Effects of acute vasodilation on the hemodynamic response to muscle metaboreflex

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1Department of Medical Sciences, Sports Physiology Laboratory, University of Cagliari, Cagliari, Italy; 2Cardiac Department, Heart Failure Unit, Guglielmo da Saliceto Polichirurgico Hospital, Piacenza, Italy; and 3Department of Medical Sciences, Unit of Cardiology and Angiology, University of Cagliari, Cagliari, Italy

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Marongiu E, Piepoli M, Milia R, Angius L, Pinna M, Bassareo P, Roberto S, Tocco F, Concu A, Crisafulli A. Effects of acute vasodilation on the hemodynamic response to muscle metaboreflex. Am J Physiol Heart Circ Physiol 305: H1387–H1396, 2013. First published August 30, 2013; doi:10.1152/ajpheart.00397.2013.—The aim of the present study was to test the contribution of stroke volume (SV) in hemodynamic response to muscle metaboreflex activation in healthy individuals. We hypothesized that an acute decrease in cardiac afterload and preload due to the administration of a vasodilating agent could reduce postexercise muscle ischemia (PEMI)-induced SV response. Ten healthy males (age 33.6 ± 1.3 yr) were enrolled and randomly assigned to the following study protocol: 1) PEMI session, 2) control exercise recovery (CER) session, 3) PEMI after sublingual administration of 5 mg of isosorbide dinitrate (ISDN), and 4) CER after ISDN. Central hemodynamics were evaluated by means of impedance cardiography. The main findings were a blunted SV response during metaboreflex following acute arterial and venous vasodilation, associated with a reduction in cardiac diastolic time and filling, and a decrement of systemic vascular resistance. These hemodynamic changes restrain blood pressure response during metaboreflex activation. Our results indicate that hemodynamic response to metaboreflex activation is a highly integrated phenomenon encompassing complex interplay between heart rate, cardiac performance, preload, and afterload and that impairment of one or more of these parameters leads to altered hemodynamic response to metaboreflex.

venous return; cardiac preload; blood pressure; myocardial contractility; stroke volume

Circulatory response arising from metabolic sensitive nerve endings in the skeletal muscle, commonly termed “muscle metaboreflex,” is attracting growing interest since it is thought to play a pivotal role in cardiovascular regulation during exercise. This reflex provides continuous feedback to the cardiovascular control areas on the metabolic status of contracting muscles (1, 5, 41), and, whenever activated, sympathetic activity increases, which in turn leads to a rise in blood pressure (19, 41).

Our group has conducted several experiments on the hemodynamic effect of metaboreflex recruitment in humans through postexercise muscle ischemia (PEMI) (8, 9, 12, 14, 36). From the quoted investigations and from results obtained by other laboratories, it could be argued that blood pressure response during metaboreflex activation in healthy individuals is the consequence of hemodynamic adjustments that encompass complex interplay between myocardial performance, cardiac preload, systemic vascular resistance (SVR), and heart rate (HR) (1, 8, 13, 14, 20a, 28, 37, 39, 40). Each of these parameters is modulated during metaboreflex, and their contribution to the resulting hemodynamic response depends on several factors, such as cardiac contractility reserve, metabolite accumulation, and exercise mode and intensity (5, 9, 11, 12, 14, 28, 39).

Overall, it appears that, at least in healthy individuals, a central role in metaboreflex-induced mean blood pressure (MBP) modulation is played by stroke volume (SV). This parameter has been shown to rise during metaboreflex, and, in turn, cardiac output (CO) is consequently increased as a result, whereas HR is not significantly involved in the phenomenon (8, 9, 11, 13), although considerable individual differences in HR response to PEMI have been reported (42). The described SV response is the consequence of improvements in both cardiac performance and ventricular filling rate. Moreover, it has been reported that the possibility of increasing SV during PEMI-induced hemodynamic response may vary depending on HR behavior, since tachycardia reduces diastolic time and consequently ventricular filling (14). In fact, changes in HR and SV may oppose each other (17), and their combined effects should therefore be investigated.

