Relationships between the extent of apnea-induced bradycardia and the vascular response in the arm and leg during dynamic two-legged knee extension exercise

Takeshi Nishiyasu,1 Rina Tsukamoto,1 Katsuhito Kawai,1 Keiji Hayashi,2 Shunsaku Koga,3 and Masashi Ichinose4

1Institute of Health and Sports Science, University of Tsukuba, Tsukuba; 2Junior College, University of Shizuoka, Shizuoka; 3Kobe Design University, Kobe; and 4School of Business Administration, Meiji University, Tokyo, Japan

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Acute apnea-induced bradycardia is observed in humans (10, 12, 14, 19, 28, 36). The response is characterized by bradycardia and vasoconstriction related to the so-called “diving reflex” (1, 8, 10, 20, 24, 36), and it has been proposed that the function of these changes is primarily to preserve an adequate O2 supply to vital organs (1, 4, 15, 18, 19, 24). Some diving animals, such as seals, show remarkable bradycardia during voluntary diving (36). In humans, the bradycardic response seen during apnea or diving is smaller than in diving animals and varies a great deal from individual to individual (5, 21, 24, 31, 32). Acute apnea-induced bradycardia is observed in humans during exercise on land (3, 4, 6, 7, 22, 25, 26, 27, 30, 33). Bjertnaes et al. (7) reported that during exercise, the decrease in cardiac output (CO) induced by apnea was nearly paralleled by a reduction in heart rate (HR). In addition, Lindholm et al. (27) reported that the extent of the bradycardia induced by apnea during exercise had a significant negative relationship with the reduction in arterial blood O2 saturation (SaO2) and suggested that the reduction in CO during apnea could conserve O2 in arterial blood during apnea in exercising humans. On the other hand, large reductions in CO during exercise could reduce blood flow to exercising muscles, thereby impairing performance. It is not known how blood flow is regulated in active muscles in exercising humans or whether the blood flow response differs between active and inactive regions.

In some people, apnea induces marked bradycardia, during which HR is reduced to levels below the resting level, even during moderate exercise (24). Bjertnaes et al. (7) suggested that, for these people, the strong bradycardia could lead to a large reduction in CO. Moreover, total vascular conductance (TVC) would need to be reduced to maintain or increase arterial blood pressure. In contrast, changes in TVC would likely be smaller in persons who do not show strong apnea-induced bradycardia. Indeed, Lindholm et al. (26) showed a negative correlation between apnea-induced changes in HR and total peripheral resistance during exercise, suggesting that individuals with the largest chronotropic response to apnea also had the greatest vasoconstriction. Furthermore, the contribution made by changes in peripheral vasoconstriction to changes in TVC during exercise could be greater in exercising muscles than in inactive muscles (29). We hypothesized that during apnea in exercising humans, the cardiovascular responses of those who show marked bradycardia differ from the responses of those who show only mild bradycardia. Moreover, we suggest that a greater apnea-induced bradycardic response during exercise will be accompanied by greater vascular responses in the exercising regions. We examined the changes in blood flow in exercising and inactive muscle regions during apnea in two groups of subjects: those who showed marked bradycardia and those who showed mild bradycardia during apnea.

METHODS

Subject selection. We conducted a preliminary experiment to select subjects who exhibited large or small apnea-induced bradycardic responses. Eighty-six subjects performed voluntary apneas during semirecumbent bicycle exercise, eliciting a HR of ~100 beats/min. We instructed the subjects to hold their breath but to keep their glottis open to avoid a Valsalva-like maneuver. All of the subjects rehearsed their breath holding numerous times and were well accustomed to the...
Cardiovascular response to apnea during exercise

Fig. 1. Results of a preliminary experiment. The histogram shows the numbers of the subjects exhibiting the indicated apnea-induced changes in heart rate (HR) during a semisupine bicycle ergometer exercise at a workload that raised the HR to ~30 beats/min over the resting level (n = 86).

