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Coupled Systolic-Ventricular and Vascular Stiffening With Age

Implications for Pressure Regulation and Cardiac Reserve in the Elderly

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Objectives. **We tested the hypothesis that age-related arterial stiffening is matched by ventricular systolic stiffening, and that both enhance systolic pressure sensitivity to altered cardiac preload.**

Background. **Arterial rigidity with age likely enhances blood pressure sensitivity to ventricular filling volume shifts. Tandem increases in ventricular systolic stiffness may also occur and could potentially enhance this sensitivity.**

Methods. **Invasive left ventricular pressure-volume relations were measured by conductance catheter in 57 adults aged 19 to 93 years. Patients had normal heart function and no cardiac hypertrophy and were referred for catheterization to evaluate chest pain. Twenty-eight subjects had normal coronary angiography and hemodynamics, and the remaining had either systolic hypertension or coronary artery disease without infarction. Data recorded at rest and during transient preload reduction by inferior vena caval obstruction yielded systolic and diastolic left ventricular chamber and effective arterial stiffness and pulse pressure.**

Results. **Left ventricular volumes, ejection fraction and heart rate were unaltered by age, whereas vascular load and stiffening increased ($p < 0.008$). Arterial stiffening (E_a) was matched by increased ventricular systolic stiffness (E_{es}): $E_{es} = 0.91 \cdot E_a + 0.53$, ($r = 0.50$, $p < 0.0001$), maintaining arterial-heart interaction (E_a/E_{es} ratio) age-independent. Ventricular systolic and diastolic stiffnesses correlated ($r = 0.51$, $p < 0.0001$) and increased with age ($p < 0.03$). Both ventricular and vascular stiffening significantly increased systolic pressure sensitivity to cardiac preload ($p < 0.006$).**

Conclusions. **Arterial stiffening with age is matched by ventricular systolic stiffening even without hypertrophy. The two effects contribute to elevating systolic pressure sensitivity to altered chamber filling. In addition to recognized baroreflex and autonomic dysfunction with age, combined stiffening could further enhance pressure lability with diuretics and postural shifts in the elderly.**

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Human aging is associated with increased vascular stiffening (1–4), which results in elevation of systolic blood pressure and progressive widening of the arterial pulse (5,6). Each is a recognized risk factor for cardiovascular disease and stroke (5,7–9), and likely contributes to the independent risk from aging in postinfarction patients with or without left ventricular (LV) dysfunction (10–13).

Chronic cardiac ejection into increasingly stiff arteries has been implicated in the evolution of LV diastolic dysfunction and structural remodeling of the aging myocardium (14,15). However, important changes in systolic function may also occur, such as a rise in maximal ventricular systolic stiffening, as measured by the end systolic elastance (E_{es}). End systolic elastance is a key determinant of heart-arterial interaction and normally matches with vascular load to achieve near optimal mechanical and metabolic function (16,17). It is therefore possible that elderly patients with vascular stiffening may have an altered E_{es} to maintain matching even in the absence of ventricular hypertrophy.

Combined ventricular-vascular stiffening could potentially have important consequences on the cardiac response to varied filling volume, since a stiff heart-arterial system generates more systolic pressure change for a given change in ejected stroke volume (SV) or ventricular volume. Superimposed upon abnormalities of autonomic/baroreflex regulation associated with aging (18–20), such stiffening would exacerbate blood pressure fluctuations from postural or postprandial stress and with diuretics or fluid/salt restriction (21–24). The present study tested the hypothesis that aging is associated with tandem changes in vascular and ventricular systolic stiffening in the absence of cardiac hypertrophy, and that both stiffnesses contribute to greater systolic pressure lability with cardiac preload alteration.