Starting from these considerations, our aim was to further investigate the contribution of metaboreflex to hemodynamic responses to exercise. Taking into consideration the fact that hemodynamic response to muscle metaboreflex activation is a highly integrated phenomenon encompassing complex interplay between myocardial performance, cardiac preload, SVR, and HR adjustments, we wondered whether the mechanism underlying the blood pressure response observed during PEMI (i.e., a SV-induced increase in CO and unchanged HR and SVR) would be the same if an acute increase in HR and a reduction in cardiac preload and SVR occurred. This situation is typically observed when arterial and venous dilation occurs simultaneously, such as after administration of vasodilator drugs. In particular, we expected that the inability to increase both SVR and cardiac preload could result in a blunted blood pressure due to reduced metaboreflex activation. Indeed, acute arterial dilation reduces blood pressure and would cause baroreflex unloading, sympathetic activation, parasympathetic withdrawal, and tachycardia, whereas venous dilation decreases cardiac filling and preload. Such research would have the practical implication to investigate the acute effects on cardiovascular regulation of vasodilator agents, which are commonly used in cardiology practice.

METHODS

Study population. Ten healthy males aged 26–44 yr (mean ± SD 33.6 ± 1.3 yr), height 174.7 ± 4.7 cm, and mass 73 ± 5.7 kg were...
enrolled in the study. None had any history of cardiac or respiratory disease or were taking any medication at the time of the experiment. All subjects were normotensive, and no abnormalities were observed on physical examination. The study was performed according to the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all subjects.

Experimental design. All experiments were carried out in a temperature-controlled, air-conditioned room (22°C, relative humidity 50%), and all subjects were randomly assigned to the following study protocol to eliminate any order effect: 1) PEMI session: 3 min of resting, followed by 3 min of exercise, consisting of rhythmic (30 compressions/min) dynamic handgrip at 30% of the maximum assessed as the peak reached during five previous maximal compressions on a hydraulic dynamometer (MAP 1.1; Kern, Balingen, Germany). Exercise was followed by 3 min of PEMI on the exercised arm induced by rapidly (in <3 s) inflating an upper arm biceps tourniquet to 50 mmHg above peak exercise systolic pressure. The cuff was kept inflated for 3 min. A further 3 min of recovery were allowed after the cuff was deflated, for a total of 6 min of recovery. This protocol has been shown to trap muscle metabolites in the exercising limb and to maintain stimulation of the metaboreceptors (8, 14); 2) control exercise recovery session (CER): the same rest-exercise protocol used for PEMI was performed followed by a control exercise recovery of 6 min without tourniquet inflation; 3) postexercise ischemia session after acute vasodilation (PEMIAV) session: subjects performed the same protocol as for PEMI; 4) control exercise recovery session after acute vasodilation (CERAV) session: subjects performed the same protocol as for CER.

Before the PEMIAV and CERAV tests, 5 mg isosorbide dinitrate (ISDN) were administered sublingually to induce acute vasodilation. Following ISDN administration, subjects remained seated until their HR increased by at least 10 beats/min above resting values and systolic blood pressure (SBP) decreased by at least 5 mmHg below resting values. This was done to obtain the typical response of ISDN administration (22), which occurred on average 15 min after administration. Next, participants underwent the scheduled protocol session. Sessions with and without ISDN administration were distanced by at least 1 day (interval 1–7 days). ISDN was chosen because of its well-known effects to reduce both cardiac preload due to pulmonary artery and venous capacity vessel dilation and afterload by increasing aortic capacity (27, 35). While the first effect principally affects SV, the second affects mainly HR by unloading baroreflex (31), although it has been reported that nitrates may lower blood pressure through a predominant venodilator effect, which reduces ventricular preload, and a quantitatively lesser effect on arteriolar resistance vessels (22, 27).

