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## **Human arterial responses to isometric exercise: the role of the muscle metaboreflex.**

Tom S. Davies<sup>\*</sup>, Michael P. Frenneaux<sup>†</sup>, Ross I. Campbell<sup>†</sup>, and Michael J. White<sup>\*</sup>

<sup>\*</sup>School of Sport and Exercise Sciences, <sup>†</sup>Department of Cardiovascular Medicine, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK.

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Correspondence to Tom Davies, School of Sport and Exercise Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK.

Tel: +44 121 414 8739

Fax: 0121 414 4121

Email: [tsd146@bham.ac.uk](mailto:tsd146@bham.ac.uk)

## Abstract

The effects of exercise on the distensibility of large and medium sized arteries are poorly understood, but can be attributed to a combination of local vasodilator effects of exercise opposed by sympathetic vasoconstrictor tone. We sought to examine this relationship at the conduit artery level, with particular reference to the role of the sympathoexcitatory muscle metaboreflex. The effect of maintained muscle metaboreflex activation on a previously passive or exercised limb femoral artery was investigated.

10 healthy volunteers performed 2 minutes of isometric ankle plantar-flexion at 40% MVC, in conjunction with 2 minutes of either non-ischemic isometric handgrip (HG, control condition) or ischemic handgrip (IHG) at 40% MVC. IHG was followed by 2 minutes of post exercise circulatory occlusion (PECO) to maintain muscle metaboreflex activation. Femoral-tibial pulse wave velocity (FTPWV) was measured in the exercised or contralateral limb at baseline and immediately following calf exercise. Blood pressure (BP) and heart rate (HR) were measured continuously throughout. In the HG condition, BP and HR returned promptly to baseline post exercise whilst exercised leg FTPWV was decreased (less stiff) by 0.6m/s ( $P<0.05$ ) and non-exercised leg PWV was not changed from baseline. PECO caused a sustained increase in BP but not HR in the IHG condition. Contralateral leg PWV increased (stiffened) during PECO by 0.9m/s ( $P<0.05$ ), whereas exercised limb FTPWV was not changed from baseline.

Muscle metaboreflex activation causes a systemic stiffening of the arterial tree, which can overcome local exercise induced decreases in arterial PWV.

## Introduction

Changes in microvascular tone during exercise and the regulatory mechanisms responsible for these changes have been well described. These mechanisms ensure diversion of blood flow to exercising skeletal muscle [1]. In contrast, the effect of exercise on large artery function has not been extensively investigated. Large artery stiffness determines central aortic systolic and pulse pressure via the Windkessel effect and via effects on the timing of reflected waves to the central aorta [2]. Large artery distensibility declines with age, resulting in an increase in systolic and pulse pressures [3]. The systolic hypertension resulting from these changes is a potent risk factor for cardiovascular disease (including myocardial infarction, heart failure and stroke) [4]. Until recently large artery function was thought to relate virtually entirely to the structural characteristics of the vessel wall, reduced distensibility with age being a consequence of loss of elastin and collagen cross-linking [5]. Over recent years there has been an increasing recognition that changes in the tone of the vascular smooth muscle in large arteries also influences their distensibility [6,7,8]. This tone is determined by endothelial, humoral and neural factors [9]. Changes in large artery distensibility may have considerable impact on cardiac performance during exercise. Acute increases in impedance are known to cause an acute impairment of LV active relaxation, and it has been proposed that this may be an important mechanism responsible for the syndrome of Heart Failure with Preserved Left Ventricular Ejection Fraction [10,11].

In the present study we investigated the role of the skeletal muscle metaboreflex in controlling femoral-tibial arterial distensibility in the exercised and non exercised leg in healthy volunteers following isometric exercise. Previous studies have shown that the skeletal metaboreflex contributes to the vasoconstriction in non-exercising microvascular beds and restrains the microvascular dilation seen in exercising limbs [12]. However the impact of this reflex on large artery distensibility is currently unknown.

