Relationship among diastolic intraventricular pressure gradients, relaxation, and preload: impact of age and fitness

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Popović, Zoran B., Anand Prasad, Mario J. Garcia, Armin Arbab-Zadeh, Allen Borowski, Erika Dijk, Neil L. Greenberg, Benjamin D. Levine, and James D. Thomas. Relationship among diastolic intraventricular pressure gradients, relaxation, and preload: impact of age and fitness. Am J Physiol Heart Circ Physiol 290: H1454–H1459, 2006. First published November 11, 2005; doi:10.1152/ajpheart.00902.2005.—Diastolic intraventricular pressure gradients (IVPGs) are a measure of the ability of the ventricle to facilitate its filling using diastolic suction. We assessed 15 healthy young but sedentary subjects, aged <50 yr (young subjects; age, 35 ± 9 yr); 13 healthy but sedentary seniors, aged >65 yr with known reductions in ventricular compliance (elderly sedentary subjects; age, 70 ± 4 yr); and 12 master athletes, aged >65 yr, previously shown to have preserved ventricular compliance (elderly fit subjects; age, 68 ± 3 yr). Pulmonary capillary wedge pressure (PCWP) and echocardiography measurements were performed at baseline, during load manipulation by lower body negative pressure at −15 and −30 mmHg, and after saline infusion of 10 and 20 ml/kg (elderly) or 15 and 30 ml/kg (young). IVPGs were obtained from color M-mode Doppler echocardiograms. Baseline IVPGs were lower (1.2 ± 0.4 vs. 2.4 ± 0.7 mmHg, P < 0.0001), and the time constant of pressure decay (τo) was longer (60 ± 10 vs. 46 ± 6 ms, P < 0.0001) in elderly sedentary than in young subjects, with no difference in PCWP. Although PCWP changes during load manipulations were similar (P = 0.70), IVPG changes were less prominent in elderly sedentary than in young subjects (P = 0.02). Changes in stroke volume and IVPGs during loading manipulations correlated (r = 0.96, P = 0.0002). PCWP and τo were strong multivariate correlates of IVPGs (P < 0.001, for both). IVPG response to loading interventions in elderly sedentary and elderly fit subjects was similar (P = 0.33), despite known large differences in ventricular compliance. The ability to regulate IVPGs during changes in preload is impaired with aging. Preserving ventricular compliance during aging by lifelong exercise training does not prevent this impairment.

aging; diastolic function; pulmonary capillary wedge pressure; isovolumic relaxation

THE PRESENCE OF EARLY DIASTOLIC intraventricular pressure gradients (IVPGs), defined as a discrete (positive) pressure difference between the base and apex of the heart, has been previously demonstrated in the normal left ventricle (LV) (18). IVPGs are directly related to LV relaxation parameters, such as the time constant of isovolumic relaxation (τ) and peak negative derivative of LV pressure (13). Studies have shown that IVPGs significantly decrease in ischemic heart disease (7, 18) and increase in response to catecholamine stimulation (13). We have recently validated a method to estimate IVPGs noninvasively, based on quantitative analysis of the spatiotemporal distribution of color M-mode Doppler velocities (8, 13, 21). Using this method, we have demonstrated that IVPGs increase during exercise and that their increase is related to maximum oxygen consumption both in normal subjects and patients with heart failure (20). Moreover, in that study (21), we found a strong inverse relationship between the increase in IVPGs and the increase in estimated left atrial (LA) pressure during exercise, suggesting that IVPGs may represent active LV suction. However, the response of IVPGs to preload-induced changes of cardiac function (i.e., Frank-Starling mechanism) with respect to ventricular compliance (9), which is a fundamental property of cardiovascular system regulation, is unknown.

Accordingly, the aims of this study were to determine 1) whether IVPGs vary in response to changes in preload; 2) whether load-induced changes in IVPGs are related to changes in stroke volume (SV); 3) whether the ability to increase IVPGs in response to preload is reduced in healthy elderly subjects with age-related changes in relaxation; and 4) whether lifelong exercise training, previously shown to preserve ventricular compliance (8), favorably impacts diastolic suction.

