR_{AUC} between the two testing conditions (placebo *vs.* alpha) (Table 1, all $P > 0.05$).

Exercise haemodynamics

Mean arterial pressure increased in response to exercise in both the placebo and the prazosin conditions (time $P < 0.001$, Fig. 1). While higher values were evident under the placebo condition during exercise, these differences were statistically insignificant ($P = 0.06$ for condition; $P = 0.12$ for interaction effect). HR was significantly elevated throughout exercise, with elevations higher under the prazosin condition (condition effect $P = 0.04$, Fig. 1). Stroke volume was also elevated throughout exercise, with higher values under the placebo condition ($P = 0.03$) and no interaction effect (interaction effect $P = 0.10$). Cardiac output and TPRi did not differ between conditions (Fig. 1).

Brachial artery SR and blood flow

Mean SR was elevated significantly in both conditions during exercise ($P < 0.001$) with a significant condition × time interaction ($P = 0.01$). *Post hoc* tests revealed significantly higher mean SR at the 5 min exercise time point under the prazosin condition ($P = 0.02$, Fig. 2), with no significant differences at any other exercise time point.

Antegrade SR increased in both conditions during exercise (time $P < 0.001$), with a significant condition × time interaction ($P = 0.03$). Similar to mean SR, *post hoc* tests demonstrated a significantly higher antegrade SR at the 5 min exercise time point in the prazosin condition. Retrograde SR also increased significantly in both conditions (time both $P < 0.001$), although no difference was evident in this increase between the conditions (interaction effect $P = 0.08$, Fig. 2).

Both mean and antegrade BF increased with exercise in both conditions (both $P < 0.001$) with both demonstrating a significant condition × time interaction ($P = 0.02$ and $P = 0.01$, respectively). *Post hoc* tests revealed that at the 5 and 10 min exercise time points, both mean and antegrade flows were higher in the prazosin condition. Finally, retrograde BF increased under both conditions ($P < 0.001$), with no condition or interaction effects apparent ($P = 0.22$ and $P = 0.14$, respectively).

Vascular conductance increased in both conditions ($P < 0.001$) but this increase was not significant between the two conditions (condition effect $P = 0.24$, Fig. 3). Finally, brachial artery diameter increased during the exercise session in both conditions ($P < 0.001$) but this effect was not different between the two conditions (condition effect $P = 0.80$, Fig. 3).

FMD parameters

Two-way ANOVA performed on baseline brachial artery diameter revealed a significant time effect ($P = 0.04$), but no condition or interaction effects (Table 1). A significant time × condition interaction was evident for FMD (%) ($P = 0.01$, Fig. 4). *Posthoc* tests indicated a significant FMD reduction immediately following the 30 min exercise intervention ($P = 0.03$) under the placebo condition, whereas an increase in FMD was observed with prazosin ($P = 0.004$, Fig. 4). In terms of the post-cuff deflation SR stimulus to FMD [FMD SR_{AUC} ($10^3 \ s^{-1}$)], prazosin was associated with elevated values both before

and after exercise (condition effect $P < 0.01$). However, when corrected for changes in both diameter and SR_{AUC} [Corrected FMD (%), Table 1], the interaction effect for FMD remained ($P < 0.01$).

Discussion

In keeping with several previous studies examining large muscle group exercise (Goel *et al.* 2007; Dawson *et al.* 2008; Jones *et al.* 2010; Johnson *et al.* 2012*b*; Birk *et al.* 2013), in the present study we observed a transient post-exercise reduction in brachial artery FMD following 30 min of cycle ergometer exercise. This effect was abolished by the ingestion of prazosin, a specific α_1-adrenoceptor blocker, suggesting that exercise-induced increases in SNS activation contribute to the acute effects of exercise on arterial function *in vivo*.