Hemodynamic assessment. Throughout all phases of the study, hemodynamic parameters were measured by means of impedance cardiography (NCCOM 3; BoMed, Irvine, CA), which allows for continuous noninvasive cardiodynamic measuring and has been previously used in similar experimental settings (8, 11, 14). The data acquisition method is described in detail in our previous work (8, 12). Briefly, NCCOM 3-derived analog traces of electrocardiogram, thorax impedance ($Z_t$), and $Z_t$ first derivative were stored by using a digital chart recorder (PowerLab 8sp; ADInstruments, Castle Hill, Australia). $Z_t$ is an inverse index of thoracic fluid volume, since reductions in its values are associated with increases in central blood volume while increases in $Z_t$ occur when central blood volume is reduced, such as during leg venous pooling (6, 10, 18). Hence, changes in $Z_t$ were used as an indirect measure of changes in central blood volume. The Sramek-Bernstein equation (3) was employed to calculate beat-to-beat SV from stored transthoracic impedance traces. The preejection period-to-left ejection time ratio (PEP/VET) was also calculated from impedance traces, as shown in previous papers (8, 9, 11, 14). This ratio correlates quite well with the angiographic ejection fraction and represents an inverse index of myocardial performance (7). HR was calculated as the reciprocal of the electrocardiogram R-R interval, and $Z_t$ first derivative were stored by using a digital chart recorder (PowerLab 8sp; ADInstruments, Castle Hill, Australia). The time (DT) was measured by subtracting the sum of PEP and VET from the cardiac cycle total period and by dividing SV by DT, the ventricular filling rate (VFR), which is a measure of the mean rate of diastolic blood flux, was obtained (8, 13, 20).

Subjects were also connected to a noninvasive automated sphygmomanometer (NIBP 7000; Colin Medical Instrument, San Antonio, TX) that provided beat-to-beat values of SBP and diastolic blood pressure (DBP) by means of a tonometer placed around the wrist, at the height of the radial artery. This device has been shown to provide continuous beat-to-beat pressure monitoring with high accuracy (25). MBP was calculated taking into account changes in the diastolic and systolic periods caused by exercise tachycardia (11, 12). In detail, the fraction of systole (FS) from the heart cycle was assessed, MBP was calculated from DBP, and the pulse pressure (PP) was adjusted for FS as follows: $DBP + FS \times PP$. SVR was derived by multiplying the MBP-to-CO ratio by 80, where 80 is a conversion factor to change units to standard resistance units.

To obtain a cardiac sympathovagal balance index, power spectral analysis was performed on 120-s consecutive time series of HR during PEMI, CER, PEMIAV, and CERAV tests. The R-R intervals at the 3rd min of PEMI and PEMIAV maneuvers and at the corresponding time point of the CER and CERAV tests were inspected for ectopic beats and analyzed using power spectral analysis based on the fast-Fourier transform (Kubios HRV analysis software 2.0; Kuopio, Finland). Two main components were considered: that within the 0.04- to 0.15-Hz frequency band (low frequency, LF) and that within the 0.15- to 0.4-Hz band (high frequency, HF). LF is widely accepted that HF power reflects vagal modulation of HR and that LF power reflects complex interplay between sympathetic and vagal modulation. The very low component (<0.03 Hz) was not taken into account because of its uncertain physiological meaning (33). The LF-to-HF ratio was also calculated and used as an index of sympathovagal balance. Results of HR spectral analysis are reported in normalized units.

Finally, the sequence method was employed to measure the sensitivity of baroreflex control on blood pressure (4, 31). In detail, regression analysis was performed on sequences of three or more consecutive cardiac cycles showing concurrent changes in SBP and R-R interval (either increasing or decreasing). A linear relationship was applied to each individual sequence, and only those sequences with $R^2 > 0.85$ were accepted and the slope was calculated. In each subject, at least three sequences (range 3–7) for each protocol session were taken into account. Next, mean slope and mean $\gamma$-intercept of the R-R/SBP relation (i.e., ms), obtained by averaging all slopes computed within a given protocol session, were calculated.

