Impact of tachycardia and sympathetic stimulation by cold pressor test on cardiac diastology and arterial function in elderly females


Heart failure with preserved ejection fraction (HFpEF) develops predominantly in women: up to 75% of patients are women, aged >65 yr (37, 60). Research in elderly patients at risk of HFpEF has demonstrated that left ventricular (LV) stiffening is paralleled by age-related changes of the properties of the arterial tree (9, 49). While, traditionally, cardiac diastolic reserve has been viewed as the culprit in this group, mechanisms such as deranged vascular-ventricular coupling have therefore been suggested to contribute (2, 38, 39, 65, 70). This concept was originally derived from pressure-volume loop analysis and posits that irrespective of cardiac diastolic stiffness, ventricular systolic stiffening arises in parallel with age-related arterial stiffening. By beating with greater force, the heart is able to overcome the elevation that occurs in afterload (1, 6, 39, 49). Afterload is a key determinant of LV output (12), and afterload mismatch may be particularly important for stroke volume (SV) regulation in this group (1, 21) as, after menopause, there is a rapid increase in arterial stiffness that is much greater in women than in men (49, 51, 57). Interestingly, dynamic alterations of arterial function have been found during exercise in elderly women, including increased blood pressure, increased systemic vascular resistance (SVR), and decreased arterial compliance (16, 18, 43, 45, 47, 52, 58). This may be important as animal research has shown that an increase in afterload can produce an immediate alteration of LV relaxation (32). An attractive hypothesis is that relaxation impairment arises secondary to adverse afterload elevation during exercise, which in turn limits SV reserve and leads to HFpEF. However, it remains to be shown that such mechanisms are operant in elderly women during circulatory stress.

Two key aspects of exercise that may both contribute to circulatory stress and altered arterial physiology are cardiovascular sympathetic excitation and elevation of heart rate (HR). While both occur during exercise, they are difficult to study in isolation since interventions designed to produce sympathoexcitation lead to tachycardia (61). Moreover, elderly women frequently suffer from depressed sinoatrial function (3, 50), which may contaminate data if HR is not carefully controlled by study design. Lastly, arterial wave reflections may add to the increase in afterload during sympathoexcitation but are directly altered by tachycardia (68) and should therefore be studied while controlling for HR.

We performed an interventional study in elderly women to clarify the respective roles of tachycardia and sympathoexcitation with regard to vascular-ventricular coupling and SV response. During steady atrial tachycardia pacing (ATP) at 100 beats/min, sympathoexcitation was induced by applying a cold pressor test (CPT; see below). This study design avoided confounding effects of altered heart rate during CPT and vice versa, and data contamination by between-subject differences in sinoatrial function were eliminated.

METHODS

Patients. We recruited female carriers of permanent pacemakers, aged >60 yr, from the Swedish National Pacemaker Registry. Exclusion criteria were right ventricular pacing >10%, depressed LV ejection, significant comorbidity affecting cardiopulmonary function including renal failure (estimated glomerular filtration rate, <50 ml/min),

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non-sinus rhythm, valvular heart disease, coronary artery disease, and obesity. Hypertension was defined as arterial blood pressure persistently elevated $>140/90$ mmHg. Information was collected before performing the experiment on the proportion of atrial pacing since the pacemaker had last been interrogated. Patients were asked to avoid intake of any vasoactive substances for at least 24 h before taking part in the study (tobacco, caffeinated drinks, antihypertensive treatments, aspirin, statins). The study was approved by the regional independent ethics committee in Stockholm, Sweden, and complied with the declaration of Helsinki. All patients gave written informed consent.

Protocol. Blood tests were drawn for creatinine (estimated glomerular filtration rate was calculated based on the Cockcroft-Gault formula) and NH$_2$-terminal pro-brain natriuretic peptide. Investigations were started after a 5-min supine rest. An oscillographic method (Omron M6 Comfort; Omron Healthcare, Kyoto, Japan) was used to measure blood pressure noninvasively at the right brachial artery, beginning at rest and repeating at least every 5 min throughout the experiment.

