Verapamil Acutely Reduces Ventricular-Vascular Stiffening and Improves Aerobic Exercise Performance in Elderly Individuals

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OBJECTIVES

We tested the hypothesis that acute intravenous verapamil acutely enhances aerobic exercise performance in healthy older individuals in association with a combined reduction of ventricular systolic and arterial vascular stiffnesses.

BACKGROUND

Age-related vascular stiffening coupled with systolic ventricular stiffening may limit cardiovascular reserve and, thus, exercise performance in aged individuals.

METHODS

Nineteen healthy volunteers with mean age 70 ± 10 years underwent maximal-effort upright ergometry tests on two separate days after receiving either 0.15 mg/kg i.v. verapamil or 0.5 N saline in a double-blind, randomized, crossover study.

RESULTS

Baseline vascular stiffness, indexed by arterial pulse-wave velocity (Doppler) and augmentation index (carotid tonometry) declined with verapamil (−2.5.9 ± 2.1% and −31.7 ± 12.8%, respectively, both p < 0.05). Preload-adjusted maximal ventricular power, a surrogate for ventricular end-systolic stiffness, also declined by −9.5 ± 3.6%. Peripheral resistance and peak filling rate were unchanged. With verapamil, exercise duration prior to the anaerobic threshold (AT) increased by nearly 50% (260 ± 129 to 387 ± 176 s) with a corresponding 13.4 ± 4.7% rise in oxygen consumption (VO2) at that time (both p < 0.01). Total exercise duration prolonged by +6 ± 2.7% (p < 0.05) with no change in maximal VO2. Baseline cardiodepression from verapamil reversed by peak exercise with net increases in stroke volume and cardiac output (p < 0.05).

CONCLUSIONS

Acute intravenous verapamil reduces ventriculovascular stiffening and improves aerobic exercise performance in healthy aged individuals. This highlights a role for heart-arterial coupling in modulating exertional capacity in the elderly, suggesting a potentially therapeutic target for aged individuals with exertional limitations. (J Am Coll Cardiol 1999;33:1602–9)

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Aerobic capacity declines with age (1), with exertional fatigue and frailty often occurring in the absence of cardiac or peripheral vascular ischemia (2). Several age-related cardiovascular changes may contribute to such altered exercise physiology (1). One potentially important factor is arterial stiffening (3–5), which increases pulsatile and non-pulsatile components of vascular load (5) imposed on the heart, resulting in systolic hypertension and enhanced systolic wave reflections (1,3–5). We recently reported that left ventricular systolic stiffness (i.e., end-systolic elastance, Ees) also increases with age, matching cardiac function to the altered arterial load (6). Coupling a stiff heart in systole with a stiff arterial system impedes the transfer of increased stroke volume (SV) from heart to artery without concomitant substantial increases in pressure load, which in turn can feed back to inhibit cardiac ejection. Furthermore, a less stiff heart and vasculature can better accommodate reduced end-systolic volumes (ESV), whereas stiffer properties may contribute to a greater reliance on preload reserve in the elderly (7,8).

If combined ventricular-vascular stiffening limits exertional tolerance, then agents such as verapamil, which lower both end-systolic stiffness (9) and arterial stiffness (10), might improve exercise capacity. In particular, more effective ventricular-to-vascular interaction could enhance SV and cardiac output reserve, prolonging aerobic exercise duration. The present study tested this hypothesis in healthy elderly subjects.
METHODS

Control subjects. Twenty-four healthy volunteers aged 50 to 90 years were recruited from the general public. Control subjects with coronary or peripheral vascular ischemia, significant valvular regurgitation or stenosis, prior myocardial infarction, atrial fibrillation and those unable to withhold vasoactive medications for at least 24 h prior to study were excluded. Informed consent was obtained from each subject and the protocol approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions. Three control subjects developed significant asymptomatic electrocardiographic ST segment depression with regional wall motion abnormalities on radionuclide ventriculography during exercise, while two subjects failed to complete the protocol (allergic reaction to verapamil, failure to return for follow-up). Data are reported from the remaining 19 subjects, comprised of 10 men and 9 women with a mean age 67.4 ± 10.5 years (range 50–84). Three individuals had hypertension treated with an angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, or alpha1-blocker. No subject was treated with a Ca2+-channel blocker.

