Abnormalities in arterial-ventricular coupling in older healthy persons are attenuated by sodium nitroprusside

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Chantler PD, Nussbacher A, Gerstenblith G, Schulman SP, Becker LC, Ferrucci L, Fleg JL, Lakatta EG, Najjar SS. Abnormalities in arterial-ventricular coupling in older healthy persons are attenuated by sodium nitroprusside. Am J Physiol Heart Circ Physiol 300: H1914–H1922, 2011. First published March 4, 2011; doi:10.1152/ajpheart.01048.2010.—The coupling between arterial elastance (EA; net afterload) and left ventricular elastance (E LV; pump performance), known as E A/E LV, is a key determinant of cardiovascular performance and shifts during exercise due to a greater increase in E LV versus E A. This normal exercise-induced reduction in E A/E LV decreases with advancing age. We hypothesized that sodium nitroprusside (SNP) can acutely ameliorate the age-associated deficits in E A/E LV. At rest and during graded exercise to exhaustion, E A was characterized as end-systolic pressure/stroke volume and E LV as end-systolic pressure/end-systolic volume. Resting E A/E LV did not differ between old (70 ± 8 yr, n = 15) and young (30 ± 5 yr, n = 17) subjects because of a tandem increase in E A and E LV in older subjects. During peak exercise, a blunted increase in E LV in old (7.8 ± 3.1 mmHg/ml) versus young (11.4 ± 6.5 mmHg/ml) subjects blunted the normal exercise-induced decline in E A/E LV in old (0.25 ± 0.11) versus young (0.16 ± 0.05) subjects. SNP administration to older subjects lowered resting E A/E LV by 31% via a reduction in E A (10%) and an increase in E LV (47%) and lowered peak exercise E A/E LV (36%) via an increase in E LV (68%) without a change in E A. Importantly, SNP attenuated the age-associated deficits in E A/E LV and E LV during exercise, and at peak exercise E A/E LV in older subjects on drug administration did not differ from young subjects without drug administration. In conclusion, some age-associated deficiencies in E A/E LV, E A, and E LV, in older subjects can be acutely abolished by SNP infusion. This is relevant to common conditions in older subjects associated with a significant impairment of exercise performance such as frailty or heart failure with preserved ejection fraction.

AGING OF THE CARDIOVASCULAR (CV) system is characterized by several structural and functional alterations in both the arteries and the heart (15–16), including increased central arterial wall thickness and stiffness, endothelial dysfunction, increased left ventricular (LV) wall thickness, and decreased early LV diastolic filling. Some age-associated CV alterations are not present at rest and can only be observed in response to a stressful stimulus. For example, LV ejection fraction (EF) does not differ between young and old individuals at rest. However, during aerobic exercise, the ability to increase EF is blunted with advancing age, such that at peak exercise there is a significant age-associated deficit in EF (9).

Although EF is usually considered an index of LV systolic function, it is governed not only by properties of the LV but also by properties of the arterial system and the interaction between the LV and arterial systems (12, 41). This interaction, termed arterial-ventricular coupling, can be indexed by the ratio of effective arterial elastance (E A; a measure of the net arterial load imposed on the left ventricle) to LV end-systolic elastance (E LV; a measure of LV chamber performance) (3). In the resting state, E A/E LV is maintained within a relatively narrow range across a broad age spectrum (23, 30) and across species (19, 42), as this range is thought to represent the optimal energetic set point of the CV system (39). An examination of E A/E LV has provided useful mechanistic insights into the CV effects of aging and diseases (3). During dynamic exercise, E A/E LV declines because of a disproportionate change in E LV versus E A with a resultant increase in LV performance so as to meet the increased demand for blood flow (23). However, there is an age-associated deficit in the ability to reduce E A/E LV during exercise, largely because of a failure of older individuals to sufficiently augment E LV (23).