After all data had been collected at rest, ATP was achieved by setting pacemakers to atrial pacing at 100 beats/min. Patients were allowed 5 min to establish a new steady state before repeating investigations. While atrial pacing at 100 beats/min continued, patients underwent CPT; the right hand of the patient was immersed to the wrist in ice water during a total of 4 min. Data collection was commenced 30 s after immersion as sympathoexcitaction begins at this point and was performed in adherence to a strict standardized protocol during 2 min (61).

Echocardiography. All echocardiograms were performed using a Vivid 7 system (GE Healthcare, Horten, Norway). Reading and postprocessing was performed at a dedicated workstation (EchoPAC; GE Healthcare) after blinding for all other data. LV dimensions and Doppler data were recorded as recommended, including LV outflow tract (LVOT) diameter, which was measured Doppler data were recorded as recommended, including LV outflow tract (LVOT) diameter, which was measured and recorded for analysis in triplicate. Volume measurements were indexed

$$LVEDV = SV/LVEF$$

(1)

as done elsewhere (2, 3, 20, 52). Dimensions, flows, and velocities were analyzed in triplicate. Volume measurements were indexed using Mosteller’s formula for body surface area as

Body surface area $= [3.660/(weight\text{-}height)^{1/2}]^{1/2}$

(2)

Tissue Doppler velocities were obtained by postprocessing color-coded tissue Doppler loops, using a $5 \times 5$ mm region of interest to record the mean velocity at basal segments of septum and lateral wall. Doppler and tissue Doppler measurements were taken at baseline but not during ATP and CPT because of tachycardia-induced fusion between E and A waves and between e’ and a’ velocities. Early diastolic function was assessed based on analysis of LV torsional mechanics by speckle tracking imaging (22, 42). In brief, torsion (twist) is defined as the summation of rotational motion in apical and basal planes of the LV, performed by helically oriented fibers. Untwist begins before aortic valve closure and is believed to create a negative pressure gradient (suction) in early diastole (48), which is traditionally quantified at the time of maximal LV pressure fall (peak $-dP/dt$) and expressed as Tau (66). Experiments in humans and animals originally showed that Tau can be estimated using rotational analysis based on speckle tracking imaging (5, 64), and Wang later externally revalidated this approach, showing that the closest estimate is obtained by maximal rate of untwist (UR$_{MAX}$) (63) in early diastole. For the purpose of computing an estimate of Tau ($e$Tau) from UR$_{MAX}$ in the present study, we digitized the scatter plot of invasive Tau versus UR$_{MAX}$ in the paper by Wang and coworkers (63) and fitted the equation

$$e\text{Tau} = -0.145 \times UR_{MAX} + 55.5$$

(3)

as this exactly followed the empirically developed linear association in Fig. 3 of the original publication ($r = -0.51; P < 0.01$).

Arterial tonometry. Applanation tonometry at the right radial artery was performed (Millar SPT-301), and brachial blood pressures were used for calibration. A generalized transfer function that synthesizes central aortic blood pressure was applied (SphygmoCor, AtCor Medical, Sydney, Australia), which has been validated for use under resting conditions (10, 25) and also during various interventions causing hemodynamic perturbation (23, 54). Augmentation pressure (AP) was defined as the pressure increase above the inflection point, and augmentation index ($AI_x$) was calculated as AP divided by central pulse pressure and expressed as a percentage (40). The time required for the forward pressure wave to return is a surrogate marker of aortic pulse wave velocity, estimated by round-trip time ($T_h$), defined as time from the beginning of the systolic upstroke to the first inflection point (36).