In addition, we told the subjects to hold their breath without performing a Valsalva-like maneuver just before the breath-holding trials. Figure 1 shows the distributions of HR changes induced by apnea during the exercise. Eleven subjects (8 men and 3 women) who developed a minimum HR during apnea that was below 65 beats/min were selected as the large bradycardia group (L group), whereas 12 subjects (11 men and 1 woman) who developed a minimum HR during apnea that was >75 beats/min were selected as the small bradycardia group (S group). There were no differences between the two groups with respect to mean age (23 ± 1 vs. 22 ± 1 yr), body weight (64 ± 2 vs. 60 ± 2 kg), or height (169 ± 3 vs. 169 ± 1 cm). None of the subjects were taking medication, and none of the subjects 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. Each subject gave informed written consent.

**Experimental protocol.** The subjects took part in an orientation session in which they were familiarized with the two-legged knee extension exercise and apnea. On the experimental day, the subjects entered the test room, which was maintained at 25°C, and adopted the semisupine position on the ergometer. Subjects maintained that rest-bearing position for at least 15 min between protocols. During each protocol, it was repeated several times, with recovery periods of at least 15 min between protocols. During each protocol, we measured one of the following: 1) aortic blood velocity, 2) aortic diameter, 3) brachial artery diameter and blood flow velocity, or 4) femoral artery diameter and blood flow velocity. Measurements 1 and 2 were conducted on 1 day, and measurements 3 and 4 were conducted on other days. For each subject, all measurements were conducted within 4 consecutive days, and the order of the measurements was randomly assigned.

**Measurements.** HR was monitored using a three-lead electrocardiogram. Changes in blood pressure were measured beat-to-beat using a finger-cuff blood pressure monitor aligned at the level of the heart (Finometer, FMS). SaO₂ was monitored using a noninvasive pulse oximeter (N550, NELLCOR) with a probe fixed to the forehead. Subjects wore a mask, enabling respiratory flow to be monitored using a hot-wire respirometer (RF-H, Minato Medical Science, Osaka, Japan), and the flow signal was displayed on an oscilloscope display (Tektronix). All data were stored in a personal computer (ThinkPad T30, IBM).

An ultrasound Doppler system (HDI 5000 Sonoc T2R, Philips), equipped with a model L12–5 transducer probe having an operating frequency of 6 MHz, was used to simultaneously measure two-dimensional artery diameter and blood velocity. Measurements were made using a hand-held transducer probe positioned over the common femoral artery, 2–3 cm distal to the inguinal ligament, or over the brachial artery, 5–15 cm proximal to the elbow. The same system, but equipped with a D2 CW transducer probe having an operating frequency of 2 MHz, was used to measure aortic blood velocity, and a P3–2 transducer probe was used to measure aortic diameter. All Doppler data were recorded on S-VHS videotape (ST-120, Maxell), after which the videotaped record of the vessel images was digitized using a digital video board (PCI-1411, National Instruments) and stored in a personal computer (ThinkPad T30, IBM) containing a program for vessel diameter measurement. The arterial diameters related to systole (Ds; in mm) and those related to diastole (Dd; in mm) were taken as the largest and smallest diameters within each cardiac cycle, respectively. Mean diameter (Dm; in mm) was calculated as follows:

\[
D_m = D_s/3 + 2 \times D_d/3
\]

Aortic, femoral, and brachial vascular diameters were calculated using the above formula, and the cross-sectional areas (CSA; in cm²) were estimated as follows:

\[
CSA = (D_m/20)^2 \times \pi
\]

Instantaneous mean blood velocity (MBV) was estimated using a computer program developed with the aid of LabView (version 6.0, National Instruments). The processes used in the calculation of MBV are outlined below. The frequency spectrum of the analog audio

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**Table 1. Cardiovascular response to apnea during exercise**