Isometric exercise lends itself to this type of study because the influence of the metaboreflex on cardiovascular function can be readily controlled [13]. It has long been established [14] that this reflex can be evaluated using the technique of post exercise circulatory occlusion (PECO), which traps metabolites in a previously exercised muscle and sustains the sympathoexcitatory stimulus at the same levels seen during exercise [15,16]. Using this technique to manipulate systemic sympathoexcitation in a controlled fashion, whilst local

dilator factors are still active in a previously exercised limb [17,18,19,20] allows their respective contributions to conduit artery function to be revealed. Additionally isometric exercise allows assessment of conduit artery function to be made immediately post-exercise (within 1 minute) using non invasive, pulse wave velocity (PWV) measures. This rapid assessment is not possible following dynamic exercise because of inevitable temporal delays and movement artefacts upon cessation of this exercise mode [17,18,19,20].

In the present study subjects performed a standardised level of ischemic handgrip exercise to evoke a reproducible level of systemic sympathetic vasoconstrictor drive and this was sustained with subsequent forearm PECO [21,22]. We investigated the effect of simultaneous one legged isometric calf plantar flexor exercise on arterial stiffness immediately following the combined handgrip and leg exercise and during recovery with PECO. This was achieved by measuring PWV in the femoral-tibial arterial segment of the exercised and contralateral limbs. As a control, these PWV measures were repeated while subjects recovered from non-ischemic handgrip without forearm PECO.

We hypothesised that in the control condition calf exercise would cause local arterial vasodilatation and therefore decrease femoral-tibial PWV in the active limb but not in the inactive limb. With the addition of sympathoexcitation, caused by forearm PECO, we hypothesised that passive limb femoral-tibial PWV would increase above resting levels. Finally, we hypothesised that this systemic sympathoexcitation would override local vasodilator responses in the active limb and attenuate the decrease in PWV seen following calf exercise.

## **Methods**

### **Subjects**

10 subjects (5 male, 5 female) aged  $22 \pm 1$  yr (mean  $\pm$  standard error of the mean, SEM) volunteered to participate in this study. None smoked, were hypertensive (blood pressure  $>140/80$ mmHG), or were taking medication. All subjects gave informed written consent and were habituated with the experimental procedures, which were approved by the local ethics committee and conformed to the Declaration of Helsinki (2002). Subjects were asked to refrain from consuming food and caffeine in the three hours preceding the experiments.

### **Experimental Protocol**

Each subject underwent four experiments in a randomised manner. Subjects lay supine in a custom built isometric dynamometer designed to measure ankle plantar flexion force. The subjects were positioned with the right knee flexed by 50 deg, the ankle flexed at 90 deg, and the foot strapped to a footplate. Straps were aligned around the ankle in order to minimise lifting of the heel away from the footplate when performing plantar flexor exercise. Isometric handgrip exercise was performed with the right hand on a Lafayette hand dynamometer. Maximal voluntary force (MVC) was determined prior to each study, with each exercise mode.

Before each trial, the subject rested for 10min in supine position to establish a stable baseline. Each protocol began with 10min of baseline recordings after which the subject performed 2mins of isometric ankle plantar flexion at 40% MVC, in conjunction with 2mins of either non-ischemic isometric handgrip (HG, control condition) or ischemic handgrip (IHG) at 40% MVC. IHG was followed by 2mins PECO to maintain metaboreflex activation. PWV in the exercised or contralateral femoral-tibial arterial segment was measured at baseline and for 5mins immediately following calf exercise. A schematic diagram of the experimental protocol is shown in Figure 1.

### **Measured Variables**

Continuous beat-to-beat BP was assessed using a non-invasive, bio-impedance monitor (Task Force® Monitor) at the middle finger of the left hand. A standard 3-lead electrocardiogram (ECG) was used to measure heart rate continuously during baseline, exercise and recovery periods. The monitor sampled at a rate of 1000Hz.

Femoral-Tibial PWV (FTPWV) was measured simultaneously and non-invasively by oscillometry (time resolution +/- 2ms; QVL P84, SciMed, Bristol, UK) using a method developed to identify waveforms by their early phase in order to improve wave recognition and timing. This technique has been shown to give within day (minute to minute variation) of 2.2% and between day reproducible (10 minute averaged) of 5.6% [18]. Non-occlusive cuffs were placed over the mid thigh (femoral) and ankle (tibial), and connected to computerised pressure transducers by non-compliant tubing. The cuffs were inflated to 65-70mmHg and pulse pressure waveforms caused by volume displacement were obtained from each cuff. Waveforms were characterised by a computer programme with respect to time at 30, 40 and

50% of peak pressure along their ascending phase. The programme was designed to discard ectopic beats and abnormally shaped waveforms. The transit time between cuffs was calculated using an average of the three points (30, 40 and 50%), for 15 continuous beats. PWV was derived as the distance between the proximal edges of each cuff (measured around the flexed knee joint) divided by pulse transit time. It is important to note that neither cuff or leg was allowed to move during either protocol. HR and BP during corresponding periods of PWV measurement (1min) were calculated from the Task Force data.