Sodium nitroprusside (SNP) is a clinically available agent that is primarily used in patients with congestive heart failure or with hypertensive crises. SNP is considered a balanced vasodilator because, at rest, it lowers LV preload by increasing venous capacitance (21) and it lowers arterial afterload predominantly by decreasing peripheral vascular resistance (PVR) (27). In the heart, SNP enhances LV relaxation via a cGMP-mediated pathway (36), and it can also increase contractility through a cGMP-independent pathway (43). The effects of SNP on arterial and ventricular properties have been amply documented in the resting state in both healthy subjects and in patients with heart failure (1, 22, 24, 25, 27, 28, 31). We have previously reported the effects of SNP on arterial stiffness and CV function during exercise in our older cohort (24). Our previous article (24), however, did not examine the effects of SNP on restoring arterial-ventricular coupling in healthy older persons, nor did it examine the effects of SNP on CV function, at rest or during exercise, in young persons.

The main aim of this study was to examine whether SNP restores the coupling between the LV and arterial system during graded aerobic exercise in healthy older individuals. A second aim of this study was to determine whether the response...
to SNP differs from young and older individuals at rest and at peak exercise.

METHODS

Fifteen older (age range, 60–84 yr; 9 men) and seventeen younger (age range, 21–38 yr; 9 men) healthy volunteers from the Baltimore Longitudinal Study of Aging participated in the study. All subjects had a resting EF ≥ 50% and were free from CV diseases as determined by a detailed history and physical examination, a normal resting and exercise electrocardiogram, and an absence of perfusion abnormality on thallium scintigraphy during treadmill stress testing in men > 40 and in women ≥ 50 yr of age. All subjects provided written informed consent to participate, and the study was approved by the Institutional Review Board. All data were collected between July 1993 and May 1995 under the supervision of the same investigators (G. Gerstenblith, L. C. Becker, and S. P. Schulman). Some of the data, exclusive of $E_A/E_{LV}$, $E_A$, and $E_{LV}$ in the older group, have been previously published (24). One older subject was excluded from the previous published article (24) since blood pressures (BPs) at maximal exercise were not available. Furthermore, only the young subjects who underwent the intervention arm of the study were included ($n = 17$).

Study Protocol

In older individuals, SNP was titrated to achieve an approximate 10% reduction in mean arterial pressure (MAP) for subjects in the supine position unless systolic BP (SBP) dropped below 90 mmHg or significant side effects were reported (24). MAP was calculated as 2/3 × diastolic BP + 1/3 × SBP. Because a prior study has shown that resting arterial responses to a given SNP dose were less in young versus older subjects (1), we stratified our young healthy cohort into two groups, each group receiving a different SNP dose. In young group 1 (YG-1; $n = 9$, 5 men), SNP was administered at the same aggregate average dose of SNP that was administered to the older individuals; in young group 2 (YG-2; $n = 8$, 7 men), SNP was administered at a dose to achieve an approximate 10% reduction in MAP following the same procedure as the older group. After the final infusion rate of the study medication was achieved, subjects were slowly raised to the upright seated position. After at least 15 min of seated rest, they underwent an assessment of arterial and ventricular properties in the resting state and during each 3-min stage of a graded symptom-limited seated upright cycle exercise test, starting at a work rate of 25 W and increasing by 25 W during successive stages until exhaustion. These tests were performed on two separate visits at least 48 h apart. On one occasion the subjects were administered SNP, and on the other they received saline placebo. The order in which SNP or placebo was administered was randomized. Because of the obvious physical effects of SNP, neither the subject nor the investigators could be blinded to the drug infusion. However, the off-line analysis of the data was performed in a blinded fashion.