While an acute impact of exercise on arterial function has been previously reported (Goel *et al.* 2007; Dawson *et al.* 2008; Jones *et al.* 2010; Johnson *et al.* 2012*b*; Birk *et al.* 2013), these studies did not fully address the mechanisms
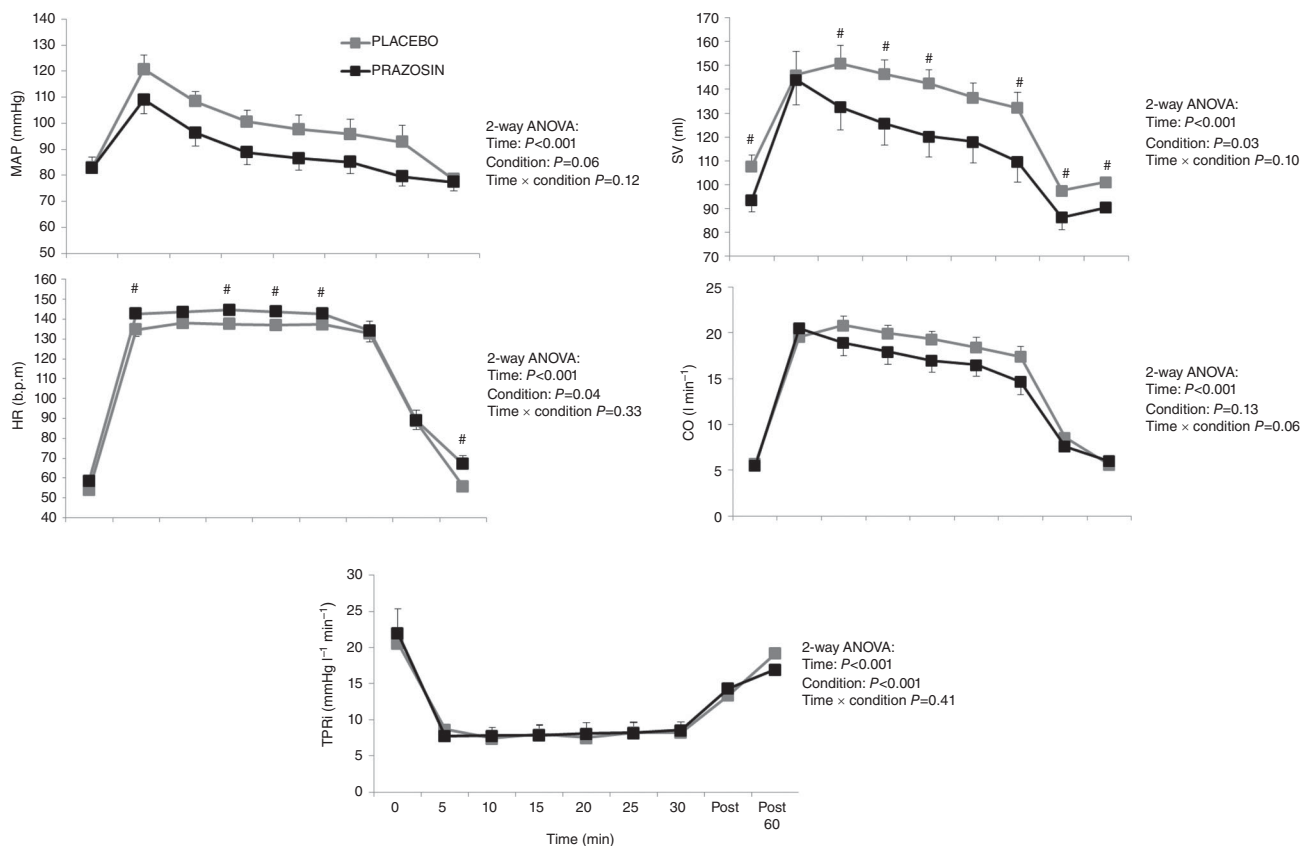

Figure 1. Mean arterial pressure (MAP), heart rate (HR), stroke volume (SV), cardiac output (CO) and total peripheral resistance index (TPRi) across 30 min of cycle exercise at 75% HR$_{max}$
Grey squares denote 'Placebo' condition and black squares denote 'prazosin' condition. Error bars represent SEM. Statistical significance was assumed at $P \leq 0.05$; #statistical significance between conditions. (NB: subjects were exercised at a target HR of 75%HR$_{max}$, resulting in mean workloads of 161 ± 16 W in the placebo condition and 140 ± 20 W in the prazosin condition.)

