Muscle Metaboreflex-Induced Increases in Stroke Volume

ANTONIO CRISAFULLI1, ADAM C. SCOTT2, ROLAND WENSEL2, COSTANTINOS H. DAVOS2, DARREL P. FRANCIS2, PASQUALE PAGLIARO3, ANDREW J. S. COATS2, ALBERTO CONCU1, and MASSIMO F. PIEPOLI2

1Interdepartmental Centre of Technologies and Environments Related to Sport, University of Cagliari, Cagliari, ITALY; 2National Heart and Lung Institute, Royal Brompton Hospital, London, UNITED KINGDOM; and 3Clinical and Biological Science Department, University of Torino, Torino, ITALY

ABSTRACT

Purpose: Accumulation of by-products of metabolism within skeletal muscle may stimulate sensory nerves, thus evoking a pressor response named muscle metaboreflex. The aim of this study was to evaluate changes in central hemodynamics occurring during the metaboreflex activation. Methods: In seven healthy subjects, the metaboreflex was studied by postexercise regional circulatory occlusion at the start of the recovery from a mild rhythmic forearm exercise. Central hemodynamics was evaluated by means of impedance cardiography. Results: The main findings of this study were that, with respect to rest, the metaboreflex: 1) raised mean blood pressure (+13%; P < 0.01); 2) enhanced myocardial contractility (−12% in prejection period/left ventricular ejection time ratio; P < 0.01); 3) prolonged diastolic time (+11%; P < 0.01); 4) increased stroke volume (+10%; P < 0.05); and 5) increased cardiac output (+6%; P < 0.05). These responses were present neither during recovery without circulatory occlusion nor during circulatory occlusion without prior exercise. Moreover, the metaboreflex did not affect systemic vascular resistance and induced bradycardia with respect to recovery without circulatory occlusion. Conclusion: These results suggest that the blood pressure response during metaboreflex activation after mild rhythmic exercise is strongly dependent on the capacity to increase cardiac output rather than due to increased vascular resistance. Key Words: MYOCARDIAL CONTRACTILITY, CARDIAC OUTPUT, BLOOD PRESSURE, EXERCISE, IMPEDANCE CARDIOGRAPHY

When O2 delivery is insufficient to meet the metabolic needs of exercising muscle, by-products of metabolism such as lactic acid, potassium, arachidonic acid products, and adenosine accumulate, due to a mismatch between metabolism and blood flow. Such a mismatch causes activation of muscle metaboreceptors (small slow-conducting group III and IV fibers), leading an increase in arterial blood pressure, through the so-called muscle metaboreflex (21,22,25). This reflex is exaggerated in patients suffering from heart failure, and it is thought to be one of the causes of the exaggerated hemodynamic, ventilatory, and autonomic responses to exercise occurring in these patients, leading to exercise intolerance (19,23,28).

In human studies, two main approaches have been used to evoke the muscle metaboreflex: 1) reducing exercising muscle blood flow during muscle work effort (6), or 2) reducing exercising muscle blood flow immediately at the cessation of effort by postexercise regional ischemia (PEI) (22). Both approaches lead to metabolite accumulation within skeletal muscles, which induces the expected blood pressure response (the so-called “metaboreflex”). However, the hemodynamic response is markedly different in the two settings mentioned. In fact, studies performed in animals showed that if the metaboreflex is activated during exercise, the blood pressure response is due to both systemic vascular resistance (SVR) and cardiac output (CO) increases (1,21). The latter effect was mainly attributed to an increase in heart rate (HR) as a consequence of the enhanced sympathetic outflow. On the contrary, during PEI, HR decreases markedly toward resting values because the baroreflex restored vagal activity counteracts the enhanced sympathetic activity. Thus, HR exhibits a course not different from recovery without PEI (9,20,22). Therefore, an increase in blood pressure during PEI is thought to be mainly due to a vasconstriction, i.e., SVR increase, rather than to a HR increase.