Data analysis. Hemodynamic responses during PEMI, CER, PEMIAV, and CERAV tests were averaged over 1 min. For each parameter, the values at the 3rd min of rest, exercise, and recovery from the tests (when a steady state was expected to be reached) were taken into account, with the exception of HR power spectral analysis, which was performed during 120-s consecutive time series of HR (i.e., the last 2 min of each period of the protocol). Next, the difference between the PEMI and CER tests and between the PEMIAV and CERAV tests was calculated. This procedure allowed for metaboreflex response to be assessed (15), i.e., the parameter response due to metaboreflex activity. Two-way analysis of variance (ANOVA) for repeated measures was used to compare hemodynamic data for the effects of settings (rest, exercise, and recovery) and conditions (PEMI, CER, PEMIAV, and CERAV) followed by Tukey’s post hoc when appropriate. One-way ANOVA was employed to find out whether there was a significant difference in slope and mean intercept of the R-R/SBP relation. Differences in measured variables due to metaboreflex response were assessed by means of the paired $t$-test. Statistical analysis was carried out by using commercially available software (GraphPad Prism). Statistical significance was established as a $P$ value of $<0.05$ in all cases.
RESULTS

The protocol was completed by all subjects, and no individual complained of unbearable pain or discomfort during the periods of arm circulatory occlusion.

Figures 1–4 show cardiovascular values and responses obtained during the various protocol sessions. Figure 1, top, shows that, in all protocol settings (i.e., rest, exercise, and recovery), the administration of ISDN caused an increase in HR with respect to the PEMI and CER tests, whereas there was no difference between the PEMI and CER tests and between the PEMIAV and CERAV tests. Figure 1 also shows that HR was significantly affected by setting, since during exercise it was higher compared with rest and recovery. Moreover, there was no difference in HR response. SV (Fig. 1, middle) was unaffected by settings and conditions, even though it showed a tendency to be higher during the PEMI phase of the recovery session with respect to the other protocol conditions. Furthermore, SV response was higher when PEMI was conducted without the administration of ISDN. As a result of HR and SV behavior, CO (Fig. 1, bottom) was higher during the PEMIAV and CERAV with respect to the PEMI and CER tests both at rest and during exercise. Differently, during the recovery session of the PEMI test, CO was at the same level as during the PEMIAV and CERAV tests. Statistics also revealed that

Fig. 1. Absolute values at rest, exercise (exe), and recovery (rec) during the postexercise muscle ischemia (PEMI), control exercise recovery (CER), postexercise ischemia session after acute vasodilation (PEMIAV), and control exercise recovery session after acute vasodilation (CERAV) tests (left) and responses to metaboreflex (right) in heart rate (HR), stroke volume (SV), and cardiac output (CO). Values are means ± SD. *Brackets, significant effect of settings. *P < 0.05 vs. PEMI; †P < 0.05 vs. CER; and ‡P < 0.05 vs. PEMIAV-CERAV.
exercise significantly affected CO values, since it was higher with respect to rest and recovery. Furthermore, CO response was higher during tests without ISDN administration.

MBP (Fig. 2, top) was significantly affected by the setting of the protocol, since it was higher during exercise than during the other phases. Furthermore, MBP was reduced by ISDN at rest and exercise with respect to tests without ISDN. During recovery, MBP maintained higher levels during PEMI than in all the other tests. In detail, this parameter maintained a mean of 92.1 ± 8 mmHg, i.e., higher than the corresponding rest value and similar to that at exercise. During the exercise phase of the CER test, this parameter achieved similar levels compared with the PEMI test. However, MBP recovered to rest during the recovery phase, when on average it was 82 ± 5.9 mmHg. Thus, during both exercise phases of the PEMI and CER tests MBP increased to a similar amount with respect to baseline (i.e., in the order of 5–6 mmHg). It did not recover toward baseline only during the circulatory occlusion period of the PEMI test. Similar behavior was observed after ISDN administration, i.e., an increase in MBP of about 5–6 mmHg during the exercise phases. However, it is noteworthy that the circulatory occlusion period of the PEMI test did not cause any MBP increment compared with the CER test. Therefore, MBP response was more elevated when metaboreflex was recruited without the vasodilator agent. Figure 2, middle, demonstrates that ISDN reduced SVR with respect to the PEMI and CER tests, without any detectable difference between the PEMI and CERAV tests. Even though it appeared that SVR response
tended to be lower when tests were conducted without ISDN, no significant difference was highlighted by statistics, probably because of the small number of individuals examined. Figure 2, *bottom*, shows that $Z_0$ (inversely related to thoracic fluid volume) was reduced after ISDN in all of the settings of the study, without any significant difference in its response.

