Hemodynamic effects of unloading the old heart

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Hemodynamic effects of unloading the old heart. Am. J. Physiol. 277 (Heart Circ. Physiol. 46):H1863–H1871, 1999.—A reduction in upright exercise capacity with aging in healthy individuals is accompanied by acute left ventricular (LV) dilatation and impaired LV ejection. To determine whether acute vasodilator administration would improve LV ejection during exercise, sodium nitroprusside (NP) was administered to 16 healthy subjects, ages 64–84 yr, who had been screened for the absence of coronary heart disease by prior exercise thallium scintigraphy. Infusion of NP (0.3–1.0 µg·kg⁻¹·min⁻¹), titrated to reduce the resting mean arterial pressure 10% (and eliminate the late augmentation of cardiac arterial pressure), increased LV ejection fraction (EF) compared with placebo during upright, maximal graded cycle exercise at all work rates and permitted an equivalent stroke volume and stroke work from a smaller end-diastolic volume. The maximum increase in exercise EF in older subjects during NP infusion was equal to that in healthy, younger (22–39 yr) control subjects. The maximum cycle work rate and cardiac index were unchanged compared with placebo. Thus combined preload and afterload reduction with NP in older individuals improves overall LV ejection phase function: exercise LV stroke work is reduced, EF is increased, and stroke volume is maintained in the setting of a reduced ventricular size. These findings suggest that at least some of the age-associated decline in cardiac function during maximal aerobic exercise may be secondary to adverse loading conditions.

AGING: MYOCARDIAL FUNCTION; PRELOAD; AFTERLOAD; EXERCISE HEMODYNAMICS

AGE-ASSOCIATED CHANGES in cardiovascular reserve mechanisms occur even among healthy individuals (15). The most salient cardiovascular changes with aging occur during stress and include a reduction in maximum heart rate (HR) and increases in left ventricular (LV) afterload and preload (9). An increase in the vascular component of LV afterload with aging consists of four components (12, 24, 25, 32): a modest increase in systemic vascular resistance (9, 25), a more marked reduction in aortic compliance (25), early return of pulse wave reflections from the periphery of the vascular system to the aortic root due to stiffening of the arterial walls and an increase in pulse wave velocity (PWV), and increased inertance due to a larger mass of blood requiring acceleration at the onset of ejection because of aortic dilatation (11, 15). The increase in the vascular component of afterload with aging, together with a decline in maximum intrinsic contractility (34) and in adrenergic augmentation of contractility (10, 16), results in a smaller reduction in LV end-systolic volume (ESV) and a blunted increase in the LV ejection fraction (EF) during vigorous exercise in older vs. younger individuals (2, 9, 27).

Previous studies of this cohort in our laboratory (9, 10, 30) have demonstrated increased LV end-diastolic volume (EDV) in older vs. younger men at seated rest and a greater increase in EDV in older than in younger individuals of both genders during exhaustive, upright exercise (9). However, the stroke volume (SV) elicited by the Frank-Starling mechanism in healthy older persons is limited because of failure of the LV to empty as completely in older persons as it does in younger ones (9, 15), resulting in an age-associated increase in ESV during exercise. Thus, during vigorous exercise, the increased LV vascular afterload and LV preload in older individuals, combined with reduced LV contractility (10, 34) and HR, cause the heart to become dilated relative to the heart in younger individuals throughout the cardiac cycle (9, 15). This cardiac dilatation increases LV wall stress throughout the cardiac cycle in older vs. younger individuals and may contribute to the reduction in maximum LV ejection capacity with aging (28).

The goal of this study was to examine (1) whether unloading the heart in healthy older persons with sodium nitroprusside (nitroprusside), a mixed vasodilator without direct inotropic effects (22, 23, 26), would improve their LV function during vigorous aerobic exercise to that attained by healthy, unmedicated, younger individuals and (2) whether this effect would permit an enhanced maximum cardiac output and maximum exercise capacity in these older individuals.