Average values for cardiovascular variables and PWV were calculated over the whole 10 minute baseline period and each successive minute of the 5 minute recovery period. In addition average values for blood pressure and heart rate at the end of the exercise period (last 10 seconds of exercise) were also calculated.

### **Statistical Analysis**

All values are expressed as mean  $\pm$  SEM. Statistical analysis was performed using repeated measures ANOVA and *post hoc* analysis using paired t-tests with Bonferroni correction. Significance levels were set at  $P < 0.05$ .

## **Results**

### **Control Condition**

Table 1 shows average heart rate and blood pressure values for the baseline, end exercise, and recovery phases of the trials performed to examine PWV in the previously exercised and contralateral limbs. Heart rate and blood pressure increased markedly during exercise and to the same extent in both trials, and in both trials heart rate and blood pressure returned promptly to baseline levels within the first minute of recovery and remained at these levels thereafter.

FTPWV data is shown in Figure 2. It is clear that immediately following combined calf and handgrip exercise, when blood pressure had recovered to baseline, FTPWV in the previously exercised leg had declined ( $p < 0.05$ ) by 0.6m/s, 0.6m/s and 0.5m/s relative to baseline, during minutes 1, 2 and 3 respectively. By minute 4 of recovery FTPWV had returned to baseline levels. In contrast, in the contralateral leg FTPWV was not significantly changed from baseline after the combined calf and handgrip exercise.

### **IHG Condition**

During exercise, heart rate and blood pressure increased in both trials. During PECO, heart rate returned to baseline, whilst blood pressure remained significantly elevated in both IHG trials. Following PECO, during the 3rd minute of recovery, blood pressure returned to baseline and in both trials remained unchanged thereafter.

During the two minutes of PECO which followed combined calf and ischaemic handgrip exercise and when blood pressure was markedly elevated above baseline, FTPWV in the exercised limb was not significantly changed from baseline ( $p=0.1$ ) Upon release of PECO and recovery of blood pressure to resting levels, FTPWV remained statistically indistinguishable from baseline.

In the contralateral limb, FTPWV was initially increased during PECO ( $p<0.05$ ) by 0.8m/s and 0.9m/s, in the first and second minutes, respectively, of recovery. It then returned to baseline upon release of the occlusion. The increase in FTPWV in this limb during PECO was in complete contrast to the unchanged FTPWV values seen in the exercised leg during PECO. It also contrasts with unaltered FTPWV in the contralateral limb in the absence of PECO in the control condition.

### **Discussion**

The present study investigated the acute effects of isometric exercise on large (conduit) artery distensibility. Immediately after exercise PWV was measured in the contralateral or exercised femoral artery to examine the influence of systemic and local factors on arterial function. In addition, the ability of exercise induced sympathoexcitation, mediated by muscle metaboreflex activation, to alter these responses was investigated.

#### **Femoral Artery Responses to Isometric Calf Exercise**

In the absence of PECO, required to sustain sympathoexcitation and elevated BP, arterial distensibility of the exercised limb was augmented for three minutes following calf exercise. This data is in accordance with all aerobic exercise studies to date [17,18,19,20]. One idea used to explain the increase in arterial distensibility post exercise is that it is caused by exercise-related regional factors. Although these factors have yet to be fully elucidated, local vasodilator mechanisms involving the muscle vascular endothelium and limited retrograde travel of dilator signals have been postulated [17,18,19,20]. Once local intramuscular



vasodilatation has occurred then flow in the femoral artery will increase and therefore cyclic wall stress on its endothelium will follow. This is a well known vasodilator stimulus [23] which would facilitate the increased muscle blood flow. Therefore the observed increase in distensibility immediately post exercise in the control condition could be attributed to endothelium dependent, vasodilation. An alternative idea to explain post exercise increases in arterial distensibility is that an exercise driven increase in sympathetic vasoconstrictor tone is decreased at this time (see below). Certainly systemic sympathoexcitation caused by muscle metaboreflex activation during the handgrip and calf exercise would be expected to oppose vasodilatation during exercise [12,21,22]. However, rapid wash out of the metabolites on cessation of exercise removes this reflex response and sympathetic activity quickly returns to baseline, as is supported by the rapid recovery of BP in the control experiments. Finally, the fact that no change was seen in FTPWV in the contralateral limb following exercise, even though it would have experienced the same increased level of sympathetic drive during exercise as the exercise limb [12], provides further support for the idea that the decrease in PWV in the exercise limb is likely dominated by local factors.