Study design. We used a double-blind, randomized, placebo-controlled crossover design. Verapamil (0.15 mg/kg) or saline control (0.5 N NaCl-D5W) was injected i.v. in 5 mL over 5 min. Baseline cardiac and vascular properties were obtained (detailed below) in the supine position prior to and 15 min after the infusion. Maximal effort upright bicycle ergometry was then performed. Cardiac volumes, arterial pressures and several derived indexes of cardiovascular function were measured immediately before and during each stage of exercise. Each control subject returned for a second study one to seven days later, using the identical protocol but with the alternative agent.

Vascular measurements. Carotid tonometry, transcutaneous Doppler flow velocity and noninvasive calibrated central arterial pressure assessed arterial vascular properties. Carotid applanation tonometry was performed with a hand-held transducer (SPC-350, Millar Instruments, Houston, Texas) (11). Signals were digitized at 200 Hz, and the ratio of pressure rise after the midlate systolic inflection to the total pulse pressure (augmentation index [AI]) (12,13) was determined. The inflection point was identified from zero-crossing timings of the fourth derivative of the pressure signal (14). Doppler flow signals (2.0 MHz nonimaging transducer, CFM 800, Vingmed Sound, Norway) were measured in the ascending aorta or right carotid artery and right femoral artery along with simultaneous electrocardiogram. The time from the R wave of the QRS complex to the foot of each flow wave (15,16) was subtracted to yield propagation time, and aortic pulse wave velocity (PWV) was the external distance between the suprasternal notch and right femoral pulse divided by this time.

Noninvasive calibrated central arterial pressures were measured using an improved version of a previously validated device (17). This system consisted of a computer-controlled sphygmomanomeric arm cuff with an internal transducer to measure cuff pressure, dual microphones over the brachial artery at the antecubital fossa and an electrocardiographic monitor. The cuff was inflated above systolic pressure and then deflated at 2 to 3 mm Hg/beat. During deflation, Korotkoff sounds were recorded and the time delay between the ECG-R wave and the Korotkoff sound determined as a function of cuff pressure. This time delay combined cardiac electromechanical delay, flow transit time from aorta to brachial artery and the time for arterial pressure to exceed cuff pressure. This last component declined with cuff pressure, so plotting cuff pressure versus time delay produced the upstroke portion of the arterial waveform. A prior version of this system employed a Doppler transducer to signal the onset of brachial flow (17); however, maintaining persistent flow signals during exercise was problematic. In contrast, detection of Korotkoff sounds was less sensitive to exact dual microphone positioning and was more reliable during exercise.

The effective arterial elastance (Ea) was also determined as a measure of total vascular load. Both mean and pulsatile components of arterial impedance are manifest in Ea, and it has been shown to quantify influences of vascular loading on heart function in intact patients better than does mean resistance (18). Effective arterial elastance is equal to the ratio of end-systolic pressure (Pes) to SV. End-systolic pressure may be estimated by 0.9 arterial-systolic pressure (Psys) (18), so that $Ea = 0.9 \times \frac{Psys}{SV}$. Psys was arterial systolic pressure. Stroke volume was determined from radionuclide ventriculography.

Cardiac measurements. Gated technetium99m pertechnetate radionuclide ventriculography blood pool scans were obtained in the left anterior oblique orientation at 32 frames/cycle at rest in the supine position before and after drug administration. Scans were gated at 16 frames/cycle during exercise. Time–activity curves from identified regions
of interest were calibrated for ventricular volume using a count-based method with peripheral blood sampling to determine counts per mL of a reference volume and with correction for attenuation of left ventricular counts (19). In addition to providing ESV, end-diastolic volume (EDV), SV and ejection fraction (EF), time-activity curves were fit to a four-term Fourier series that was analytically differentiated to yield flow (20).

Left ventricular power equaled the product of ascending aortic pressure and ventricular systolic flow. Signals were adjusted so the onset of flow and the arterial end-diastolic pressure were synchronous. Maximal power (PWRmax) was the peak pressure-flow product. Maximal power varies with preload volume but is relatively insensitive to arterial load (20,21), and PWRmax/EDV has been shown to be both preload-adjusted so the onset of flow and the arterial end-diastolic pressure (20) and afterload insensitive in normal sized hearts (22). Importantly, changes in preload-adjusted PWRmax correlate with those of chamber end-systolic stiffness (20) (i.e., Ees), but unlike Ees, PWRmax can be measured noninvasively during exercise (22). In the present study, PWRmax/EDV was used as a surrogate for Ees changes.