Noninvasive measures of vascular-ventricular coupling. Effective arterial elastance ($E_A$) was calculated as an estimate of global afterload as previously validated against frequency domain measures of arterial input impedance (8, 55, 56):

$$E_A = LVESPV/SV.$$  

(4)

This method was validated by Kelly and coworkers (27) who also showed that an approximation of LV end-systolic pressure (LVP$^{ESP}$) could be obtained as

$$LVP^{ESP} = 0.9 \times \text{brachial SBP}$$

(5)

where SBP is systolic blood pressure.

End-systolic LV elastance ($E_{LV}$) was calculated using estimates of group-averaged normalized elastance values [$E_{ND(est)}$] derived noninvasively from brachial blood pressures, SV, LVEF, and the ratio between prejection period and total systolic time. As experimentally validated by Chen and coworkers (8),

$$E_{LV} = (DBP - [E_{ND(est)} \times SBP \cdot 0.9])/(SV \cdot E_{ND(est)}),$$

(6)

where DBP is diastolic blood pressure.

As $E_{LV}$ follows the equation for a straight line, its volume axis intercept ($V_0$) is

$$V_0 = (LVESV \cdot E_{LV} - LVESPV)/E_{LV},$$

(7)

Arterial hemodynamic parameters. LVOT Doppler jet velocity was analyzed using a semiautomatic approach where Doppler envelopes were traced manually, followed by interpolation by a custom MATLAB program. After data export, central pressure was aligned so as to allow time domain calculation of aortic characteristic impedance ($Z_C$) as the early systolic pressure-to-flow ratio over the interval $t_1$ to $t_2$, where $t_1 = 10$ and $t_2 = 30$ ms (13, 28),

$$Z_C = |p(t_2) - p(t_1)|/[q(t_2) - q(t_1)]$$

(8)

SVR was calculated based on a three-element windkessel:

$$SVR = MAP/\text{cardiac output} - Z_C$$

(9)

where MAP is mean arterial pressure. Arterial compliance is defined as the ratio between volume and pressure in the arterial compartment. As this relation is inherently nonlinear due to pressure dependency,
the method of Yin was chosen since it enables compliance to be estimated as a function of pressure (35, 69),

\[
\text{compliance}(p) = \frac{(b \cdot SV \cdot e^{b \cdot p})}{\left| (A_S + A_D)/A_D - Z_c \cdot SV / A_D \right| (e^{b \cdot ESP} - e^{b \cdot EDP})}
\]

(10)

where the nonlinear parameter b was set to \(-0.0131\) (35), ESP and EDP denote end-systolic and end-diastolic aortic pressures, and \(A_S\) and \(A_D\) represent the systolic and diastolic areas under the pressure waveform. In the present study, we recorded compliance at end-systolic pressure which will henceforth be referred to as \(C_{ES}\) (52).

Statistics. One-way repeated-measures analysis of variance was used to study the changes induced by ATP and CPT (baseline vs. ATP vs. CPT were categories of the nominal variable time). Patients were dichotomized based on SV response to ATP, which created two groups (maintained SV vs. SV failure as categories of the variable group). Two-way repeated-measures analysis of variance was performed, entering time as main variable and group as fixed factor. This allowed the interaction term “time” to be analyzed (time \(\times\) group).

The variables \(V_0\) and \(C_{ES}\) were strongly skewed and could not be transformed to normality, necessitating nonparametric analyses: one- or two-sample Wilcoxon's \(Z\) test applied to data that were normal variables, and their association with SV response to ATP were studied using univariable linear regression analysis. Multivariable linear regression analysis was used to study the changes induced by ATP and CPT (baseline vs. ATP vs. CPT were categories of the nominal variable time). Patients were dichotomized based on SV response to ATP, which created two groups (maintained SV vs. SV failure as categories of the variable group). Two-way repeated-measures analysis of variance was performed, entering time as main variable and group as fixed factor. This allowed the interaction term “time” to be analyzed (time \(\times\) group).