responsible. The impact of SNS activation on FMD may be due to direct interactions between neurotransmitters and endothelium-dependent vasodilators (Kolo *et al.* 2004) or secondary impacts of sympathetic vasoconstriction on arterial SR during exercise, or both. In this context, we recently demonstrated that FMD reduction during LBNP was ameliorated by applying a forearm heating stimulus that normalised the brachial artery retrograde
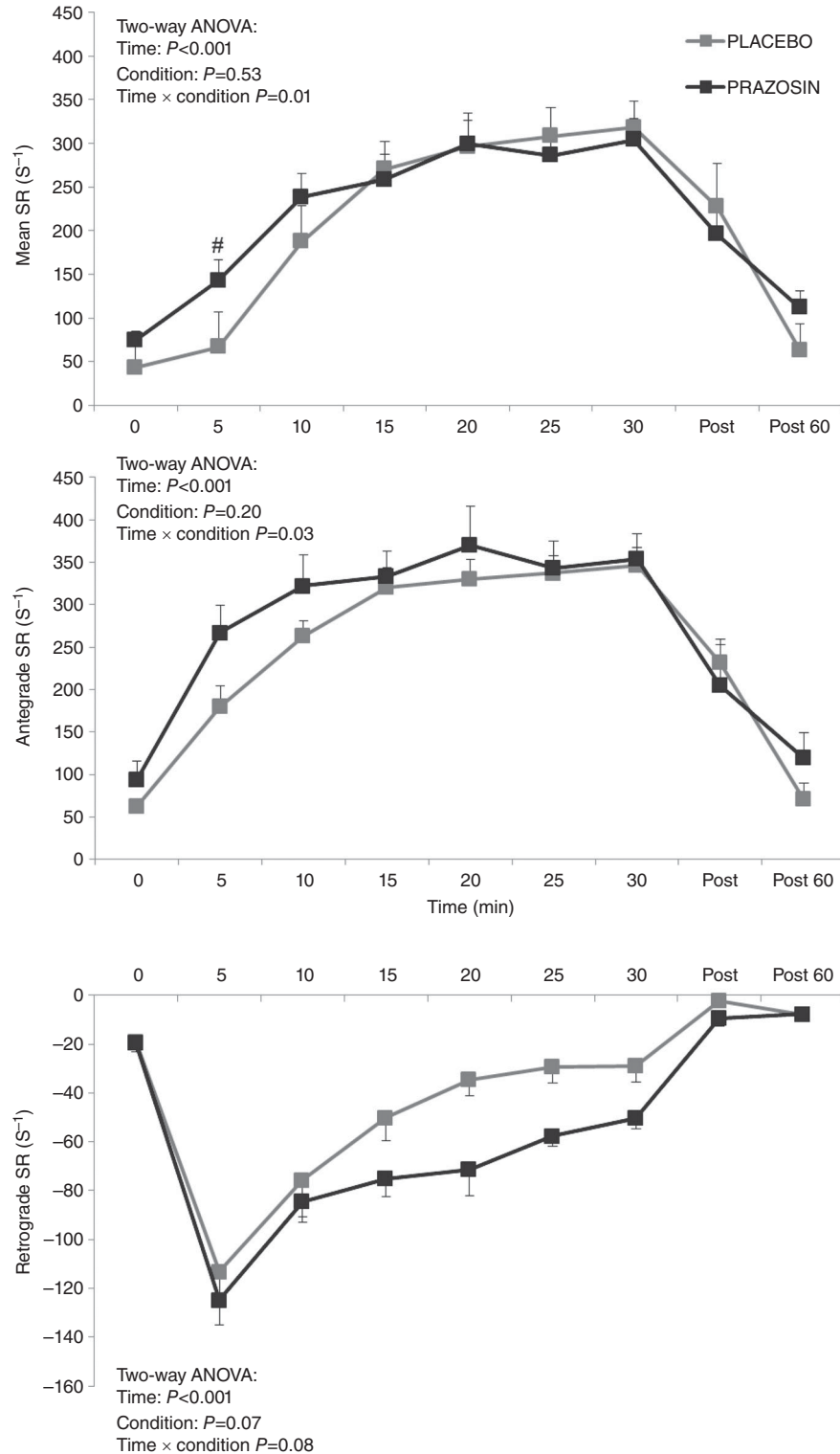
Figure 2. Mean, antegrade and retrograde shear rate (SR) comparisons across 30 min of cycle exercise at 75% HR$_{max}$ under 'Placebo' (grey squares) and 'prazosin' (black squares)