### **The Effects of Metaboreflex Activation**

Sympathetic nerve activity has been reported to exert a tonic stiffening influence on the arterial walls [24,25]. Arterial distensibility can be reduced by an increased sympathetic drive, as shown by the effects on the radial and carotid arteries during cold-pressor and mental arithmetic tests [26], and smoking [27], i.e. manoeuvres that cause sympathetic activation. A period of circulatory occlusion following isometric exercise has been widely used to maintain muscle metaboreflex activation and cause sympathoexcitation [28]. PECO entraps the metabolic results of exercise and therefore sustains afferent feedback from the exercised muscle [14]. Muscle metaboreflex activation typically evokes parallel sympathetic activation in exercising and resting human skeletal muscle [12] that maintains or elevates arterial pressure [29].

In the present study, elevated sympathetic outflow was associated with a stiffening of the arterial tree, as observed in the increased FTPWV of the contralateral limb femoral artery during PECO. The decrease in femoral artery distensibility in the contralateral limb during PECO, mirroring the BP rise at this time, is consistent with sustained muscle metaboreflex-mediated vasoconstriction. This data, to our knowledge, is the first to show a stiffening of the large conduit arteries during muscle metaboreflex activation. As the muscles were relaxed

and there was no intention to perform exercise, we can rule out any contribution from muscle mechanoreflex or central command.

### **Local Dilatory Mechanisms Vs Increased Sympathetic Outflow**

The interaction between functional vasodilation and sympathetic vasoconstriction and the phenomenon of “functional sympatholysis” has long driven studies of blood flow control [1,30,31,32,33]. Of particular interest to the present study are recent findings that the interaction between sympathetic nerve activity and vasodilatory stimuli seems to vary with vessel branch order [34]. The present study measures femoral-tibial arterial PWV between the mid thigh and ankle. As subjects performed isolated calf exercise these measures will provide information about the artery passing through the exercising muscle and also the conduit artery (mid femoral) proximal to the exercising muscle itself.

The ability of muscular contractions to limit the amount of vasoconstriction appears to be a local regulatory mechanism, particularly arising in the arterioles embedded within active muscle fibres, to ensure adequate blood flow and oxygen delivery to the contracting muscle [35,36]. Further upstream however, vasoconstriction is sustained, as sympathetic nerve activity seems able to impair ascending vasodilation of the feed arteries [34,35,36,37]. Data from the present study further extends this idea to the large conduit artery level, as following exercise with PECO; metaboreflex activation abolished the increase in distensibility that was seen in the femoral-tibial arterial segment of the exercised limb in the control condition. If this observation can be extrapolated to exercise conditions, then it suggests that the proximal branches of the network serve as key sites for regulating the distribution of cardiac output and the maintenance of arterial pressure.

### **The Potential Influence of Blood Pressure Changes on PWV**

Arterial compliance is reduced with a rise in mean arterial pressure (MAP) [38]. Therefore changes in arterial compliance occurring in the presence of MAP changes may simply be a consequence of the nonlinearity of the vascular pressure-volume relationship rather than an intrinsic change in vessel wall properties [38]. It is therefore difficult to exclude the possibility that the rise in MAP seen during PECO will account for any increases seen in PWV during this period. However, despite similar MAP increases during both IHG protocols, the PWV responses of exercised and contralateral femoral arteries were markedly different. It is therefore unlikely that the arterial responses observed were entirely BP dependent.

Furthermore in the control condition, exercised leg FTPWV significantly decreased despite unchanged BP during the recovery period. Changing pressure cannot thus be wholly responsible for the observed changes in FTPWV seen during these experiments. The PWV responses thus appear to reflect acute changes in vascular tone, which occur during recovery from exercise.