**Cardiopulmonary exercise testing.** Maximal effort upright bicycle exercise was performed, starting at a 25 W, and increasing 25 W every three minutes until exhaustion. Standard 12-lead electrocardiographic monitoring was performed. Breath-by-breath levels of oxygen consumed (VO2) and carbon dioxide produced (VCO2) were measured (CPX, MedGraphics, St. Paul, Minnesota). Maximal oxygen consumption at the anaerobic threshold (AT) (23) was determined by the V-slope method (24) and peak VO2 defined as the mean value over 15 s prior to termination of exercise. Exercise capacity was assessed by total exercise duration, time-to-reach AT, VO2 at the AT and maximal VO2. Gated blood pool acquisitions were obtained during the last 2.5 min of each 5-min exercise load, and noninvasive central arterial pressures were recorded during the last minute of each stage.

**Statistical analysis.** Data are presented as mean ± SD. Within subject effects comparing verapamil to saline infusion before and after infusion at rest and during exercise, between intervention studies and their interaction (i.e., different responses between verapamil vs. placebo) were tested by a repeated measures one-way analysis of variance. Post-hoc tests between individual means were then performed using Tukey’s test for multiple comparisons. Differences of baseline hemodynamics and exercise capacity between the two studies were compared by Student’s two-tailed paired t test.

**RESULTS**

**Baseline data and response to verapamil.** Table 1 provides baseline data for each of the two sequential studies. There were no significant differences in any parameter. Arterial systolic pressure averaged 140 ± 10 mm Hg and arterial pulse pressure 66.7 ± 10 mm Hg, consistent with age-related vascular changes (25).

Figure 1 compares the effects of verapamil with saline administration. Figure 1A shows a representative tracing from a subject randomized to verapamil and saline, and Figure 1B shows the effects of verapamil on arterial pulse pressure. Figure 1C shows the effects of verapamil on arterial pulse pressure. Figure 1D shows the effects of verapamil on arterial pulse pressure.
declined from 905 ± 192 to 847 ± 173 cm/sec (−5.9 ± 2.1%, p < 0.05), and PWR max/EDV declined from 6.04 ± 1.19 to 5.38 ± 1.17 watts/mL (−2.5.9 ± 3.6%, p < 0.05). Compared with saline, verapamil also lowered P sys (141 ± 16 to 136 ± 16 mm Hg) but not mean pressure, E a (1.38 ± 0.21 to 1.35 ± 0.18 mm Hg/mL), EF (69 ± 8 to 67 ± 7%) and raised EDV (135 ± 19 to 139 ± 23 mL) and ESV (42 ± 14 to 47 ± 15 mL). Verapamil did not significantly change heart rate (66 ± 11 vs. 65 ± 10 min⁻¹), SV (6.1 ± 0.92 vs. 5.95 ± 0.91 L/min), mean arterial resistance (1271 ± 182 vs. 1269 ± 209 dynessec cm⁻⁵) or peak filling rate/EDV (PFR EDV, 2.99 ± 0.72 vs. 2.87 ± 0.59 sec⁻¹).

Hemodynamic responses to intravenous verapamil during exercise. All subjects achieved 90% predicted heart rate and/or peak VO2 plateau. Despite initial cardiodepression from verapamil reflected by reduced PWR max/EDV and EF and higher ESV, exercise reserve was similar in both treatment and saline control studies (Fig. 2, Table 2). Arterial load was lower throughout exercise (total peripheral resistance: −9%, E a: −7%), whereas EDV and SV were significantly increased (Fig. 2). Improved cardiac output and EDV was not accompanied by enhanced diastolic filling, as verapamil tended to lower PFR EDV during exercise (p = 0.08). Systolic pressure rose similarly during exercise in both studies. Cardiac output was slightly greater with verapamil (+6% averaged over exercise, Table 2, p < 0.05) despite slightly slower heart rates (−4%, p < 0.05).

Effect of intravenous verapamil on exercise tolerance. Hemodynamic differences during exercise were accompanied by significant improvement in aerobic exercise performance. Exercise duration prior to achieving the AT increased from 260 ± 129 to 387 ± 176 s (+43.4 ± 16%, p = 0.007) with verapamil, and VO2 at this time rose from 11.2 ± 2.8 to 12.5 ± 3.8 mL/min/kg (+13.2 ± 4.6%, p = 0.018). Total exercise time increased modestly from 803 ± 300 to 845 ± 293 sec (+5.8 ± 2.8%, p = 0.06) whereas maximal VO2 remained unchanged (+2 ± 3%, p = NS).