RESULTS

Patients. The study population included \(n = 28\) elderly female patients whose basic characteristics are shown in Table 1. More than one-half of the population had been diagnosed with essential arterial hypertension. While all medications were stopped ≥24 h before the study, blood pressures in this subgroup were still within the normal range (brachial SBP and DBP, 132 and 76 mmHg, respectively) and both blood pressure (\(P > 0.62\)) and age (\(P > 0.83\)) were similar to nonhypertensive patients. In 8 patients (29%), an NH3-terminal pro-brain natriuretic peptide level > 220 ng/l was found. URMAX correlated strongly and inversely to LV mass (\(r = -0.67, P < 0.01\)), and eTau did not exceed 48 ms in any patient (range 10–47 ms).

Echocardiography and blood pressure. Representative waveform data and Doppler flow from a patient are shown in Fig. 1. Main alterations induced by ATP and CPT are shown in Table 2. Indexed SV (SVi) decreased as expected during ATP (−16 ± 19% from baseline; \(P = 0.001\)) because of smaller end-diastolic (−17 ± 19%; \(P = 0.001\)) and end-systolic volumes (−18 ± 23%; \(P < 0.01\)). SVi, indexed LVEDV (LVEDVi), and indexed LVESV (LVESVi) all significantly increased again during CPT; however, whereas SVi and LVEDVi remained significantly smaller than at baseline (−8 ± 15%, \(P < 0.01\) and −6 ± 17%, \(P = 0.035\)), LVESVi was restored to levels nonsignificantly different from baseline (\(P = 0.35\)). Early diastolic suction as measured by URMAX increased during ATP (+105 ± 104%, \(P = 0.01\)) and remained elevated from baseline during CPT (+67 ± 101, \(P = 0.023\)). As SBPs and DBPs were differentially affected by ATP (brachial SBP, −4 ± 7%, \(P < 0.01\); brachial DBP, +3 ± 15%, \(P = 0.41\); central SBP, −8 ± 7%, \(P < 0.001\); and central DBP, +4 ± 15%, \(P < 0.22\)), there was no change in MAP from baseline (0 ± 10%, \(P = 0.75\)). During CPT, however, there were simultaneous increases relative to baseline in SBP (+20 ± 14%, \(P < 0.001\)) and DBP (+24 ± 22, \(P < 0.001\)), leading to an increase in MAP (+25 ± 17%, \(P < 0.001\)).

Arterial hemodynamics. Global afterload defined as \(E_A\) increased during ATP (+22 ± 40%, \(P < 0.001\)) and more still during CPT (+34 ± 25%, \(P < 0.001\)). Across the group as a whole, neither \(Z_c\) nor \(C_{ES}\) changed from baseline during ATP (\(P = 0.20\) and \(P = 0.86\), respectively), but both did change during CPT (−53 ± 67%, \(P < 0.01\) and −31% (median; inter-quartile range, −3 to −54%), \(P = 0.049\)). At group level, SVR exhibited no change in response to either ATP or CPT (−3 ± 48%, \(P = 0.062\) and +189 ± 298%, \(P = 0.57\)). Pulse waveform analysis demonstrated that ATP led to decreases in AP and AIX (−47 ± 23%, \(P < 0.001\); and −30 ± 28%, \(P < 0.001\), respectively) despite an increase in pulse wave velocity as evidenced by a fall in \(T_R\) (−2 ± 9%, \(P = 0.037\)). During CPT, AP and AIX were found to increase again but were still below baseline (−5 ± 45%, \(P = 0.028\), and −30 ± 28%, \(P = 0.001\)). During ATP there was a further decrease in \(T_R\) (\(P = 0.024\) from APT) to levels well below baseline (−5 ± 7%, \(P < 0.001\)).

