Individual differences in cardiac and vascular components of the pressor response to isometric handgrip exercise in humans

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Watanabe K, Ichinose M, Tahara R, Nishiyasu T. Individual differences in cardiac and vascular components of the pressor response to isometric handgrip exercise in humans. Am J Physiol Heart Circ Physiol 306: H251–H260, 2014. First published November 8, 2013; doi:10.1152/ajpheart.00699.2013.—We tested the hypotheses that, in humans, changes in cardiac output (CO) and total peripheral vascular resistance (TPR) vary considerably among individuals and that the individual differences are related to differences in muscle metaboreflex and arterial baroreflex function. Thirty-nine healthy subjects performed a 1-min isometric handgrip exercise at 50% of maximal voluntary contraction. This was followed by a 4-min postexercise muscle ischemia (PEMI) period to selectively maintain activation of the muscle metaboreflex. All subjects showed increases in arterial pressure during exercise. Interindividual coefficients of variation (CVs) for the changes in CO and TPR between rest and exercise periods (CO: 95.1% and TPR: 87.8%) were more than twofold greater than CVs for changes in mean arterial pressure (39.7%). There was a negative correlation between CO and TPR responses during exercise (r = −0.751, P < 0.01), but these CO and TPR responses correlated positively with the corresponding responses during PEMI (r = 0.568 and 0.512, respectively, P < 0.01). The CO response during exercise did not correlate with PEMI-induced changes in an index of cardiac parasympathetic tone and cardiac baroreflex sensitivity. These findings demonstrate that the changes in CO and TPR that occur in response to isometric handgrip exercise vary considerably among individuals and that the two responses have an inverse relationship. They also suggest that individual differences in components of the pressor response are attributable in part to variations in muscle metaboreflex-mediated cardioaccelerator and vasoconstrictor responses.

During isometric exercise, arterial blood pressure, heart rate (HR), and sympathetic nerve activity all increase in association with increases in the intensity and duration of the exercise. This pressor response is governed mainly by neural mechanisms: central command (52) as well as a feedback system operating via afferent input from exercising skeletal muscle receptors (muscle metaboreflex and mechanoreflex) (40, 41, 51) and from arterial and cardiopulmonary baroreceptors (arterial and cardiopulmonary baroreflexes) (51, 52). While the increase in arterial pressure during isometric exercise is a well-established response, the responses of the components mediating the pressor response, cardiac output (CO) and total peripheral vascular resistance (TPR), remain controversial. In fact, previous studies have shown that, during isometric handgrip exercise in healthy humans, the pressor response occurs via an increase in CO (16, 32, 34–36, 57), an increase in TPR (6, 17), or both of those (3, 31, 58, 59, 61, 62). The variability of those findings leads one to speculate that there are considerable individual differences in the components of the pressor response to exercise, which is in stark contrast to the nearly invariant arterial pressure response. To the best of our knowledge, however, individual differences in CO and TPR responses to exercise have never been systematically investigated, and the regulatory mechanism underlying those individual differences remains unknown.

Presumably, one of the important contributors to individual differences in arterial pressure regulatory mechanisms during isometric exercise, especially during the fatiguing phase, is the muscle metaboreflex. This reflex is a feedback system operating via chemosensitive afferents (group III and IV fibers) that can elicit a reflex pressor response (7, 29, 38). When the reflex is selectively activated in humans by postexercise muscle ischemia (PEMI) after isometric handgrip exercise, the pressor response occurs mainly via peripheral vasoconstriction; CO remains at the resting level (16, 27, 31, 44, 57). However, humans can also reportedly show an increase in CO during PEMI after leg cycling (5), dynamic knee extension (10), and dynamic handgrip exercise (9, 11). Although differences in the type of exercise and muscle mass used in the exercise could potentially affect the results, an alternative explanation for this inconsistency is that the components of the muscle metaboreflex-mediated pressor response vary widely among human subjects. Previous studies (25, 26, 30, 67) have shown that activation of the muscle metaboreflex during submaximal treadmill exercise in dogs with reduced hindlimb blood flow elicits a pressor response mediated primarily by an increase in CO. However, the mechanism of the pressor response shifts to increased peripheral vasoconstriction when the ability to increase CO is limited, such as in heart failure or during maximal exercise (2, 20). In addition, that shift has also been observed when the normal rise in CO is either pharmacologically or mechanically removed (26, 54). Based on these findings, it is conceivable that individuals with a small or no increase in CO during PEMI, and maybe even during isometric exercise, may show substantial peripheral vasoconstriction.