METHODS

Study Subjects

To assess the effects of normal aging, we compared a group of 15 young, sedentary healthy volunteers <50 yr (young subjects; age, 35 ± 9 yr; 12 men) with a group of 13 sedentary healthy seniors >65 yr (elderly sedentary subjects; age, 70 ± 4 yr; 7 men). The study of the characteristics of subjects has already been described in detail (1). None of the subjects were involved in an exercise-training program, and their estimated average weekly activity was <90 min of endurance exercise.

To discern whether the effects of aging on relaxation are dependent on underlying changes in ventricular compliance, we compared our elderly sedentary subjects with 12 highly trained master athletes in whom ventricular compliance has been demonstrated previously to be normal and similar to young control subjects (elderly fit; age, 68 ± 3 yr; 6 men) (1). We have already published data on the compliance of our groups on elderly fit and elderly sedentary subjects, using a three-parameter monoeponential equation that fits pulmonary capillary wedge pressure (PCWP) to corresponding LV end-diastolic volume data (1). We have shown that elderly fit subjects have a LV stiffness index of 0.013 ± 0.020, which was significantly lower than 0.029 ± 0.026 detected in elderly sedentary subjects. Because stiffness is the inverse of compliance, it follows that elderly fit subjects as a group have a higher compliance than elderly sedentary subjects.

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All subjects were rigorously screened for the presence of arterial hypertension, obstructive coronary artery disease, or structural heart disease, using 24-h blood pressure recordings and baseline and exercise ECGs and echocardiograms. Subjects were excluded if any of the following were present: mean daytime blood pressure $>140/90$ mmHg, ECG changes suggestive of ischemic heart disease, left bundle branch block, atrial flutter/fibrillation, atrioventricular block greater than first degree, baseline or exercise-induced wall motion abnormalities, valvular heart disease other than mild valvular insufficiency, right ventricular or LV hypertrophy, untreated thyroid disorders, chronic lung disease, regular cigarette smoking within the previous 10 yr, body mass index of $\geq 30$, or use of any cardiovascular medications (e.g., β-blockers, etc.). All subjects signed an informed consent approved by the institutional review boards of the University of Texas Southwestern Medical Center at Dallas and Presbyterian Hospital of Dallas.

**Loading Maneuvers and Hemodynamic Assessment**

A 6-Fr balloon-tipped fluid-filled catheter was placed under fluoroscopic guidance through an antecubital vein into the pulmonary artery. The catheter was connected to a pressure transducer with the zero reference point set at 5 cm below the sternal angle. The wedge position of the catheter was confirmed by both fluoroscopy and the presence of typical waveforms. Mean PCWP and right atrial pressures were determined visually at the end of expiration.

Lower body negative pressure (LBNP) was applied to decrease PCWP as previously reported (16). Briefly, the subject was placed in a Plexiglas box sealed at the level of the iliac crest. The suction was provided with the use of a vacuum pump with a variable autotransformer. Measurements of PCWP, thermocillion SV, cardiac output, heart rate, and blood pressure were made after 5 min of LBPNP at $-15$ and $-30$ mmHg. The negative pressure was then released. After repeated baseline measurements to confirm a return to hemodynamic steady state, cardiac filling was increased by rapid infusion (100 ml/min) of warm (37°C) isotonic saline. Measurements were repeated, after 10 and 20 ml/kg (elderly) or 15 and 30 ml/kg (young) had been infused, to attain similar increases in PCWP in both groups.

**Graded Low-Level Exercise Testing**

Nine (of 12) of elderly fit and 11 (of 13) of elderly sedentary subjects underwent graded low-level upright bicycle stress testing at rest and during the 5-min stages of 30 and 60 W. At each stage, we collected color M-mode data. In 10 (of 11) elderly sedentary and 7 (of 9) elderly fit subjects, the data were of satisfactory quality both at rest and at least one stage of exercise.