METHODS

Study Population

Sixteen participants who received nitroprusside infusion were healthy, sedentary, older (64–84 yr) community-dwelling volunteers selected from the Baltimore Longitudinal Study of Aging (BLSA) panel. All younger (22–39 yr, n = 81) BLSA subjects, who exercised in the absence of drug, served as a reference control group. All participants in the BLSA undergo extensive physiological, psychological, and clinical testing at the Gerontology Research Center for 2.5 days biennially. Criteria for inclusion in the present study were as follows: 1) no clinical evidence of cardiovascular disease, 2) absence of cardiovascular medication, 3) normal resting electrocardiogram (ECG), 4) normal exercise ECG, 5) normal thallium myocardial perfusion scan (in subjects >40 yr of
age) performed using standard methodology after peak treadmill exercise with use of a modified Balke protocol, 6) resting EF = 0.50 and no segmental wall motion abnormality at rest or during exercise on the radionuclide ventriculogram, and 7) no regular participation in exercise training (e.g., running, cycling, swimming), defined as ≥30 min of such activity at least three times per week.

Study Protocol

The study protocol involved measurement during supine rest of two indexes of arterial stiffness, carotid augmentation index (AGI) and carotid femoral PWV, followed by determination of cardiac volumes by radionuclide ventriculography (RNV) at seated rest and during exhaustive upright cycle ergometry. Oxygen consumption (V\(_{\text{O}}\)\(_{2}\)) was monitored throughout exercise. All studies were performed on two separate occasions 48 h apart. On one occasion each subject received an infusion of nitroprusside sufficient to lower mean arterial pressure by 10% and, on the other day, saline placebo. The order in which each individual received active drug or placebo was randomized. Because of the obvious physical effects of nitroprusside, neither the subject nor the investigators were blinded to whether the drug or placebo was being infused, but analysis of the data was blinded. The protocol was approved by the Institutional Review Board of the Johns Hopkins Hospital, and informed consent was obtained from all subjects. Studies were begun between 8:00 and 10:00 AM, ≥2 h postprandially. After arrival in the laboratory, the subject rested in the supine position for ≥15 min. Brachial arterial pressure was measured until stable. Baseline measurements of HR, AGI, PWV, and supine cardiac volumes were then obtained. After completion of baseline measurements, nitroprusside or saline placebo infusion was started. On the day the subject received active drug, the dose was slowly titrated until one of the following occurred: 1) 10% reduction in mean blood pressure (MBP), 2) systolic blood pressure (SBP) of 90 mmHg, or 3) significant side effects (usually light-headedness). On the placebo day the infusion rate was also increased in a stepwise fashion for ≥20 min. After the final infusion rate was achieved, this rate was maintained constant while supine measurements of arterial stiffness and cardiac volumes were repeated. The subject was then slowly raised to the sitting position. After ≥15 min of seated rest, cardiac volumes were measured again. Cycle ergometry was then started, and cardiac volumes, HR, blood pressure, and \(V_{O2}\) were measured during each 3-min exercise stage until exhaustion. The drug infusion was stopped immediately on completion of exercise.

Carotid-Femoral PWV

Flow waves were recorded from the right common carotid artery and right femoral artery with the use of nondirectional transcutaneous Doppler flow probes (model 810-A, 10 MHz, Parks Medical Electronics, Aloha, OR), as previously described (32). Measurements were made in the postabsorptive state in a quiet, temperature-controlled room (23–24°C) after a 15-min equilibrium period before and then during drug infusion. The PWV is determined by the quotient of a distance and time measure. The distance measure is the distance between the midpoint of the manubrium (taken as a locator of the aortic arch) and the femoral pulse transducer minus the distance between the manubrium and the carotid pulse transducer. The time measure is the interval from the QRS onset to the foot of the femoral pulse wave minus the time from the QRS onset to the foot of the carotid pulse recording (3).

Noninvasive Determination of the Carotid Artery AGI

Carotid arterial pressure waveforms were obtained from the right common carotid artery by applanation tonometry with use of a pencil-sized probe over the pulsation of the artery, as previously described (12, 32). The AGI was used to quantify the augmentation of systolic pressure in central arteries due to early return of wave reflections (12, 24, 32). The early return of wave reflections causes an inflection in the ascending portion of the pressure wave of central arteries (Fig. 1). We constructed a computer algorithm using the derivatives of the pressure wave to determine the timing and amplitude of the foot, inflection, and peak of the pressure wave contour. To calculate AGI, ≥10 sinus beats were averaged, with the peak of the R wave from the simultaneously recorded ECG as a timing marker. The AGI was defined for each averaged waveform as the height from the inflection point to the peak of the pressure waveform divided by the total height from foot to the peak and expressed as a percentage (Fig. 1, inset). The use of AGI derived from noninvasively recorded pressure waveforms of the carotid artery as an index of the contribution of wave reflections to late systolic pressure augmentation in central arteries was previously validated (12). Because of technical limitations, high-quality AGI and PWV measurements can be made only in the supine position; therefore, these indexes were obtained only at supine rest, before saline placebo or nitroprusside infusion and after achievement of the final infusion rate with the subject recumbent.