Noninvasive Determination of LV and Arterial Variables

LV end-diastolic volume (EDV) and end-systolic volume (ESV) were noninvasively determined at rest and during each stage of exercise with radionuclide ventriculography as previously described (33). Stroke volume (SV) was calculated as EDV – ESV, and EF was calculated as SV/EDV. $E_A$ was calculated as end-systolic pressure (ESP)/SV, where ESP is approximated as 0.9 × brachial SBP (13). Measured or derived determinants of $E_A$ include the following: heart rate (HR); PVR (PVR = MAP/C0 × 80), where CO is cardiac output; and total arterial compliance (TAC = SV/pulse pressure) (5, 29). Additional important determinants of CV performance are as follows: $E_{LV}$ ($E_{LV} = ESP/ESV$), a measure of LV chamber performance (41); arterial-ventricular coupling ratio ($E_A/E_{LV} = ESV/SV$) (41); CO = SV × HR; stroke work (SW = SV × ESP); and pressure volume area (PVA), an index of myocardial oxygen consumption (39) [$PVA = SW + [(ESP × (ESV – Vo))/2]$, where Vo is the volume-axis intercept of the ESP volume relationship and is assumed to be negligible compared with ESV (7). LV work efficiency (WE) was defined as the ratio of the SW performed and the total mechanical energy required to perform this work (WE = SW/PVA) (40). Peak aerobic capacity was measured using the Medgraphics CPX-D system (Medgraphics, St. Paul, MN).

Statistical Analysis

The anthropomorphic characteristics of the older and combined younger groups were compared with independent sample t-tests. The CV parameters measured during SNP administration in the older group were compared with the placebo trial of the combined younger groups using an independent t-test. The effects of SNP versus placebo within each group (older, YG-1, and YG-2) were compared with paired t-tests. The effects of drug, group, and drug/group interactions on the CV parameters at rest and at peak exercise were evaluated with two- or three-way repeated-measures ANOVA. All analyses were performed with the statistical package SPSS version 17 (SPSS, Chicago, IL). Values shown in the tables represent means ± SD. A $P < 0.05$ was defined as significant.

Several of the CV parameters that were evaluated can be influenced by body size. Thus all the aforementioned analyses were repeated after the arterial and cardiac variables were scaled to body surface area either ratiometrically or allometrically as previously described (2). The results of the analyses were essentially unchanged using either method of scaling these data to body size. Therefore, only the nonscaled values of the parameters are reported.

RESULTS

Age and anthropometric characteristics of the older and younger groups are shown in Table 1. The younger and older subjects were similar in body size and body mass index.

Effects of Age on Arterial-Ventricular Coupling

At rest. In the absence of SNP, $E_A/E_{LV}$ did not differ between young and old subjects, but both $E_A$ and $E_{LV}$ were higher in old (11 and 15%, respectively) versus young (Fig. 1). $E_A$ was higher in the old group, in part, because of an increased PVR (12%) and, in part, to a lower TAC (13%), since HR did not differ between groups (Fig. 2).

During exercise. Unlike at rest, age-associated differences in $E_A/E_{LV}$ were evident during exercise. From rest to peak exercise, old subjects manifest a blunted reduction in $E_A/E_{LV}$, resulting in a 36% higher $E_A/E_{LV}$ in old versus young at peak exercise (Fig. 1A). However, the higher $E_A$ noted at rest in the old versus young group was no longer evident at peak exercise. As for $E_{LV}$, despite a similar initial increase in the old and young groups, from 50 W of exercise, the old group had a

Table 1. Demographic and anthropometric characteristics of the study cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Older Group</th>
<th>Younger Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>70 ± 7.5</td>
<td>30 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>9 (60)</td>
<td>9 (53)</td>
<td>0.48</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171 ± 12.0</td>
<td>172 ± 10.1</td>
<td>0.85</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.0 ± 16.9</td>
<td>76.3 ± 13.3</td>
<td>0.90</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.1 ± 3.3</td>
<td>26.0 ± 4.8</td>
<td>0.96</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.89 ± 0.19</td>
<td>1.88 ± 0.19</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Values are means ± SD (or %); n, number of subjects.
reduction in $E_A$ (27%), which in turn contributed to the reduction in $E_{LV}$ (Fig. 1). But, importantly, between 50 W and peak exercise, the rate of increase in $E_A$ on drug in the older subjects was greater than that on placebo, driving $E_A$ to reach the same level noted at peak exercise while on placebo. A further examination of the determinants of $E_A$ revealed that the exercise-induced increase in $HR$ and reduction in $TAC$ on placebo were not influenced by SNP at any exercise intensity (Fig. 2). Thus the effect of SNP to reduce $E_A$ at rest and during moderate exercise was solely due to a reduction in PVR, and the loss of this SNP effect to lower $E_A$ from 50 W to peak exercise is attributable to the inability of the SNP to lower PVR versus placebo at more intense exercise levels.