Moreover, in dogs, it has been found that the magnitude of the metaboreflex pressure response is also dependent on the ability to increase CO. This is particularly true for mild to moderate exercise, whereas peripheral vasoconstriction is thought to become more important during severe exercise (1). As CO is the product of HR and stroke volume (SV), changes in HR alone may not accurately reflect changes in CO. Therefore, to assess fully cardiovascular changes
occurring during metaboreflex activation, the knowledge of both HR and SV changes is necessary. Besides, strong evidence has recently arisen that sympathetic activity remains elevated despite HR reduction during PEI (16,20); thus, it is conceivable that ventricular performance is also enhanced in this setting. In particular, O'Leary and Augustyniak (21) have recently shown during dynamic exercise in dogs that the muscle metaboreflex induced increases in ventricular performance, which, in turn, kept SV constant despite the concomitant increase in HR and the consequent reduction in diastolic time and cardiac filling. If this response was present also during PEI, i.e., when HR declines toward resting values and diastolic time and cardiac filling increase, then a rise in SV would be expected.

The aim of this study was to evaluate changes in hemodynamics during metaboreflex activation at the start of recovery after mild forearm rhythmic exercise by the PEI method. Moreover, as it was found that stimulation of mechanosensitive afferents in form of external compression is capable of causing cardiovascular reflexes (30), we also evaluated hemodynamics during arm circulatory occlusion not preceded by forearm exercise. We found that the muscle metaboreflex is capable of increasing SV, so keeping CO higher with respect to resting conditions despite a concomitant HR decreases toward resting values. This response was present neither during control recovery (i.e., without PEI) nor during circulatory occlusion (i.e., not proceeded by exercise). These results may be explained by the observed increases in myocardial contractility and in diastolic time, which, in turn, caused a more efficient cardiac filling during metaboreflex activation after rhythmic exercise.

METHODS

Study population. Seven male volunteers between the age of 25 and 38 yr (mean 30.1 ± 1.9 yr; height 177.7 ± 2.7 cm; weight 73.4 ± 2.5 kg) (mean ± SEM) agreed to participate to this study. None had any history of cardiac or respiratory disease or were taking any medication. All subjects were normotensive, and none showed any abnormalities on physical examination. The study was performed according to the Declaration of Helsinki and was approved by a local ethics committee. All subjects gave written informed consent.

Protocol. All experimental sessions were carried out in a temperature-controlled, air-conditioned room. Each subject underwent the following study protocol in a random order, while seated on a chair:

a) Postexercise ischemia session (PEI session): 3 min of resting, followed by 5 min of exercise, consisting of a rhythmic handgrip achieved by squeezing the balloon of a phymgomanometer (30 squeezes per minute) at 30% of the predetermined maximal capacity followed by 3 min of PEI on the exercising arm. We induced PEI by using an automated pneumatic device (Hokanson E20 Rapid Cuff Inflator and AG101 Air Source, Bellevue, WA), which allows inflating a biceps tourniquet in less than 1 s. The cuff was inflated to 50 mm Hg above peak exercise arm systolic pressure just at the end of exercise. This protocol has been shown to trap the muscle metabolites in the exercising limb and to maintain the stimulation of the metaboreceptors (10,23,26). We chose this light exercise intensity because it was found that CO is mainly involved in metaboreflex pressure response when there is a sufficient cardiac reserve (i.e., mild or moderate exercise) (1).

b) Control exercise recovery session (CER session): the same rest-exercise protocol used for PEI was performed followed by a control exercise recovery without tourniquet inflation.

c) Rest circulatory occlusion session (RCO session): after an 8-min resting period, 3 min of regional circulatory occlusion was applied, to verify whether this condition “per se,” without any exercise, could affect hemodynamics.

As it can be inferred, each protocol session had the same length (11 min). Approximately, 15 min of recovery was allowed between trials.