As concerns PEP/VET (inversely related to myocardial performance; Fig. 3, *top*), an increment was observed (i.e., performance decreased) during all settings of the protocol in the PEMI$_{AV}$ and CER$_{AV}$ tests compared with tests conducted without vasodilators. Moreover, the response of this parameter was lower when tests were performed without ISDN, thereby indicating that there was an increase in cardiac performance only in this condition. During the exercise phases of the protocol, DT (Fig. 3, *middle*) was reduced compared with rest and recovery. Moreover, DT was always higher in the PEMI and CER tests than in the PEMI$_{AV}$ and CER$_{AV}$ tests, whereas no significant difference in DT response was observed between the two experimental conditions. Figure 3, *bottom*, shows that VFR was significantly increased during the exercise phase compared with the other two protocol settings. Furthermore, VFR was higher after ISDN compared with the CER and the PEMI tests. However, during the PEMI condition of the recovery, VFR maintained a value similar to those achieved during the PEMI$_{AV}$ and CER$_{AV}$ tests. VFR response was higher when tests were conducted without ISDN.

Figure 4, *top*, illustrates changes in the power of LF and HF expressed in normalized units. In detail, the exercise setting increased LF power compared with rest and recovery. This parameter was elevated by the administration of ISDN at rest and recovery.
and during exercise compared with the PEMI and CER conditions, whereas during the recovery setting of the PEMI test it was at the same level as during the PEMIAV and CERAV tests. There was no difference in terms of LF response between tests conducted with and without ISDN. Figure 4, middle, demonstrates that during exercise there was a reduction in HF power with respect to both rest and recovery, whereas conditions did not induce any difference in this parameter. Furthermore, ISDN did not lead to any change in HF response to circulatory occlusion maneuvers. The LF-to-HF ratio (Fig. 4, bottom) was increased during exercise compared with rest and recovery. At rest and during exercise, ISDN increased this parameter with respect to the PEMI and CER conditions. It is noteworthy that during recovery the LF-to-HF ratio was similar between the PEMI and PEMIAV tests and that both tests induced an increase in this variable compared with the corresponding recovery condition. Yet, ISDN did not affect the LF-to-HF ratio response to the PEMI and PEMIAV tests.

Finally, Fig. 5, top, shows there was no difference in the slope of the R-R/SBP relation between protocol sessions,
whereas the intercept of this relation was higher during the PEMI test compared with all the other protocol phases (Fig. 5, bottom).

**DISCUSSION**

The present investigation was devised to test the hypothesis that metaboreflex-induced SV response in healthy individuals is blunted by acute arterial and venous vasodilation. In accordance with this hypothesis, administration of ISDN impaired the SV response during metaboreceptor activation, in this setting. This blunted SV response was likely the consequence of the shortening in DT that occurred following ISDN administration as a consequence of tachycardia. This fact could have impaired cardiac preload by reducing the time available to fill cardiac ventricles, thereby limiting the possibility to recruit the Frank-Starling mechanism, although we have to acknowledge that this hypothesis remains speculative since we were unable to gather direct measures of cardiac preload, i.e., end-diastolic volume.

It must also be considered that, despite DT reduction, VFR was higher during the PEMI<sub>AV</sub> and CER<sub>AV</sub> tests with respect to the CER test. The DT reduction in the presence of a slightly reduced venous return probably resulted in an increase in VFR that in turn maintained a constant SV level during the PEMI<sub>AV</sub> and CER<sub>AV</sub> tests compared with the CER test. Therefore, after the acute vasodilation, which resulted in a combination of both arteriolar and venous dilation, the cardiovascular apparatus successfully defended SV in the face of tachycardia, thereby augmenting CO and counteracting the reduction in SVR. Indeed, during the PEMI<sub>AV</sub> and CER<sub>AV</sub> tests, MBP was kept at the same level as during the CER test, thus indicating that cardiovascular regulatory mechanisms successfully avoided blood pressure drops. This compensation was the consequence of HR elevation, likely because of baroreflex unloading-induced increase in sympathetic outflow, and to the maintained SV, that together increased CO and counterbalanced SVR reduction due to the ISDN. The fact that SV was maintained was probably also the consequence of the reduction in afterload, which facilitated ventricular emptying.