Error bars represent SEM. Statistical significance was assumed at $P \le 0.05$; #statistical significance between conditions. (NB: subjects were exercised at a target HR of 75%HR$_{max}$, resulting in mean workloads of 161 ± 16 W in the placebo condition and 140 ± 20 W in the prazosin condition.)
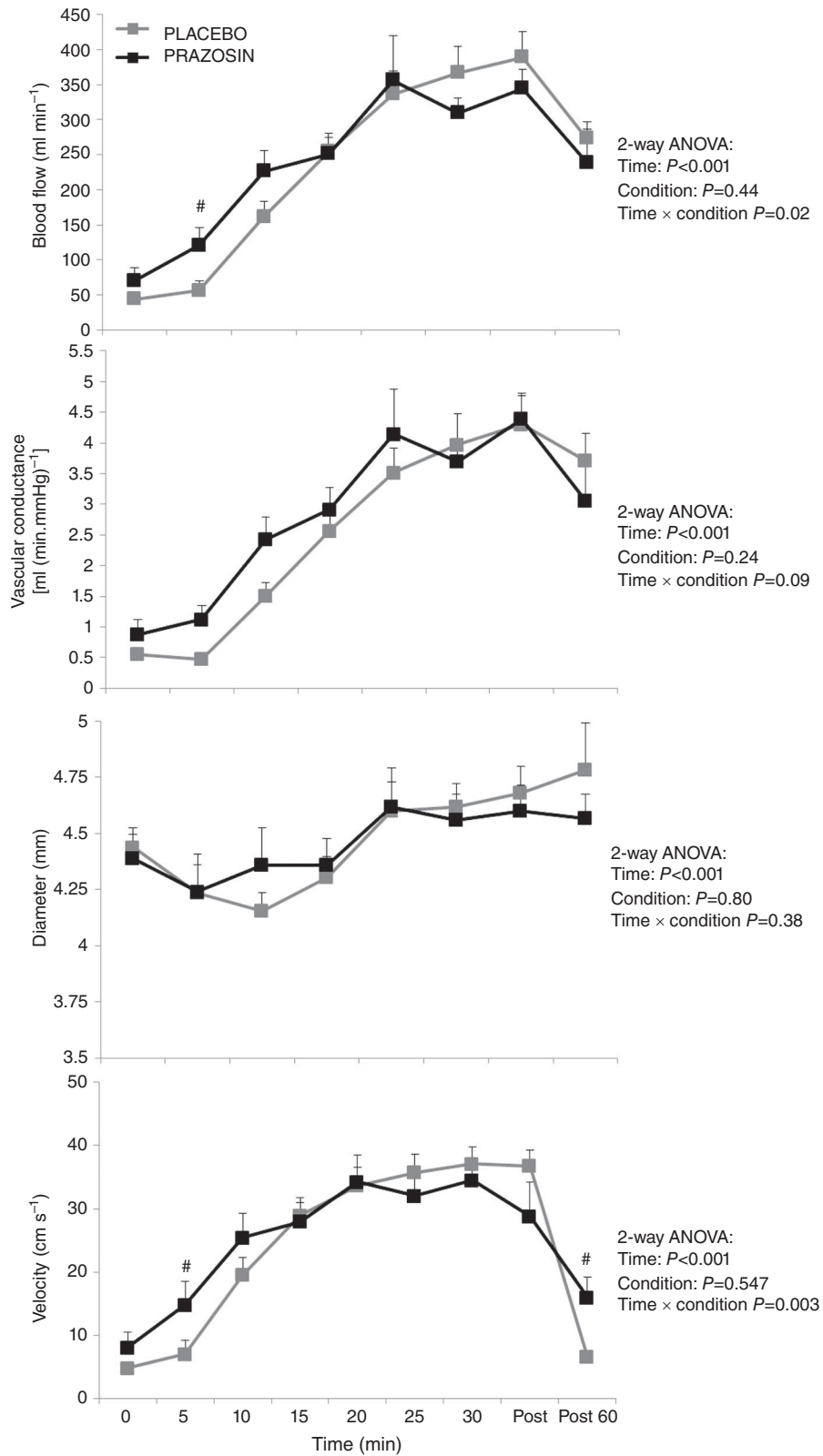
Figure 3. Blood flow, conductance, brachial artery velocity and arterial diameter across 30 min of cycle exercise at 75% HR_max under 'Placebo' (grey squares) and 'prazosin' (black squares)
Error bars represent SEM. Statistical significance was assumed at $P \leq 0.05$; #statistical significance between conditions. (NB: subjects were exercised at a target HR of 75%HR_max, resulting in mean workloads of 161 ± 16 W in the placebo condition and 140 ± 20 W in the prazosin condition.)

