Cardiac mechanics are impaired during fatiguing exercise and cold pressor test in healthy older adults

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Muller MD, Mast JL, Patel H, Sinoway LI. Cardiac mechanics are impaired during fatiguing exercise and cold pressor test in healthy older adults. J Appl Physiol 114: 186–194, 2013. First published November 15, 2012; doi:10.1152/japplphysiol.01165.2012.—We sought to determine how the aging left ventricle (LV) responds to sympathetic nervous system (SNS) activation. Three separate echocardiographic experiments were conducted in 11 healthy young (26 ± 1 yr) and 11 healthy older (64 ± 1 yr) adults. Tissue Doppler imaging was used to measure systolic myocardial velocity (Sm), early diastolic myocardial velocity (Em), and late diastolic myocardial velocity (Am) during isometric fatiguing handgrip (IFHG), a 2-min cold pressor test (CPT), and 5 min of normobaric hypoxia. Heart rate (HR) and mean arterial pressure (MAP) were also monitored on a beat-by-beat basis; rate pressure product (RPP) was used as an index of myocardial oxygen demand. At peak IFHG, the groups had similar increases in RPP, but the ΔSm was significantly greater (i.e., larger impairment) in the older subjects (−0.82 ± 0.13 cm/s) compared with the young subjects (0.37 ± 0.30 cm/s). At peak IFHG, the ΔEm was similar between older (−1.59 ± 0.68 cm/s) and young subjects (−1.06 ± 0.76 cm/s). In response to the CPT, both Sm and Em were reduced in the older adults but did not change relative to baseline in the young subjects. Normobaric hypoxia elevated HR and RPP in both groups but did not alter Tissue Doppler parameters. These data indicate that Sm and Em are reduced in healthy older adults during IFHG and CPT. We speculate that suboptimal LV adaptations to SNS stress may partly explain why acute heavy exercise can trigger myocardial ischemia.

Doppler echocardiography; myocardial contraction; autonomic nervous system; cold temperature; hypoxemia

The sympathetic nervous system (SNS) plays an important role in the control of cardiac output and peripheral vascular resistance during exercise. While much attention has been devoted to SNS effects on heart rate (HR) and mean arterial pressure (MAP), the effects on the heart muscle itself (i.e., myocardium) are less clear. Experiments in chronically instrumented dogs have indicated that α-adrenergic constriction impairs coronary blood flow (i.e., O2 delivery to the myocardium) and limits increases in left ventricular contractility during treadmill exercise (i.e., in the face of an increased myocardial O2 demand that should elicit metabolic dilation) (6, 16, 27, 58). This sympathetically mediated “braking mechanism” to the heart is not well understood in humans. Aging is associated with increased SNS activity at rest (55, 69, 77), and older adults also have decreased left ventricle (LV) compliance (increased stiffness) (5); either factor could lead to ischemia when faced with an acute increase in afterload. However, it is currently unknown how the aging LV will respond to sympathetic stress.

Pulsed-wave tissue Doppler imaging (TDI), an echocardiographic technique that can detect subclinical LV abnormalities, may be able to address this issue in healthy older adults.

TDI allows for quantification of regional myocardial contraction and relaxation along the longitudinal plane of the LV (51, 63). A typical TDI waveform includes systolic myocardial velocity (Sm), early diastolic myocardial velocity (Em), and late diastolic myocardial velocity (Am). These noninvasive measures of endocardial excursion have been used clinically to detect LV wall motion abnormalities and are considered to be less preload dependent than Doppler transmitral inflow values (14, 51, 72). The temporal resolution of TDI also makes it useful in physiological experiments to quantify acute LV adaptations to stress (e.g., thermal, postural) (7, 10, 12, 53, 54, 82). We, therefore, reasoned that TDI could be used to clarify how acute SNS-mediated increases in HR and MAP impact LV function.

The purpose of this investigation was to determine the effect of healthy aging on myocardial function during SNS activation. We hypothesized that myocardial function would be impaired in healthy older adults at baseline and during three laboratory stressors known to activate the SNS: isometric fatiguing handgrip (IFHG), cold pressor test (CPT), and normobaric hypoxia. To test these hypotheses, we used TDI as a noninvasive measure of LV function at the physiological level (i.e., reflecting the combined effects of changes in loading conditions and contractility). Overall, these experiments indicate that sympathetic activation (particularly acute increases in MAP) reduces systolic and diastolic function in healthy older adults.