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Abbreviations and Acronyms

Ea = arterial elastance
E_d = end diastolic elastance
EDV = end diastolic volume
E_{es} = end systolic elastance
EF = ejection fraction
LV = left ventricular
PP = pulse pressure
PV = pressure volume
SBP_{EDV} = slope of systolic blood pressure-end diastolic volume relation
SV = stroke volume

Methods

Study population. Cardiac catheterization was performed in 57 patients (Johns Hopkins Hospital, Baltimore, Maryland [n = 36], Veterans General Hospital-Taipei, Taiwan [n = 12], Instituto di Coração, São Paolo, Brazil [n = 9]). Most subjects were referred for chest pain syndrome, with the remaining having unexplained exertional dyspnea or borderline hypertension. Patients were screened by echocardiography, left ventriculography and electrocardiography for the absence of LV and valvular dysfunction, prior myocardial infarction and chamber hypertrophy. The Institutional Review Board at each respective medical center approved the protocol, and all procedures were conducted similarly using similar equipment and analyses. At least one investigator (DAK) was involved with all studies performed at each institution.

Left ventricular ejection fraction (EF) was in a normal range in all patients (mean 64 ± 7%). Twenty-eight subjects (group 1) had no discernible coronary artery disease and were normotensive. Chronic medications in this group were a beta-blocking agent (n = 4), nifedipine (n = 1) and diltiazem (n = 1). Of these subjects, ~25% had a positive stress-thallium study, mostly on the basis of perfusion defects and often without symptoms. The remaining 29 subjects (group 2) had a history of systolic hypertension or coronary artery disease without infarction and were included to reflect the high prevalence of both conditions in the aging population. Chronic medications in this group were beta-blockers (n = 7), nifedipine (n = 4), verapamil (n = 2) and diltiazem (n = 4). All medications were withheld 24 h prior to study. Table 1 provides clinical characteristics of the study subjects (40 men, 17 women, aged 19 to 93 years) in the two groups. The groups were comparable except for a greater proportion of men, slower heart rate and very slightly higher EF for group 2.

Procedures. Continuous LV pressure-volume (PV) data were obtained by conductance catheter method as described and validated (25,26). The catheter combines a micromanometer to measure high-fidelity cavity pressure (PC-330A; Millar, Houston, Texas) and multiple electrodes arranged 1 to 2 cm apart for generating the volume signal. The catheter was inserted retrograde across the aortic valve to the ventricular apex, and a low-amplitude, high-frequency alternating current was applied at apical and root electrodes to generate a local field (Sigma-V; Cardiodynamics, Rijnsburg, The Netherlands). Conductance between intervening electrodes was proportional to chamber blood volume. Signal calibration matched the amplitude (SV) to thermodilution-derived cardiac output divided by heart rate and end diastolic volume (EDV) to SV/EF, with EF determined by contrast ventriculography.

Pressure volume data were recorded at rest and during changes in ventricular filling induced by balloon obstruction of inferior vena caval inflow. An occlusion catheter (SP-09168; Cordis, Miami, Florida) was advanced to the right atrium and rapidly inflated with 10 to 20 ml CO_2 to impede blood return for ~10 s. Data recorded during this maneuver provided assessment of LV systolic and diastolic chamber elastance (e.g., stiffness) and the sensitivity of systolic pressure to varied chamber filling.

Data analysis. Data were digitized at 200 Hz and analyzed using custom software. Rest hemodynamics were determined from cardiac cycles just prior to vena caval obstruction. End systolic elastance was the slope of the end systolic PV relation (26) (Fig. 1A), with end systole defined as the point of maximal stiffness for each beat. End diastolic elastance (E_d) was assessed from the lower PV boundary using data from the mid-third of filling from the same multiple beats, and fit to a linear regression (Fig. 1A). These data also quantified the sensitivity of systolic pressure to changes in ventricular end diastolic filling volume. For each beat during preload decline, peak systolic pressure was determined and plotted against EDV for the same cycle. The linear regression slope of this relation defined the sensitivity.