It should, however, be noted that after vasodilator administration the cardiovascular apparatus lost the possibility to increase VFR and SV in response to metaboreflex, as testified by the PEMI<sub>AV</sub>-CER<sub>AV</sub> difference in these two parameters. In fact, during the recovery period of the protocol, there was significant enhancement in VFR and SV during the PEMI test with respect to the CER test, whereas during the PEMI<sub>AV</sub> test these variables were at the same level as in the CER<sub>AV</sub> test, i.e., metaboreflex could not elicit any response in SV and VFR.

As concerns the PEP-to-VET ratio, the response to metaboreflex demonstrates that this parameter could not decrease (i.e., cardiac performance could not increase) after the administration of nitrate. This is in line with the concept that a reduced capacity to increase cardiac preload occurred in this setting. Indeed PEP/VET is sensitive to enhancements in both cardiac inotropism and preload (24). Hence, PEP/VET decreases when an enhancement in cardiac inotropism takes place and/or when there is an increase in cardiac preload, which recruits the Frank-Starling mechanism. Moreover, PEP/VET is also sensitive to afterload (24), which recruits the Anrep effect. Each of these variables (preload, afterload, and inotropism) can independently affect PEP/VET, thereby rendering their single contribution difficult to detect. During the circulatory occlusion of the PEMI session, a contemporary increase in sympathetic discharge, preload, and afterload likely took place, and decreased PEP/VET, whereas during the circulatory occlusion of the PEMI<sub>AV</sub> session an increase in afterload did not occur because of arteriolar vasodilation, which along with reduced capacity to sustain ventricular filling could have limited the capacity to decrease PEP/VET. This fact may explain why PEP/VET did not decrease during the PEMI<sub>AV</sub> with respect to the CER<sub>AV</sub> test, since it is likely that the PEP/VET is not sensitive enough to detect changes in cardiac performance due to sympathetic activation when two of these three components (i.e., preload and afterload) are not operating. Moreover, it has recently been proposed that a portion of the rise in contractility when metaboreflex is activated may be directly attributable to enhanced blood volume mobilization (40). Thus, in our setting, the reduction in cardiac preload after ISDN may have played a pivotal role in preventing PEP/VET from decreasing.

Therefore, because it was unlikely that ISDN affected cardiac contractility, it could be hypothesized that a reduction in the ability to propel blood volumes toward the heart took place after ISDN. However, as previously stated, we could not directly measure cardiac preload, since impedance cardiography cannot assess end-diastolic volume; this hypothesis remains speculative. The fact that venous and arteriolar dilation took place after ISDN is testified by Z<sub>0</sub>, which is an inverse index of thoracic fluid volume, that is, reductions in its values are associated with increases in central blood volume, whereas increases in Z<sub>0</sub> occur when central blood volume is reduced, such as during leg venous pooling (6, 10, 18). The reduction in this parameter indicated that an increase in thoracic blood volume was present after ISDN, a phenomenon coherent with the ISDN effects, i.e., artery and venous capacity vessel dilatation.

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**Fig. 5.** Mean values of slope and intercept of the R-R/SBP relation during the PEMI, CER, PEMI<sub>AV</sub>, and CER<sub>AV</sub> tests. Values are means ± SD. *P < 0.05 vs. PEMI and †P < 0.05 vs. CER.
Collectively, the hemodynamic scenario arising from our data suggests that the normal flow-mediated increase in MBP that normally occurs during PEMI could not take place after acute vasodilation occurring both at arteriolar and venous levels. In fact, ISDN administration prevented MBP from increasing in response to PEMI, as shown by the reduced MBP difference between the PEMIAV and the CERAV tests. In our opinion, this fact is to be ascribed to the impossibility to increase cardiac preload and SV during metaboreflex, which, along with HR behavior that does not normally participate in this response, could not compensate for the SVR decrease and sustain MBP. It could be speculated that the vasodilator stimulus induced by ISDN was too robust to allow the autonomic nervous system to correct the arteriolar and venous dilation, thereby preventing MBP to respond during metaboreflex activation.