Hemodynamic and ventilatory data. Hemodynamic and ventilatory data were recorded throughout all phases of the protocol. Subjects breathed through a mouthpiece and wore a nose clip. Pulmonary ventilation (VE), oxygen uptake (VO2), and carbon dioxide production (VCO2) were measured breath-by-breath by using a mass spectrometer (Amis, Innovation, Odense, Denmark). Hemodynamics were continually measured using an impedance cardiograph (NCCOM 3, BoMed Inc., Irvine, CA) connected to the subject by arranging eight spot electrodes (18). This noninvasive method is commonly utilized to assess hemodynamics either in resting or exercising subjects (2,7,34). As previously shown (13), through traces of electrocardiogram (ECG), transthoracic electric impedance (Z0), and its first derivative (dZ/dt), we measured the following time intervals: prejection period (PEP), left ventricular ejection time (VET), and their ratio (PEP/VET), which is inversely correlated with myocardial contractility (15), and diastolic time (DT), calculated subtracting the sum of PEP and VET from the cardiac cycle total period. SV was calculated using the Sramek-Bernstein equation (3):

\[
SV = (VEPT \cdot Z0) \cdot \frac{dZ/dt}{max} \cdot (\text{VET})
\]

where VEPT was the volume of tissues electrically participating in thoracic impedance, computed as the difference between the actual and ideal body weights of the subject multiplied by the quantity L (17% of subject’s cubed height divided by 4.2) (3). HR was calculated as the reciprocal of the electrocardiogram R-R interval and CO was obtained by multiplying SV·HR. Arterial systolic (SBP) and diastolic blood pressure (DBP) were obtained by using a noninvasive device (Finapres, Ohmeda, CA). Mean arterial blood pressure (MBP) was calculated as DBP + 1/3 (SBP – DBP). By dividing MBP by CO, we obtained SVR. Variables were averaged over a period of 1 min. Ventilatory and hemodynamic responses are reported as the mean ± SEM percent changes from corresponding resting values. We considered as the resting values the mean of the 3 min preceding the exercise runs for PEI and CER sessions, and the mean of the first 3 min of rest for RCO session. We chose the use of
percent changes instead of absolute values to describe time courses of variables because we expected that the mild exercise we used would cause little changes in hemodynamics and metabolism. Thus, percent changes would allow to curtail the interindividual variance and to highlight small perturbations better than absolute values.

**Data analysis.** Changes in each variable were compared across conditions by two-way ANOVA for repeated measures (factors: conditions and times) followed by Newman–Keuls post hoc analysis when significant F-values were obtained. A P value < 0.05 was considered statistically significant.

**RESULTS**

All subjects completed the protocol and none of them complained of significant pain or discomfort during circulatory occlusions. No significant differences in resting variables before the three tests were observed (Table 1).

As it can be seen in Figure 1 (top panel), starting from the third minute of both exercise runs, HR significantly increased on average of 10% with respect to the corresponding resting values and to the corresponding time point of RCO session (P < 0.01 in both cases), whereas no differences were noticed between the two exercise tests. Then, during CER, HR returned to values no different from rest and RCO; differently, during PEI, starting from the second minute of recovery, it showed lower values than rest (on average −7%), CER (−8%), and RCO (−8%) (P < 0.01 in all cases).

Figure 1 (middle panel) shows that SV was unaffected by both exercises, CER, and RCO session but it rose significantly during the latter 2 min of PEI with respect to the others protocol phases (on average +9% and +10% with respect to CER and RCO) and to the corresponding resting values (on average +10%) (P < 0.05 in all cases). CO was risen by both of the exercises runs versus rest (on average +7% and +8% for PEI session and CER session exercises, respectively; P < 0.05) and versus RCO session (on average +8% and +9% for PEI session and CER session exercises respectively; P < 0.05 in both cases) starting from the third minute of the exercises. Then, during CER, cardiac output progressively decreased toward resting values. On the contrary, during PEI it kept higher values than rest (on average +6%; P < 0.05), RCO (on average +7%; P < 0.05), and CER, to a limited extent of the third minute of recovery (+6%; P < 0.05) (Fig. 1, bottom panel).