As was the case for $E_A$, the effect of SNP on $E_{LV}$ at rest persisted throughout submaximal exercise (Fig. 1B). Importantly, in contrast to its effect on $E_A$, SNP increased $E_{LV}$ to a greater extent than placebo from 50 W to peak exercise. Thus peak $E_{LV}$ was greater (68%) on drug versus placebo in older subjects. This was accompanied by reductions in SW and PVA and an improved WE (93 vs. 89%) (Table 2). Most importantly, SNP infusion in the older subjects was sufficient to restore peak exercise $E_A/E_{LV}$ and $E_{LV}$ to levels in young subjects (Fig. 1).

Effects of SNP Infusion in Young Subjects

At rest. In the younger subjects (YG-1), infusion of the same SNP dose administered to the older group (0.90 ± 0.17 μg·kg⁻¹·min⁻¹) reduced $E_A/E_{LV}$, PVR, TAC, SBP, MAP, ESV, and EDV and increased HR and CO (Fig. 3). However, SNP infusion in YG-1 did not alter $E_A$ because the reduction in PVR was offset by an increase in HR. SNP infusion in YG-1 increased $E_{LV}$, which accounted for the SNP-induced reduction in $E_A/E_{LV}$.

Infusion of an SNP dose (2.92 ± 0.97 μg·kg⁻¹·min⁻¹) in younger subjects (YG-2) to lower resting MAP to a similar extent as in the older group (by ~10%) reduced $E_A/E_{LV}$, PVR, TAC, SBP, MAP, ESV, and EDV and increased HR and CO (Fig. 3). However, unlike YG-1, SNP reduced $E_A$ mainly because of a greater reduction in PVR than the accompanying increase in HR in YG-2. Furthermore, in YG-2, the SNP-induced reduction in $E_A/E_{LV}$ was greater than identified in YG-1 (43 vs. 27%) ($P = 0.019$ for the interaction term between drug and YG-2) and was attributed to the greater increase in $E_{LV}$ (63 vs. 27%) ($P = 0.04$ for the interaction term between drug and young group) in YG-2 versus YG-1 during SNP infusion.

At peak exercise. In YG-1, SNP reduced $E_A/E_{LV}$ at peak exercise; while no change in $E_A$ was noted (Fig. 5), $E_{LV}$ on drug was higher versus placebo because SNP reduced ESV. Peak exercise BP, EDV, HR, PVR, and TAC during SNP infusion did not differ from placebo in YG-1 (Fig. 4).

In YG-2, SNP also reduced peak exercise $E_A/E_{LV}$ and increased $E_{LV}$ as in YG-1, although the reduction in $E_A/E_{LV}$ (36 vs. 22%) and increase in $E_{LV}$ (59 vs. 43%) tended to be greater in YG-2 versus YG-1 (Fig. 4). Furthermore, YG-2 also tended to have a greater reduction in EDV (12 vs. 7%), ESV (43 vs. 29%), and CO (11 vs. 5%) versus YG-1. Finally, a
reduction in peak oxygen consumption was only identified in YG-2 during SNP versus placebo infusion (14 vs. +1%).

Age Differences in the Response to SNP

At rest. In the older group and YG-1, SNP infusion exerted similar effects on $E_A/E_{LV}$, PVR, TAC, and SBP. However, a greater reduction in $E_A$ was evident after SNP infusion in the older versus YG-1 (similar SNP dose to the old) group and can be attributed to the greater effects of SNP to reduce BP in the older versus young group and the lack of drug effect on HR in the older subjects. Indeed, this increase in HR in YG-1 also induced a greater increase in CO (20 vs. 5%) compared with the older group. In contrast, the effect of SNP on $E_{LV}$ at rest was greater in the older group than in YG-1 (Fig. 3). In the older group and YG-2, SNP infusion effected similar responses in $E_A/E_{LV}$, $E_A$, PVR, TAC, BP, and cardiac volumes (Fig. 4), although there was a slightly larger increase in $E_{LV}$ (63 vs. 27%) in YG-2 than in the older group. Furthermore, unlike in the older group, SNP also induced a greater increase in CO in YG-2 (22 vs. 5%).