### **Method of PWV Measurement**

Pulse transit time measurement critically depends on accurately identifying potential changes in the waveform. Conventionally this is achieved by measuring the timing of the foot of the wave. The present technique, which characterises and times the waveform by averaging 3 points along the first 50% of its rising phase during which its upstroke should be relatively uncontaminated by reflected waves and wave propagation [39], and is likely to bring advantage over techniques relying on the identification of a single point [18]. PWV measured with the present technique has been shown to be sensitive to acute changes of vascular tone, independently of any associated change in blood pressure. PWV in the upper limb, for example, is decreased or increased ~10% by local intra-arterial acetylcholine or *NG*-monomethyl-L-arginine, whereas lower limb PWV, heart rate, and blood pressure are unchanged [9,40,41]. It is acknowledged, that a variety of other techniques exist which can be employed to assess the mechanical properties of arteries, e.g. the windkessel 'area method' approach of Liu et al. [38] referred to above. However it is difficult to compare the different indices produced by these methods with changes in PWV. Nevertheless, in the present study PWV was measured over the same defined sections of the femoral-tibial arterial segment before and immediately after exercise. The results therefore provide evidence of relative arterial distensibility changes, and as such the technique provides an objective, sensitive but robust and reproducible measure of acute changes in arterial distensibility as influenced by changes in vascular tone [18]

### **Conclusions**

Isometric exercise induced an acute, local augmentation in large artery distensibility. Increased sympathetic outflow during muscle metaboreflex activation causes a systemic stiffening of the arterial tree. This sympathetically induced stiffening is able to overcome the local increase in distensibility in an exercised artery.

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## Tables

Table 1. Blood pressure and heart rate changes following combined calf and handgrip exercise (control conditions) or following calf and ischemic handgrip with PECO (IHG conditions).

	Baseline	End Ex	Post 1	Post 2	Post 3	Post 4	Post 5
<b>SBP (mmHg)</b>							
Exercised	116±4	148±6*	123±4	117±4	115±5	113±5	112±5
Contralateral	119±3	149±9*	130±8	126±6	125±4	125±3	126±4
Contralateral (IHG)	121±3	152±7*	138±5*	135±4*	125±3	121±3	121±3
Exercised (IHG)	120±3	163±7*	146±6*	144±6*	132±6	127±6	124±5
<b>DBP (mmHg)</b>							
Exercised	67±2	92±3*	66±3	63±2	61±3	59±3	59±3
Contralateral	65±2	89±3*	71±3	69±3	68±2	68±3	70±3
Contralateral (IHG)	70±2	96±3*	79±3*	80±2*	70±2	67±2	67±2
Exercised (IHG)	65±2	99±7*	80±4*	81±4*	70±5	66±4	65±4
<b>HR (bpm)</b>							
Exercised	64±3	87±4*	71±3	62±3	61±3	60±3	60±3
Contralateral	64±5	86±6*	72±5	62±5	60±5	61±5	61±4
Contralateral (IHG)	65±4	90±4*	71±5	62±4	62±3	60±3	60±3
Exercised (IHG)	64±3	88±4*	72±4	65±4	63±4	62±3	59±3

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate;

\* indicates significantly different from respective baseline value.

## Figures

**Figure 1.**

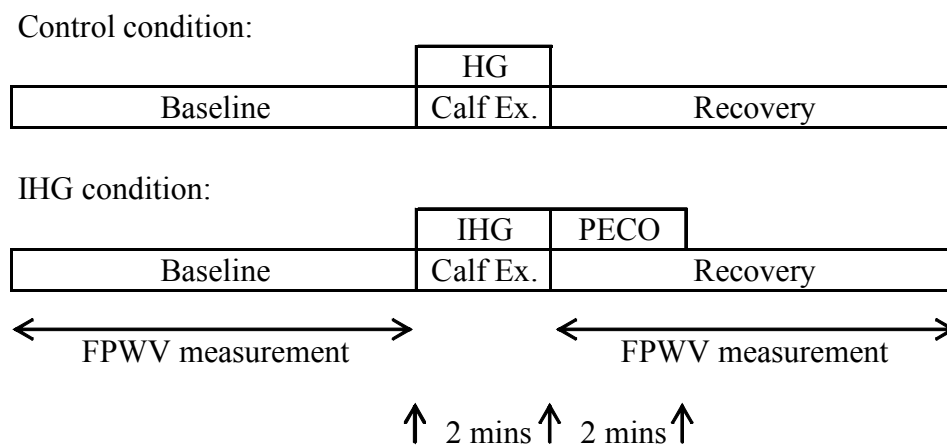


Figure 1. Schematic of experimental protocol. HG, handgrip; IHG, ischemic handgrip; PECO, post exercise circulatory occlusion.