**Echocardiographic Studies**

**Data acquisition.** Complete two-dimensional (2-D) and Doppler echocardiographic studies were performed at baseline to exclude any structural heart disease (HDI 5000, ATL, Bothell, WA). Subsequently, apical two- and four-chamber views, pulsed-wave Doppler interrogation of inflow and outflow LV tracts, and color M-mode of the LV inflow tract were performed at each stage of load protocols. Care was taken to avoid foreshortening of image views and to record images with optimal endocardial definition. All images were stored digitally for off-line analysis by a blinded, experienced observer.

**Data analysis.** Noninvasive measurement of IVPGs has been previously described (13). Briefly, we simplified three-dimensional Navier-Stokes equations for incompressible fluid flow by assuming that the viscous term is very small and can be neglected and that the gravitational force is balanced by hydrostatic buoyancy. If we consider flow along a streamline only, this results in the Euler equation (Eq. 1), in which the vector notation has been dropped because the focus has shifted to the velocity in one direction.

\[
\frac{dp}{ds} = -\rho \left[ \frac{\partial v}{\partial t} + v \cdot \nabla v \right] = -\rho \left[ \frac{\partial v}{\partial t} + \nabla p \right]
\]  

(1)

where \(p, s, t, \) and \(v\) are pressure, distance, time, and velocity, respectively.

Integrating the Euler equation from the LV base to apex yields an estimate of the IVPGs (Eq. 2).

\[
\Delta P_{IV}(t) = \int_{base}^{apex} \frac{dp}{ds} \, ds
\]  

(2)

where \(\Delta P_{IV}\) represents IVPG.

We applied this equation to color M-mode data, because they closely approximate the spatiotemporal velocity distribution, \(v(s, t)\), along an inflow streamline from the LV base to apex. To obtain spatiotemporal velocity distribution, digital images of the color M-mode data were calibrated by custom software developed in the LabView environment (National Instruments, Houston, TX), and the resulting 2-D matrix was used to calculate time-varying intraventricular pressure drop over a fixed 4-cm distance. The peak pressure drop during early diastole was defined as IVPG. This method was validated extensively both in animal studies and in clinical population (8, 13, 21).

The time constant of isovolumic pressure decay with a zero asymptote assumption (\(\tau_0\)) was estimated by using the following equation (26):

\[
\tau_0 \text{(in ms)} = \frac{IVRT}{\ln P - \ln PCWP}
\]  

(3)

where \(P\) is systolic blood pressure and IVRT is isovolumic relaxation time by echocardiography (22). To further validate this equation, we analyzed LV, LA, and aortic pressure tracings obtained by a micro-manometer-tipped catheter (Millar, Houston, TX) from 1,327 individual beats recorded in seven mongrel dogs under a variety of hemodynamic conditions. We compared \(\tau_0\) calculated from the IVRT (calculated as a time interval between LV minimum pressure derivate and mitral valve opening), peak aortic pressure, and mean LA pressure with a gold-standard time constant of isovolumic pressure decay calculated by a shifting asymptote method. Although \(\tau_0\), as described (22), underestimates true time constant, there was a very strong correlation between the two parameters \((r = 0.90, P < 0.0001;\) see Fig. 1), indicating that changes in \(\tau_0\) adequately reflect changes in ventricular relaxation over a wide range of values.

All IVPGs and pulsed-wave Doppler measurements were averaged over six consecutive beats.

**Intra- and Interobserver Variability of IVPG Measurements**

To assess intra- and interobserver variability of IVPG measurements, six data sets of individuals were measured twice, after a time interval of $>1$ mo, by the same observer and, at that time, also by a second observer blinded to the measurements of the first observer. Inter- and intraobserver variability was then quantitated as absolute and relative difference between the two measurements. Absolute intraobserver variability of measurements obtained by integrating reconstructed pulsed-wave Doppler tissue-imaging signal was $0.1 \pm 0.1$ mmHg (4.4 ± 3.7% for relative value). The absolute interobserver variability of measurements was $0.4 \pm 0.7$ mmHg (15.2 ± 21.7% for relative value).