It has been previously demonstrated that the arterial baroreflex buffers the muscle metaboreflex-mediated pressor response (30, 55). Nishiyasu et al. (44) showed that cardiac parasympathetic tone increases during PEMI in humans and suggested that this increase may form part of a counteraction by the arterial baroreflex in response to the rise in blood pressure induced by the muscle metaboreflex. In addition, Ichinose et al. (22) reported that, in humans, cardiac baroreflex sensitivity (BRS), determined using transfer function analysis,
is increased during PEMI, which would enhance the buffering effects of the arterial baroreflex. In line with these findings, our group (65) recently showed that the HR response during PEMI varies considerably from individual to individual and that individuals with greater increases in cardiac parasympathetic tone and/or BRS during PEMI will likely show a greater bradycardic response to PEMI, and vice versa. This raises the possibility that, for individuals in whom the muscle metaboreflex is strongly buffered by the arterial baroreflex during PEMI, any rise in CO during PEMI may be limited by a large bradycardic response. However, despite the need to understand this relationship if one is to fully understand an individual’s blood pressure regulation during muscle metaboreflex activation, it has never been examined. Furthermore, it remains unknown whether buffering by the arterial baroreflex contributes to individual differences in the cardiac component of pressor responses (e.g., during isometric exercise), which could also be accompanied by activation of central command and the muscle mechanoreflex.

With this background in mind, the aim of the present study was to test our hypotheses that, in humans, CO and TPR responses to handgrip exercise vary considerably from individual to individual and that individual differences in components of the pressor response are associated with variations in muscle metaboreflex and arterial baroreflex function.

**METHODS**

**Subjects.** We studied 39 healthy volunteers (32 men and 7 women) with a mean age of 23.1 ± 0.4 yr, body weight of 63.6 ± 1.7 kg, and height of 169.7 ± 1.3 cm (means ± SE). None of the subjects was taking any medication, and none smoked. This study was carried out in accordance with the Declaration of Helsinki and was approved by the Human Subjects Committee of the University of Tsukuba. All subjects provided informed written consent.

**Procedures.** Before the actual experimental day, we familiarized each subject with the procedures during an orientation session in which they experienced the isometric handgrip exercise and PEMI. Subjects were asked to abstain from alcohol intake for at least 24 h before the experiment, from caffeine intake on the experimental day, and from everything except water during 2 h before the experiment. On the experimental day, subjects entered the test room, which was maintained at 25°C, and assumed a supine position. They then performed a maximum voluntary contraction (MVC) using a handgrip dynamometer held in the right hand, which enabled us to determine 50% MVC. Thereafter, a rapidly inflatable cuff for arterial occlusion was placed on the right upper arm (for the production of PEMI), and a respiratory mask was fitted. Subjects then had a rest period of at least 15 min before data collection began.

Subjects were instructed to maintain a constant respiration rate of 15 cycles/min and a constant tidal volume of 0.4–0.7 liters throughout the experiment. Auditory signals and an oscilloscope display of the respiratory volume were supplied to assist the subjects with this. In preliminary tests, we established that the tidal volume used did not cause dyspnea at a respiratory frequency of 15 cycles/min for any subject. Throughout the measurement period, an occlusion cuff on the ankle was kept inflated to a supersystolic pressure (>240 mmHg) to impede the foot circulation. Because the foot has a rich skin vasculature, including arteriovenous anastomoses, which can be affected by changes in the level of arousal, circulatory arrest in the foot can minimize alterations in leg vascular resistance (LVR) and leg blood flow (LBF) elicited by changes in arousal level. Resting baseline data were acquired for 4 min before the handgrip exercise was started. Subjects then performed a 60-s isometric handgrip exercise at 50% MVC with visual feedback showing the achieved force on an oscilloscope display. Five seconds before cessation of the exercise, the occlusion cuff on the arm was inflated to a supersystolic pressure (>240 mmHg), and the cuff remained inflated long enough to produce a 4-min period of PEMI. After PEMI, the cuff was deflated, and recovery data were acquired for 4 min. In the first 12 subjects tested, the protocol was performed twice on separate days. We measured aortic and common femoral artery blood velocities separately on different days, and duplicate variables detected in each protocol were averaged. Subsequently, we established a system to measure aortic and common femoral artery blood velocities simultaneously. In the remaining subjects, therefore, we were able to measure both variables within a single performance of the protocol.