Ventricular PV data also yielded assessments of arterial afterload and stiffness. Central aortic pulse pressure (PP) was estimated by the difference in the pressure at the onset of ejection to ventricular peak pressure. The latter generally overestimated arterial diastolic pressure since inertial forces

Table 1. Patient Characteristics

Variable	Group 1 (n = 28)	Group 2 (n = 29)	p
Sex (M/F)	16/12	25/5	0.029
Age (yrs)	51 ± 19	54 ± 11	0.44
Heart rate (beats/min)	81 ± 21	65 ± 12	< 0.001
Systolic pressure (mm Hg)	142 ± 19	143 ± 26	0.95
Pulse pressure (mm Hg)	57 ± 17	62 ± 16	0.40
End diastolic volume (ml)	109 ± 26	107 ± 25	0.71
End systolic volume (ml)	41 ± 13	37 ± 14	0.27
Stroke volume (ml)	68 ± 17	70 ± 13	0.70
Ejection fraction (%)	62 ± 6	66 ± 7	0.04
End systolic elastance (E_{es}) (mm Hg/ml)	2.3 ± 1.0	2.6 ± 1.2	0.60
End diastolic elastance (mm Hg/ml)	0.20 ± 0.11	0.22 ± 0.07	0.34
Arterial elastance (E_a) (mm Hg/ml)	2.2 ± 0.8	2.2 ± 0.7	0.78
Ea/Ees	1.0 ± 0.36	0.92 ± 0.36	0.39
SBP_{EDV} (mm Hg/ml)	0.88 ± 0.39	0.85 ± 0.40	0.79

SBP_{EDV} = the slope of relations between systolic pressure and left ventricular end diastolic volume.

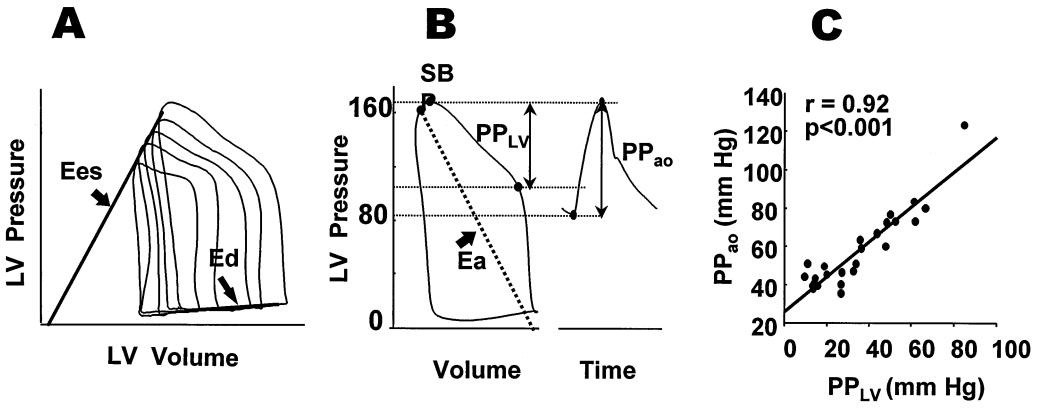

Figure 1. **(A)** Pressure volume loops used to derive ventricular end systolic chamber stiffness (E_{es}) and end diastolic chamber stiffness (E_d). Multiple cardiac cycles measured at different levels of filling are recorded. The slope of the relation linking the upper left-hand corner of these beats (end systole) is E_{es}. The slope of the relation linking late diastolic points from these beats is E_d. **(B)** Relation between aortic arterial pulse pressure and the pulse pressure estimated from the ventricular pressure volume loop. For the loop, the pulse pressure is given by the difference between the pressure at the onset of ejection and the peak pressure (PP_{LV}), and it somewhat underestimates the measured arterial pulse pressure (PP_{ao}). However, PP_{LV} is highly correlated with PP_{ao} among individuals. **(C)** shows data from a separate group of 25 patients in which both ventricular pressure volume and aortic pressure data were recorded. This regression was $PP_{ao} = 0.91 \times PP_{LV} + 26.5$, $r = 0.91$, $p < 0.0001$ (SEE = 8 mm Hg), and this relation was then used to predict PP_{ao} from PP_{LV}.

required to accelerate blood upon valve opening resulted in ongoing pressure rise despite minimal ejection, resulting in an underestimated PP (Fig. 1B). However, this was a consistent discrepancy, as shown in Figure 1C, which compares the two PP measures derived from 25 separate studies from simultaneous recordings of ventricular PV and proximal aortic pressures ($y = 0.91x + 26.5$, $r = 0.92$, $p < 0.0001$, SEE = 8). This regression relation was used to better estimate aortic PP from the loop data.