**Statistical Analysis**

Data are presented as means ± SD, except in figures where means ± SE were used. A comparison of baseline hemodynamic parameters (e.g., R-R interval, PCWP, IVPG, and \(\tau_0\)) between young, elderly sedentary, and elderly fit subjects was performed by unpaired
for both). Similarly, the time constant of pressure decay (0.4 and 1.1
and elderly fit subjects compared with young subjects (1.2
significance was determined as
RESULTS
change of IVPG, R-R interval, and PCWP values during two loading
groups was also performed by unpaired test. The significance of a
occurring during LBNP and during volume loading) between the same
licated by summing the absolute values of the maximum change
\[ t-test. \] A comparison of change in hemodynamic parameters (calcu-
lated by summing the absolute values of the maximum change
occurring during LBNP and during volume loading) between the same
groups was also performed by unpaired test. The significance of a
change of IVPG, R-R interval, and PCWP values during two loading
interventions within studied groups was assessed by a paired t-test.
Bonferroni correction for multiple comparisons was applied if appro-
To compare the impact of PCWP on IVPGs in patient groups, as
well as to describe the relation between changes in IVPGs and
changes in SV, we performed repeated-measures linear regression,
assuming different slopes and intercepts in two subject groups (young
and elderly sedentary, or elderly sedentary and elderly fit; SPSS 10.00,
SPSS, Chicago, IL) (12). To assess the predictive value of PCWP and
\( \tau_0 \) on IVPGs, a standard multiple stepwise linear regression was used.
Finally, for bicycle exercise testing data, within-group changes
were evaluated by Wilcoxon paired test, whereas between-group
differences were evaluated by Mann-Whitney U-test. Statistical sig-
nificance was determined as \( P < 0.05 \).
RESULTS
Baseline IVPGs were 50% lower in both elderly sedentary
and elderly fit subjects compared with young subjects (1.2 ±
0.4 and 1.1 ± 0.5 vs. 2.4 ± 0.7 mmHg; \( P < 0.002 \) vs. young,
for both). Similarly, the time constant of pressure decay (\( \tau_0 \))
was longer in both elderly sedentary and elderly fit subjects
compared with young subjects (60 ± 10 and 60 ± 6 vs. 46 ±
6 ms; \( P < 0.0001 \) vs. young, for both). Baseline PCWP was
similar in elderly sedentary, elderly fit, and young subjects
(11 ± 2 and 10 ± 1 vs. 11 ± 2 mmHg; \( P > 0.05 \), for all
comparisons). R-R interval duration was expectedly shorter in
elderly sedentary and young subjects compared with elderly fit
subjects (999 ± 193 ms and 987 ± 151 ms vs. 1,082 ± 156
ms; \( P < 0.01 \) vs. elderly fit, for both).

**Effects of Aging and Preload on IVPG**

Preload manipulations led to comparable changes of PCWP
in elderly sedentary and young groups (\( P = 0.7 \)). In addition,
although RR interval decreased during both LBNP (by 150 ms,
\( P < 0.001 \)) and saline infusion (by 119 ms, \( P < 0.001 \)), R-R
changes in both groups were similar (\( P = 0.26 \)).

IVPGs decreased with LNB and increased with saline
infusion (Fig. 2). The change of IVPG values recorded during
loading interventions was twice as large in young (\( \Delta IVPGs =
1.6 ± 0.3 \text{ mmHg} \)) than in elderly sedentary (\( \Delta IVPGs =
0.8 ± 0.2 \text{ mmHg}, \ P = 0.02 \) subjects). Figure 2 illustrates the relation
between IVPGs and PCWP in elderly sedentary versus young
subjects. The IVPGs were strongly influenced by PCWP (\( P <
0.0001 \)) in young but less in elderly sedentary subjects, as
demonstrated by the difference in slope (\( P = 0.0006 \)) and
intercept (\( P = 0.0002 \)) of these correlations: IVPGs =
(0.069 − 0.031 · Y) · PCWP + 1.18 − 0.42 · Y, where \( Y \) equals
−1 for young subjects and 1 for elderly sedentary subjects.