Subgroup analysis. As one aim of the present study was to study altered arterial hemodynamics in patients with poor SV

### Table 1. Basic characteristics of study population

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>70 ± 4.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>28 (100)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27 ± 4.8</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>15 (54)</td>
</tr>
<tr>
<td>Pain experienced during CPT, visual analog scale</td>
<td>6.6 ± 2.5</td>
</tr>
<tr>
<td>Blood tests</td>
<td></td>
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<tr>
<td>Creatinine, μg/l</td>
<td>65 ± 18</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, ml/min</td>
<td>84 ± 24</td>
</tr>
<tr>
<td>Drug treatment</td>
<td></td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
<td>10 (36)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor/receptor blocker, n (%)</td>
<td>11 (39)</td>
</tr>
<tr>
<td>Calcium blocker, n (%)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Vasodilator treatment, n (%)</td>
<td>11 (39)</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>5 (18)</td>
</tr>
<tr>
<td>Pacemaker interrogeration</td>
<td></td>
</tr>
<tr>
<td>Atrial pacing, %</td>
<td>42 ± 39</td>
</tr>
<tr>
<td>Right ventricular pacing, %</td>
<td>1.0 (0.0–4.6)</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
</tr>
<tr>
<td>Interventricular septal thickness, mm</td>
<td>10 ± 1.7</td>
</tr>
<tr>
<td>Posterior wall thickness, mm</td>
<td>8.1 ± 1.3</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>85 ± 20</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>30 ± 10</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.0 ± 0.4</td>
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<tr>
<td>e’, septum, cm/s</td>
<td>6.7 ± 1.8</td>
</tr>
<tr>
<td>e’, lateral wall, cm/s</td>
<td>6.3 ± 2.3</td>
</tr>
<tr>
<td>E/e’</td>
<td>12 ± 3.5</td>
</tr>
<tr>
<td>eTau, ms</td>
<td>35 ± 11</td>
</tr>
<tr>
<td>Phynomyocor data quality control operator index</td>
<td></td>
</tr>
<tr>
<td>Baseline, %</td>
<td>99 (96–100)</td>
</tr>
<tr>
<td>ATP, %</td>
<td>97 (95–100)</td>
</tr>
<tr>
<td>CPT, %</td>
<td>90 (86–96)</td>
</tr>
</tbody>
</table>

Continuous data are shown as means ± SD or median (interquartile range). Categorical data are shown as n (%). ATP, atrial tachycardia pacing, CPT, cold pressor test; LV, left ventricular.
reserve during tachycardia, patients were identified in whom SV decreased more than 15% during ATP (SV failure). This created two subgroups of approximately equal size (SV failure, n = 15 vs. non-SV failure, n = 13). At baseline, patients with SV failure during ATP were characterized by greater AP (21 ± 8 vs. 14 ± 7 mmHg; P = 0.029) and greater AIX (41 ± 7 vs. 30 ± 10%; P = 0.013), but there was no difference in TR (P = 0.24). Chamber size was similar between subgroups [SVi (P = 0.20), LVEDVi (P = 0.17), and LVESVi (P = 0.52)] as were conventional indexes of LV diastology, including E/A ratio (P = 0.53), e’ (P > 0.56), and E/e’ (P = 1.0). Patients with SV failure had a higher proportion of atrial pacing (55 ± 38 vs. 24 ± 34%; P = 0.029) and a lower HR at baseline (65 ± 7 vs. 76 ± 14 min⁻¹; P = 0.040). Hemodynamics differed in this subgroup over time as shown in Fig. 2. There was a differential response of groups as evidenced by statistical significance for interaction terms (time × group) in the case of Ees, SVR, and AIX. Owing to the nonnormality of Ees, the response of this variable to ATP and CPT was analyzed separately (please see Statistics). ATP induced a differential response between subgroups (P = 0.033) but not CPT. As for Ees and AIX, there were significant between-group differences, demonstrating the presence of overall higher levels of global afterload (mean Ees across all categories of time, 2.6 ± 0.7 vs. 2.4 ± 0.4 mmHg/ml) and greater arterial augmentation (mean AIX, 33.9 ± 7.3 vs. 26.3 ± 7.6%) in these individuals. Importantly, HR did not differ during ATP or CPT (P = 0.19 and 0.36, respectively), showing that differences in AIX could not be explained by differences in HR (68). Moreover, ELV differed over time as patients with SV failure had higher ELV during ATP (4.7 ± 2.0 vs. 3.2 ± 1.0 mmHg/ml; +35 ± 44 vs. −5 ± 32%; P for interaction = 0.01) but was similar at rest and during CPT (between-subgroup, P = 0.29).