Arterial load and stiffness were also indexed by the effective arterial elastance (E_a), which is equal to the ratio of ventricular end systolic pressure divided by SV (27,28) (Fig. 1B). Since ventricular end systolic pressure varies directly with mean aortic pressure (28), E_a is similar to the product of heart rate times the ratio of mean pressure to cardiac output (27), and reflects mean and pulsatile components of arterial load (28). The ratio of E_a/E_{es} indexes ventricular-arterial matching (27,29), with a normal ratio at 0.6 to 1.2 (16,17).

Statistical analysis. Data are presented as mean ± SD. Between-group comparisons were performed using an unpaired Student *t* test or chi-square test. Age effects on ventricular-arterial hemodynamics and the influence of age and ventricular-vascular stiffening on systolic pressure and work-cardiac volume dependencies were performed using univariate and multivariate linear regression models. Covariance analysis revealed that patient group had no interaction effect, influencing neither slope nor offset for any of the regressions. Therefore, results are generally reported from analysis of the combined 57 patients.

Results

Effect of age on hemodynamics. Consistent with prior studies for ascending aortic data (30), systolic pressure increased significantly with age ($r = 0.41$, $p = 0.001$) at an average rate of 6.2 mm Hg per decade. There were no significant age-dependent changes in aortic diastolic ($p = 0.97$) or mean pressure ($p = 0.13$), heart rate ($p = 0.97$), end diastolic ($p = 0.10$) or end systolic volume ($p = 0.20$), cardiac output ($p = 0.19$) or EF ($p = 0.95$). Mean resistance tended to rise with age ($r = 0.27$, $p = 0.042$) (data not shown).

Age-dependent ventricular-vascular stiffening. Aortic PP and E_a both significantly increased with age ($p < 0.008$; Fig. 2), supporting age-dependent pulsatile load increase. As expected from its defining equation, E_a correlated with peripheral resistance and heart rate, but also varied with arterial PP ($p < 0.0001$ for each contributor by multivariate analysis, $r = 0.92$ for total regression), supporting influences of mean and pulsatile load on this parameter.

Age-related rise in E_a was associated with a modest but significant rise in ventricular E_{es}. Figure 3A displays example data from a young and from an elderly patient. Arterial elastance was higher in the elderly subject and corresponded with an increased E_{es}. Simultaneous ventricular-vascular stiffening maintained an E_a/E_{es} ratio near unity. These PV loops also show differences in the diastolic PV relation slope (diastolic stiffness), which was higher in the elderly patient.

Group data (Fig. 3B) revealed a significant correlation between E_{es} and E_a ($E_{es} = 0.91 \times E_a + 0.5$, $p < 0.0001$, $r = 0.51$), so that the E_a/E_{es} ratio was maintained unchanged with age (Fig. 3C, mean ratio of 0.96 ± 0.36). End systolic elastance also correlated with diastolic elastance ($E_{es} = 6.0 \times E_d + 1.1$, $r = 0.50$, $p < 0.0001$; Fig. 3D), and each correlation was significant for individual subgroups as well. Finally, E_{es} and E_d both rose with age ($r = 0.29$, $p < 0.03$, for each) by separate regression analysis.