SR (Thijssen *et al.* 2014). These findings suggested that changes in FMD may, at least partly, result from LBNP effects on retrograde shear rather than direct impacts on endothelium-mediated dilatation *per se*. In the present study, the impact of prazosin on FMD cannot be ascribed to impacts of this drug on SR responses during exercise, as it was associated with small but significant increases in retrograde shear across the exercise period. These findings therefore infer that the α_1-blockade may have direct impacts on the nitric oxide–dilator pathway and FMD response during large muscle group lower limb exercise. Indeed, several studies in animals have indicated that nitric oxide interacts with noradrenaline, thereby directly modifying arterial vasoactivity (Vo *et al.* 1991; Chowdhary & Townend, 1999; Zanzinger, 1999; Kolo *et al.* 2004). Our data suggest that a balance exists between SNS-mediated vasoconstriction and endothelium-dependent dilatation, with large muscle group lower limb exercise associated with a transient increase in systemic SNS activation, and consequent reduction in FMD. Prazosin-induced blockade of α_1-adrenoceptors altered this balance in favour of nitric oxide-mediated vasodilatation and consequently increased FMD, as observed immediately following exercise in the present experiment.

By virtue of its α-blocking action, prazosin is a vaso-dilator and it is possible that the stimulus to brachial arterial dilatation following cuff deflation during the FMD tests was affected by this drug. Indeed, directly measured SR_{AUC} following cuff deflation was higher in the prazosin condition, although no interaction effect existed for SR_{AUC} between the conditions and the magnitude of change

in SR after exercise was similar between the conditions (from 15.87 to 30.34×10^3 s^{-1}: 90% increase; 20.15 to 37.42×10^3 s^{-1}: a 86% increase). Furthermore, the significant impact of prazosin on FMD% persisted after we corrected for differences in the SR stimulus before and after exercise. It seems unlikely that the effect of prazosin on FMD that we observed can be fully or even largely explained by effects on the SR stimulus *per se*.

Vascular function and FMD can be modulated by inflammation and oxidative stress and several studies have reported improvements in FMD following treatments that ameliorate oxidation and inflammation (Ellis *et al.* 2000; Silvestro *et al.* 2002; Donato *et al.* 2010; Johnson *et al.* 2012*a*,2013; Wray *et al.* 2012). Improvements in FMD following the ingestion of anti-oxidants have been observed in the elderly (Donato *et al.* 2010; Johnson *et al.* 2012*a*), patients with hypertension (Plantinga *et al.* 2007), peripheral artery disease (Silvestro *et al.* 2002) and heart failure (Ellis *et al.* 2000). Conversely, studies in healthy individuals have typically not demonstrated increases in FMD with administration of oral anti-oxidants (Richardson *et al.* 2007; Donato *et al.* 2010), although Johnson and colleages suggested that vitamin C supplementation in the presence of increased retrograde SR induced by either cuff placement (Johnson *et al.* 2013) or cycle exercise (Johnson *et al.* 2012*a*) can enhance FMD responses. We cannot exclude the possibility that the exercise performed in our study had impacts on inflammatory or oxidative factors. However, the acute impact of prazosin is specific to α_1-adrenoceptor blockade and we are unaware of any direct effects of this agent on
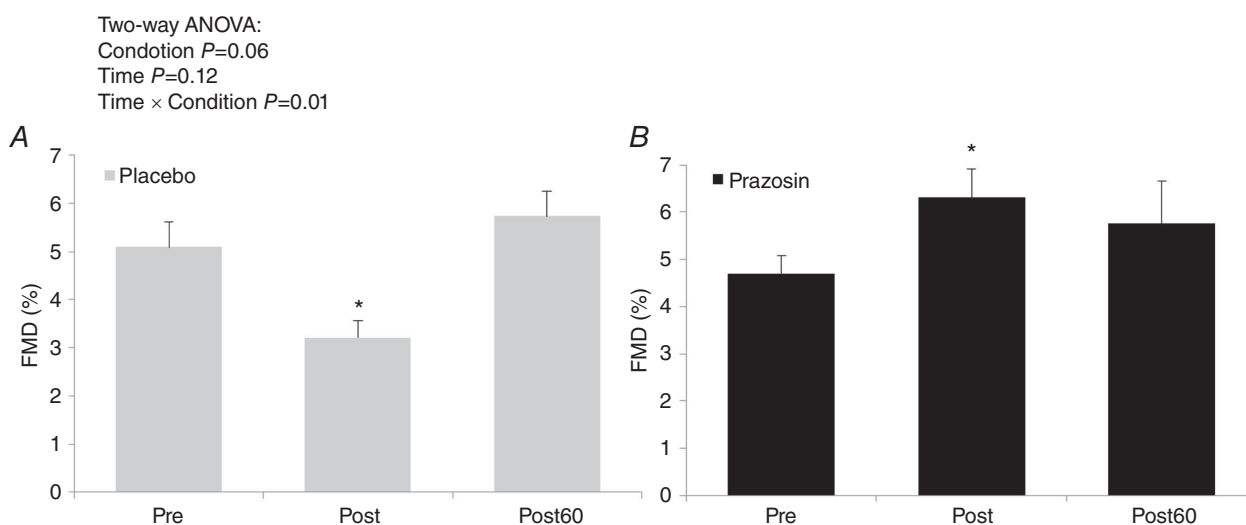
Figure 4. Brachial artery flow-mediated dilatation (FMD) prior to, immediately post and 60 min following 30 min cycle exercise at 75%HR$_{max}$