In addition, to ensure that individual differences in cardiovascular responses to exercise and PEMI did not arise incidentally, we also examined the test-retest reproducibility of individual differences over the 2 sessions in 12 subjects.

**Measurements.** HR and R-R intervals (RRIs) were monitored via a three-lead ECG. Beat-to-beat changes in arterial blood pressure were assessed using finger photoplethysmography (Finometer, Finapres Medical Systems). The monitoring cuff was placed around the middle finger with the forearm and hand supported so that the cuff was aligned at the level of the heart. Subjects wore a mask connected to a respiratory flow meter (RF-H, Minato Medical Science), and the flow signal was displayed on an oscilloscope display (TDS2002, Tektronix).

CO and LBF were measured using Doppler ultrasound as previously described in detail (22, 23, 43). Briefly, a Doppler ultrasound system (HDI 3500, Philips) equipped with a hand-held transducer probe (model D2 CW) with an operating frequency of 2 MHz was used to measure aortic blood velocity in the suprasternal notch. Aortic diameter was measured in a separate resting session using the same Doppler system with a sector probe (S5-1) with an operating frequency of 5 MHz. A similar system (u22, Philips) but equipped with a linear probe (L12-5) with an operating frequency of 6 MHz was used to simultaneously measure two-dimensional common femoral artery diameter and blood velocity at a position 2–3 cm distal to the inguinal ligament. All Doppler data were recorded continuously on S-VHS videotape (ST-120, Maxell) or a hard-disk video recorder (DMR-BR670V, Panasonic). Videotape and hard-disk records of the MBV (in cm/s) and LBF (in cm2/s) were digitized using a digital video board (P4-1411, National Instruments) and stored on a personal computer equipped with software for measuring vessel diameter. Artery diameters related to systole (Ds; in mm) and diastole (Dd; in mm) were taken as the largest and smallest diameters within each cardiac cycle. The mean diameter (Dm; in mm) was calculated as follows: Dm = Ds/2 + Dd/2. Aortic and common femoral artery diameters were calculated using the above formula, and cross-sectional areas (CSAs; in cm²) were estimated as follows: CSA = (Dm/10/2)² × π. Instantaneous mean blood velocity (MBV) was continuously estimated using a computer program developed with the aid of LabView (version 6.0, National Instruments), as previously described in detail (23, 43). Our system collects MBV at 100 Hz together with analog signals representing the ECG, blood pressure waveform, and respiratory flow. Beat-to-beat MBV was calculated using an offline data-analysis program. Stroke volume (SV) was calculated as the product of the beat-to-beat aortic MBV (in cm/s) and aortic CSA (in cm²), and CO was calculated from the product of SV and HR. Similarly, LBF was calculated as the product of the beat-to-beat common femoral artery MBV (in cm/s) and common femoral artery CSA (in cm²) and was multiplied by 60 to obtain values expressed in terms of milliliters per minute. TPR and LVR were calculated as follows: TPR = MAP/CO and LVR = MAP/LBF, where MAP is mean arterial pressure.