Rest and Exercise Cardiac Volumes

RNVs were obtained after equilibrium of red blood cells with 99mTc (12 mCi/m\(^2\) body surface area), as previously described (9). The camera was placed in a position to best define the ventricular septum, usually the 40° left anterior oblique view, with the subject at rest in the supine position before baseline recording during the infusion of the drug, 15 min after the assumption of an upright seated position, and throughout graded, upright bicycle exercise to exhaustion. Images were acquired with a high-sensitivity parallel-hole collimator attached to a standard Anger camera interfaced with a commercial Nuclear Medicine computer (Sopha DST-NXT) system. Data were acquired on a magnetic disk (64 × 64 matrix, 1.9× zoom).

![Fig. 1. A representative carotid pulse pressure (PP) recording in an older subject before and during nitroprusside infusion. Inset: method for calculating augmentation index (AGI).](http://ajpheart.physiology.org/ by 10.2.20.33.4 on October 30, 2017)
LV volumes were determined by standard methods (20). Briefly, end-diastolic count rate was obtained from a large manually drawn region of interest and was corrected for background activity with the use of a region of interest drawn lateral and inferior to the LV in the end-systolic frame. Attenuation correction was determined individually in each subject by the use of the opposed static view to measure the attenuation distance from a chest wall marker to the count center of the LV, with the assumption that the linear attenuation coefficient was equal to that of water. A blood sample was drawn after cessation of exercise, counted with the same camera-collimator system used for the scintigraphic study, and corrected for the time delay between the scintigram and the counting of the blood sample. LV EDV was obtained from the ratio of the attenuation-corrected end-diastolic count rate from the gated cardiac images to the count rate per milliliter from the sample of venous blood drawn 5–10 min after the completion of exercise. EF was calculated, after background subtraction, by a validated, fully automated algorithm. ESV was calculated from the measured EF and EDV. LV volumes calculated by this method have been validated against invasive measurements (20).

All radionuclide-derived LV volumes were normalized to body surface area, yielding their respective indexes: EDV index (EDVI), ESV index (ESVI), SV index (SVI), and cardiac index (CI). The following blood pressure measurements were measured or derived: SBP, diastolic blood pressure (DBP), MBP [calculated as (2·SBP + DBP)/3], pulse pressure (PP), and end-systolic pressure [ESP, estimated as (2·SBP + DBP)/3] (14). Total systemic vascular resistance (TSVR) was calculated as the ratio of MBP/CI, and stroke work index (SWI) was calculated as the product of SVI and SBP.

Exercise Protocol
Seated, upright exercise was begun on an electronically braked cycle ergometer at 25 W and was increased by 25 W every 3 min until exhaustion. Pedal speed was maintained at 60 rpm throughout exercise. Radionuclide images were acquired during the last 2.5 min of each period. Brachial arterial cuff pressures were measured at the end of each exercise period, and a 12-lead ECG was recorded each minute. All participants exercised to exhaustion without cardiac symptoms or ischemic ECG changes.

On-line analysis of expired gases throughout the entire cycle exercise protocol was performed with a metabolic cart (Medical Graphics, St. Paul, MN), in which expired gases and cycle exercise protocol was performed with a metabolic cart.

Results

Baseline Characteristics and Measurement Reproducibility
Sixteen subjects (10 men and 6 women), ages 60–84 yr (mean 71 ± 7 yr), participated in the nitroprusside infusion study. Forty-one healthy, young subjects (46 men and 35 women), ages 22–39 yr (mean 32 ± 0.5 yr), served as a control group. Their anthropometric measurements are listed in Table 1. Two internal controls permitted evaluation of the reproducibility of the resting measurements; values of all variables measured before drug administration on day 1 were compared with those on the placebo day; on the placebo day, preinfusion values were compared with those after saline infusion. Worse-case examples of the reproducibility of RNV measurements on two different days were as follows: EDV₁ = 3.66 ± 0.93EDV₂ (r² = 0.78, P = 0.0001) and EF₁ = 14.6 ± 0.79EF₂ (r² = 0.77, P = 0.001). The reproducibility of cardiac volume measurements and derived parameters during maximum cycle exercise was validated previously (29).