Subgroup analysis. While PFR EDV did not significantly change with verapamil in the total study group, individual responses varied according to baseline value. Control subjects with slower early diastolic filling displayed increases with verapamil whereas filling rates declined in patients.
with higher resting values. This dependence was given by:
\[ \Delta \text{PFR}_{\text{EDV}} = -0.35 \times \text{PFR}_{\text{EDV, Basal}} + 0.93, \ r = 0.58, \ p = 0.009. \] To test if improved early filling related to enhanced exercise capacity, patients were subdivided into those with a baseline \( \text{PFR}_{\text{EDV}} \leq 3.0 \text{ s}^{-1} \) (mean 2.4 ± .44, \( n = 10 \)) and those with higher initial values (mean 3.6 ± 0.4, \( n = 9 \)). Verapamil increased \( \text{PFR}_{\text{EDV}} \) by 11 ± 17% in the first group but reduced it by −12 ± 11% in the latter group.

### Table 2. Systolic Function Response During Exercise in Placebo and Verapamil-Treated Patients

<table>
<thead>
<tr>
<th></th>
<th>Preexercise</th>
<th>Exercise-25 W</th>
<th>Exercise-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Output (L/m)</td>
<td>Placebo</td>
<td>5.8 ± 0.26</td>
<td>10.0 ± 0.36</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>6.43 ± 0.24</td>
<td>10.5 ± 0.48</td>
</tr>
<tr>
<td>PWR_{max}/EDV (watts/mL(10^2))</td>
<td>Placebo</td>
<td>7.13 ± 0.34</td>
<td>9.3 ± 0.49</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>6.65 ± 0.26</td>
<td>9.3 ± 0.58</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>Placebo</td>
<td>67 ± 2</td>
<td>72 ± 2</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>67 ± 2</td>
<td>72 ± 2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>Placebo</td>
<td>69.8 ± 2.7</td>
<td>96.8 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>67.9 ± 2.4</td>
<td>92.6 ± 4.4</td>
</tr>
</tbody>
</table>
(p < 0.003). However, none of the exercise performance variables significantly differed between subgroups.

In contrast, exercise duration was greater in patients in whom both ventricular and vascular stiffness declined (reflected by PWRmax/EDV, Eₐ, PWV and AI). In 13 subjects with reductions in both parameters from verapamil, exercise duration increased 8.6 ± 11.4% whereas the remaining subjects had less change in duration (−0.08 ± 12.4%, p < 0.05 by Mann-Whitney U test).

**DISCUSSION**

This is the first study to report that acute i.v. verapamil reduces ventricular-vascular stiffening and improves exercise capacity in healthy elderly individuals. Enhanced performance principally reflected an ability to exercise longer and reach a higher VO₂ prior to the anaerobic threshold. There was far less change in overall exercise duration or maximal VO₂. This suggests that exercise efficiency was improved rather than absolute capacity. Importantly, these changes occurred without an increase in cardiac per minute-work. Verapamil lowered preload-corrected PWRmax (a surrogate for ventricular chamber systolic stiffness) and reduced vascular stiffness as evidenced by AI, PWV and Eₐ. These data support the hypothesis that age-related arterial and ventricular stiffening may partially limit exercise performance even in healthy individuals and that this capacity can improve from interventions that diminish this stiffening.

**Comparison with prior studies.** Prior studies regarding the effects of verapamil on cardiac function and exercise capacity in nonhypertrophied hearts have mostly employed oral therapy and highlighted influences on diastolic filling. For example, Arrighi et al. (26) administered verapamil for 3 to 4 days to middle-aged and older individuals and found enhanced early diastolic filling whereas this was not observed in younger subjects. That such changes might translate into better exercise capacity was suggested by Petrella et al. (27) who compared acute (4-h) to chronic (12-week) effects of oral verapamil in normotensive and hypertensive elderly subjects. They also observed enhanced diastolic filling (i.e., reduced isovolumic relaxation time, increased E:A ratio) associated with higher maximal VO₂ in both groups. Interestingly, similar results were achieved with acute and chronic treatment. Setaro et al. (28) treated elderly patients with symptomatic heart failure, EF > 45% and abnormal baseline PFREDV (<2.5) with five weeks of oral verapamil. They reported a 30% rise in PFREDV and 33% increase in exercise duration.

Our study demonstrates that exercise performance can be enhanced by even acute i.v. verapamil in elderly individuals, and that this response does not require increasing early diastolic filling rates. The lack of an overall change in PFREDV likely reflected heterogeneity of basal values in our study group, consistent with prior data (26). Acute i.v. verapamil also induces more pronounced systolic cardiodepression (9) and can have variable effects on relaxation (29) and thus, early peak filling while arterial load reduction may be less pronounced. This is consistent with the finding that pulsatile load, rather than mean resistive load, was mainly lowered by i.v. verapamil at baseline while contractility indexed by PWRmax/EDV fell approximately 10%.