**Data analysis.** From the 4-min resting recordings, 3.5 min of steady-state data were averaged as rest data. During exercise, data from the final 10 s were averaged as exercise data. From the 4-min recordings made during the PEMI and recovery periods, the final 3.5 min of data from each period were averaged as PEMI and recovery...
data, respectively. Subjects with frequent ectopic beats (>1% of all beats, n = 2) or excessive respiratory sinus arrhythmia (RRI fluctuations of >400 ms each respiratory cycle, n = 2) were eliminated from all analyses. Common femoral artery MBV data during exercise were successfully collected from 31 of the remaining 35 subjects, and data for the LBF and LVR responses to exercise shown here are from those 31 subjects. We used the 3.5 min of steady-state data collected during the rest and PEMI periods for spectral and cross-spectral analyses. Beat-to-beat RRI and systolic arterial pressure (SAP) data at rest and during PEMI were interpolated and resampled. This process provided 512 points of equidistant time interval data. Data were then divided into five equal overlapping segments of 256 data points, the linear trend was removed from each segment, and a Hanning window was applied. Thereafter, fast Fourier transforms were implemented in each segment and then averaged to calculate the autospectrum. The spectral resolution for these estimates was ~0.0095 Hz. The low-frequency (LF; ~0.03–0.15 Hz) and high-frequency (HF; ~0.15–0.35 Hz) powers of all of the variables were calculated from the integration of the autospectra. It is known that the HF power of the RRI variability reflects the level of cardiac parasympathetic tone, whereas the LF power is influenced both by cardiac sympathetic and parasympathetic nerve activities (1, 4, 47, 60). We used transfer function analysis to evaluate the relationship between SAP and RRI. The transfer function \[ H(f) \] between the two signals was calculated as follows:

\[
H(f) = \frac{S_{xy}(f)}{S_{xx}(f)}
\]

where \( S_{xy}(f) \) is the cross-spectrum of SAP variability and \( S_{xx}(f) \) is the cross-spectrum between SAP and RRI. The transfer function magnitude \( |H(f)| \) and phase \( \Phi(f) \) were obtained from the real \( H_R(f) \) and imaginary \( H_I(f) \) parts of the complex function as follows:

\[
|H(f)| = \sqrt{H_R(f)^2 + H_I(f)^2}
\]

\[
\Phi(f) = \tan^{-1}(H_I(f)/H_R(f))
\]

and the squared coherence function \( \text{Coh}(f) \) was estimated as follows:

\[
\text{Coh}(f) = \left| \frac{S_{xy}(f)}{\sqrt{S_{xx}(f) S_{xy}(f)}} \right|^2
\]

where \( S_{xy}(f) \) is the cross-spectrum of the changes in RRI. The squared coherence function reflects the fraction of the output power that can be linearly related to the input power at each frequency. Like a correlation coefficient, the squared coherence function varies from 0 to 1 and reflects the validity of the transfer function estimates. For this purpose, the LF transfer function gain and phase only at frequency data points of coherence \( \geq 0.5 \) were accepted as significant responses and were averaged in the frequency range of 0.05–0.15 Hz. The coherence data reflect average values from all data points in the frequency range. For phase value interpretation, a negative phase suggests that changes in the input variable preceded changes in the output response, whereas a positive phase suggests the reverse. From a baroreflex perspective, a negative phase value for SAP-RRI means that changes in SAP are followed by changes in RRI in the same direction, which can be taken as a baroreflex relationship. Previous studies (46, 50) have shown that the transfer function gain for the SAP-RRI relationship in the LF range reflects the BRS in the control of HR.

**Statistical analyses.** Data are presented as means ± SE. One-way repeated-measures ANOVA with Tukey’s post hoc test was used to compare the hemodynamic data obtained during the rest, exercise, PEMI, and recovery periods. For variables derived from the spectral and cross-spectral analyses, comparisons were made between the rest and PEMI periods using Student’s paired t-tests. A coefficient of variation (CV; in %) was used to assess the magnitude of the variance in individual changes in MAP, CO, and TPR (as a magnitude of interindividual differences) between the rest period and the exercise or PEMI periods. This enabled us to compare the degree to which individuals differed in their responses among parameters. The relationships between selected physiological variables were evaluated using Pearson’s product-moment correlation analysis. Intraclass correlation coefficients (ICCs) across two repeated sessions were calculated as a measure of intrasubject reproducibility. This measure indicates excellent agreement when >0.75, fair to good agreement when between 0.4 and 0.75, and poor agreement when <0.4 (21, 68). P values of <0.05 were considered significant.

**RESULTS**

*Mean cardiovascular responses.* Figure 1 shows mean values for MAP, HR, SV, CO, TPR, LBF, and LVR in subjects at rest and during isometric handgrip exercise, PEMI, and recovery. Significant pressor responses occurred during exercise. Although SV was slightly but significantly reduced, HR was markedly increased, resulting in an increase in CO. TPR did not differ between the rest and exercise periods, although we did observe an increase in LVR during exercise. There was no significant change in LBF during the exercise period. During PEMI, MAP remained higher than at rest; although HR, SV, CO, and LVR all returned to their resting levels, TPR and LBF were higher during PEMI than at rest.