SBP, DBP, and MBP increased during the exercise runs compared to the corresponding rest and to RCO session (P < 0.01 in both cases). In particular, mean arterial pressure (MAP) was increased by about 13% during both exercises with respect to rest. However, whereas during CER, the blood pressure rapidly decreased toward resting values, during PEI all the pressure parameters remained higher than rest, CER, and RCO (on average +13%, +11%, and +16% in MAP, respectively; P < 0.01 in all cases) (Fig. 2, top, middle, and bottom panel).

SVR (Fig. 3 top panel) did not show any statistical difference among the protocol periods, even if it tended to increase during exercise phases and PEI PEP/VET (inversely related to myocardial contractility) decreased during the two exercise runs with respect to rest (on average −7% for PEI and −6% for CER; P < 0.05 in both cases) and to RCO session (P < 0.05). During CER and PEI, the contractility index gradually restored toward resting values, but this increment was more marked during CER, which showed, starting from the second minute of recovery, values no different from rest and RCO. On the contrary, during post-exercise ischemia, PEP/VET remained lower than rest (on average −12%; P < 0.01) and RCO (−13%; P < 0.01) for the entire recovery period (Fig. 3, middle panel).

Both of the exercises lowered DT with respect to the corresponding rest (on average −12% for PEI session and −14% for CER session exercises; P < 0.01 in both cases) and to RCO session (on average −10% for PEI and −12% for CER session exercises; P < 0.01 in both cases). Then, CER led DT to increase reaching values no different from rest and RCO. DT increased also during PEI, but the increment was more pronounced than during CER. This fact caused DT to be higher during the latter 2 min of PEI than rest, CER, and RCO (on average +11%, +13%, and +13%, respectively; P < 0.01 in all cases) (Fig. 3, bottom panel).

Finally, both exercise runs increased in a similar way VO2, VCO2, and VE versus rest and RCO session (P < 0.01 in all cases). During PEI and CER, all the aforementioned variables returned to values similar to baseline (Fig. 4, top, middle, and bottom panel).

**DISCUSSION**

In this study, performed in healthy subjects, we were able to evoke a typical blood pressure response after forearm exercise due to metaboreflex activation: a persistent increase in
SBP, DBP, and MBP during muscle circulatory occlusion after effort. This response was not present during recovery without circulatory occlusion. These data confirm previous observations concerning the presence of neural signals from exercising muscle eliciting a reflex increase in blood pressure when blood flow is insufficient to meet the metabolic demands of the muscles, i.e., the metaboreflex (22).

The main findings of our study were that the metaboreflex during PEI: 1) enhanced myocardial contractility, 2) prolonged DT, 3) induced bradycardia with respect to CER, 4) increased SV, 5) increased CO, and 6) did not affect SVR. On the other hand, RCO did not lead to any hemodynamic differences with respect to rest, supporting the concept that these reflex responses were due to the accumulation of

FIGURE 1—Time courses of heart rate (HR), stroke volume (SV), and cardiac output (CO) during rest, 5 min of exercise, and 3 min of postexercise performed with regional ischemia (PEI) induced by tourniquet inflation (■) or without ischemia (CER) (□). Filled triangles (▼) denote 5 min of rest followed by 3 min of regional ischemia (RCO). Values are mean ± SEM of rest; ‡ significant different from the corresponding rest; § significant different from CER; * significant different from RCO session.

FIGURE 2—Time courses of systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) during rest, 5 min of exercise, and 3 min of postexercise performed with regional ischemia (PEI) induced by tourniquet inflation (■) or without ischemia (CER) (□). Filled triangles (▼) denote 5 min of rest followed by 3 min of regional ischemia (RCO). Values are mean ± SEM of rest; ‡ significant different from the corresponding rest; § significant different from CER; * significant different from RCO session.
metabolites of exercising muscle (the "metaboreflex") and not simply due to muscle ischemia.

The significant increase in myocardial contractility found in our study was not unexpected. In fact, some works have reported similar findings both in animals and humans (5,21). The index we used to evaluate myocardial contractility (PEP/VET decrease) may, indeed, underestimate the real increase in contractility during PEI, as the PEP shortening may be limited by the increase in DBP. The increase in myocardial contractility is in line with the sustained sympathetic activation described for this reflex (20). Moreover, also the increased after-load may have taken place in enhancing myocardial contractility during PEI (i.e., Anrep effect).