<table>
<thead>
<tr>
<th>Variable</th>
<th>L group</th>
<th>S group</th>
<th>L group</th>
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<th>L group</th>
<th>S group</th>
</tr>
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<tbody>
<tr>
<td>HR, beats/min</td>
<td>59 ± 7</td>
<td>68 ± 4</td>
<td>90 ± 5*</td>
<td>100 ± 3*</td>
<td>54 ± 7†</td>
<td>92 ± 10‡</td>
<td>71 ± 3*</td>
<td>45 ± 5*</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>51 ± 1.3</td>
<td>59 ± 1.5</td>
<td>9.7 ± 2.3*</td>
<td>9.2 ± 2.8*</td>
<td>4.5 ± 1.5† ‡</td>
<td>7.1 ± 2.4‡</td>
<td>7.1 ± 2.4‡</td>
<td>7.1 ± 2.4‡</td>
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<tr>
<td>SV, ml</td>
<td>91.5 ± 26.0</td>
<td>90.2 ± 22.0</td>
<td>110.3 ± 29.6*</td>
<td>99.6 ± 30.7*</td>
<td>66.1 ± 3.0† ‡</td>
<td>72.3 ± 8.0‡</td>
<td>72.3 ± 8.0‡</td>
<td>72.3 ± 8.0‡</td>
</tr>
<tr>
<td>TVC, ml/min−1·mmHg−1</td>
<td>63.9 ± 14.7</td>
<td>74.1 ± 21.4</td>
<td>99.9 ± 22.7*</td>
<td>110.9 ± 35.1*</td>
<td>35.2 ± 2.2† ‡</td>
<td>63.0 ± 6.5*</td>
<td>63.0 ± 6.5*</td>
<td>63.0 ± 6.5*</td>
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<tr>
<td>MAP, mmHg</td>
<td>82 ± 6</td>
<td>82 ± 6</td>
<td>97 ± 8*</td>
<td>91 ± 7*</td>
<td>148 ± 3.3* ‡</td>
<td>125 ± 10†</td>
<td>125 ± 10†</td>
<td>125 ± 10†</td>
</tr>
<tr>
<td>LBF, ml/min</td>
<td>405.5 ± 187.3</td>
<td>672.4 ± 285.6</td>
<td>2229.5 ± 311.0*</td>
<td>2379.5 ± 413.9*</td>
<td>571.5 ± 92.6‡</td>
<td>1220.5 ± 342.4‡</td>
<td>1220.5 ± 342.4‡</td>
<td>1220.5 ± 342.4‡</td>
</tr>
<tr>
<td>LVC, ml/min−1·mmHg−1</td>
<td>4.9 ± 2.3</td>
<td>8.0 ± 3.5</td>
<td>23.1 ± 3.6*</td>
<td>25.7 ± 5.9*</td>
<td>4.3 ± 2.3† ‡</td>
<td>10.8 ± 3.0† ‡</td>
<td>10.8 ± 3.0† ‡</td>
<td>10.8 ± 3.0† ‡</td>
</tr>
<tr>
<td>FBF, ml/min−1·mmHg−1</td>
<td>111.8 ± 52.7</td>
<td>111.2 ± 49.2</td>
<td>115.1 ± 35.9</td>
<td>154.7 ± 55.3*</td>
<td>17.3 ± 11.5† ‡</td>
<td>52.5 ± 48.5*</td>
<td>52.5 ± 48.5*</td>
<td>52.5 ± 48.5*</td>
</tr>
<tr>
<td>FVC, ml/min−1·mmHg−1</td>
<td>1.4 ± 0.7</td>
<td>1.4 ± 0.7</td>
<td>1.2 ± 0.4</td>
<td>1.7 ± 0.7*</td>
<td>0.1 ± 0.1† ‡</td>
<td>0.5 ± 0.4‡</td>
<td>0.5 ± 0.4‡</td>
<td>0.5 ± 0.4‡</td>
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</tbody>
</table>

Values are means ± SD. L group, large bradycardia group; S group, small bradycardia group; time at the peak response is from the end of apnea; in † HR, heart rate; CO, cardiac output; SV, stroke volume; TVC, total vascular conductance; MAP, mean arterial pressure; LBF, leg blood flow; LVC, leg vascular conductance; FBF, forearm blood flow; FVC, forearm vascular conductance. *P < 0.05 vs. rest; †P < 0.05 vs. the preapnea baseline; ‡P < 0.05 vs. the corresponding value in the S group.
output signal of our ultrasound Doppler unit robustly reflects the Doppler shift frequency spectrum within the audio range (<7.5 kHz in this study). The analog audio output signal was digitized at a sampling frequency of 20 kHz through an analog-to-digital converter (DAQCard-6062E, National Instruments) for processing on the personal computer (ThinkPad T30, IBM) containing our program. The power spectrum of the digitized audio signal was obtained using fast Fourier transform analysis techniques, using a Hanning smoothing window with a 512-data point segment. The mean frequency of a data segment \( f_{\text{me}} \) was derived from the spectral data using the following equation:

\[
 f_{\text{me}} = \frac{\sum_{i=0}^{N/2} (f_i \times P_i)}{\sum_{i=0}^{N/2} f_i}
\]

where \( f_i \) is the spectral frequency, \( P_i \) is the power related to \( f_i \), and \( N \) is the number of data points. We began an analysis of the next data segment of the digitized audio signal, which was advanced 200 data points from the beginning of the previous segment, so that 312 data points (15.6 ms) overlapped. Our program repeated the above processes in real time and continuously produced 100 values of \( f_{\text{me}} \) per second (100 Hz). The calculated \( f_{\text{me}} \) correlated very well with the actual mean Doppler-shift frequency when an electrically generated arbitrary ultrasound wave was transmitted to the transducer probe and measured using our ultrasound Doppler unit. We therefore regarded \( f_{\text{me}} \) as the mean Doppler shift frequency and used it to calculate instantaneous MBV. The analog signals representing the electrocardiogram were digitized at a sampling frequency of 100 Hz and stored together with \( f_{\text{me}} \), enabling all data for the same time period to be analyzed together. HR and MBV were calculated using an offline data-analysis program. MBV was derived from the stored \( f_{\text{me}} \) data using the following equation:

\[
 \text{MBV} = \frac{f_{\text{me}} \times C}{2 \times f_e \times \cos \theta} \times 100
\]

where \( f_e \) is the emitted frequency from the transducer probe (6 MHz for femoral and brachial blood flow and 2 MHz for aortic blood flow), \( C \) is the sound velocity in the tissues (we used 1,530 m/s), and \( \theta \) is the angle between the blood flow direction and the ultrasound beam (we kept \( \theta \) below 60° for femoral and brachial blood flow and below 20° for aortic blood flow). We applied the above formula to all of the stored \( f_{\text{me}} \) data and obtained an instantaneous MBV profile over the entire measurement period. The instantaneous MBV profile was then integrated over each cardiac cycle to acquire the beat-by-beat velocity-time integral (VTI; in cm/beat). Mean blood flow (MBF; in ml/min) was then derived as follows:

\[
 \text{MBF} = \text{CSA} \times \text{VTI} \times \text{HR}
\]

where MAP is mean arterial pressure (in mmHg).

While the subject rested, 1 min of data (from 30 to 90 s) was averaged as the rest data. During exercise, data from the 15 s preceding breath holdings were averaged as the preapnea baseline. During and after apnea, the greatest apnea-induced change in HR was detected as the peak of the response. Also recorded were CO, SV, TVC, LBF, LVC, FBF, and FVC at the peak HR response. To exclude the noise caused by ventilation from the measurements, most of the values for CO, SV, and TVC at the peak HR response during the apnea were adopted as the peak responses. Subjects performed the

### Table 2. Cardiovascular response at peak HR response during apnea

<table>
<thead>
<tr>
<th>Variable</th>
<th>At Peak HR</th>
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<tbody>
<tr>
<td></td>
<td>L group</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>54 ± 7†‡</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>7.2 ± 3.4*</td>
</tr>
<tr>
<td>SV, ml</td>
<td>137.2 ± 66.4*‡</td>
</tr>
<tr>
<td>TVC, ml·min⁻¹·mmHg⁻¹</td>
<td>59.6 ± 31.5†</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>129 ± 12*‡</td>
</tr>
<tr>
<td>LBF, ml/min</td>
<td>1013.7 ± 378.6*‡</td>
</tr>
<tr>
<td>LVC, ml·min⁻¹·mmHg⁻¹</td>
<td>8.1 ± 3.3*‡</td>
</tr>
<tr>
<td>FBF, ml/min</td>
<td>33.4 ± 18.1*‡</td>
</tr>
<tr>
<td>FVC, ml·min⁻¹·mmHg⁻¹</td>
<td>0.3 ± 0.1*‡</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.05 vs. rest; †P < 0.05 vs. the preapnea baseline; ‡P < 0.05 versus the corresponding value in the S group.
breath-hold maneuver five times during each exercise protocol, and the respective preapnea baseline data and peak response data were averaged over the five maneuvers. Because all of the variables of interest could not be measured within a single performance of this protocol, it was repeated several times, which meant that HR, MAP, and SaO\textsubscript{2} were measured more than once. That is, the resting, preapnea baseline, and peak values of the response to apnea were detected in each protocol. The HR, MAP, and SaO\textsubscript{2} data were averaged through all of the protocols, whereas CO, SV, TVC, LBF, LVC, FBF, and FVC were averaged from each protocol.