*Mean data from spectral and cross-spectral analyses.* Table 1 shows mean values of the autospectral power for RRI and SAP variability as well as the transfer function gain, phase, and coherence for the SAP-RRI relationship during the rest and PEMI periods. During PEMI, HF RRI power and transfer function gain (i.e., BRS) were significantly higher than at rest, whereas LF and HF SAP power were lower than at rest. The phase was negative and did not significantly differ between the two conditions. The coherence during PEMI was lower than at rest, but the values were above 0.5 under both conditions.

**Variance in MAP, CO, and TPR responses.** Figure 2 shows beat-to-beat changes in MAP, CO, and TPR during the rest, exercise, and PEMI periods in two representative subjects. Although these two subjects showed similar increases in MAP during exercise and PEMI, their CO and TPR responses differed considerably. Figure 3 shows distributions of the changes in MAP, CO, and TPR from the rest period to the exercise and PEMI periods and interindividual CVs for the absolute values of those changes. All subjects showed increases in MAP during the exercise and PEMI periods, but the responses of the components mediating those pressor responses (CO and TPR) varied widely. More specifically, during exercise, 11 subjects showed an increase in CO and a decrease in TPR, whereas 5 subjects showed an increase in TPR and a decrease in CO, and 19 subjects showed increases in both CO and TPR. During PEMI, 5 subjects showed an increase in CO and a decrease in TPR, whereas 19 subjects showed an increase in TPR and a decrease in CO, and 11 subjects showed increases in both CO and TPR. CVs for changes in CO and TPR from the rest period to the exercise and PEMI periods were 1.7- to 2.4-fold greater than the CV for the change in MAP. This indicates that the components contributing to the pressor responses during isometric handgrip exercise and PEMI varied to a much greater degree among subjects than the blood pressure response itself.

**Relationships among pressor, central hemodynamic, and peripheral vascular responses.** Table 2 shows correlations between the changes in MAP, CO, TPR, and LVR from the rest period to the exercise and PEMI periods for all subjects. The MAP response during exercise correlated positively with the exercise-induced changes in CO but not with the changes in
TPR or LVR. The MAP response during PEMI correlated positively with the PEMI-induced changes in TPR but not with the changes in CO or LVR. The CO response during exercise correlated negatively with the exercise-induced changes in TPR but did not correlate with the changes in LVR. On the other hand, the CO response during PEMI correlated negatively with the PEMI-induced changes in both TPR and LVR. The TPR response to PEMI correlated positively with the LVR response to PEMI, but that was not the case with the relationship between those responses during exercise.

Relationships between cardiovascular responses to exercise and responses to PEMI. Figure 4 shows the correlations between the changes in MAP, HR, SV, CO, TPR, LBF, and LVR from the rest period to the exercise period and those changes from the rest period to the PEMI period. MAP, SV, CO, and TPR responses during exercise correlated positively with the corresponding responses during PEMI. On the other hand, HR, LBF, and LVR responses during exercise did not correlate with the corresponding responses during PEMI, although the LVR responses tended to be correlated ($P = 0.072$).

Relationships between CO responses and cardiac autonomic tone or arterial baroreflex function. Figure 5 shows correlations between the changes in CO from the rest period to the exercise period and changes in LF and HF autospectral power for RRI variability ($A$ and $B$) as well as the LF transfer function gain for the SAP-RRI relationship (i.e., BRS) from the rest period to the PEMI period ($C$). Also shown in Fig. 5 are the correlations between the changes in CO from the rest period to the PEMI period and the changes in those parameters derived from the spectral and cross-spectral analyses ($D$–$F$). PEMI-induced changes in CO correlated negatively with the changes in LF RRI power (an index of cardiac parasympathetic tone) and BRS (Fig. 5, $E$ and $F$) but not with the changes in LF RRI power (Fig. 5D). There were no significant correlations between the exercise-induced changes in CO and the PEMI-induced changes in LF and HF RRI power or BRS (Fig. 5, $A$–$C$).