At peak exercise. In both the YG-1 and the older group, the effects of SNP were similar on $E_A/E_{LV}$, $E_A$, $E_{LV}$, PVR, TAC, HR, CO, and ESV at peak exercise (Fig. 4). However, unlike in the older group, SNP did not lower EDV at peak exercise in YG-1.

In both the YG-2 and the older group, SNP had similar effects on $E_A/E_{LV}$, $E_A$, $E_{LV}$, PVR, TAC, HR, EDV, and ESV. A reduction in peak CO, however, occurred in YG-2 but not in the older group. Furthermore, unlike in the older cohort, SNP infusion in YG-2 reduced peak oxygen consumption (14 vs. 6%).

DISCUSSION

To our knowledge, this is the first study to examine the effects of SNP on $E_A/E_{LV}$ and its components, both at rest and
during exercise, in both young and older subjects, and whether SNP infusion in older subjects can normalize the age-associated changes in $E_A/E_LV$.

The interaction, or the coupling, between the LV and arterial system is an important and largely underappreciated determinant of cardiac performance and energetics. The principal insight that $E_A/E_LV$ provides is a determination as to whether changes in CV performance with drugs and/or exercise are due to alterations in arterial properties, LV properties, or both. An examination of $E_A/E_LV$ has provided mechanistic insights into the age-associated decline in LV performance during exercise (23). In the present study, SNP unloaded the aged heart and lowered $E_A$ at rest to the same level noted in the young individuals without drug administration. $E_A$ is a steady-state arterial parameter that is derived from the three-element Windkessel model and integrates the overall effects of peripheral arterial resistance, TAC, characteristic impedance, and systolic and diastolic time intervals (i.e., cardiac cycle) (41). In addition, the combined effects of SNP to lower EDV, ESV and BP, and PVR at rest resulted in a marked increase in $E_LV$ in the older individuals at rest. The increase in $E_LV$, in turn, resulted in a reduction in $E_A/E_LV$ and an improvement in LV WE.

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Table 2. The effects of SNP versus placebo on cardiac energetics at seated rest and at peak exercise

<table>
<thead>
<tr>
<th></th>
<th>Stroke Work, mmHg/ml</th>
<th>Pressure Volume Area, mmHg·ml</th>
<th>Work Efficiency</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Peak exercise</td>
<td>Rest</td>
</tr>
<tr>
<td>Older group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>10,120±1,974</td>
<td>19,331±4,066</td>
<td>12,614±2,163</td>
</tr>
<tr>
<td>SNP</td>
<td>8,418±1,948**</td>
<td>9,111±2,244**</td>
<td>9,829±2,159***</td>
</tr>
<tr>
<td>YG-1 Placebo</td>
<td>10,620±3,086</td>
<td>22,132±7,256</td>
<td>11,072±3,402</td>
</tr>
<tr>
<td>SNP</td>
<td>9,546±2,230</td>
<td>10,985±2,277</td>
<td>11,183±2,451*</td>
</tr>
<tr>
<td>YG-2 Placebo</td>
<td>8,121±1,833</td>
<td>17,617±3,971</td>
<td>10,187±2,225</td>
</tr>
<tr>
<td>SNP</td>
<td>7,431±1,369*</td>
<td>14,816±3,087*</td>
<td>8,465±1,405*</td>
</tr>
</tbody>
</table>

Values are means ± SD. SNP, sodium nitroprusside; YG-1, young group 1; YG-2, young group 2. *P < 0.05, **P < 0.01, and ***P < 0.001 compared with placebo within the same group.