To study the predictors of a fall in SV during ATP, the most closely associated variables were entered into linear regression. As shown in Table 3, there was a nonsignificant trend to an association between baseline HR and the SV response in univariable analysis (P = 0.09); however, there was no discernible association between URM, SV response (P = 0.62). In multivariable analysis, the leading independent predictor of the magnitude of ATP-induced SV failure was AIX, followed by the proportion of atrial pacing found at pacemaker interrogation (Table 3).

DISCUSSION

While poor vascular-ventricular coupling is often cited as a potential cause of HFpEF (65, 70), the exact underlying mechanism has not been clarified. Based on reports from our group (52) and others (45, 47, 58), dynamic afterload elevation appears to occur during exercise in elderly women. As principles of vascular-ventricular coupling posit that primary afterload elevation may produce secondary SV failure, we investigated in isolation the respective impacts of tachycardia and sympathoexcitation on SV regulation during circulatory stress in elderly women.

Impact of afterload and tachycardia on SV regulation. Altered afterload can adversely influence SV regulation in several principally different ways. Ventriculoarterial mismatch occurs when afterload (ELV) increases relatively more than contractility (Ees), producing a deranged arterial-to-LV elastance interaction (6). As this is an important determinant of myocardial stroke work efficiency (6, 26, 41), SV failure may hypothetically arise because of systolic dysfunction. In the present study, however, we found no evidence of contractile failure in subjects with SV failure, since the 35% increase in ELV in this subgroup was significantly larger than the 5% decrease in subjects with maintained SV.

On the contrary, animal research has suggested that cardiac diastology, especially early diastolic relaxation, may be influenced by cardiac afterload. In our subjects, early diastolic suction was enhanced during ATP and CPT (URMAX, +65 and +67%, respectively) despite augmentation of global afterload (Ees, +22 and +34%, respectively). The apparent absence of afterload-dependent impairment of relaxation is also supported by the fact that URM did not differ between patients with versus without SV failure during ATP.

While this finding was contrary to our original hypothesis, previous reports have not consistently described that elevated afterload produces an attenuation of relaxation. Hori et al. (24), in fact, found enhanced relaxation during increased systolic pressure in isolated perfused canine hearts. Eichhorn et al. (15) catheterized human subjects and noted that the impact of end-systolic pressure elevation on relaxation was variable and found in computer modeling that the response depended on LV contractility (R² = 0.62). Likewise, Leite-Moreira and Gillesbert (33) did not observe a change in relaxation after partial aortic clamping in healthy dogs, but there was significant slowing of relaxation in postischemically stunned hearts. This suggests that relaxation in our
compliance decreases early in the course of myocardial aging. Cardiac diastology is that no established method exists for the measurement of diastolic function as it shortens Tau. Wachter et al. (62) performed a study in which they proposed to be due to perturbations in calcium cycling, recruitment of cross bridges, and delayed inactivation (17).

Initial relaxation has tentatively been attributed to release of prediastolic potential energy by backrotation of myosin head cross bridges and has been found to be enhanced by pressure augmentation especially in mid- to late systole (34). Subsequent, decelerative relaxation, on the contrary, has been shown to slow down in response to an increase in arterial pressure in early systole, whereas acceleration is preserved in mid- to late systole (34). The normal initial accelerative phase and a subsequent decelerative phase, occurring at the transition between the two (34).