METHODS

Subjects and design. All study protocols were approved in advance by the Institutional Review Board of the Penn State Milton S. Hershey Medical Center and conformed to the Declaration of Helsinki. A total of 11 young (26 ± 1 yr) and 11 older (64 ± 1 yr) subjects volunteered to participate and provided written informed consent. All subjects were normotensive, nonasthmatic, nonobese, nonsmokers, not taking any prescription or vasoactive medication, and were in good health, as determined by history and physical examination. All subjects reported being physically active, but none were competitive athletes. After the consent process, but before enrollment, the older adults underwent a modified Bruce protocol with 12-lead ECG monitoring. The test was then interpreted by a cardiologist to rule out coronary artery disease.

Subjects refrained from caffeine, alcohol, and exercise for 24 h before the study and arrived to the laboratory in a semistated fasted state (i.e., 4–6 h after their last meal). All experiments were conducted in a dimly lit thermoneutral laboratory (22°C–25°C), and subjects were situated in the supine or left lateral position to facilitate acquisition of echocardiographic images. For experiments 1–3, subjects were outfitted with a 3-lead ECG (Cardiocap5, GE Healthcare) to monitor HR, a finger blood pressure cuff (Finometer, FMS), and a pneumotrace to monitor respiratory movement. These parameters (as well as additional parameters listed below) were sampled at 200 Hz by a data monitor respiratory movement. These parameters (as well as additional parameters listed below) were sampled at 200 Hz by a data...
acquisition system (PowerLab, ADInstruments). Doppler echocardiographic parameters were synchronized to the PowerLab on a beat-by-beat basis using a Doppler audio transformer (30). Verbal and written time stamps were also used to match hemodynamic and echocardiographic parameters during off-line analysis. The Finometer blood pressure values (i.e., MAP, systolic, and diastolic pressure) were each determined separately and calibrated to match the blood pressure obtained with automated sphygmonanometer (Philips SureSigns Vs3) obtained before each stimulus.

**Baseline echocardiographic measurements.** Upon arrival at the Clinical Research Center, two-dimensional and Doppler measurements of LV structure and function were obtained using a commercially available system (Vivid 7, GE Healthcare and M4S transducer) following 15–20 min of quiet supine rest. Left atrial diameter was measured in the parasternal long-axis view, and then M-mode imaging was obtained as previously described (68). LV end-diastolic diameter and end-systolic diameter were measured using ProSolv 3.0, and fractional shortening was calculated. Pulsed Doppler transmittal early and late diastolic flow velocities were also measured, and the early-to-late diastolic flow ratio was derived (61). An index of LV filling pressure was also derived using the ratio of early diastolic mitral inflow to Em (51). These aforementioned parameters were measured at baseline in an effort to confirm age-related differences in heart structure and function. However, these parameters were not measured during experiments 1–3 to keep the sample volume within the same part of the myocardium.

TDI was used to quantify LV regional systolic and diastolic function on a beat-by-beat basis during SNS activation. Pulsed Doppler images were acquired in the apical four-chamber view with the sample volume placed within the intraventricular septum at the mitral annulus (59, 60, 72). To minimize the angle between the beam and the direction of annular motion, care was taken to keep the ultrasound beam perpendicular to annulus plane (12). Measurements were obtained at end-expiration, and averages of three cardiac cycles were used in analysis. The same investigator (M. D. Muller) performed all TDI measurements. The TDI technique is relatively insensitive to changes in preload (1, 51, 72) and is able to detect both systolic and diastolic dysfunction within 5 s after an acute reduction in coronary blood flow (17), as well as impaired LV myocardial velocities in patients with myocardial infarction (3). On the basis of previous human experiments, we considered acute tissue velocity changes ≥0.5 cm/s to be physiologically meaningful (7, 10, 53, 54, 82). To account for potential altered timing of mechanical events, velocity time integrals were also measured for SEm, EEm, and AEm, consistent with previous experiments (25, 62, 66). For SEm and EEm, larger values are considered to be more optimal.

**Experiment 1: IFHG in young and older subjects.** Participants were familiarized to the Borg rating of perceived exertion scale (where 6 = very light, very light and 20 = maximal exertion) (9), and it was emphasized that the upcoming IFHG trial should continue until the hand and forearm reached a score of “20”. Maximal voluntary contraction (MVC) of the right hand was determined in triplicate with a dynamometer (Lafayette Instrument), and 30% of this value was calculated. Following a 2-min baseline, IFHG proceeded at 30% MVC until the forearm reached a score of “20”. Maximal voluntary contraction (MVC) was also derived using the ratio of early diastolic mitral inflow to Em (51). These aforementioned parameters were measured at baseline in an effort to confirm age-related differences in heart structure and function.