The significant DT elongation we observed during PEI is a novel finding which suggests that not only an increase in

![Figure 3](image1)

**FIGURE 3**—Time courses of systemic vascular resistance (SVR), myocardial contractility (PEP/VET), and diastolic time (DT) during rest, 5 min of exercise, and 3 min of postexercise performed with regional ischemia (PEI) induced by tourniquet inflation (◼) or without ischemia (CER) (□). Filled triangles (▼) denote 5 min of rest followed by 3 min of regional ischemia (RCO). Values are mean ± SEM of rest; † significant different from the corresponding rest; § significant different from CER; * significant different from RCO session

![Figure 4](image2)

**FIGURE 4**—Time courses of oxygen consumption (VO₂), carbon dioxide production (VCO₂), and pulmonary ventilation (VE) during rest, 5 min of exercise, and 3 min of postexercise performed with regional ischemia (PEI) induced by tourniquet inflation (◼) or without ischemia (CER) (□). Filled triangles (▼) denote 5 min of rest followed by 3 min of regional ischemia (RCO). Values are mean ± SEM of rest; † significant different from the corresponding rest; * significant different from RCO session
contractility may take place during metaboreflex activation (4,9) but also a greater ventricular filling with a consequent Frank-Starling effect. In our setting, the rise in DT may have been evoked by the rise in blood pressure that occurred during PEI, which in turn may have stimulated the arterial baroreflex inducing the significant fall in HR with respect to CER.

The HR fall below baseline values induced by PEI is an unusual phenomenon that was probably mediated by metaboreflex-induced changes in sympathetic and parasympathetic activity, which are the primary mediators of HR modulation. In animal studies, it has been proposed that parasympathetic tone could be increased during PEI via the arterial baroreflex or by unknown mechanisms, which leads HR to decrease in spite of the enhanced sympathetic outflow to the heart due to muscle metaboreflex activation (20). The importance of baroreflex-mediated increase in parasympathetic tone in HR regulation during PEI was also confirmed in a human study showing that a vagally mediated baroreflex mechanism was responsible for the return of HR toward resting values despite the maintained sympathetic activation (11). Therefore, a simultaneous increase in sympathetic and parasympathetic tones may occur during PEI. However, it should be noted that the HR behavior may become remarkably unstable during stressful situations that result in accentuated sympathovagal antagonism, as acetylcholine and noradrenaline have complex interaction at the presynaptic and postsynaptic level of sinus node (14). A critical aspect of the sympathetic-parasympathetic interaction is represented by the phenomenon of “accentuated antagonism,” which consists in a more pronounced bradycardia in response to vagal stimulation while sympathetic activity is elevated (31,32). Thus, if during situations involving increase in sympathetic activity, such as PEI, there was a concomitant increase in parasympathetic tone, then a deep negative chronotropic effect could occur. This is a possible explanation of the drop in HR below baseline found in our setting, because a simultaneous rise in both sympathetic and parasympathetic tone likely took place. This particular autonomic condition could affect not only HR behavior, but it could result in the apparently paradoxical hemodynamic effect of causing a constant or even increased cardiac contractility while HR decreases. For example, during the early exercise recovery, when the sympathetic tone is still high and the cardiac parasympathetic outflow rises, it is not uncommon to find that ejection fraction (which is directly related to myocardial contractility) and SV are kept constant or even increased whereas HR decreases (12,24). In summarizing, in our experiment, it may have been that during PEI the parasympathetic outflow to the heart increased causing bradycardia, whereas the sympathetic activity remained elevated, thus keeping high the myocardial contractility, because it is known that the vagal activity produces only a small effect on ventricles contractility. These results are in line with the findings of Nishiyasu and coworkers (16), who found in humans that the parasympathetic tone was enhanced during the metaboreflex activation and balanced the enhanced cardiac sympathetic activity leading to a decrease in PEP/VET (i.e., contractility increase), whereas HR was unchanged with respect to a control situation.