Fig. 3. The relative difference between placebo and SNP infusion in younger and older individuals at rest. A: $E_A$, LV $E_LV$, and $E_A/E_LV$. B: EDV, SV, and ESV. C: systolic (SBP), mean (MAP), and pulse (PP) pressures. D: PVR, TAC, and HR in the older and younger groups at rest. *P < 0.05 SNP vs. placebo within the same group; †P ≤ 0.08 and ††P < 0.05 for interaction between drug (SNP vs. placebo) and group [old vs. young group 1 (YG-1) or old vs. young group 2 (YG-2)]; P < 0.07 and ##P < 0.05 for interaction between drug (SNP vs. placebo) and group (YG-1 vs. YG-2).
At rest, in the old heart, CV performance was improved through reductions in arterial afterload and LV wall stress and an augmentation in LV contractility.

During exercise, $E_A/E_{LV}$ decreases (23) largely through an increase in $E_{LV}$. We have previously shown that the decrease in $E_A/E_{LV}$ during exercise is blunted in older versus younger healthy individuals (23). This limited decrease in $E_A/E_{LV}$ during exercise was also evident in this study and was due to a blunted increase in $E_{LV}$. However, SNP augmented the change in $E_A/E_{LV}$ and $E_{LV}$ in the older group. The lowering of $E_A/E_{LV}$ and augmentation of $E_{LV}$ after SNP infusion at rest essentially shifted the operating point for $E_A/E_{LV}$ down and $E_{LV}$ up during exercise (Fig. 1). Thus, from 25 W of exercise, the change in $E_A/E_{LV}$ and $E_{LV}$ on drug tracks the change in $E_A/E_{LV}$ and $E_{LV}$ on placebo, albeit at a different operating point (Fig. 1). Importantly, the effects of SNP on $E_A/E_{LV}$ and $E_{LV}$ restored peak exercise values to levels noted in the younger individuals.

Although SNP lowered the operating point of $E_A$ at rest and during submaximal exercise, the effects of SNP on $E_A$ waned at higher levels of exercise, such that peak $E_A$ was similar during both SNP and placebo infusions. SNP did not alter compliance but lowered resting PVR, which remained reduced during submaximal exercise. Similar to peak exercise $E_A$, SNP had no effect on PVR at peak exercise. A shift in the PVR curve was evident at rest and persisted up to 50 W of exercise; however, no further reductions in PVR were noted at higher workloads (Fig. 3), suggesting that the physiological responses to peak exercise, rather than the responses to SNP, govern these variables. Thus, at peak exercise in the old heart, SNP was able to augment the CV performance predominately through an improvement in LV contractility and a reduction in LV wall stress. Nitric oxide donors, within a specific concentration range, have been previously shown to augment LV contractility (43).

Effect of SNP at Rest and during Exercise in Young Subjects

At rest, a multitude of studies have examined the effects of SNP on the CV system, with most conducted in the resting state and in patients with CV diseases (1, 22, 25, 27–28). Another novel aspect of this study examined the effects of SNP both at rest and peak exercise in younger individuals at two different SNP infusion rates: dose 1 was a similar dose given to the older individuals (YG-1); dose 2 was administered to decrease MAP by ≈10% (YG-2).

At rest, SNP lowered $E_A/E_{LV}$ in both YG-1 and YG-2, although this reduction was more pronounced in YG-2 versus YG-1 and can be attributed to the larger SNP dose in YG-2, exerting a marked increase in $E_{LV}$ in YG-2 versus YG-1. The greater increase in $E_{LV}$ can be attributed to a greater reduction in ESV in YG-2 versus YG-1 (45 vs. 28%). $E_{LV}$, as characterized in the present study, is a measure of LV pump performance (32) and reflects the combined effects of SNP on LV preload (lowering EDV), LV wall stress (lowering both EDV and ESV), and vascular afterload. However, $E_{LV}$ is also highly dependent on chamber geometry (3). Although we did not assess LV wall thickness or wall-to-cavity ratio in this study, it...
is highly unlikely that an infusion of SNP would acutely alter LV remodeling pattern in a given individual. SNP may also affect intrinsic cardiac muscle performance, as low doses of SNP in animal models increase cardiac muscle performance through cGMP-independent mechanisms (43). Of note, studies in isolated cardiac muscle have shown that cardiac muscle performance or “contractility” is modulated by muscle length (preload or stretch and afterload) (14). Thus the effects of SNP on LV contractility, preload and afterload, in the intact organism are essentially intertwined.