A, placebo condition (grey bars); *B*, prazosin condition (black bars). Error bars represent SEM. Statistical significance was assumed at $P \leq 0.05$; *statistical significance from 'Pre' value. (NB: subjects were exercised at a target HR of 75%HR$_{max}$, resulting in mean workloads of 161 ± 16 W in the placebo condition and 140 ± 20 W in the prazosin condition.)

inflammation or oxidative stress. The complete reversal in FMD we observed with prazosin strongly implies that interaction between SNS activation and nitric oxide plays a role in the acute impact of exercise on arterial function in humans.

An important limitation of our study was that no direct assessment of SNS activation was undertaken. It is not technically possible to perform muscle sympathetic nerve activity (MSNA) assessments from the common peroneal nerve during cycle exercise, and upper limb MSNA assessments are also challenging to maintain at higher cycle exercise intensities. While it is possible that any impact of whole body exercise would be greater during the immediate post-exercise period than at later time points (e.g. 1 h), and some human evidence exists to support this contention (Cleroux *et al.* 1992), there is also evidence that MSNA is lower following large muscle mass exercise (Halliwill *et al.* 1996; Kulics *et al.* 1999) and this question has not been resolved in the literature. Another limitation is that prazosin provides specific α_1-receptor blockade and therefore we cannot exclude the possibility that differential β-adrenoceptor-mediated dilatation or α_2-mediated vasoconstriction occurred in the downstream microvasculature in our study. Some studies suggest that functional sympatholysis is mainly due to blunting of α_2-adrenoceptor-mediated vasoconstriction (Wray *et al.* 2004) although both α_1- and α_2-adrenergic receptor-mediated vasoconstriction are blunted in contracting human skeletal muscle (Rosenmeier *et al.* 2003). Our findings indicate that, at the level of the conduit arteries, α_1-blockade impacts on FMD and this effect is not due to changes in arterial shear stress (as a result of downstream vascular effects), given that the impact of prazosin on flows and shear were directionally opposite to those that might enhance FMD. Nonetheless, there remains a possibility that increases in retrograde shear with prazosin may be due to greater α_2-mediated constriction when α_1-receptors are blocked, and multiple blockade with non-specific α- and β-blockade could be addressed in future studies.

A final limitation of our study relates to differences between the conditions in exercise intensity. We exercised subjects to a target HR (75% HR_{max}), due mainly to our previous study (Birk *et al.* 2013) which indicated that exercise at ~70%HR_{max} resulted in a significant decrease in FMD following cycling. We did not anticipate that prazosin would induce differences in workload of ~20 W between the conditions. This could theoretically contribute to the differences we observed in post-exercise FMD. However, in the study by Birk *et al.*(2013), cycling performed at lower workloads resulted in a decrease in FMD, whereas in our study post-exercise FMD increased when prazosin was administered. Furthermore, a correlation performed on differences between conditions in workload and exercise-impact on FMD revealed no relationship ($r = 0.18$, $P = 0.62$). We suggest that, while distinct workloads may have contributed to some extent to the FMD differences between conditions, it seems that a primary impact of prazosin on nitric oxide-mediated dilator function predominated.

Conclusions

Our findings suggest that changes in vascular function following cycle exercise reflect a balance between sympathetically driven vasoconstriction and nitric oxide-mediated vasodilatation. The acute impairment in FMD observed following exercise in the current study suggests that cycle exercise, at the intensity used in this study, transiently alters this balance in favour of SNS-mediated vasoconstriction. When taken in context with previous studies utilising LBNP, the findings of the present study suggest that a direct interaction between noradrenaline and endothelium-dependent dilators, and/or SNS-mediated changes in SR patterns, can both influence artery function *in vivo*. The contribution of these direct and indirect pathways may differ according to which stimulus of SNS activation is adopted: previous studies suggest that LBNP contributes to FMD changes via shear stress-related mechanisms, whereas our current results cannot be explained via this secondary impact.

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Additional information

Competing interests

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