Reproducibility of individual differences in cardiovascular responses. Table 3 shows test-retest ICCs for the absolute values of MAP, HR, SV, CO, TPR, LBF, and LVR during the resting, isometric handgrip exercise, postexercise muscle ischemia (PEMI), and recovery periods. *$P < 0.05$ vs. rest.

TPR or LVR. The MAP response during PEMI correlated positively with the PEMI-induced changes in TPR but not with the changes in CO or LVR. The CO response during exercise correlated negatively with the exercise-induced changes in TPR but did not correlate with the changes in LVR. On the other hand, the CO response during PEMI correlated negatively with the PEMI-induced changes in both TPR and LVR. The TPR response to PEMI correlated positively with the LVR response to PEMI, but that was not the case with the relationship between those responses during exercise.

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Table 1. Mean values of the spectral power for RRI and SAP variability and transfer function gain, phase, and coherence for the SAP-RRI relationship during the rest and PEMI periods

<table>
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<th>Rest</th>
<th>PEMI</th>
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<tr>
<td></td>
<td>Autospectral data</td>
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<tr>
<td>RRI power, ms$^2$</td>
<td>LF 691 ± 102</td>
<td>805 ± 156</td>
</tr>
<tr>
<td></td>
<td>HF 1.679 ± 344</td>
<td>2.225 ± 447*</td>
</tr>
<tr>
<td>SAP power, mmHg$^2$</td>
<td>LF 10.2 ± 1.2</td>
<td>7.6 ± 1.0*</td>
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<tr>
<td></td>
<td>HF 5.1 ± 0.8</td>
<td>4.3 ± 0.6*</td>
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<td></td>
<td>Cross-spectral data</td>
<td></td>
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<tr>
<td>LF gain, ms/mmHg 10.5 ± 1.0</td>
<td>12.3 ± 1.3*</td>
<td></td>
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<tr>
<td>LF phase, ° −52.8 ± 4.1</td>
<td>−48.1 ± 3.6</td>
<td></td>
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<tr>
<td>LF coherence 0.66 ± 0.02</td>
<td>0.61 ± 0.02*</td>
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Values are means ± SE; $n = 35$ subjects. RRI, R-R interval; SAP, systolic arterial pressure; PEMI, postexercise muscle ischemia; LF, low-frequency range; HF, high-frequency range. *$P < 0.05$ vs. rest.
cardiovascular responses to the exercise and PEMI periods, except the SV response to PEMI, were $>0.4$. The low ICC for the SV response to PEMI, despite reproducible absolute values at rest and during PEMI, reflects the marginal random changes in SV from the rest period to the PEMI period in each trial ($\sim 4$ ml). These findings demonstrate that all absolute values of measurements and the significant cardiovascular responses to isometric handgrip exercise and PEMI were well reproduced in the same subjects.

**DISCUSSION**

To the best of our knowledge, this is the first study investigating person-to-person differences in the components of the pressor response to isometric handgrip exercise in healthy humans. The major findings of this study are that there are much greater individual differences in CO and TPR responses to exercise than in MAP responses and that CO and TPR responses are negatively correlated with each other. In addition, CO and TPR responses during exercise correlate positively with the corresponding responses during PEMI. Taken together, these results indicate that CO and TPR responses to isometric handgrip exercise vary considerably from individual to individual and that these two responses have an inverse relationship, which reduces the variation in the pressor response. Our results also suggest that the individual differences in components of the pressor response are attributable in part to variations in muscle metaboreflex-mediated cardioaccelerator and peripheral vasoconstrictor responses.

