Aging and the Exercise Pressor Reflex in Humans

Troy A. Markel, BA; Joseph C. Daley III, MD; Cynthia S. Hogeman, BSN, RN; Michael D. Herr, PhD; Mazhar H. Khan, MD; Kristen S. Gray, MS; Allen R. Kunselman, MA; Lawrence I. Sinoway, MD

Background—Blood flow limitation to exercising muscles engages the muscle reflex during exercise, evoking an increase in heart rate (HR), blood pressure (BP), and muscle sympathetic nerve activity (MSNA).

Methods and Results—In the current study, we examined forearm flow and autonomic responses to ischemic handgrip in young and older subjects. We studied 6 younger subjects (mean age 23.5±2.2 years) and 7 older subjects (mean age 65.0±2.4 years). Subjects performed rhythmic handgrip (thirty 1-sec contractions/min) at 30% maximal voluntary contraction during six 1-minute stages: freely perfused exercise (E1) and exercise with forearm pressure of +10, +20, +30, +40, and +50 mm Hg (E2 through E6). We measured HR, BP, MSNA, forearm flow velocity, forearm venous oxygen saturation, H⁺, and lactate. Compared with E1, ischemic exercise (E2 through E6) increased HR, BP, and MSNA, reduced forearm velocity, lowered venous oxygen saturation, and raised venous lactate and H⁺. Compared with the younger subjects, the older subjects had attenuated BP at E6, attenuated MSNA indices (%Δbursts, bursts/100 heart beats and signal averaged MSNA), attenuated H⁺ at E6, a trend toward higher levels of oxygen saturation, and similar forearm velocity and HR responses.

Conclusions—Aging attenuates the muscle reflex. (Circulation. 2003;107:675-678.)

Key Words: aging ■ exercise ■ reflex ■ blood flow

During exercise, the sympathetic nervous system is activated. This helps redistribute blood flow to active muscle and aids in preventing blood pressure (BP) from falling.1 Two neural systems contribute to sympathetic activation: central command,2 a feed-forward process, and a muscle reflex termed the exercise pressor reflex.3 The muscle reflex is engaged when mechanically or metabolically sensitive thin fiber afferents within contracting muscle increase their discharge.4 During forearm exercise, the muscle reflex is engaged when a mismatch occurs between blood supply and metabolic demand.5

In the present study, we examined the effects of aging on the exercise pressor reflex in humans. Despite the fact that this reflex is an important determinant of exercise flow regulation, little is known about the effects of aging on this reflex. The reflex is evoked by a muscle work/blood flow mismatch. Therefore, to engage the reflex, a paradigm was employed in which the level of work was kept constant as external impedance to muscle flow was progressively increased. We examined whether age affects the BP response to reflex engagement and if sympathetic nerve responses to reflex engagement is different in young and older subjects. The results of these studies support the concept that the muscle reflex becomes attenuated with age.

Methods

Subjects
Six young (4 males, 2 females; mean age 23.5 years; mean body mass index 23.5) and 7 older subjects (4 males, 3 females; mean age 65.0; body mass index 26.2) were studied. All were normotensive non-smokers on no medications. Each signed an Institutional Review Board-approved consent.

Forearm Pressure
Subjects performed handgrip in a sealed wooden arm tank (33 in × 9 in × 10 in). The forearm was placed in the tank through a neoprene sleeve that provided an adequate seal without obstructing flow. Forearm pressure was delivered via a gas regulator and monitored via a gas pressure transducer.

Exercise Trial
The handgrip paradigm used was a variant of a previously described protocol.6 After a 5-minute baseline measurement, subjects performed rhythmic handgrip exercise using a Stoelting dynamometer. Handgrip was performed at 30% maximal voluntary contraction (MVC) with thirty 1-sec contractions/min. After 1 minute of handgrip (E1), arm tank pressure was increased to +10 mm Hg (E2), and then by 10 mm Hg each minute until +50 mm Hg (E3 through E6). Measurements included heart rate (HR), BP, muscle sympathetic nerve activity (MSNA), venous blood metabolite concentrations, and mean blood velocity (MBV). The perceived level of exertion was also determined using the Borg scale.7 The protocol was performed in both forearms of all subjects.

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From the Cardiology Division (T.A.M., C.S.H., M.D.H., M.H.K., K.S.G., L.I.S.), the Pulmonary, Allergy and Critical Care Division (J.C.D.), and the Department of Health Evaluation Sciences, (A.R.K.), Penn State College of Medicine, Hershey, Pa; and VA Medical Center, Lebanon, Pa (L.I.S.).

Correspondence to Lawrence Sinoway, MD, Cardiology, MC H047, Hershey Medical Center, P.O. Box 850, Hershey, PA 17033. E-mail lsinoway@psu.edu

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HR was continuously monitored and collected on-line via a 4-lead ECG. BP was measured with a Finapres (Ohmeda). Resting Finapres values were compared with Dinamap (Critikon) before and after each study.