We found a significant correlation between changes in SV
and in IVPGs (\( P = 0.0002 \)) (Fig. 3) but with no effect of age
on either the slope or the intercept of this relationship. The \( r \)
value for linear regression of average data was 0.96, whereas
the linear regression equation was \( \Delta SV \) (in ml) =
49 · \( \Delta IVPGs \) − 6.

A multiple linear regression showed that both PCWP (\( P <
0.0001 \)) and \( \tau_0 \) (\( P < 0.0001 \)) are independent predictors
of IVPGs, with the multiple regression correlation coefficient \( r =
0.58 \) (\( P < 0.0001 \))(Fig. 4).

**Diastolic Ventricular Compliance and IVPG in Aging LV.**

Figure 5 illustrates the relation between IVPGs and PCWP
in elderly sedentary versus elderly fit subjects. Overall, the
IVPGs were strongly influenced by PCWP (\( P = 0.001 \)).
However, no difference between groups in either slopes (\( P =
0.33 \)) or parameter intercepts (\( P = 0.94 \)) could be demon-
strated, indicating that an IVPG decrease with aging occurs
even when passive diastolic properties remain preserved.
Upright Bicycle Stress Echocardiography.

Figure 6 displays rest and exercise testing data in elderly sedentary and elderly fit groups, along with the number of subjects at each stage. As can be seen, only three elderly sedentary subjects exercised at the stage of 60 W. The heart rates at rest, 30 W, and 60 W were 67 ± 8, 96 ± 14, and 104 ± 18 beats/min for the elderly sedentary group and 56 ± 5, 84 ± 10, and 100 ± 13 beats/min for the elderly fit group ($p = 0.01$ and 0.03 for the difference between groups at rest and at 30 W, respectively). IVPG increased in both groups at 30 W ($p = 0.02$, for both), with the increase equivalent in both groups ($p$ = not significant); however, at 60 W, it showed a tendency to decrease in the elderly sedentary group and increase in the elderly fit group ($p = 0.17$).

DISCUSSION

The results of this study demonstrate that IVPGs vary directly and predictably in response to alterations in preload. Normal aging dramatically impairs this relationship, probably through age-dependent decline in relaxation, and is independent of changes in ventricular compliance. It should be emphasized that impaired sensitivity of IVPGs to preload in the sedentary elderly occurs in parallel with the already reduced ability to augment SV via the Starling mechanism. A coupling of these two phenomena may become important during exercise as when heart rate increases the ability to fill depends on the establishment of IVPGs and diastolic suction, particularly in the elderly who have reduced ventricular compliance.

Impact of Loading on Relaxation

It is well known that an increase of afterload during contraction inhibits the relaxation process (19), which may influence...
ence the basoapical pressure gradient by increasing the pressure in the regions close to the incoming fluid front. Interestingly, despite numerous studies, controversy still exist about the impact of preload on the subsequent isovolumic LV relaxation (4). Starling et al. (24) have shown that relaxation is unaffected by modest alterations in preload or afterload. Eichhorn et al. (6) built on these findings, showing that although this is valid if contractility is normal, relaxation decreases with increasing preload in the presence of heart failure. This load dependency in the presence of heart failure, however, was recently questioned (23). It has also been proposed that load-relaxation relations may be U-shaped (11).

Impact of Aging on Diastolic Function

A multitude of studies (2, 15) have described profound effects that aging exerts on LV filling patterns. Because impaired LV relaxation may bring about similar changes (27, 28), effects that aging exerts on LV filling patterns. Because increasing preload in the presence of heart failure, however, was recently questioned (23). It has also been proposed that load-relaxation relations may be U-shaped (11).