**RESULTS**

The two groups in this study were similar (P > 0.05) with regard to height (young: 1.71 ± 0.02 m; older: 1.74 ± 0.03 m), weight (young: 73 ± 3 kg; older: 75 ± 5 kg), body surface area (young: 1.89 ± 0.08 m²; older: 1.85 ± 0.05 m²), and body mass index (young: 24.7 ± 0.7 kg/m²; older: 24.3 ± 1.0 kg/m²). Left atrial diameter was also not different between young (2.8 ± 0.1 cm) and older subjects (3.1 ± 0.2 cm) at rest. In a similar way, baseline measures of fractional shortening...
were not different between young (36 ± 2%) and older (34 ± 3%) subjects. Early diastolic mitral inflow velocity was reduced in older adults (69.4 ± 4.5 cm/s) compared with controls (94.6 ± 5.8 cm/s, \( P = 0.003 \)), while late diastolic mitral inflow velocity was augmented in older adults (60.4 ± 4.5 vs. 48.1 ± 3.7 cm/s, \( P = 0.048 \)). The ratio of early to late mitral inflow to \( E_m \) was impaired with age (young: 2.03 ± 0.20; older: 1.19 ± 0.10, \( P < 0.001 \)), but the ratio of early mitral inflow to \( E_m \) was not statistically different between groups (young: 6.82 ± 0.47; older: 8.08 ± 0.70, \( P = 0.194 \)).

Baseline measures of \( S_m \), \( E_m \), and \( A_m \) demonstrated high test-retest reliability (Cronbach’s \( \alpha = 0.864 \), 0.919, and 0.964, respectively) in the combined group of subjects. In a similar way, baseline TDI velocity time integrals were significantly correlated (\( R = 0.522 \), \( P = 0.026 \), \( A_m = 0.598 \), \( P = 0.009 \)). As expected, TDI velocity time integrals demonstrated age differences at baseline for \( S_m \) (young: 2.02 ± 0.07; older: 1.80 ± 0.04 cm, \( P = 0.010 \), \( E_m \) (young: 1.64 ± 0.10; older: 1.16 ± 0.06 cm, \( P < 0.001 \)), and \( A_m \) (young: 0.58 ± 0.04; older: 0.81 ± 0.06 cm, \( P = 0.008 \)).

**Experiment 1: IFHG in young and older subjects.** Maximal voluntary contraction tended to be lower in the older subjects (31 ± 2 kg) compared with the young subjects (38 ± 3 kg), but this did not reach statistical significance (\( P = 0.053 \)). Grip duration was not different between older (288 ± 16 s) and young (294 ± 25 s) subjects (\( P = 0.853 \)). MAP, HR, and RPP demonstrated expected increases across time (main effect \( P < 0.001 \), Table 1). MAP revealed a main effect of group (\( P = 0.022 \)), such that older subjects had higher MAP regardless of time but \( \Delta MAP \) (i.e., at fatigue) was not different between young (29 ± 4 mmHg) and older (32 ± 4 mmHg) subjects (\( P = 0.588 \)). HR revealed a group × time interaction (\( P < 0.001 \)), such that the \( \Delta HR \) at fatigue was blunted in the older adults (11 ± 2 vs. 23 ± 2 bpm). As shown in Fig. 1, TDI parameters of systolic and diastolic function were impaired in the older subjects at baseline and remained impaired across time as RPP increased (main effect of group \( P < 0.05 \)). The \( \Delta S_m \) was significantly greater (i.e., larger impairment) in the older subjects (−0.82 ± 0.13 cm/s) compared with the young subjects (0.37 ± 0.30 cm/s, \( P = 0.001 \)). The \( \Delta E_m \) was similar between older (−1.59 ± 0.68 cm/s) and young subjects (−1.06 ± 0.76 cm/s, \( P = 0.616 \)), while \( \Delta A_m \) was significantly augmented (i.e., greater atrial contribution to filling) in young subjects (\( P = 0.001 \)).

