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

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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 sympatho-excitatory muscle metaboreflex. The effect of maintained muscle metaboreflex activation on a previously passive or exercised limb femoral artery was investigated. A total of ten healthy volunteers performed 2 min of isometric ankle plantar-flexion at 40% MVC (maximal voluntary force), in conjunction with 2 min of either non-ischaemic isometric HG (handgrip; control condition) or IHG (ischaemic HG) at 40% MVC. IHG was followed by 2 min of PECO (post-exercise circulatory occlusion) to maintain muscle metaboreflex activation. FTPWV [femoral–tibial PWV (pulse wave velocity)] was measured in the exercised or contralateral limb at baseline and immediately following calf exercise. BP (blood pressure) and HR (heart rate) were measured continuously throughout. In the HG condition, BP and HR returned promptly to baseline post-exercise, whereas exercised leg FTPWV was decreased (less stiff) by 0.6 m/s (P < 0.05) and the 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 0.9 m/s (P < 0.05), whereas exercised limb FTPWV was not changed from baseline. In conclusion, 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 investigated extensively. 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

Key words: arterial response, conduit artery, exercise, metaboreflex, pulse wave velocity (PWV), sympathetic nervous system.

Abbreviations: BP, blood pressure; HG, handgrip; HR, heart rate; IHG, ischaemic HG; LV, left ventricular; MAP, mean arterial pressure; MVC, maximal voluntary contraction; PECO, post-exercise circulatory occlusion; PWV, pulse wave velocity; FTPWV, femoral–tibial PWV.

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influences their distensibility [6–8]. 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 (left ventricular) active relaxation, and it has been proposed that this may be an important mechanism responsible for the syndrome of heart failure with preserved LV 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 PECO (post-exercise circulatory occlusion), which traps metabolites in a previously exercised muscle and sustains the sympatho-excitatory stimulus at the same levels seen during exercise [15,16]. Using this technique to manipulate systemic sympatho-excitation in a controlled fashion, while local dilator factors are still active in a previously exercised limb [17–20], 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 min) using non-invasive PWV (pulse wave velocity) measures. This rapid assessment is not possible following dynamic exercise, because of inevitable temporal delays and movement artefacts upon cessation of this exercise mode [17–20].

In the present study, subjects performed a standardized level of IHG [ischaemic HG (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 HG 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-ischaemic HG without forearm PECO.

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

MATERIALS AND METHODS

Subjects

A total of ten subjects (five male and five female) aged 22 ± 1 years (mean ± S.E.M.) volunteered to participate in this study. None were smokers, were hypertensive [BP (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 3 h preceding the experiments.

Experimental protocol

Each subject underwent four experiments in a randomized 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°, the ankle flexed at 90°, and the foot strapped to a footplate. Straps were aligned around the ankle in order to minimize lifting of the heel away from the footplate when performing plantar-flexor exercise. Isometric HG exercise was performed with the right hand on a Lafayette hand dynamometer. MVC (maximal voluntary contraction) was determined prior to each study, with each exercise mode.

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

Variables measured

Continuous beat-to-beat BP was assessed using a non-invasive bioimpedance monitor (Task Force® Monitor; CNSystems) on the middle finger of the left hand. A standard three-lead ECG was used to measure HR (heart rate) continuously during baseline, exercise and recovery periods. The monitor sampled at a rate of 1000 Hz.
FTPWV was measured simultaneously and non-invasively by oscillometry (time resolution \( \pm 2 \text{ ms} \); QVL P84; SciMed) 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 a within-day reproducibility (min-to-min variation) of 2.2%, and a between-day reproducibility (10 min averaged) of 5.6% [18]. Non-occlusive cuffs were placed over the mid-thigh (femoral) and ankle (tibial), and were connected to computerized pressure transducers by non-compliant tubing. The cuffs were inflated to 65–70 mmHg and pulse pressure waveforms caused by volume displacement were obtained from each cuff. Waveforms were characterized by a computer program with respect to time at 30, 40 and 50% of peak pressure along their ascending phase. The program 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 the pulse transit time. It is important to note that neither the cuff nor the leg was allowed to move during either protocol. HR and BP during corresponding periods of PWV measurement (1 min) were calculated from the Task Force data.