Figure 2.

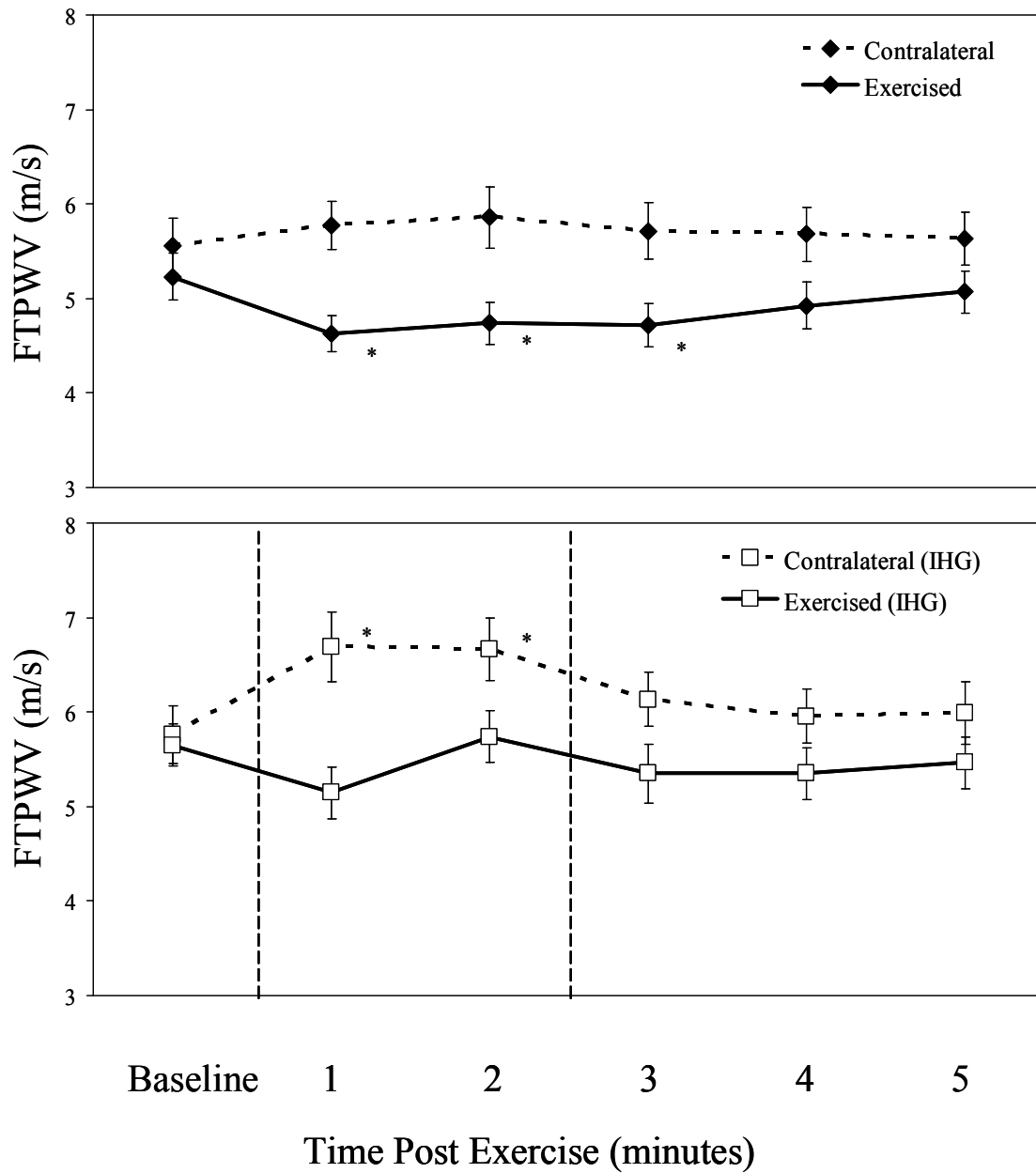


Figure 2. FTPWV in exercised and contralateral limbs following calf and handgrip exercise (top) or following calf and ischemic handgrip exercise with PECO (IHG) (bottom). Dashed vertical lines indicate PECO period. \* indicates significantly different from respective baseline value.