Effects of Nitroprusside on Hemodynamics and PWV and AGI in the Supine Resting Position

By study design the nitroprusside infusion rate was titrated to achieve a target reduction in MBP of 10%, if tolerated. This was achieved with very small doses of the drug (0.3–1.0 μg·kg⁻¹·min⁻¹, mean 0.85 ± 0.10 μg/min). The effects of nitroprusside on all study parameters, measured in the supine position, are listed in Table 2. With the exceptions of CI and HR, nitroprusside effected a reduction in all measured parameters. There was a nonstatistically significant trend for HR to increase and for PP to decrease; EF significantly increased, and CI did not change. The relative changes induced by the drug in selected parameters were as follows: SBP and DBP were reduced by 12%, TSVR was reduced 8.4%, PWV was reduced 14%, and AGI was reduced by 94.4%. Thus, in this older population, a...
modest reduction in PWV by the low dose of nitroprusside employed is accompanied by an order of magnitude higher reduction in AGI. As a consequence of these changes, particularly the substantial reduction in reflected waves and AGI, the shape of the carotid pressure waveform changed significantly (Fig. 1). This was accompanied by an increased EF while EDV and ESV were reduced.

The central PP was calculated by calibrating the applanation tonometry, with the mean and diastolic pressures from the applanation tonometry waveform set equal to the mean and diastolic brachial artery measurements. The calculated central systolic pressure was 118.40 ± 4.26 and 106.37 ± 4.32 mmHg before and during infusion, respectively. The difference in the amplitude of the calculated central systolic pressure and the cuff pressure in each person varied directly with the amplitude of the cuff pressure. The calculated central PP was 40.79 ± 2.70 and 40.01 ± 3.2 mmHg before and after drug, respectively. The calculated central ESP was 104.80 ± 3.73 and 93.03 ± 3.38 mmHg before and during drug infusion, respectively. The SBP/ESVI calculated from the calibrated tonometry measurement was 5.07 ± 0.42 and 8.43 ± 0.95 before and during drug infusion, respectively. With the use of the calculated central pressure, the estimated SWI was 6,111.85 ± 343.63 and 4,971.77 ± 265.18 before and during drug infusion, respectively.

Effects of Nitroprusside on Hemodynamics at Seated Rest, During Submaximal Exercise Workloads, and at Maximum Exercise

The effect of nitroprusside on blood pressure, HR, and cardiac volumes at rest in the sitting position, during graded submaximal workloads, and at peak upright cycle exercise are shown in Figs. 2–4.

Seated upright rest. At rest in the sitting position, SBP (Fig. 2A), DBP (Fig. 2B), MBP (Fig. 2C), and TSVR (Fig. 2D) were reduced by nitroprusside, as were EDVI and ESVI (Fig. 3C); EF significantly increased (Fig. 4A), whereas HR (Fig. 3B), SVI (Fig. 2A), and CI (Fig. 3A) were not changed significantly. Thus the effect of nitroprusside in the upright position was essentially the same as in the supine position.

Seated upright exercise. In older persons the maximum exercise work rate during drug infusion was not different from that during placebo infusion (Table 3). V̇O₂ and the arteriovenous O₂ difference during graded submaximal exercise and at maximum effort did not significantly differ during control and nitroprusside infusion. At maximum effort, V̇O₂ was 1.59 ± 0.21 and 1.48 ± 0.18 l/min and the arteriovenous O₂ difference was 0.11 ± 0.2 and 0.11 ± 0.01 ml during control and nitroprusside drug infusion, respectively.

HR and arterial pressures during rest and exercise in the presence and absence of nitroprusside are depicted in Figs. 2 and 3. SBP increased progressively with exercise, but at any workload it is lower during nitroprusside infusion (Fig. 2A). DBP was also lower during nitroprusside infusion at all workloads (Fig. 2B). Interestingly, PP was not changed by the drug at seated rest or at any exercise workload (Fig. 2C). The modest acceleration of HR at seated rest persisted at common submaximal workloads (Fig. 3B), and at maximum exercise a small (5 beats/min) but statistically significant drug-induced reduction in HR was observed.