Statistical analysis. Data are presented as means ± SD. One-way ANOVA was used to compare the variables among the resting baseline, preapnea baseline, and peak of the response. Two-way ANOVA was performed to compare the variables between the two groups. Fisher’s post hoc test was used to assess differences between group means and to assess differences. P values of <0.05 were considered statistically significant.

RESULTS

Apnea-induced, beat-to-beat changes in HR and MAP in representative subjects from the L and S groups are shown in Fig. 2. The average breath-holding period did not differ between the two groups (26.1 ± 1.6 s in the L group and 22.5 ± 2.3 s in the S group), nor did the average workloads (35 ± 3 W in the L group and 30 ± 3 W in the S group).

Table 1 shows the mean values for variables measured while the subjects were at rest, during exercise, and at the peak response to apnea, with the delay time from the end of apnea. There were no differences in these variables between the two groups at rest. In the L group, HR increased to 90 ± 5 beats/min during exercise (preapnea baseline), and subjects showed marked apnea-induced bradycardia at the peak of the response, with HR reaching a level lower than the resting value.

Fig. 3. Changes in MAP, HR, arterial O\textsubscript{2} saturation (SaO\textsubscript{2}), leg vascular conductance (LVC), stroke volume (SV), cardiac output (CO), total vascular conductance (TVC), and forearm vascular conductance (FVC) from the preapnea baseline (Pre) to the peak response in the L group (solid bars) and S group (open bars). *P < 0.05, L group vs. S group.
(59 ± 7 vs. 54 ± 7 beats/min, P < 0.05). In the S group, HR increased to 100 ± 3 beats/min during exercise, and apnea induced only a small bradycardic response; at the peak of the response, HR was only 8 beats/min slower than the preapnea baseline value (92 ± 10 beats/min, P < 0.05). During exercise, MAP increased from the resting level, and a significant pressor response was evoked by apnea in both groups. At the peak of the response, however, MAP was higher in the L group than in the S group (148 ± 13 mmHg in the L group vs. 125 ± 10 mmHg in the S group, P < 0.05). During exercise, TVC increased in both groups, but had declined by the peak response to apnea, and was lower in the L group than in the S group. \( \text{Sao}_2 \) declined gradually during apnea and continued to decline for \(-6\) s after breathing resumed in both groups, and there was no difference in the peak response values between the two groups (84 ± 2% in the L group vs. 88 ± 2% in the S group). Aortic, femoral, and brachial vascular diameters all tended to increase during exercise. LBF and LVC increased during exercise but declined during apnea and were lower in the L group than in the S group (LBF: 571.5 ± 292.6 vs. 1,220.5 ± 342.4 ml/min and LVC: 4.3 ± 2.3 vs. 10.8 ± 3.0 ml·min\(^{-1}\)·mmHg\(^{-1}\)). Similarly, FBF and FVC increased in the L group during exercise and during apnea, but both had declined by the peak of the response to apnea in the two groups and were much lower in the L group than in the S group.

Table 2 shows mean values for the variables at the time of the peak HR response to apnea. During apnea, SV initially declined in the L group (Table 1), but by the peak of the HR response, it tended to be higher than the preapnea level. In the S group, in contrast, SV declined and remained lower than in the L group, even at the peak of the HR response. MAP was higher in the L group than in the S group, and LBF, LVC, FBF, and FVC were lower in the L group than in the S group (\( P < 0.05 \)).

The changes in the variables from the preapnea baseline to the peak of the response to apnea are shown in Fig. 3. The changes in the L group were greater than in the S group for MAP, HR, CO, TVC, and LVC. Figure 4 shows the percent changes in blood flow (A) and vascular conductance (B) from the preapnea baseline to the peak response in the L group (solid bars) and S group (open bars). LBF, leg blood flow; FBF, forearm blood flow. *\( P < 0.05 \), L group vs. S group; †\( P < 0.05 \), CO (A) or TVC (B); §\( P < 0.05 \) vs. LBF (A) or LVC (B).