Given the conflicting evidence regarding the respective roles of CO and TPR in mediating the pressor response to isometric handgrip exercise (3, 6, 16, 17, 31, 32, 34–36, 57–59, 61, 62), we speculated that CO and TPR responses would vary significantly from individual to individual, and our results confirm that idea. Interestingly, the individual variations in CO and TPR responses are about twofold greater than the variation in the MAP response. In addition, individuals showing greater increases in CO had smaller increases in TPR during exercise, and vice versa. This balance contributed to the relatively narrow range of variation in the MAP response. Moreover, these observations suggest that arterial pressure is the controlled entity, whereas CO and TPR are manipulated to adjust arterial pressure to the desired level during exercise and PEMI. In this context, it has been demonstrated that during isometric handgrip exercise, the arterial baroreflex operating point is reset to higher blood pressures and, as a result, autonomic nerve activity is modulated to elevate arterial pressure to a new operating pressure (13, 24, 28). Our results thus suggest that the physiological strategies used to accomplish the task of elevating arterial pressure to the new operating pressure are not uniform among individuals. Furthermore, it may be that the arterial baroreflex works to mitigate the increase in CO and vasoconstriction responses to maintain arterial pressure at a target level. For example, in an individual showing a large increase in CO, the arterial baroreflex may inhibit peripheral vasoconstriction to prevent an excess rise in arterial pressure above the operating pressure. But while the arterial baroreflex...
is an attractive mechanism for explaining our observations, the mechanisms underlying the obvious difference between the person-to-person variations in MAP and the variations in CO and TPR remain unclear, and further studies will be needed to address that issue.

To gain insights into the mechanism(s) underlying the large individual differences in the components of the pressor response to isometric handgrip exercise, we examined the activity of the muscle metaboreflex. Previous studies (5, 9–11, 16, 27, 31, 44, 57) in humans have come to different conclusions about the respective roles of CO and TPR in mediating the pressor response to PEMI-induced muscle metaboreflex activation. One possible explanation is that there is substantial variation in the muscle metaboreflex-mediated vasoconstrictor responses. Although the origin of the individual variations in muscle metaboreflex-mediated CO and TPR responses is not clear from the present study, we speculate that it will be a consequence of the combination of several factors. It has been postulated, for example, that cardiovascular responses to muscle metaboreflex activation can be influenced by the types of muscle fibers comprising the working muscles and by their training status (19). Additionally, differences in other factors, including the sensitivity and/or density of group III and IV muscle afferent endings, integration of afferent neural input, regulation of autonomic nervous activity within the central nervous system, and end-organ responsiveness, including α- and β-adrenergic receptor function (16, 31, 37), may also contribute to individual differences in cardiovascular responses to muscle metaboreflex activation.

We found that, although LBF or LVR responses during exercise did not correlate significantly with the corresponding responses during PEMI, the LVR responses tended to relate to each other \( (P = 0.072) \). This suggests that the individual differences in the vascular response of the inactive lower limbs during handgrip exercise would, to some degree, reflect variations in the muscle metaboreflex-mediated vasoconstrictor effects. It should be noted, however, that the linkage between LBF or LVR responses during the exercise and PEMI periods was clearly weaker than the linkage between TPR responses during those periods. It therefore appears that individual differences in vascular responses in the lower limbs do not necessarily correspond to those in other regions during isomet-

Table 2. Correlations among MAP, CO, TPR, and LVR responses during the exercise and PEMI periods

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<th>Exercise</th>
<th>PEMI</th>
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<tr>
<td></td>
<td>△CO</td>
<td>△TPR</td>
</tr>
<tr>
<td>△MAP</td>
<td>0.375*</td>
<td>0.196</td>
</tr>
<tr>
<td>△CO</td>
<td>-0.751†</td>
<td>0.014</td>
</tr>
<tr>
<td>△TPR</td>
<td>0.308</td>
<td>0.549†</td>
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</tbody>
</table>

Values are Pearson’s correlation coefficients between changes (△) in mean arterial pressure (MAP), cardiac output (CO), total peripheral vascular resistance (TPR), and leg vascular resistance (LVR) from the rest period to the exercise and PEMI periods. For correlations between △LVR and △MAP, △CO, or △TPR from the rest period to the exercise period, \( n = 31 \) subjects; for all other correlations, \( n = 35 \) subjects. * \( P < 0.05 \); † \( P < 0.01 \).
PEMI-induced changes in those variables. Fig. 4. Relationships between isometric handgrip exercise-induced changes in MAP (A), HR (B), SV (C), CO (D), TPR (E), LBF (F), or LVR (G) and PEMI-induced changes in those variables. ΔMAPEx, ΔHREx, ΔSVEx, ΔCOEx, ΔTPREx, ΔLBFEx, and ΔLVREx are the respective changes in MAP, HR, SV, CO, TPR, LBF, and LVR from the rest period to the exercise period; ΔMAPPEMI, ΔHRPEMI, ΔSVPEMI, ΔCOPEMI, ΔTPRPEMI, ΔLBFPEMI, and ΔLVRPEMI are the respective changes in MAP, HR, SV, CO, TPR, LBF, and LVR from the rest period to the PEMI period. Symbols denote data from individual subjects; lines are regression lines.