**Experiment 2: CPT in young and older subjects.** The ratings of cold perception (young: 9 ± 1; older: 9 ± 1) and hand pain (young: 7 ± 2; older: 7 ± 1) were not different between groups in response to the CPT. As shown in Table 2, CPT for 2 min increased MAP and RPP in both young and older subjects (\( P < 0.001 \)), while having a modest effect on HR. The change in systolic blood pressure (young: from 107 ± 3 to 128 ± 5 mmHg; older: from 120 ± 2 to 146 ± 4 mmHg) and the change in diastolic blood pressure (young: from 68 ± 3 to 85 ± 6 mmHg; older: from 75 ± 2 to 87 ± 3 mmHg) were not different between groups. In the older subjects, \( S_m \) was reduced across time (main effect \( P = 0.010 \)), and 9 out of 11 subjects had a reduced \( S_m \) at the end of the second minute compared with baseline. In a similar way, \( E_m \) was reduced across time (main effect \( P = 0.019 \)), and 10 out of 11 subjects had a reduced \( E_m \) at the end of the second minute of CPT. The TDI velocity time integral for \( E_m \) was reduced during the second minute of CPT, relative to baseline (\( \Delta = −0.23 ± 0.05 \) cm, \( P < 0.001 \)). In the young subjects, neither \( S_m \) (\( P = 0.247 \)) nor \( E_m \) (\( P = 0.611 \)) demonstrated a main effect for time, despite the fact that MAP and RPP were significantly elevated above resting levels.

**Experiment 3: normobaric hypoxia in young and older subjects.** As expected, hypoxia caused a reduction in arterial oxygen saturation, while eliciting increases in minute ventilation, HR, and RPP in both groups (Table 3). By the end of the fifth minute of hypoxia, minute ventilation increased from 8.90 ± 0.92 to 11.51 ± 0.98 l/min in the young subjects and from 9.23 ± 0.89 to 11.49 ± 0.65 l/min in the older subjects. Five minutes of poikilocapnic hypoxia lowered end tidal CO₂ from 35 ± 1 to 32 ± 1 mmHg in the young subjects and 36 ± 1 to 31 ± 1 mmHg in the older subjects. As shown in Table 3, the \( \Delta RPP \)

### Table 1. Hemodynamic responses to isometric fatiguing handgrip

<table>
<thead>
<tr>
<th>Group</th>
<th>Base</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>100%</th>
<th>Time</th>
<th>Group</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
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<td></td>
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</tr>
<tr>
<td>Young</td>
<td>109 ± 2</td>
<td>113 ± 1</td>
<td>126 ± 3</td>
<td>135 ± 4</td>
<td>146 ± 6</td>
<td>&lt;0.001</td>
<td>0.070</td>
<td>0.530</td>
</tr>
<tr>
<td>Older</td>
<td>116 ± 3</td>
<td>124 ± 4</td>
<td>134 ± 4</td>
<td>147 ± 5</td>
<td>158 ± 6</td>
<td></td>
<td></td>
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<tr>
<td>DBP, mmHg</td>
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</tr>
<tr>
<td>Young</td>
<td>64 ± 3</td>
<td>68 ± 3</td>
<td>76 ± 3</td>
<td>83 ± 3</td>
<td>86 ± 4</td>
<td>&lt;0.001</td>
<td>0.063</td>
<td>0.628</td>
</tr>
<tr>
<td>Older</td>
<td>73 ± 3</td>
<td>79 ± 3</td>
<td>84 ± 3</td>
<td>89 ± 3</td>
<td>95 ± 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>79 ± 2</td>
<td>84 ± 3</td>
<td>93 ± 3</td>
<td>100 ± 3</td>
<td>108 ± 4</td>
<td>&lt;0.001</td>
<td>0.022</td>
<td>0.754</td>
</tr>
<tr>
<td>Older</td>
<td>88 ± 3*</td>
<td>95 ± 3*</td>
<td>103 ± 3*</td>
<td>111 ± 4*</td>
<td>120 ± 5</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HR, bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>62 ± 4</td>
<td>72 ± 4</td>
<td>75 ± 3</td>
<td>83 ± 3</td>
<td>85 ± 3</td>
<td>&lt;0.001</td>
<td>0.022</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Older</td>
<td>59 ± 2</td>
<td>65 ± 2</td>
<td>66 ± 2*</td>
<td>69 ± 2*</td>
<td>70 ± 2*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. Workload was set at 30% Maximal voluntary contraction (MVC) and participants (n = 10 young and n = 10 older) gripped until a rating of perceived exertion of 20. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) were measured using a Finometer device. *Significant group difference at a given time point (\( P < 0.05 \)).
and HR were blunted in older adults compared with the young subjects at the end of the 5 min (P < 0.01). Despite the increase in RPP in both groups, neither showed a change in Sm (main effect P = 0.6), Em (main effect P = 0.5), or Am (main effect P = 0.1).