Tachycardia per se has a primary effect on cardiac early diastolic function as it shortens Tau. Wachter et al. (62) performed atrial pacing in 17 patients with HFpEF (13 women). While Tau was longer in HFpEF patients than controls (median 55 vs. 42 ms), there was similar shortening of Tau during tachycardia (51 vs. 34 ms; P not significant for interaction). Because of shorter diastole and longer Tau, incomplete relaxation was found in patients with HFpEF but not in controls (62). In the present study, the duration of diastole was ~10-eTau during tachycardia. This exceeds 3.5-Tau, i.e., the most commonly used definition of complete relaxation, demonstrating that early diastolic filling did not occur late in diastole.

An important limitation of noninvasive investigations into cardiac diastology is that no established method exists for the analysis of late filling. This is potentially important since LV compliance decreases early in the course of myocardial aging and/or hypertensive heart disease, a process that does not strictly require the presence of either hypertension or LV hypertrophy (11, 29, 71). Indeed, data from laboratory work in HFpEF patients as well as registry research into community-dwelling patients suggest that LV end-diastolic (Frank-Starling) reserve is important for SV reserve during exercise (7, 46). Moreover, historical data have suggested that tachycardia per se induces a low compliance state as end-diastolic volume decreases relatively more than EDP (4) especially in patients with structural heart disease (14). Nonetheless, in the aforementioned contemporary study by Wachtet al. (62), stiffness index β was measured and, while being higher in HFpEF patients than controls, was not actually altered by atrial pacing (62). The role of load, on the contrary, for end-diastolic function was studied invasively by Leite-Moreira and Correia-Pinto (31) in rabbits. The end-diastolic pressure-volume relation was found to vary with load (both preload and afterload), suggesting that acutely afterloading the LV does alter diastolic tone and/or viscous properties of the LV. Future research in this field should analyze late-diastolic function since more data are needed in this area (59).

Altered arterial function during stress. Interestingly, we found dynamic changes in $E_A$, SVR, and $C_{ES}$ in patients with SV failure during ATP and/or CPT. $A_0$ emerged as an independent predictor of SV failure irrespective of HR. This demonstrates that individuals with arterial stiffening exhibit significant adverse changes in arterial physiology and increased global afterload as a direct consequence of primary LV failure to maintain SV.
Patients with intact stroke volume (SV) during ATP are shown in gray bars; patients whose SV fell during ATP (SV failure) are shown in black. Whiskers show SE of the mean. EA, effective arterial elastance; SVR, systemic vascular resistance; CES, arterial compliance at end-systole; AIX, augmentation index. P values from analysis of variance are shown by symbols: single symbol indicates P < 0.05; double, P < 0.01; and triple, P < 0.001. Statistical main effect (baseline to ATP to CPT) is shown by horizontal bracket and asterisk, between-group effect (SV intact vs. SV failure) is shown by dagger, and interaction effect is shown by double-dagger. In the case of CES, owing to nonnormality, P values for between-subgroup testing were obtained from Mann-Whitney U-test: section symbol denotes P < 0.05 from baseline to ATP. ns, Not significant.

Table 3. Predictors of fall in SV during ATP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>95% CI</td>
</tr>
<tr>
<td>Constant</td>
<td>0.002</td>
<td>−0.041 to −0.002</td>
</tr>
<tr>
<td>Atrial pacing</td>
<td>0.002</td>
<td>−0.041 to −0.002</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>0.001</td>
<td>−0.011 to 0.124</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.001</td>
<td>−0.017 to 0.011</td>
</tr>
<tr>
<td>Maximal untwist rate</td>
<td>0.001</td>
<td>−0.011 to 0.124</td>
</tr>
</tbody>
</table>

Increments for independent variables: atrial pacing, increments of 10%; augmentation index, increments of 10%; heart rate, increments of 10 beats/min; maximal untwist rate, increments of 10°/s. *R² for model = 0.41; adjusted R² = 0.35. †P < 0.05; ‡P < 0.10. β, standardized B; CI, confidence interval.
DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES

30. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pelliika PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 18: 1440–1463, 2005.