DISCUSSION

The major findings of this investigation were that 1) during dynamic two-legged knee extension exercise, apnea induces reductions in HR, CO, LVC, FVC, and TVC while increasing MAP in both the L and S groups; 2) the changes in HR, CO, LVC, SV, TVC, and MAP are greater in the L group than in the S group; and 3) there are significant positive linear relationships between the extent of the apnea-induced bradycardia and the changes in TVC, LVC, FVC, and MAP. We therefore suggest that cardiovascular responses in exercising humans who show strong apnea-induced bradycardia differ from the responses of those who show only mild bradycardia. Furthermore, the greater bradycardia was accompanied by greater vascular responses in both exercising and inactive muscle regions. This coordination between HR and peripheral vasomotor tone would be expected to play a significant role in defending vital organs against apnea-induced hypoxemia during exercise.

HR responses. HR is reduced during apnea in exercising humans (4, 7, 26, 27, 33), and the extent of the apnea-induced...
HR response varies substantially from individual to individual (24, 26). We selected 2 groups from among the 86 subjects tested in preliminary experiments: those in the L group showed strong apnea-induced bradycardia during dynamic exercise, whereas those in the S group showed a mild bradycardic response. In the L group, apnea reduced HR during exercise by 36 beats/min to a level lower than the resting level. In contrast, HR was reduced by only 8 beats/min in the S group. It is thought that an increase in the activity of parasympathetic nervous efferents is involved in the bradycardia induced by apnea in resting individuals (9, 13), and this could also be true during exercise (16). The magnitude of a bradycardic response is known to be affected by several factors, including exercise intensity and the duration of the apnea (24). However, there were no differences in exercise intensity, apnea duration, levels of SaO₂, or resting HR between the L and S groups. That apnea-induced changes in MAP were also greater in the L group suggests that the arterial baroreflex might account for the difference in the responses to apnea in the two groups. However, the peak of the MAP response occurred ~3 s after the peak HR response. This suggests that although apnea-induced bradycardia may be influenced to some extent by the arterial baroreflex, it is not a major factor, which is consistent with earlier reports (27, 33).

**SV and CO responses.** In the L group, SV declined slightly at first, but by the peak of the HR response to apnea, SV had recovered to a level that tended to be higher than the preapnea level. This is in contrast to the finding of an earlier study (26) in which SV was calculated over 10 heart beats and no apnea-induced change in SV was seen during exercise. In the present study, apnea-induced changes in MAP were also greater in the L group suggests that the arterial baroreflex might account for the difference in the responses to apnea in the two groups. However, the peak of the MAP response occurred ~3 s after the peak HR response. This suggests that although apnea-induced bradycardia may be influenced to some extent by the arterial baroreflex, it is not a major factor, which is consistent with earlier reports (27, 33).

**MAP, TVC, LVC, and FVC responses.** Apnea reportedly increases MAP in exercising humans (2, 4, 7, 26, 27, 33, 35). In the present study, we found that MAP was greatly increased during apnea in both the L and S groups, but the increase in MAP was larger in the L group than in the S group. Because CO was reduced during apnea, we can infer that the increase in MAP was mainly due to the reduction in TVC. In resting humans, apnea stimulates muscle sympathetic nervous activity (23), which suggests substantial sympathetic vasoconstriction could occur during apnea in exercising humans. Diving animals, such as penguins and seals, show strong vasoconstriction in active muscles during their dives (10, 17). During exercise in the present study, LBF in the L group was 2,229.3 ml/min just before apnea and was reduced to 571.5 ml/min during apnea, which is about the resting level (405.8 ml/min). The reduction in LVC could reflect vasoconstriction in the active muscles in the lower legs due to increased muscle sympathetic activity. It is thought that several local vasodilatory mechanisms are activated in exercising muscles (11, 34). That we observed apnea-induced reductions in LVC during exercise suggests that sympathetic vasoconstriction can override local vasodilatory mechanisms in exercising muscles. LBF and LVC were smaller in the L group than in the S group during apnea.

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**Fig. 5. Relationships between apnea-induced changes in HR during exercise and the percent changes in MAP (A), TVC (B), LVC (C), and FVC (D) from the preapnea baseline to the peak response.**
and the percent changes in LBF and LVC were greater in the L group than in the S group. This suggests that subjects who showed greater apnea-induced bradycardia experience greater vasosconstriction (perhaps reflecting greater sympathetic activation) in active muscles during dynamic exercise than those who showed only a small bradycardic response.