**Ventricular-vascular stiffening.** By lowering both vascular and ventricular systolic stiffness, verapamil may facilitate cardiac-arterial interaction, increasing functional reserve by providing more effective transfer of blood from the heart to periphery. It seems remarkable that the changes in both ventricular and vascular stiffnesses by verapamil were modest, yet improvement in aerobic exercise capacity was substantial. However, when volume is transferred into or out of stiff chambers there are correspondingly greater changes in accompanying pressures. Increasing cardiac SV during exercise would therefore be associated with a greater rise in arterial systolic pressure, and, in a closed-system, this can feedback and amplify inhibition of net cardiac ejection. With verapamil, both PWRmax/EDV declined and ESV increased, yet they reached similar values at peak exercise as with saline controls, suggesting increased reserve. Such recovery during exercise of basal contractile depression from verapamil has been previously proposed (30) but never as directly shown as in the present study employing cardiac-specific power indexes.

Exercise-induced increases in contractile function are thought to decline in aged hearts (7). This is thought to be partly due to lower beta-adrenergic responses, but it could also stem from age-dependent changes in basal ventricular end-systolic stiffness (Ees) (6). Since acute contractile reserve is linked to further increases in Ees (i.e., increasing slope of the end-systolic pressure-volume relation [31]), a higher baseline value of Ees limits further change and thus systolic reserve. By lowering basal contractile function but not inhibiting increases during exercise, verapamil may restore some of this reserve.

Verapamil also reduced effective ventricular afterload (Eₐ) during exercise due both to a decline in heart rate and fall in pulsatile and resistive vascular loading. This further enhanced cardiac ejection. Our hypothesis that the major cardiovascular effect from i.v. verapamil was more effective cardiac output transfer (with similar total cardiac per min-work) is supported by the type of exercise changes observed, i.e., aerobic exercise duration and VO₂. Prior studies performed in younger patients (mean age 52 years) treated for ~1 month with oral verapamil have also displayed reduced heart rates and arterial load during exercise similar to that observed in the present study yet, without any improvement in exercise performance. The effects of verapamil on improving ventricular-arterial interaction likely depend upon the baseline state (i.e., age-dependent), as was the case for its effects on PFREDV in the present and earlier studies (26).

**Methodological limitations.** Ventricular end-systolic stiffness (Ees) was not directly measured as there are no...
current methods to do this noninvasively during exercise. \( P_{\text{WRmax}}/EDV \) was used as it is measurable during exercise, minimally load-dependent (32), and prior studies have shown that relative changes correlate with \( E_{\text{s}} \) (20,21) with the data including effects from i.v. verapamil (20).

Effective arterial elastance was based on an estimate of \( P_{\text{es}} \) which, while validated at rest and with preload reduction in patients of varying ages (18), nonetheless has not been verified during exercise. Effective arterial elastance has been reported to decline in younger individuals undergoing supine exercise (33) whereas it rose in the present study. This may reflect differences in systolic pressure augmentation during exercise in older versus younger individuals, faster heart rates with upright versus supine exercise and methodologic differences from using dicrotic notch pressure to estimate \( P_{\text{es}} \).

Clinically occult coronary artery disease is a concern for any investigation of asymptomatic elderly individuals in whom invasive coronary arteriography cannot be justified. Beneficial effects of verapamil on exercise tolerance in patients with coronary artery disease are well known (34–36). We cannot entirely rule this factor out, although we did identify several patients with silent ECG changes associated with wall motion abnormalities during the initial stress testing, and these subjects were excluded from further testing and analysis. None of the remaining patients demonstrated these changes.

Conclusions. We demonstrated that aerobic exercise capacity is acutely enhanced in elderly healthy individuals by intravenous verapamil. The dose of verapamil principally lowered basal pulsatile vascular load and ventricular systolic contractile function—reflecting reductions of systolic ventricular and vascular stiffening. Such changes may improve the functional coupling of the heart with the systemic vascular system, enhancing reserve capacity. While this study was performed in healthy individuals, the results may apply to those with baseline exertional intolerance. Heart failure symptoms in the elderly are often associated with preserved systolic function (37), and vascular stiffening is well-documented in elderly heart failure patients (38). Combined vascular and ventricular–systolic stiffening would further constrain reserve function. Reducing ventricular–vascular stiffening may therefore be a logical therapeutic target, particularly in elderly patients with limited exertional capacity.

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