Correlation analysis. Both acute (i.e., reflex changes in HR and MAP) and chronic processes (i.e., aging) might affect cardiac mechanics as measured by TDI, so both absolute physiological parameters and changes from baseline were considered in analysis. As shown in Fig. 2, both Sm and Em were inversely related to MAP across a variety of stimuli (resting, both minutes of CPT, 100% IFHG, 5th min of hypoxia), such that higher MAP was associated with reduced (i.e., slower) myocardial tissue velocities. Furthermore, isolating just the healthy older subjects, we found that MAP was related to Sm and Em in response to IFHG, CPT, and hypoxia (Fig. 3). Changes in MAP were not related to changes in myocardial function in the group of young subjects. Lastly, neither absolute HR values nor changes from baseline were related to Sm or Em in either group (P > 0.2).

DISCUSSION

We conducted this study to determine how healthy aging affects LV systolic and diastolic function during SNS activation (i.e., IFHG, CPT, normobaric hypoxia). The current data indicate that healthy aging is associated with impaired Sm and Em in response to both IFHG and CPT. Furthermore, greater pressor responses to these laboratory stressors were associated with larger decrements in myocardial systolic and diastolic LV function in the older adults. To our knowledge, this is the first experimental evidence that LV function can be acutely impaired across different sympathoexcitatory stimuli in older adults. Considering that older adults have baseline impairments

Table 2. Hemodynamic and myocardial responses to a two-minute cold pressor test

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>1 min</th>
<th>2 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>81 ± 3</td>
<td>86 ± 7</td>
<td>102 ± 8†</td>
</tr>
<tr>
<td>HR</td>
<td>57 ± 5</td>
<td>75 ± 5</td>
<td>66 ± 5†</td>
</tr>
<tr>
<td>RPP</td>
<td>6132 ± 605</td>
<td>8661 ± 571</td>
<td>8545 ± 1026†</td>
</tr>
<tr>
<td>Sm</td>
<td>7.83 ± 0.36</td>
<td>7.33 ± 0.71</td>
<td>7.28 ± 0.43</td>
</tr>
<tr>
<td>Em</td>
<td>12.91 ± 0.84</td>
<td>13.41 ± 0.93</td>
<td>12.22 ± 0.98</td>
</tr>
<tr>
<td>Am</td>
<td>5.79 ± 0.78</td>
<td>6.80 ± 0.57</td>
<td>6.85 ± 0.71</td>
</tr>
<tr>
<td>Older</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>89 ± 2</td>
<td>107 ± 4</td>
<td>109 ± 4†</td>
</tr>
<tr>
<td>HR</td>
<td>59 ± 2</td>
<td>64 ± 2</td>
<td>61 ± 2†</td>
</tr>
<tr>
<td>RPP</td>
<td>7126 ± 232</td>
<td>9228 ± 549</td>
<td>8877 ± 425†</td>
</tr>
<tr>
<td>Sm</td>
<td>6.52 ± 0.21</td>
<td>6.09 ± 0.21</td>
<td>6.14 ± 0.25†</td>
</tr>
<tr>
<td>Em</td>
<td>8.91 ± 0.42</td>
<td>7.85 ± 0.48</td>
<td>8.29 ± 0.53†</td>
</tr>
<tr>
<td>Am</td>
<td>9.02 ± 0.45</td>
<td>9.40 ± 0.41</td>
<td>8.72 ± 0.40</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. The right hand was submerged into 1°C water in both young (n = 5) and older (n = 11) subjects. Rate pressure product (RPP) is considered to be a valid index of myocardial oxygen demand (23). Systolic (Sm), early diastolic (Em), and late diastolic (Am) myocardial tissue velocities were measured continuously. †Denotes significant main effect for time (P < 0.05).
in many structural and functional cardiovascular parameters (38, 46) a further worsening of cardiac mechanics during sympathetic activation may have clinical relevance.