FBF and FVC remained at their resting levels during exercise, suggesting that sympathetic activation of inactive regions was little affected by exercise at an intensity that raised HR to 90–100 beats/min. In the L group, FBF declined from 115.1 ml/min just before apnea to 17.3 ml/min during apnea, whereas FVC declined to 0.1 ml·min⁻¹·mmHg⁻¹. Both FBF and FVC were smaller during apnea in the L group than in the S group, and the percent apnea-induced changes in FBF and FVC were greater in the L group than in the S group. Thus, subjects who showed greater apnea-induced bradycardia during dynamic exercise also showed greater vasosconstriction in inactive muscle regions than those who showed a milder bradycardic response.

The percent change in blood flow during apnea was smaller in active limbs (LBF) than in inactive limbs (FBF) in both groups, and the percent changes in LBF and FBF were greater than the corresponding changes in CO (Fig. 4). Similarly, the percent change in LVC during apnea was smaller than that in FVC in both groups, and the percent changes in LVC and FVC were greater than the corresponding changes in TVC (Fig. 4).

The reductions in blood flow in both the legs and forearms during apnea (respectively calculated as decreases in LVC and FVC from the preapnea baseline to the lowest HR during apnea) accounted for ~79% and 51% of the decrease in TVC in the L and S groups, respectively (Table 2). This suggests that the decrease in blood flow, especially in active muscles, could contribute substantively to the changes in systemic vascular conductance and blood pressure evoked by apnea during dynamic exercise.

Because SV was not greatly affected by apnea in the L group, the large bradycardic response seen in the L group caused a large reduction in CO. To maintain the blood pressure in that situation, TVC was necessarily reduced. The apnea-induced HR changes during exercise and the percent changes in MAP, TVC, LVC, and FVC from the preapnea values were linearly related (Fig. 5). Those linear relationships reveal that a large apnea-induced bradycardic response during exercise is accompanied by pronounced vascular responses in both exercising and inactive muscle regions. During exercise, the reduction in blood flow in the active muscles would likely increase anaerobic metabolism and shorten the period before fatigue, but such coordination between HR and vasomotor tone, especially that seen in active muscles, could be important for preventing a rapid drop in SaO₂ and maintaining or increasing blood flow in the active muscles. Thus, those who showed the largest diving responses to apnea during exercise may possess the largest diving responses and may best tolerate arterial desaturation during underwater activity.

Although it is beyond the scope of the present study, our data may provide some insight into the mechanism(s) underlying the large individual differences in the cardiovascular response to apnea during exercise. HRs at rest, as well as during exercise at similar workloads, were ~10 beats/min lower in the L group than in the S group, although this difference was not significant. This could be an indication that the subjects in the L group were more aerobically fit than those in the S group. Therefore, our results may be indicative of an association between the cardiovascular response to apnea during exercise and aerobic fitness, and, if so, physical training may enhance the response. Further studies will be needed to address this issue, however.

Limitations. Because all of the variables of interest could not be measured within a single performance of the experimental protocol, it was repeated several times. Consequently, values were not measured only once, and the resting baseline, preapnea baseline, and peaks of the apnea-induced responses were detected in each protocol. The HR, MAP, and SaO₂ data were then averaged across all protocols, whereas CO, SV, TVC, LBF, LVC, FBF, and FVC were averaged for each protocol, so that the parameters are not always perfectly matched. However, because most of the findings were derived from the changes in each parameter, the aforementioned inconsistency would not affect our conclusion.

Conclusions. In summary, CO, FVC, LVC, and TVC were reduced and MAP was increased during apnea in both the L and S groups, but these apnea-induced changes were larger in the L group than in the S group. Moreover, there was a significant positive linear relationship between the reduction in HR and the reduction in LVC during apnea. We therefore suggest that apnea-induced hemodynamic responses during exercise differ between those who show marked bradycardia and those who show only a mild bradycardic response. Moreover, those individuals showing larger bradycardic responses also show larger vascular responses in both exercising and inactive muscle regions. This coordination between HR and vasomotor tone would be expected to play an important role in defending blood flow to vital organs against apnea-induced hypoxemia during exercise in humans.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

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REFERENCES

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