SNP also lowered $E_A$ in YG-2, but not significantly in YG-1. HR is another important determinant of $E_A$ (3–4, 35), and in YG-1 the reduction in PVR was accompanied by a similar increase in HR; thus no change in $E_A$ was found, whereas in YG-2 the reduction in PVR exceeds the increase in HR leading to a reduced $E_A$. In young subjects, the increase in HR during SNP is a normal baroreceptor reflex response to a fall in arterial pressure.

At peak exercise. SNP lowered $E_A/E_{LV}$ at peak exercise in the young subjects because of a higher $E_{LV}$ at submaximal and peak exercise workloads during SNP versus placebo administration, although once again the changes in $E_A/E_{LV}$ and $E_{LV}$ tended to be greater in the higher SNP-dose group (i.e., YG-2 vs. YG-1). The augmentation of $E_{LV}$ in the younger groups is mainly related to a reduction in LV wall stress resulting in an augmentation of LV ejection, with YG-2 demonstrating a greater reduction in both EDV and ESV.

Unlike its effects at rest, compared with placebo, SNP did not alter peak arterial function, namely, $E_A$, PVR, and TAC in either young group, although a reduction in SBP and MAP was noted in YG-2. Once again, this suggests that the physiological responses to peak exercise, rather than the responses to SNP, govern these variables. Thus, at peak exercise in the young heart, SNP augmented the CV performance predominantly through an improvement in LV contractility and a reduction in LV wall stress.

Age-Associated Differences in the Response of SNP

At rest. A major difference noted in the SNP response between young and old was that younger subjects required 1.7 higher SNP dose compared with older subjects to reduce MAP at rest by $\approx 10\%$. This smaller SNP dose requirement in the old may be due to the increased arterial stiffness. Increased stiffness of the carotid and aorta may reduce the arterial stretch (stimulus) applied to the baroreceptors during a given change in BP, resulting in a blunted baroreflex-mediated CV response in the older group. Indeed, autonomic and baroreflex dysfunction are often present in older healthy subjects (10, 34), resulting in a greater BP sensitivity to diuretic therapy (11, 44) and volume changes (6). This reflex pressure control is amplified in older subjects with increased arterial and LV stiffness (6). Furthermore, this impaired baroreflex response in the older group likely accounts for the lack of HR response in the older compared with both younger groups (10, 38). This is consistent with Simon et al. (37) who also found that SNP increased HR in younger, but not older, men with systolic hypertension.

SNP was found to lower $E_A$ at rest in the older subjects but not in the YG-1 because of the modest effects of SNP on lowering PVR in the absence of a change in TAC in older subjects. Whereas in hypertensive subjects, Simon et al. (37) showed that SNP increased total systemic arterial compliance. Using more direct measures of total systemic compliance in heart failure, some (17, 45), but not all (27, 37), studies have shown that SNP does not alter aortic input impedance. We have previously reported that in the supine position, SNP did not significantly influence carotid-femoral pulse wave velocity in older persons (24), which is considered the “gold standard” noninvasive measure of arterial stiffness (18). The administration of a higher SNP dose to young subjects (YG-2) did lower $E_A$, albeit through a greater reduction in PVR versus the increase in HR during SNP versus placebo.

Although SNP exerted modest effects on $E_{LV}$ in all groups, the increase in $E_{LV}$ in older subjects was greater than in YG-1, but less than in YG-2, and can be attributed to the greater effects of reducing LV wall stress and arterial afterload in the older group versus YG-1 and in reducing LV wall stress in YG-2 versus the older group.

At peak exercise. The mechanisms by which SNP improved peak exercise $E_A/E_{LV}$ were similar in the older group and YG-2. Although SNP infusion in YG-1 reduced $E_A/E_{LV}$ and augmented $E_{LV}$ at peak exercise, the magnitude of these changes was less in YG-1 compared with the older group and YG-2. This dampened response is, in part, due to a lack of change in peak BP in YG-1. In both older subjects and YG-2, the magnitude of the reduction in SBP and MAP during SNP infusion were similar at rest and peak exercise, suggesting a reduction in peak exercise arterial load despite the absence of a change in PVR. Furthermore, unlike YG-1, both older subjects and YG-2 noted a significant reduction in peak EDV. Our data suggest that in both older subjects and YG-2, arterial-ventricular interactions were enhanced through a reduction in total LV load to facilitate LV ejection.