Of particular consideration is the fact that conflicting results exist in scientific literature on the role of SV and CO in mediating blood pressure response to metaboreflex. While some papers have reported that SV does not significantly participate in this response (see, for example, Refs. 2, 21, and 26), we have demonstrated on more than one occasion that SV and CO may actually increase during PEMI. Various reasons may account for this different outcome: first, it should be noted that in this study as well as in other others rhythmic forearm exercise was employed to evoke the metaboreflex, whereas in the experiments reporting a pivotal role of peripheral vasoconstriction static exercise (handgrip) was employed, which is expected to induce a substantially greater pressor response and increase in afterload than the exercise protocol used in the present investigation. This fact could have limited the SV increment, thus explaining the different outcome. Second, protocols employed were very different in terms of workloads imposed and duration. Moreover, at least one other investigation (39) reported a substantial muscle metaboreflex-induced increase in SV during ischemic exercise. Thus, our results are in line with the concept that cardiovascular adjustments to metaboreflex stimulation rely mainly on an increased-flow mechanism rather than on vasoconstriction, as also suggested by recent findings by Amann and coworkers (1) supporting the idea that hemodynamic reflex arising from type III and IV nerve endings are predominantly mediated via CO rather than via SVR.

Taken together, results of the present investigation confirm that hemodynamic response to metaboreflex activation is a highly integrated phenomenon and that complex interplay between HR, cardiac performance, preload, and afterload occurs when this reflex is recruited (2, 8, 9, 14, 38, 39). In this context, impairment in one or more of these parameters leads to altered hemodynamic response, as has been reported when cardiac performance, venous return, and SVR cannot be enhanced during metaboreflex recruitment (11, 13, 29, 30, 32, 36). Hence, results of the present investigation support the concept that hemodynamic response during metaboreflex is not solely the consequence of an increase in SVR and that SV and CO responses should also be taken into consideration.

The LF and HF components of the HR power spectrum and the LF-to-HF ratio suggest that the ISDN administration induced a substantial increase in sympathetic activity compared with tests without ISDN. It is noteworthy that the PEMI maneuvers conducted with and without ISDN increased sympathetic tone similarly with respect to the corresponding control recovery condition, as testified by the fact that power spectrum response of these parameters was not statistically different between tests conducted with and without ISDN. This fact indicated that the sympathetic system was activated to a similar extent during both metaboreflex recruitment phases.

As concerns baroreflex activity, in agreement with previous studies, we found no evidence of muscle metaboreflex-mediated alterations in baroreflex sensitivity (16, 19). Rather, our data seem to indicate that muscle metaboreflex would produce a rightward and upward relocation of the baroreflex operating point (34). Indeed, the R-R/SBP relationship slope did not show any difference among protocol sessions, whereas its intercept was increased during the PEMI session compared with all the other settings. Moreover, the intercept was reduced during the PEMIAV and the CERAV sessions with respect to the PEMI and the CER tests, thus indicating that the baroreflex was unloaded after vasodilation.

A practical implication of the present study is that the administration of a vasodilator agent alters the capacity of the cardiovascular apparatus to properly respond to hemodynamic stresses, such as during metaboreflex activation. In particular, it appears that the incapacity to centralize blood volume and to increase venous return plays a pivotal role in the cardiovascular adjustment to metaboreflex activation and that an impairment in this capacity leads to altered hemodynamic response (2, 38).
SV response during metaboreflex recruitment. This is mainly the consequence of a shortening in DT and a reduced time available to fill cardiac ventricles, which reduces VFR. This fact, along with the impossibility to vasoconstrict the arteriolar beds, prevents the normal blood pressure increase normally observed during PEMI. These results indicate that the hemodynamic response to metaboreflex activation by PEMI is a highly integrated phenomenon encompassing complex interplay between HR, cardiac performance, preload, and afterload.

REFERENCES

AUTHOR CONTRIBUTIONS


Raviele A, Menozzi C, Brignole M, Gasparini G, Alboni P, Musso F. Value of head-up tilt testing potentiated with sublingual nitroglycerin to