As concerns SV, to the best of our knowledge, this is the first study reporting an increase of SV induced by the metaboreflex in humans. A similar increase in SV was seen in dogs in which the HR was maintained constant (21). The few works that have evaluated the SV response during PEI in humans (4,9) found that metaboreflex activation induced an increase in ventricular performance, which kept SV constant despite an increase in the after-load and despite an unchanged HR. However, in our study, during PEI (i.e., during metaboreflex stimulation), a drop in HR toward baseline values was observed: this, together with the enhancement in myocardial contractility (i.e., the PEP/VET decrease), which shortened the systolic time intervals, led to an increase in DT above baseline values that could have improved cardiac filling, which in turn caused an increase in cardiac diastolic volume. The consequent involvement of the Frank-Starling mechanism, together with the enhanced myocardial contractility, could explain the rise in SV found. The involvement of Frank-Starling mechanism in metaboreflex-induced changes in central hemodynamics has been suggested by Sheriff and coworkers (27), who found that the muscle chemoreflex was capable of increasing right atrial pressures. We think that the DT prolongation and the enhancement in myocardial contractility observed during PEI may have played an important role in achieving a more efficient cardiac filling and the consequent increase in CO. Our findings of significant increase in SV confirm that HR alone may not accurately depict changes in hemodynamics during situations such as metaboreflex activation after mild exercise. This may be considered a step forward with respect to previous studies in paced dogs that also showed an increase in SV during metaboreflex (21).

The combined increase in contractility and Frank-Starling mechanism is in line with the findings of Nobrega et al. (17), who demonstrated that, during exercise, an increase in SV, due to the aforementioned mechanism, could compensate for the lack of HR response in patients suffering from atrium-ventricular block. Besides, we confirmed these findings in a recent case report in which we showed that, during a complete exercise-induced atrium-ventricular block, an increase in SV can compensate for the lack of HR response and thereby maintain normal CO values during exercise (8). Therefore, it seems that reflexes, which control cardiovascular apparatus operate with sufficient plasticity to modify hemodynamic variables to increase blood pressure under various circumstances. In the present study, it appears that the bradycardia occurred during PEI was compensated by the SV increase that, by keeping CO at levels higher than rest, successfully maintained the blood pressure response induced by metaboreflex activation.

Because of the absence of changes in SVR, the blood pressure response was not due to peripheral vasoconstriction but to the CO response itself. This is in line with the recent findings of Augustyniak and coworkers (1), who found, in dogs, that the pressor response during metaboreflex activation is dependent
on the ability to increase CO, especially during mild and moderate exercise.

Another finding is that regional circulatory occlusion alone was not capable of inducing any changes in hemodynamics with respect to resting values. This means that all the hemodynamic changes we reported were not due either to a reflex arising from mechanical stimulation of skeletal muscle or to the occlusion of muscle circulation at rest. So, we suggest that the muscle must be exercised to produce metabolites capable of stimulating chemosensitive afferent nerve endings.

With respect to respiratory data, it should be noted that PEI did not induce any change in VO$_2$, VCO$_2$, and VE with respect to CER. The absence of any modification in these parameters during PEI lead us to assume that in this experimental setting the hemodynamic response was unaffected by changes in metabolism or in ventilatory pattern.