**Microneurography**

Microneurography provides multiunit recordings of post-ganglionic MSNA. Peroneal nerve recordings were obtained with an insulated tungsten electrode (1 to 5 μm uninsulated tip). MSNA was amplified, filtered (700 to 2000 Hz), rectified, and integrated, yielding a mean voltage neurogram. Activity was measured as bursts/min, bursts/100 HB, and Δ% bursts.

The data were also analyzed as normalized signal averaged MSNA. One-minute segments of MSNA were analyzed using Signal-Averaged ECG (SAECG) software (PowerLab v.4.1, AD Instruments). The ECG was used to parse MSNA into 1 cardiac cycle intervals and to sum these into a composite MSNA waveform. Dividing this composite by the number of cycles yielded an average MSNA signal/cycle that was integrated, expressed in arbitrary units, and normalized for the baseline value.11

**Mean Blood Velocity**

Brachial artery MBV was measured immediately above the arm-tank using a 4 MHz continuous wave Doppler probe (Model 500 M, Multigon Industries) that was manually adjusted to obtain the maximal frequency shift. During exercise, the last 10 seconds of each min was analyzed to obtain MBV.

**Blood Samples**

Venous blood was obtained from 20-gauge retrograde catheters placed in deep forearm antecubital veins. Blood was analyzed for lactate (Stat Plus), oxygen saturation, and H⁺ (Radiometer A/S Copenhagen NV).

**Statistical Analysis**

Resting and E1 values in the subject groups were compared using non-paired t tests. Variables measured with forearm pressure (E2 through E6) were compared with E1 and expressed as Δ from E1. Repeated measures ANOVA models were fit to the age and forearm pressure data. Tests of simple effects comparing young versus older patients at each level of forearm pressure were performed. Because the simple effects tested were determined a priori, and because the simple effects were all orthogonal contrasts, no multiple comparison adjustments were performed. Analyses were performed using SAS software (SAS Institute Inc). Values are expressed as the mean±SEM, and P<0.05 was considered significant.

**Results**

Resting and E1 data are presented in the Table. Resting MSNA (burst count) and bursts/100 HB were higher in the older subjects than in the young subjects. Lactate and H⁺ were lower in the older subjects.

During handgrip, an interaction was noted for BP, and the interaction value for H⁺ was P=0.051 (Figure 1). Simple effects demonstrated that mean arterial pressure (MAP) and H⁺ were lower at E6 in the older group (Figure 1A and 1B). All MSNA indices evaluated (Figure 1D through 1G) showed evidence of attenuated responses in the older group (Δbursts, interaction: P=0.001; Δbursts/100 HB, interaction: P=0.001; Δ% bursts, interaction: P=0.001; Δ signal-averaged MSNA age main effect: P=0.012, interaction P=0.001). Although flow velocity was not different in the 2 subject groups (Figure 1H), venous oxygen saturation tended to be higher in the older subjects (interaction P=0.063; Figure 1I). The heart rate and Borg scales rating were not different in the 2 groups.

In Figure 2, X-Y plots of ΔMAP versus ΔH⁺ and Δburst versus ΔH⁺ are presented. Clearly, aging is not associated with an attenuated increase in BP or MSNA for a given H⁺. Linear regression analyses for MVC versus ΔBP and for ΔMSNA (E6) were performed and no correlation was found. Thus, the attenuated BP and MSNA responses (Figure 1) are not due to age-related MVC differences. We also compared MVC with Δlactate and ΔH⁺, and no correlation was found.

**Discussion**

The main finding of this study is that older subjects respond differently to ischemic exercise than do younger subjects. Differences between the 2 groups include attenuated BP and MSNA responses in the older group. These findings suggest that the intensity of exercise pressor reflex decreases with age.
What are the mechanisms for these findings? It has been suggested that skeletal muscle becomes phenotypically more oxidative with age.\textsuperscript{12,13} A more oxidative profile would explain the reduced H\textsuperscript{+}/H\textsubscript{1001} response, as well as the attenuated BP and MSNA responses. Compared with oxidative muscle, glycolytic muscle evokes a larger reflex response.\textsuperscript{14}

Of note, despite the fact that the older subjects’ velocity response to ischemia was not different than that of young subjects, venous oxygen saturation tended to be higher in the older group. Diminished oxygen extraction with age has been shown previously\textsuperscript{15,16} and may be related to aging-induced mutations of mitochondrial DNA.\textsuperscript{17}

A prior report has suggested that attenuated MSNA response to handgrip in the aged is due to higher resting MSNA and not to muscle reflex attenuation per se.\textsuperscript{18} Our study also demonstrates higher resting MSNA in older subjects.\textsuperscript{18} However, we have shown that progressive ischemia used to progressively and systematically engage the muscle reflex led to multiple attenuated indices of MSNA (Figure 1D through 1G) as well as BP in the aged (Figure 1A). The fact that both BP and MSNA were attenuated and the fact that data in Figure 1 were compared with E1 and not baseline leads us to believe that differences in resting MSNA between young and old subjects cannot totally explain our findings. Thus, we conclude that attenuated MSNA responses to exercise in older subjects are due to attenuated muscle reflex activity. Furthermore, we speculate that the greater skeletal muscle oxidative potential in the aged contributes to this effect.

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