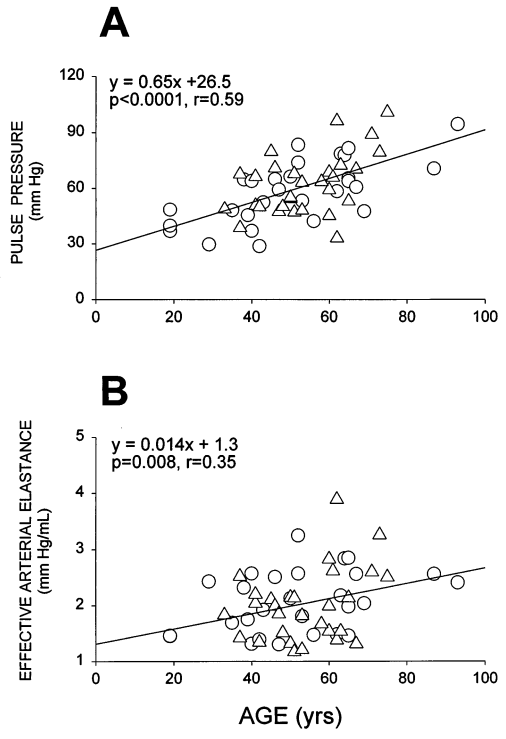

Figure 2. Effects of age on vascular stiffening and load. **A** shows pulse pressure versus age, and **B** shows arterial elastance, a measure of total (mean and pulsatile) arterial load, versus age. Both parameters significantly increased with age. **Open circles** = group 1 subjects with no demonstrable cardiovascular disease. **Open triangles** = those with coronary artery disease and no infarction or a history of systolic hypertension. **Solid lines** = linear regression for combined data.

Sensitivity of systolic pressure to cardiac preload. Combined ventricular-vascular stiffening had a major influence on the sensitivity of systolic pressure to altered preload volume. Figure 4A displays systolic pressure versus EDV for the same patients whose PV data are shown in Figure 3A. This relation was steeper for the elderly patient, indicating greater changes in systolic pressure for any relative change in EDV. Group data plotting the relation slope (SBP_{EDV}) versus age is shown in Figure 4B, and shows a 2.5-fold increase in slope over a 70-year life span.

To further test the contribution of E_{es}, E_a, age and sex to SBP_{EDV}, multivariate regression was performed (Table 2). Sex had no independent effect. The sensitivity of systolic pressure on cardiac preload was directly dependent upon both vascular and ventricular systolic stiffnesses, with a borderline residual age influence. This is compatible with model-based analysis (see Appendix). Similar results were obtained with analysis of only group 1 patients. Thus, age-related changes in SBP_{EDV} were principally mediated by its influence on E_{es} and E_a.

Discussion

This study provides the first direct evidence that age-related increases in E_{es} (i.e., chamber systolic stiffness) accompany increases in E_a (mean and pulsatile arterial load) even without cardiac hypertrophy. Increased E_{es} maintained heart-arterial matching independent of age, but imposed a limitation on net ventricular-arterial interaction. Specifically, varying cardiac filling led to disproportionately greater changes in systolic pressure in older individuals. This may amplify effects of autonomic and baroreflex dysfunction often present in the elderly (18–20,31) that are linked to greater blood pressure sensitivity to diuretic therapy, altered fluid intake and postural or postprandial stress (21–24,31).

Ventricular-vascular coupling with age. Although tandem elevation of E_{es} and E_a was statistically significant, there was considerable scatter, with only about 25% of an E_{es} change predicted by an altered E_a. This is not surprising given the sample size, the fact that E_{es} (and E_a) have multiple determinants and the heterogeneous condition represented by aging. Nonetheless, the data supported the hypothesis that patients with greater vascular stiffening were more likely to have increased ventricular stiffness. As demonstrated by univariate regression and supported by prior data (32), aging raised E_a principally by its effects on pulsatile loading, with an additional but smaller age-dependent effect from mean resistance (1,3,6). Only one prior study has reported how such changes might influence heart-arterial interaction (32); however, E_{es} was determined from a single-beat end systolic PV ratio, which can be unreliable in patients with normal or increased E_{es} values (33).