**Methodological considerations and limitation of the study.** The impedance method for measurement of hemodynamic variables at rest and during exercise is still the subject of criticism (33). One problem is that the increase in respiration with exercise may generate artifact signals due to chest movements. We used a visual inspection of impedance signals by a skilled physician to avoid poor quality signals to be recorded. Moreover, we chose a mild exercise protocol that did not generate either great enhancement in ventilation or marked chest movements. Another criticism inherent in impedance cardiography is its underestimation of high CO values, such as those occurring during exercise (33). Nevertheless, our exercise protocol was expected to produce small increase in CO, inasmuch it involved small muscle masses at mild strain engagement. Moreover, the aim of this work was not to study the absolute values of cardiodynamic variables but to evaluate relative changes. The sensibility of impedance cardiography also appears from our study (Figs. 1 and 3). In fact, SV resulted slightly increased during exercise before PEI than during exercise before CER. These apparently contradicting results indeed further validate the impedance cardiography. In fact, during exercise before PEI diastolic time and contractility are slightly greater, whereas HR is slightly lower than during exercise before CER. Although all the above differences were not significant, the higher DT and contractility may well explain the higher SV during exercise before PEI as opposed to a decreasing SV during exercise before CER.

The present study employed rhythmic forearm exercise whereas the other studies performed in humans involved dynamic cycling or static handgrip (4,9) to investigate hemodynamics during metaboreflex activation, thus making a direct comparison difficult. In fact, dynamic cycling and static handgrip are expected to cause substantially larger pressor responses and larger increases in after-load than the exercise protocol used in our study. This could have limited increases in SV, thus explaining the differences in SV behavior from those seen in our study. Furthermore, these previous studies showed little contribution of CO in mediating the pressor response, the opposite of what shown in the present study. This could be workload dependent, as shown for responses when the metaboreflex was activated during exercises at different intensities (1). A limitation of the present study is that we did not perform exercise protocol of different intensity. However, PEI effects after more intense exercise have been object of a large number of investigations and are already well defined. In particular, it is well known that high workloads (4,9) cause substantially larger pressor responses and larger increases in after-load than the light exercise intensity protocol used in our study. Because SVR increases during metaboreflex (29) and a high after-load could limit the increases in SV, and because in dogs it was found that CO is mainly involved in metaboreflex pressure response when there is a sufficient cardiac reserve (i.e., during mild or moderate exercise) (1), we chose to study the PEI effect after light exercise intensity to enhance the chance to see whether also in humans CO may contribute to metaboreflex. Finally, it should be considered that our study was performed in the seated position, whereas the majority of human investigations studying the metaboreflex were performed in the supine position and the majority of animal studies employed dogs, whom hemodynamics is known to be less stressed by postural changes. The seated position could be in part responsible of the SV response in our study. In fact, it is likely that the reduction in central blood volume in the seated position may have increased the volume reserve compared with supine position, thus allowing a greater increase in ventricular volume during PEI with a consequent increase in SV. Future researches will address whether SV can also increases with more moderate exercise in seated position, assisting in further dissection of the effects attributed to SV from that attributed to SVR. It may be speculated that metaboreflex-mediated blood pressure responses rely mainly on CO when SV reserve can be still used (i.e., when the volume reserve was not fully used in the exercise and/or the postural position facilitate its use), whereas when SV reserve cannot be used (i.e., during heavy exercise and/or during supine position), the metaboreflex-mediated pressure responses rely mainly on SVR increase.

Another difference of our study from previous works (4,9) is that the HR drop we found during PEI is unusual during metaboreflex activation. This unusual result could make the interpretation of the SV behavior during PEI difficult since it may be argued that bradycardia alone was responsible for the increased SV via the Frank-Starling mechanism. However, it should be noted that, in our study, also CO was increased during PEI. Thus, the increase in SV was higher than it could be expected if the hemodynamic response was due by a Frank-Starling effect alone. Therefore, an enhancement in myocardial contractility should have taken place during this SV response. In this light, it may be speculated that the SV increase during PEI should be a compensatory mechanism that kept CO higher than rest in spite of bradycardia in order to maintain the blood pressure response.

In conclusion, our study performed in healthy individuals showed that activation of the metaboreflex after mild forearm exercise may lead to an increase in SV. This effect was due to an improved ventricular contractility and to length-
enning of DT, which may have caused a more efficient cardiac filling. This response kept CO elevated, whereas SVR was not affected. These results also suggest that the blood pressure response during metaboreflex activation, when the SV reserve can be still used, is dependent on the capacity to increase CO rather than to peripheral vasoconstriction.

REFERENCES