Physiological Significance

The physiological implications of the present study relate to the improved arterial-ventricular coupling in older subjects. Our data highlight that in older subjects, SNP can lower arterial afterload and LV wall stress and enhance LV contractility, which restores resting and exercise arterial-ventricular interactions back to levels noted in younger subjects without drug administration. These beneficial changes would help to normalize the excessive changes in pressure that are noted during the transfer of blood from the LV to the periphery in older subjects with increased arterial stiffness. Indeed, SNP infusion in older subjects reduced myocardial oxygen demand and improved LV WE, both at rest and peak exercise.

The infusion of SNP in younger subjects in our study also provides some mechanistic insights into the underlying CV deficits in older subjects. Younger subjects required a higher SNP dose to achieve a similar reduction in MAP as the older group. This, in turn, increased HR at rest in the younger but not in the older subjects. These findings may explain why older subjects are more sensitive to pressure changes to diuretic therapy and volume changes. Thus interventions aimed at improving baroreceptor reflex responses in the older subjects may help to further improve CV performance.

Despite these improvements in arterial-ventricular coupling and cardiac energetics, the acute effects of SNP did not improve aerobic capacity in the older or younger groups and actually reduced aerobic capacity in YG-2. This would suggest
that the administration of a high concentration of SNP in young healthy subjects without arterial stiffening may have negative effects on aerobic capacity. Indeed, excessive vasodilation in congestive heart failure patients limits CO through peripheral pooling of blood. However, in older subjects, a reduction in total LV load through SNP likely facilitated LV ejection and improved cardiac function and energetics without negatively impacting on aerobic capacity. Additional studies are also needed to evaluate whether chronic, as opposed to acute, interventions that produce salutary hemodynamic and energetic effects similar to those of SNP can improve cardiopulmonary exercise capacity.

**Limitations**

The noninvasive techniques for estimation of $E_A/E_LV$ and its components have several limitations that have been extensively reviewed (3). This study was conducted before devices that allow convenient noninvasive estimations of central arterial pressures during exercise became available. The present study relied on brachial rather than central pressures measured at rest. Brachial pressures overestimate central pressures. ESP has been previously estimated as 0.9 (13) or 0.75 (26) × brachial SBP measured at rest. In the present study, using either value to estimate central SBP yielded similar results with respect to the effects of age, SNP infusion, and their interaction (although we only show data for ESP estimated from 0.9 × brachial SBP). Furthermore, it should be noted that this limitation does not influence the $E_A/E_LV$ values, as the coupling ratio is independent of ESP (because ESP is in both the numerator and the denominator and therefore cancels out). We estimated arterial compliance as the ratio of SV to pulse pressure, which as with most noninvasive measures of TAC, has several limitations (8, 20), particularly since central pulse pressure was not directly assessed in our study. Finally, because of the small number of women in each group, we were unable to examine whether there is a sex difference in the CV response to SNP. This would be an important future question to address.

**Conclusion**

We showed that the age-associated differences in $E_A$, $E_LV$, and in $E_A/E_LV$ at rest and exercise during placebo infusion were attenuated by the administration of SNP. These results provide further evidence that an evaluation of arterial-ventricular coupling and its components can provide useful mechanistic insights into the relative contributions of the arterial and LV properties to pharmacological-induced alterations in CV performance at rest and during exercise. Our findings provide “proof of principle” that at least some of the age-associated deficits in CV performance during exercise are reversible. Our findings should serve as an impetus for exploration or development of interventions that can be more readily administered than SNP and that can be tested in common conditions in older subjects associated with significant impairment of exercise performance such as frailty or heart failure with preserved EF.

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**DISCLOSURES**

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**REFERENCES**