CI increased progressively during submaximal exercise, but in a similar fashion during placebo and nitroprusside infusion (Fig. 3A). The maximum CI in the presence of the drug was slightly, but significantly (P < 0.04), reduced compared with placebo because of the trend for a smaller SVI and a slightly lower HR at any workload (Fig. 2C). The modest acceleration of HR at seated rest persisted at common submaximal workloads and at maximum effort (Fig. 2D). MBP during drug infusion was lower than during placebo infusion at submaximal work rates and at maximum effort (not shown).

EDVI during nitroprusside infusion (Fig. 3C) remained lower across all exercise workloads and at maximum effort; this reduction in EDVI was paralleled by a reduction in ESVI. The change in the LV ESVI from rest to maximum exercise, i.e., the ESVI “reserve capacity,” correlated with the change in EDVI reserve capacity before and during drug infusion (r = 0.59, P < 0.001) such that the greater the increase in EDVI, the smaller the reduction in ESVI. As was the
case at rest, SVI during exercise was not significantly altered by the drug. Cardiac ejection phase function, as assessed by EF (Fig. 4A) and ventricular function curves (Fig. 4B), was enhanced by nitroprusside at rest and during exercise. EF increased progressively with exercise but at any workload was always higher with nitroprusside (Fig. 4A). Ventricular function, characterized as the SWI vs. EDVI relation, at rest and during exercise, shifted leftward (Fig. 4B): a given exercise stroke work during nitroprusside infusion was achieved from a smaller EDV.

Table 3 compares the cardiac function at peak exercise in older individuals in the presence and absence of nitroprusside with that of unmedicated, younger individuals. Most notably, in the absence of nitroprusside, peak exercise ESVI was higher and EF was lower in older than in younger subjects. EDVI trends higher in the older group, but this did not reach statistical significance (as it does when a larger number of older individuals are compared with younger ones) (9). These age differences in the absence of nitroprusside were abolished when older subjects exercised in the presence of the drug. However, the age-associated decrease in
peak HR, peak cardiac output, and maximum exercise capacity before drug were still present when older subjects exercised during nitroprusside infusion. Exercise SV did not differ with age in the presence or absence of nitroprusside, but during drug infusion in older subjects, a given SV was delivered from a smaller LV EDV, i.e., utilizing a greater EF. Thus nitroprusside shifts the ejection characteristics of the older heart toward those of the younger heart at all levels of effort.

**DISCUSSION**

Substantial limitations of cardiovascular reserve occur with aging even in healthy individuals. In rigorously screened, healthy, older vs. younger sedentary individuals, a reduction in aerobic work capacity during maximal upright cycle exercise is accompanied by LV dilatation at end diastole and a reduction in maxi-
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In the central arteries and is responsible for the late
wave reflections further increases systolic pressure
in the central arteries and is responsible for the late
systolic pressure peak observed in the central pressure
waves of older but not younger individuals (Fig. 1).
Dilatation of conduit arteries with advancing age also
imposes an age-associated increase in the inertance
component of vascular afterload. In addition to these
increased vascular components of afterload, the in-
creased LV size at end diastole, attributable in part to
a longer LV diastolic filling period accompanying a
reduced HR (10) and throughout the cardiac cycle, in
older individuals during exercise increases the cardiac
component of LV afterload in older individuals. Reduc-
ting total LV load, i.e., cardiac and vascular components,
therefore, might be expected to facilitate ventricular
erection and improve cardiac function in older individu-
als during exercise.

Vascular stiffness and, in particular, early wave
reflection can be dramatically reduced by vasodilators
(6, 8, 13, 19, 33). To assess the effect of unloading the
older heart, we infused sodium nitroprusside, a bal-
canced vasodilator, at a rate sufficient to lower MBP by
~10% in healthy, older, sedentary community-dwelling
subjects. As shown in the supine position (Table 2), this
intervention significantly reduced systemic vascular
resistance, the AGI and PWV indexes of pulsatile load,
and EDVI and ESVI and increased the LV EF. Similar
drug effects on cardiac volumes (Fig. 3) and EF (Fig.
4A) occurred at rest in the upright position. In older
patients with dilated cardiomyopathy, a reduction in
PWV similar in magnitude to that in the present study
was observed during low-dose nitroprusside infusion
(6). The reduction in PWV in that and in the present
study is probably related to a reduction in arterial
stiffness and pressure, inasmuch as PWV is known to
be pressure dependent (1, 5, 6). However, the relation-
ship between blood pressure and PWV, albeit linear, is
steeper in older than in younger individuals (6). Thus,
for the same reduction in blood pressure, the potential
benefits of pulsatile load reduction are greater in older
individuals (6). The most striking effect of nitroprus-
side was on AGI, which was reduced by 94%. Thus, at
supine rest, a modest pharmacological vasodilatation
in healthy older individuals markedly attenuates the
age-associated increase in pulsatile arterial load and
reduces heart size throughout the cardiac cycle.