Average values for cardiovascular variables and PWV were calculated over the whole 10 min baseline period and each successive minute of the 5 min recovery period. In addition, average values for BP and HR at the end of the exercise period (last 10 s of exercise) were also calculated.

**Statistical analysis**

All values are expressed as means \( \pm \text{S.E.M.} \). Statistical analysis was performed using repeated measures ANOVA and post-hoc analysis using paired Student’s \( t \) tests with Bonferroni correction. Significance levels were set at \( P < 0.05 \).

**RESULTS**

**Control condition**

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

The results of the FTPWV are shown in Figure 2. It is clear that immediately following combined calf and HG exercise, when BP had recovered to baseline, FTPWV in the previously exercised leg had declined (\( P < 0.05 \)) by 0.6, 0.6 and 0.5 m/s relative to baseline during 1, 2 and 3 min respectively. By 4 min 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 HG exercise.

**IHG condition**

During exercise, HR and BP increased in both trials. During PECO, HR returned to baseline, whereas BP remained significantly elevated in both IHG trials. Following PECO, during the third minute of recovery, BP returned to baseline and, in both trials, remained unchanged thereafter.

During the second minute of PECO which followed combined calf and IHG exercise and when BP 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 BP to resting levels, FTPWV remained statistically indistinguishable from baseline.

In the contralateral limb, FTPWV was initially increased during PECO (\( P < 0.05 \)) by 0.8 and 0.9 m/s at 1 and 2 min 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 with 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 sympatho-excitation, mediated by muscle metaboreflex activation, to alter these responses was investigated.
Table 1  BP and HR changes following combined calf and HG exercise or calf and IHG exercise with PECO

*Significantly different from the respective baseline value. Control HG, control conditions (combined calf and non-ischaemic HG exercise); IHG, combined calf and IHG exercise with PECO. DBP, diastolic BP; SBP, systolic BP.

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<td>Baseline</td>
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<td><strong>SBP (mmHg)</strong></td>
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<td>116 ± 4</td>
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<td>Exercised</td>
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<td><strong>DBP (mmHg)</strong></td>
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<td>67 ± 2</td>
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<td>65 ± 2</td>
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<td>Exercised</td>
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<td><strong>HR (beats/min)</strong></td>
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Femoral artery responses to isometric calf exercise

In the absence of PECO, required to sustain sympatho-excitation and elevated BP, arterial distensibility of the exercised limb was augmented for 3 min following calf exercise. These findings are in accordance with all aerobic exercise studies to date [17–20]. 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 [17–20]. 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 vasodilatation. 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 sympatho-excitation caused by muscle metaboreflex activation during the HG 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 probably dominated by local factors.

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 sympatho-excitation [28]. PECO entraps the metabolic results of exercise and, therefore, sustains afferent feedback from the exercised muscle [14]. Muscle metaboreflex
Arterial stiffness and the 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 by 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. These findings, to our knowledge, are 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 and increased sympathetic outflow

The interaction between functional vasodilatation and sympathetic vasoconstriction and the phenomenon of ‘functional sympatholysis’ has long driven studies of blood flow control [1,30–33]. 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 FTPWV 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 [34–37]. Findings from the present study extend this idea further 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.

Potential influence of BP changes on PWV

Arterial compliance is reduced with a rise in MAP (mean arterial pressure) [38]. Therefore changes in arterial compliance occurring in the presence of MAP changes may simply be a consequence of the non-linearity 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 HG 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 technique used in the present study characterizes and times the waveform by averaging three 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 have advantages over techniques relying on the
identification of a single point [18]. PWV measured with the technique used in the present study has been shown to be sensitive to acute changes of vascular tone, independently of any associated change in BP. PWV in the upper limb, for example, is decreased or increased approx. 10% by local intra-arterial acetylcholine or Nω-monomethyl-L-arginine, whereas lower limb PWV, HR and BP 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 described by 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 and 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 caused 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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