Although maintenance of the E_a/E_{es} ratio with age would seem beneficial, a rise in both parameters meant that systolic pressures became more sensitive to chamber volume manipulation. With increased E_{es}, even small blood volume shifts from heart to arteries translated to greater arterial pressure changes. Since contractile reserve is also linked to increases in E_{es}, basal elevation with age might limit some of this reserve and could contribute to a reported blunting of end systolic volume decline during exercise (34). Thus, "preserved" heart-artery matching does not necessarily mean cardiovascular reserve adaptability is also maintained.

The present data may be relevant to the increased prevalence of hypotension with normal physiologic stresses such as postural or postprandial fluid shifts (23,24,35–37) and enhanced pressure changes with excess sodium intake or restriction (21,38) and diuretics (22,39). Interestingly, these symptoms occur more frequently in patients with resting supine systolic hypertension (35,36), suggesting a potential link with vascular stiffening. Many of these patients have normal EFs but abnormalities of diastolic filling and relaxation, and thus may have diastolic dysfunction. The present data show that ventricular/arterial stiffening also contributes to such sensitivity.

Factors other than ventricular-vascular stiffening also likely contribute to the regulation of systolic arterial pressure when cardiac filling volumes are altered. The baroreflex is blunted with aging (18,19), and this can compromise blood pressure homeostasis with postural changes or after meals (18,31). Downregulation of beta-adrenergic responsiveness (20) also