The present study is the first to demonstrate im-
proved exercise LV function during pharmacological
vasodilatation in healthy older adults. The drug effect
is manifested by a significant reduction in cardiac
volumes (Fig. 3), an augmentation of LVEF (Fig. 4A),
and an improvement in cardiac function depicted by a
leftward shift in the SWI vs. EDVI relation. EDVI and
ESVI, and thus heart size throughout the cardiac cycle,
were reduced during exercise (Fig. 3). However, be-
because of the approximately similar reductions in EDVI
and ESVI, SVI was not appreciably changed (Fig. 2).

Technical considerations preclude noninvasive assess-
ment of vascular stiffness indexes during exercise. If
reflected pulse waves were to reappear in the central
tissues during exercise, the systolic stress integral and
ESP would be greater than if the AGI were to remain
low. However, it is likely that a reduction in arterial

Table 3. Hemodynamic variables at maximum
exercise in older subjects in presence or absence
of nitroprusside infusion and in a younger
reference group in absence of drug

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<th>Control</th>
<th>Nitroprusside</th>
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<tr>
<td></td>
<td>Younger</td>
<td>Older</td>
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<td></td>
<td>group</td>
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<tr>
<td>MWR, W</td>
<td>153±4.3†</td>
<td>116±12.5</td>
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<tr>
<td>SBP, mmHg</td>
<td>188±3.0</td>
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<tr>
<td>DBP, mmHg</td>
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<td>MBP, mmHg</td>
<td>123.5±1.8</td>
<td>123.5±2.8</td>
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<tr>
<td>PP, mmHg</td>
<td>97.9±3.2</td>
<td>108.5±7.2</td>
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<tr>
<td>TSVR, mmHg/l</td>
<td>545±16‡</td>
<td>694±33.2</td>
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<tr>
<td>HR, beats/min</td>
<td>175±1.6†</td>
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<tr>
<td>Cl, l/min</td>
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<td>EDVI, ml/m²</td>
<td>70.4±1.5</td>
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<tr>
<td>ESVI, ml/m²</td>
<td>11.3±0.6*</td>
<td>15.3±1.4</td>
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<tr>
<td>SVI, ml/m²</td>
<td>59.3±1.3</td>
<td>60.7±2.5</td>
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<tr>
<td>EF, %</td>
<td>84.6±0.8*</td>
<td>80.6±1.3</td>
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<tr>
<td>SBP/ESVI</td>
<td>25.1±3*</td>
<td>14.5±1.5</td>
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Values are means ± SE. MWR, maximum work rate. *P < 0.05,
younger vs. older group (control); †P < 0.05, younger vs. older group
(nitroprusside); §For trend for SVI to decrease during drug infusion to reach
statistical significance at α = 0.05 and with a power of 0.80, 113 subjects
would have been required for study.
stiffness by the drug persisted during exercise for the following reasons. The magnitude of the reduction in SBP by nitroprusside throughout exercise is similar to that observed at rest. The reduction in SBP by nitroprusside is not caused by reduced LV contractility, as evidenced by higher EF and SBP/ESVI before than during drug infusion. The nonsignificant 4 ml/m² reduction in SVI by nitroprusside relative to placebo at peak exercise is identical to that seen at rest and is therefore unlikely to contribute substantially to the decline in SBP. Although the reduction in DBP during exercise by nitroprusside vs. placebo could itself contribute to a lower SBP if SV and contractility were unchanged, this reduction in DBP during exercise is virtually identical to that observed at rest. Thus, although direct proof of reduced large artery stiffness by nitroprusside during exercise is lacking, the parallel changes in the measured determinants of SBP at rest and at peak exercise during drug infusion strongly suggest that arterial stiffness was reduced to a similar extent during exercise by the drug.