Fig. 5. Relationships between ΔCOEx or ΔCOPEMI and PEMI-induced changes in the spectral power for R-R interval variability in the low-frequency range [ΔCOEx or ΔCOPEMI (A) and ΔCOPEMI (D)] and high-frequency range [ΔCOEx or ΔCOPEMI (B) or cardiac baroreflex sensitivity (ΔCOEx or ΔCOPEMI (F))]. ΔLF-powerPEMI and ΔHF-powerPEMI are the respective changes in spectral power for R-R interval variability in the low-frequency and high-frequency range from the rest period to the PEMI period; ΔBRSPEMI is the change in cardiac baroreflex sensitivity from the rest period to the PEMI period. Symbols denote data from individual subjects; lines are regression lines.
cardiovascular variables during the rest, exercise, and PEMI periods and for cardiovascular responses during the exercise and PEMI periods.

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
<th>PEMI</th>
<th>Changes From Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>0.552</td>
<td>0.712</td>
<td>0.795</td>
<td>0.852</td>
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<tr>
<td>HR</td>
<td>0.860</td>
<td>0.724</td>
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<td>0.768</td>
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<td>SV</td>
<td>0.606</td>
<td>0.614</td>
<td>0.692</td>
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<tr>
<td>CO</td>
<td>0.772</td>
<td>0.716</td>
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<td>0.766</td>
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<tr>
<td>TPR</td>
<td>0.575</td>
<td>0.567</td>
<td>0.571</td>
<td>0.732</td>
</tr>
<tr>
<td>LBF</td>
<td>0.424</td>
<td>0.664</td>
<td>0.513</td>
<td>0.596</td>
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<tr>
<td>LVR</td>
<td>0.430</td>
<td>0.403</td>
<td>0.558</td>
<td>0.468</td>
</tr>
</tbody>
</table>

Values are intraclass correlation coefficients for the absolute values of MAP, heart rate (HR), stroke volume (SV), CO, TPR, leg blood flow (LBF), and LVR during the rest, exercise, and PEMI periods and those for changes from the rest period to the exercise and PEMI periods; n = 12 subjects.

Table 3. Test-retest intraclass correlation coefficients for cardiovascular variables during the rest, exercise, and PEMI periods and for cardiovascular responses during the exercise and PEMI periods

We observed marked person-to-person variation in CO and TPR responses to isometric handgrip exercise, and the responses were correlated with each other. However, correlational analyses do not address causality; consequently, it remains unclear whether the cause of the variation is the CO or TPR response. In addition, we focused primarily on the muscle metaboreflex and arterial baroreflex as mechanisms that determine the individual differences in those responses. However, other mechanisms, including neural and non-neural factors, could also be involved. Further studies will be needed to deepen our understanding of the integrative mechanisms underlying the individual differences in the components of the pressor response during exercise.

Conclusions. In summary, our findings demonstrate that, in humans, CO and TPR responses to isometric handgrip exercise vary considerably from individual to individual, and these responses are inversely related to each other. Moreover, our results show that CO and TPR responses to exercise are positively related to the corresponding responses to PEMI. We therefore suggest that variations in the muscle metaboreflex-mediated cardioaccelerator and peripheral vasoconstrictor responses are associated with the marked individual differences in the components of the pressor response to isometric handgrip exercise.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).
AUTHOR CONTRIBUTIONS

Author contributions: K.W., M.I., and T.N. conception and design of research; K.W. and R.T. performed experiments; K.W. and R.T. analyzed data; K.W., M.I., and T.N. interpreted results of experiments; K.W. prepared figures; K.W. drafted manuscript; K.W., M.I., R.T., and T.N. edited and revised manuscript; K.W., M.I., R.T., and T.N. approved final version of manuscript.

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