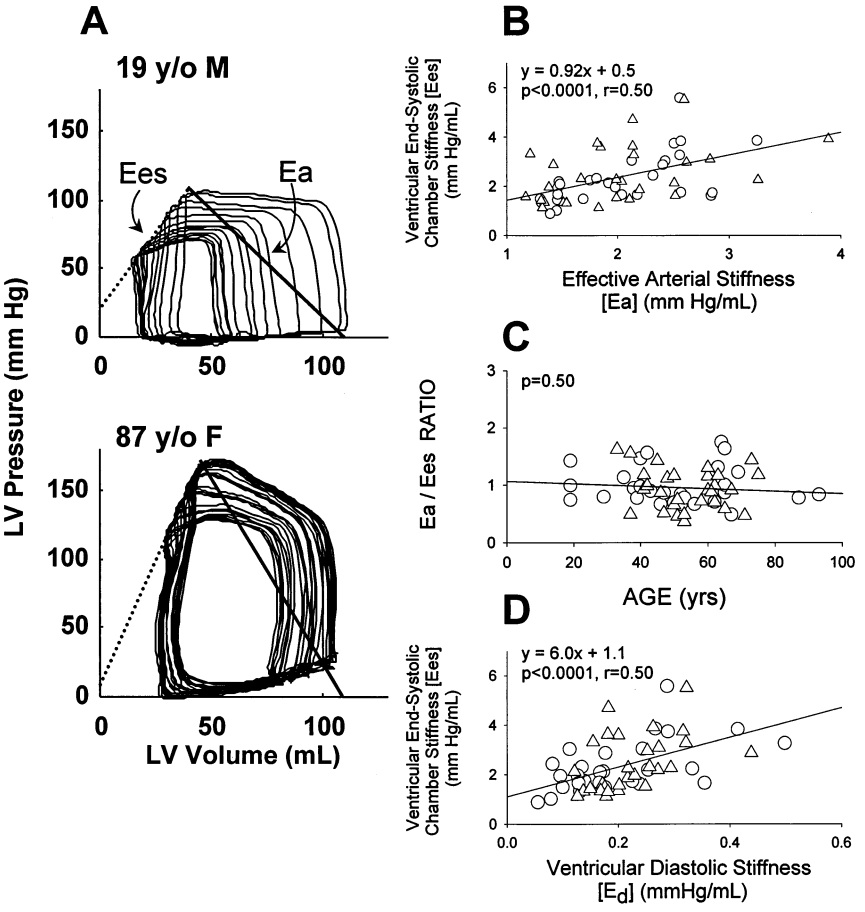

Figure 3. (**A**) Pressure volume loops and relations derived by preload reduction maneuver in a young and in an elderly patient. End systolic elastance (E_{es}) measures chamber systolic stiffness and is the slope of a line connecting the upper left-hand corners (end systole) from each pressure volume loop (**dotted line**). Arterial elastance (E_a) measures arterial load and stiffness and is depicted by the negative slope of the diagonal solid line shown in the figures. As noted in Figure 2, vascular stiffening was higher in the aged individual (E_a = 2.4 vs. 1.6 mm Hg/ml in these examples). This was accompanied by increases in ventricular stiffness (E_{es} = 3.6 vs. 2.1 mm Hg/ml, respectively). As a result, ventricular and vascular properties remained matched. (**B**) Group data showing positive correlation between ventricular systolic stiffness and arterial stiffness. See text for regression results. (**C**) Combined ventricular and vascular stiffening resulted in matching of the two systems (defined by the E_a/E_{es} ratio) that is independent of age. (**D**) Increased ventricular chamber systolic stiffness (E_{es}) also correlated with elevations in diastolic chamber stiffness (E_d). Both variables independently rise with age (data not shown).

may limit mechanisms of pressure control. In addition to its direct effect, ventricular-vascular stiffening would amplify such abnormal reflex pressure control.

Aging, E_{es} and E_d. Cardiac structural changes from aging have been reported, including increased LV mass, reduced myocyte content, apoptosis and an increased fraction and cross-linking of collagen (14,15,40). Such changes, as well as Doppler evidence of reduced early diastolic filling, have led to the notion that diastolic stiffness increases with age (15). The present study is the first to test and confirm this hypothesis directly from measured PV relations. We also found that such stiffness occurred in the absence of clinically apparent cardiac hypertrophy or LV dysfunction and without coronary artery disease or systolic hypertension (group 1 patients).

End systolic elastance depends both on active contraction and on diastolic and passive structural factors (41). End systolic elastance is traditionally considered a measure of contractility, as it directly varies in response to inotropic agents and is less influenced by volume and resistance load (42). However, a higher E_{es} with age may not mean greater contractility, since passive structural and geometric changes could also contribute. One would anticipate that an effect from factors reducing chamber distensibility in diastole, when muscle cells are relaxed and more easily distended, would become greater as systolic tension developed. This is consistent with the correlation observed between E_{es} and E_d, the former being primarily related to structural changes and remodeling.

Limitations. This study could not determine cause-and-effect relationships between ventricular-arterial stiffening, and such implications should be avoided. Thus, while ventricular stiffening may be a consequence of chronically increased pulsatile-plus-resistive vascular loads, it may equally be related to primary changes in ventricular material properties. Considerable variance in the relevant regressions supports a mutifactorial interaction.

The patient population was referred for cardiac catheterization, and despite having normal-appearing ventricles, the data may not reflect pure effects of aging. In addition, a subset of patients received medications that could have chronic effects on the heart or arterial system. However, features of the data suggest the results likely did reflect aging physiology in a general population. First, there was generally no difference in findings for the two subgroups, and both groups contributed patients with similar distributions of vascular stiffness and age. Drug therapy was varied and randomly distributed across age, making it unlikely to influence the regressions. It is always possible that group 1 subjects had some coronary flow limitations despite normal epicardial vessels. There was no evidence for limited diastolic flow, however, as the diastolic period was near 50% of the cardiac cycle in these subjects. Finally, aging