Impact of Loading on IVPG Development in Aging vs. Normal Human LV

Hoit et al. (14) have shown that increase of LA pressure (preload) increases peak lengthening rate while decreasing time from minimum of the change of pressure over time (dP/dtmin) to peak lengthening. Furthermore, they (14) have shown that this process is more evident in the apex of the LV. LeWinter et al. (17) have demonstrated that preload augmentation increases the difference between standard end-diastolic pressure and the pressure of the fully relaxed but nonfilling LV. Although the authors did not assess IVPGs, their data support the hypothesis that preload should directly and positively relate to IVPGs. In this study, we have shown decisively that IVPGs indeed increase with volume loading and that this phenomenon is blunted in elderly subjects with impaired relaxation. We (13), as well as others (25), have previously shown that the IVPG changes in response to alterations in inotropy and lusitropy are more significant than those related solely to an increase in preload. Interestingly, increased contractility and relaxation are associated with increased equilibrium volume. Thus increased contractility may increase restoring forces even without decreasing end-systolic volume (17), which is consistent with our data. It should be pointed out that, despite larger number of subjects, limitations of clinical research prohibit a rigorous comparison between these experimental studies and our data. The results of our study suggest that 1) IVPGs are influenced by preload, 2) LV relaxation modulates the IVPG response to preload in the normal LV, and 3) impaired relaxation with aging overrides the beneficial effect of preserved passive ventricular properties sustained by lifelong exercise training. Thus IVPGs are both influenced by LA pressure as a driving force and likely are related to changes in calcium reuptake during relaxation.

IVPGs During Exercise

We have recently shown that in heart failure IVPG increase during exercise predicts subject’s aerobic capacity (20). Similarly, our current data also show that to support ventricular filling during exercise, IVPGs must increase. Although this increase was equivalent at low levels of exercise in two elderly groups, our data suggest that, to sustain higher exercise levels that elderly fit subjects are capable of sustaining, IVPGs must continue to augment. It should be pointed out that the seeming equivalence of IVPGs at low levels of exercise in the two elderly groups should be taken cautiously, because the same absolute work rate of 30 W translates into a much greater relative work rate (expressed as a percentage of peak oxygen consumption) for the sedentary subjects (1). This is further strengthened by the higher heart rate increase during exercise in elderly sedentary subjects, indicating a more potent mobilization of cardiac (catecholamine) reserve in this group.

Although we cannot separate out the cause from the effect in this study, it is certainly clear that to fill the heart fast at high filling volumes (and therefore high SVs), such as those seen in fit individuals, the large IVPGs are necessary. This is another example as to how systolic function critically interacts with diastolic function by increasing restorative forces in hearts with relatively large equilibrium volumes under high catecholamine support.

Study Limitations

We estimated preload by measuring pulmonary capillary pressure, which we use as an estimate of LA and LV end-diastolic pressure. Although end-diastolic volume represents a gold standard for measuring within-subject changes of preload, the presence of large between-group differences in resting end-diastolic volume precluded its use for group comparison (1). PCWP was equivalent among all subject groups and closely tracked the carefully quantified and induced changes in central blood volume, justifying its use as an estimate of preload in these in vivo experiments.

The differences between groups may be influenced by the differences of sympathetic activation in elderly versus young individuals (15). However, although we documented R-R interval decreases mediated by Bainbridge (during volume loading) and baroreflex (during LBNP), there was no difference in response between the two groups, and plasma norepinephrine levels were not different (1), suggesting that differences in the observed changes were not due to different activation patterns of the autonomic nervous system. Also, some differences may have been mediated by LV remodeling that occurs with aging.
Clinical Implications

An increase of IVPGs in the setting of a preload challenge may be viewed as a physiologically important phenomenon that would imply that the LV appropriately modulates its function to increase output in response to increased venous return while limiting the increase in LA pressure. It is known that the incidence of diastolic dysfunction increases with aging (3). Furthermore, it is known that filling pressures during exercise increase more in elderly individuals (5). Thus it is possible that the IVPG decrease that occurs with aging may be a contributing mechanism to these phenomena.

In conclusion, we have shown that IVPGs are modulated by central blood volume and preload and that this preload modulation is attenuated in elderly individuals with documented abnormalities in relaxation independent of the preservation of ventricular compliance that occurs with lifelong endurance training. This may be a contributing physiological mechanism to an inordinate diastolic pressure rise under a preload challenge in elderly individuals.

GRANTS

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