**Experiment 1: IFHG in young and older subjects.** The effect of IFHG on HR and MAP responses has been widely studied in both young and older people (32, 40, 64, 67, 78). This exercise mode is similar to some daily activities (e.g., carrying a briefcase, using hand tools) and mechanically impedes blood flow into the working forearm muscles. As the person becomes fatigued, metabolite accumulation stimulates muscle afferents, which eventually augments sympathetic outflow to several vascular beds (2). HR and MAP increase with IFHG in both young and older subjects; the ΔHR is blunted with age due to decreased β-adrenergic sensitivity (20, 36, 56, 83). We have recently demonstrated that the coronary blood flow velocity response (left anterior descending artery) to a 2-min bout of IFHG at 30% maximal voluntary contraction was attenuated in healthy older adults (49). However, the supply-demand ratio (i.e., relating coronary flow to RPP) was similar between groups. It should be noted that in the current study, subjects performed IFHG for nearly 5 min, and RPP was ~30% greater

### Table 3. Hemodynamic and myocardial responses to hypoxia

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>1 min</th>
<th>2 min</th>
<th>3 min</th>
<th>4 min</th>
<th>5 min</th>
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<tbody>
<tr>
<td>Young</td>
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<tr>
<td>MAP</td>
<td>80 ± 2</td>
<td>83 ± 3</td>
<td>82 ± 2</td>
<td>80 ± 4</td>
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<td>80 ± 3</td>
</tr>
<tr>
<td>HR</td>
<td>57 ± 5</td>
<td>63 ± 5</td>
<td>72 ± 6</td>
<td>72 ± 6</td>
<td>76 ± 5</td>
<td>78 ± 5†</td>
</tr>
<tr>
<td>RPP</td>
<td>6294 ± 507</td>
<td>7345 ± 584</td>
<td>8389 ± 648</td>
<td>8347 ± 767</td>
<td>8925 ± 593</td>
<td>8933 ± 639†</td>
</tr>
<tr>
<td>S&lt;sub&gt;m&lt;/sub&gt;</td>
<td>8.04 ± 0.40</td>
<td>7.75 ± 0.42</td>
<td>8.00 ± 0.30</td>
<td>7.70 ± 0.47</td>
<td>7.83 ± 0.49</td>
<td>7.72 ± 0.47</td>
</tr>
<tr>
<td>E&lt;sub&gt;m&lt;/sub&gt;</td>
<td>13.77 ± 0.74</td>
<td>13.54 ± 0.76</td>
<td>13.38 ± 0.53</td>
<td>13.26 ± 0.56</td>
<td>13.32 ± 0.56</td>
<td>13.05 ± 0.55†</td>
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<tr>
<td>A&lt;sub&gt;m&lt;/sub&gt;</td>
<td>5.89 ± 0.48</td>
<td>6.07 ± 0.58</td>
<td>6.51 ± 0.39</td>
<td>6.78 ± 0.54</td>
<td>7.05 ± 0.63</td>
<td>6.88 ± 0.76†</td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt; sat</td>
<td>98 ± 1</td>
<td>92 ± 2</td>
<td>87 ± 3</td>
<td>85 ± 3</td>
<td>82 ± 4</td>
<td>81 ± 4†</td>
</tr>
<tr>
<td>Older</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>90 ± 3</td>
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<td>92 ± 3</td>
<td>85 ± 5</td>
<td>87 ± 5</td>
<td>86 ± 4</td>
</tr>
<tr>
<td>HR</td>
<td>62 ± 3</td>
<td>67 ± 3</td>
<td>69 ± 3</td>
<td>68 ± 3</td>
<td>72 ± 3</td>
<td>71 ± 2†</td>
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<tr>
<td>RPP</td>
<td>7430 ± 569</td>
<td>8210 ± 747</td>
<td>8508 ± 692</td>
<td>7874 ± 668</td>
<td>8505 ± 826</td>
<td>8455 ± 585†</td>
</tr>
<tr>
<td>S&lt;sub&gt;m&lt;/sub&gt;</td>
<td>6.76 ± 0.51</td>
<td>6.89 ± 0.33</td>
<td>6.49 ± 0.31</td>
<td>6.73 ± 0.43</td>
<td>6.56 ± 0.60</td>
<td>6.56 ± 0.45</td>
</tr>
<tr>
<td>E&lt;sub&gt;m&lt;/sub&gt;</td>
<td>9.31 ± 0.91</td>
<td>9.73 ± 0.94</td>
<td>9.01 ± 0.98</td>
<td>9.26 ± 0.97</td>
<td>9.30 ± 0.99</td>
<td>8.80 ± 0.96†</td>
</tr>
<tr>
<td>A&lt;sub&gt;m&lt;/sub&gt;</td>
<td>9.95 ± 0.97</td>
<td>9.92 ± 0.95</td>
<td>10.30 ± 0.84</td>
<td>9.60 ± 0.90</td>
<td>9.83 ± 0.76</td>
<td>9.53 ± 0.73†</td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt; sat</td>
<td>98 ± 1</td>
<td>93 ± 3</td>
<td>88 ± 4</td>
<td>85 ± 5</td>
<td>82 ± 5</td>
<td>80 ± 5†</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. The subjects (n = 7 young and n = 6 older) underwent 5 min of normobaric poikilocapnic hypoxia (10% oxygen, CO2 not controlled) in the left lateral position. †Denotes main effect for time (P < 0.05).