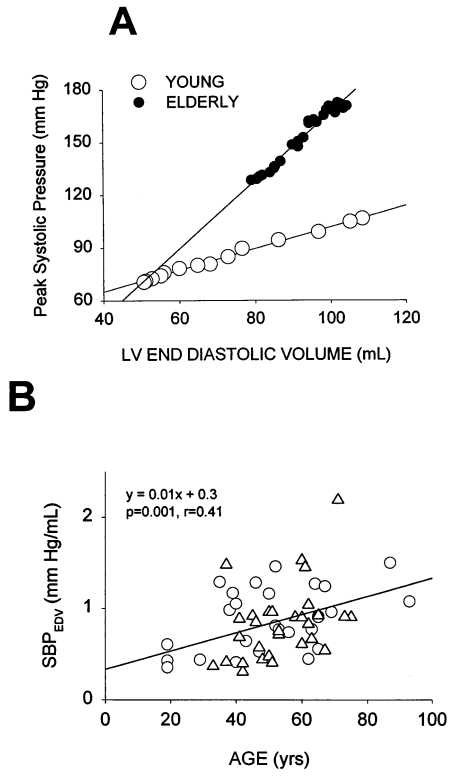

Figure 4. (**A**) Example of changes in systolic pressure to alterations in ventricular diastolic volume in a young and in an elderly patient. Data are derived from the same set of pressure volume loops shown in Figure 2. There is much greater sensitivity of systolic pressure to volume changes in the elderly patient, indicated by the steeper slope. (**B**) Group results showing effects of age on the slope of the systolic pressure LV end diastolic volume dependence (SBP_{EDV}). This relation slope increased significantly with age.

influences on the arterial vasculature have been well established by many general aging population studies (1–3,32) and were similarly observed in the present investigation. In particular, the per-decade rate of systolic and PP increase in the ascending aorta was similar to that previously reported (2,30). The gradual rise in both parameters even in patients younger than 50 years distinguishes these data from those derived from brachial arterial pressure, where values plateau below age 50 (6).

Table 2. Multivariate Regression Analysis of Influence of E_{es}, E_a and Age on the Cardiac Volume Sensitivity of Systolic Blood Pressure and Cardiac Stroke Work

			Partial Coefficients	p Value
Combined groups 1 and 2 (n = 57)				
SBP_{EDV}	ANOVA	E_{es}	0.127	0.003
	r = 0.721	E_a	0.256	0.001
	p < 0.000001	Age	0.004	0.095
Group 1 only (n = 28)				
SBP_{EDV}	ANOVA	E_{es}	0.142	0.0292
	r = 0.784	E_a	0.283	0.0253
	p = 0.000035	Age	0.004	0.2215

ANOVA = analysis of variance; other abbreviations as in Table 1.

Conclusions. The recognition that changes in both vascular load and ventricular systolic stiffness contribute to an enhanced sensitivity of arterial systolic pressures and cardiac work to ventricular volume changes may have important therapeutic significance. Combining negative inotropic agents to reduce systolic stiffness with vasodilators to lower vascular stiffness would be expected to substantially diminish these sensitivities of blood pressure and cardiac work to volume change. Thus, in elderly patients in whom volume management is problematic, or arterial pressures display marked lability with salt loading, diuretics, fluid intake or exertional stress, the combination vasodilator/negative inotropic therapy might prove beneficial. Larger-scale prospective studies will be needed to directly test this hypothesis in elderly patients.

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Appendix

One starts with the defining equations for the end systolic elastance (E_{es}) and effective arterial elastance (E_a) based on end systolic pressure (P_{es}), end systolic and diastolic volumes (V_{es}, V_{ed}), stroke volume (SV) and the volume axis intercept of the ESPVR (V_o) (28,43):

$$E_{es} = P_{es}/(V_{es} - V_o) = P_{es}/(V_{ed} - SV - V_o) \quad [1]$$

$$E_a = Pes/SV. \quad [2]$$

Rearranging Eq. 2 for Sv, and substituting this into Eq. 1, yields an expression relating $P_{es}$to both elastances and end-diastolic volume, given by:

$$P_{es} = \alpha(V_{ed} - V_o), \text{ where } \alpha = 1/[(1/E_{es}) + (1/E_a)] \quad [3]$$

Thus, the sensitivity of P_{es} to V_{ed} is linear and the slope varies inversely with both E_{es} and E_a. The higher both factors the greater the slope, consistent with the measured data.

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