Whereas in the absence of drug, older individuals maintain the same peak exercise SVI as their younger counterparts, but with a larger ESVI and reduced EF, nitroprusside infusion permits a higher EF from a smaller EDVI, without compromising SVI or maximum exercise capacity. In fact, the LV EF and ESVI at maximum exercise in older persons during drug infusion do not differ from those in a young, unmedicated BLSA cohort (Table 3) (9, 30). The finding that EF remains higher and the ESVI remains lower during drug infusion than on placebo at maximum exercise, despite the absence of a change in TSVR (Fig. 2D), points to a greater role of pulsatile afterload or preload reduction in the improvement of EF and ESVI parameters. The reduction in EDVI induced by nitroprusside appears, in part, to be attributable to a reduction in venous return, because a pure dilatation of the arterial system is not likely to produce a significant change in cardiac chamber filling, since the total volume that can be displaced into the arterial capacitance per se is rather small. It is certainly possible that the reduction in EDVI effected by nitroprusside was due, in part, to the known increase in venous capacitance induced by nitroprusside (21). The fact that a significant decline in EDVI occurred at higher levels of exercise during drug infusion, when TSVR was similar to placebo levels, also suggests a direct drug effect on preload.

As shown in Fig. 4B, nitroprusside caused a leftward shift in the SWI-EDV relation; thus any given SWI was achieved from a smaller EDVI. Additionally, the estimated ESP, which correlates highly with that measured directly (14) and reflects the lumped vascular elastance at end systole, was reduced at any given ESVI. Although it is thus plausible to assume that LV wall stress was reduced by the drug, the latter and some of its determinants, e.g., LV wall thickness and the time course of pressure development, were not measured in the present study. It might be argued that the overall augmentation of LV pump performance during exercise with nitroprusside infusion is attributable, in part, to a sympathetic reflex-mediated increase in LV contractility associated with the reduction in arterial pressure. However, if it were of a substantial magnitude, a reflex increase in LV function would be accompanied by a significant increase in HR, but only a minimal increase in HR occurred in the presence of drug at upright rest or during low-level exercise, and even this minimal increase was blunted as exercise workload increased. In fact, the HR at maximum exercise was less in the presence of nitroprusside than with placebo. Additionally, any difference in reflex sympathetic activity due to the arterial pressure reduction elicited by the drug at rest would be expected to lessen as the exercise workload progresses, because dynamic exercise per se elicits sympathetic and other reflexes to augment cardiovascular function. Additionally, reduced ESVI and increased EF observed at rest during nitroprusside infusion persisted throughout exercise, even at the maximum workload. Such an effect cannot be attributable to reflex cardiac stimulation caused by the drug. Finally, the slope of the change in EDV relative to ESV from rest to peak exercise, which shifts with increases in LV contractility during exercise (28), was unchanged by nitroprusside.

Despite the reduction in cardiac size and improvement in LV function in older persons during nitroprusside infusion, maximum work capacity during this type of cycle exercise did not appreciably change and remained less than in their unmedicated younger counterparts (Table 3). The lack of an effect of nitroprusside to increase maximum work capacity in these older subjects is due to an inability to increase the maximum cardiac output, i.e., SV was not augmented by the drug and the maximum HR was slightly reduced. An increase in SV was likely precluded by the concomitant drug-induced reduction in the preload, manifest by a reduction in EDVI. Thus it might be postulated that reducing vascular afterload during exercise, in the absence of a reduction in preload, would permit an increase in SV in older subjects. Indeed, it has recently been reported that acute lowering of arterial pressure and vascular afterload by verapamil permits older subjects to augment SV during exercise and to improve their exercise capacity (7).

In conclusion, significant reductions in vascular load at rest and cardiac size at rest and during exercise can be effected in healthy, older persons by a low dose of a mixed vasodilator, nitroprusside. At all exercise levels, heart size is reduced and LV EF increases to levels comparable to those in younger, unmedicated individuals. The same SVI at rest and during any level of exercise is attained by an increase in LV EF at reduced LV volume and, thus, at reduced LV wall stress and myocardial Vo₂. However, maximum cardiac output and exercise capacity are not improved. These findings likely have implications in the treatment of older individuals whose exercise capacity is limited because of symptoms associated with normal or abnormal increases in LV wall stress with activity.
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