Fig. 2. Relationship between systemic mean arterial pressure (MAP; x-axis) and left ventricular systolic tissue velocity (y-axis; top) and diastolic tissue velocity (y-axis; bottom). Data points include resting baseline, minutes 1 and 2 of the cold pressor test (CPT), peak IFHG, and the 5th min of hypoxia for both young (■) and older (○) subjects. The trendline reflects the pooled data.

Fig. 3. Relationship between changes in mean arterial pressure (ΔMAP) and changes in systolic (y-axis; top) and diastolic (y-axis; bottom) tissue velocities in response to IFHG, CPT, and hypoxia in older adults (n = 11).
than in our past experiment. At peak exercise, RPP (an index of myocardial O₂ demand) was not different between groups, but Sₘ and Eₘ were both reduced in the older subjects.

The reasons for age-associated LV impairments during IFHG in older adults are not entirely clear, but three physiological mechanisms are possible. First, acute reductions in coronary blood flow can cause acute reductions in TDI parameters (17), and therefore, the current IFHG data may be explained by transient cardiac ischemia (i.e., a mismatch between myocardial O₂ supply and demand caused by a sympathetic “brake” on the coronary vasculature). Second, acute increases in afterload coupled with increased aortic stiffness in older adults may mechanically impair LV performance. Indeed, a recent publication demonstrated that acute increases in MAP (i.e., IFHG at 40% MVC for 3 min) impaired echocardiography-derived LV twist mechanics in young people (81). Third, SNS activation augments ventricular contraction and relaxation via stimulation of cardiac β-adrenergic receptors (42); decreased adrenergic responsiveness in older people (18, 20) may partly explain why LV systolic and diastolic function was impaired relative to younger people, despite similar levels of RPP. It should be emphasized that echocardiographic parameters reflect the net effect of increased afterload, increased inotropy, aortic stiffness, ventricular-vascular coupling, cardiac sympathetic nerve activity, coronary adrenergic receptor sensitivity, and coronary vasoconstriction in response to IFHG. Thus, a reduction in TDI parameters in the older subjects suggests and impairment at least one of these physiological levels.

With aging, the LV fills later in the cardiac cycle, predominantly due to increased fibrosis and LV stiffness (5). The augmented late diastolic mitral inflow velocity and the augmented Aₘ are considered to be a normal compensatory response in these individuals (8). It is also interesting to note that in the current study Aₘ increased by ~50% during IFHG in young people. This finding is consistent with previous studies using dynamic exercise (13, 24, 76). To our knowledge, this study is the first to document that Aₘ also increases during IFHG in older adults, despite a blunted ΔHR compared with the young. An increase in preload, MAP, and/or HR during dynamic exercise may elicit differences in contractility and elastic recoil compared with IFHG (57), and future studies may quantify this process in healthy older individuals.

**Experiment 2: CPT in young and older subjects.** The CPT is an experimental stimulus used to activate the SNS. Contrary to IFHG in which SNS activation is initiated by mechanically and metabolically sensitive muscle afferents (41), the CPT elicits sympathoexcitation due to painful and/or thermal stimulation of the skin (21). Within the first minute of the CPT, HR, MAP, and muscle sympathetic nerve activity typically increase, and during the second minute, HR returns toward baseline (34, 47, 80). The CPT also elicits coronary artery dilation in healthy vessels and vasoconstriction in coronary vessels with atherosclerosis (50). For these reasons, we chose this test to acutely increase RPP while keeping HR relatively constant (experiment 2). Indeed, the RPP at the end of the second minute was similar between groups, and older subjects had a reduction in both Sₘ and Eₘ. In previous experiments, our laboratory has demonstrated that the CPT elicits an increase in coronary blood flow velocity in both young and older people and that the supply-demand ratio was not different between groups (45, 49). This dilation is mediated by β-adrenergic receptors, as well as endothelial cells and local metabolic dilation (i.e., due to increased RPP) (33). In the current study, reduced Sₘ and Eₘ in older people during CPT may be due to transient reductions in coronary blood flow, even though our subjects were clinically free of coronary artery disease (see METHODS).

With regard to cardiac mechanisms during CPT, a previous study showed that individuals (50 ± 9 yr) with coronary artery disease had acute reductions in early diastolic transmitral inflow velocity and reduced echocardiography-derived measures of contractility (37). Our data from experiment 2 are consistent with this study and indicate that acute changes in afterload due to SNS activation impair LV function in healthy older adults.

**Experiment 3: normobaric hypoxia in young and older subjects.** Hypoxemia elicits SNS activation (73, 74), elevates HR and ventilation (74, 75), and locally dilates blood vessels (31) while having no effect on MAP (74). For these reasons, we used 5 min of hypoxia to clarify age difference in LV function that may be influenced by changes in HR, MAP, or myocardial O₂ delivery. In experiment 3, HR and RPP both increased relative to baseline, but this increase was blunted in the older adults. This finding is consistent with a previous study using isocapnic hypoxia in older adults (35). Our laboratory recently demonstrated a 22% increase in coronary blood flow velocity (left anterior descending artery) in young individuals in response to a similar poikilocapnic hypoxia protocol (45). This coronary hyperemia may explain why LV function did not change across time, despite increases in RPP (and presumably SNS activation). It should be noted that our individuals became modestly hypocapnic in these protocols, which was an expected finding (45, 74, 75). Had we used isocapnic hypoxia, changes in minute ventilation would have been greater (making it more challenging to obtain high-quality images), but SNS activation would have been less. The data from experiment 3 indicate that the net effect of hypoxemia-mediated SNS activation (and presumably coronary dilation) did not acutely change TDI parameters in either group.

The influence of the SNS on resting LV function has been studied in hypertensive patients with diastolic dysfunction (26). Specifically, the ratio of early diastolic-to-late diastolic mitral inflow was correlated with resting muscle sympathetic nerve activity, such that greater SNS activity was associated with worse LV diastolic function. Considering that heightened SNS activity is involved in a number of cardiovascular diseases (39, 43, 52), relating SNS activity to LV function during an acute stressor could have clinical relevance. The current data demonstrate that both systolic and diastolic LV function is inversely related to absolute MAP across a wide range of ages and stimuli (Fig. 2). Furthermore, acute changes in MAP were also related to acute changes in Sₘ and Eₘ, such that larger pressor responses to stress were linked with larger decrements in LV function (Fig. 3). Therefore, we provide novel evidence that increasing afterload via physiological stress impairs LV function in healthy older adults. Many previous TDI experiments using exercise or pharmacological manipulation of preload and afterload failed to quantify changes in MAP (11, 19, 24, 65, 76) or did not account for the underlying reflex changes that occur when altering blood volume status or infusing vasoactive drugs (4, 19, 62). Considering that the human body senses and integrates a variety of signals (i.e., HR, MAP, preload, SNS activity, aortic stiffness) that might affect echo-
cardiography-derived LV parameters, we suspect that it will be necessary for future TDI studies to account for these changes.

**Experimental considerations.** The current investigation employed a noninvasive approach to understand how acute SNS-mediated increases in HR and MAP impact LV function. Previous experiments from our laboratory and others have indicated that IFHG, CPT, and hypoxia increase SNS activity to skeletal muscle, the cutaneous circulation, and the renal vasculature. Despite reflex increases in MAP being similar between groups, it is possible that the degree of sympathoexcitation was not the same between young and older subjects. Measuring muscle sympathetic nerve activity may have partly addressed this issue, but SNS control of the coronary circulation likely differs from that of other vascular beds. Direct measurement of cardiac sympathetic nerve activity is technically not feasible in humans.

Both α- (18) and β-receptor (83) responsiveness is blunted in older people. We did not perform intracoronary infusions in this experiment because the risks of cardiac catheterization outweighed the benefits for our healthy subjects. Moreover, we did not infuse an α-blocker systemically because it is known to cause baseline hypotension (6, 71), thereby activating the baroreflex and causing tachycardia, which would confound the base-

**Conclusion.** The use of TDI to quantify LV systolic and diastolic function is becoming more popular in clinical care as well as in physiological experiments. Our data indicate that S_m and E_m are reduced in healthy older adults during IFHG and CPT. Furthermore, greater pressor responses to these laboratory stressors were associated with larger decrements in myocardial systolic and diastolic function in the older adults. Taken together, suboptimal LV adaptations to SNS stress may partially explain why acute heavy exertion (i.e., acute increases in afterload and myocardial O_2 demand in the face of a sympathetically “brake” on the coronary vasculature) can trigger myocardial ischemia in certain individuals (44). Future studies evaluating the effects of healthy aging and aerobic exercise training on LV function during sympathetic stress are much needed.

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