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Prolonged mechanical systole and increased arterial wave reflections in diastolic dysfunction

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Objective: To evaluate whether left ventricular ejection time indexed for heart rate (left ventricular ejection time index (LVETI)) and arterial wave reflections (augmented pressure (AP)) are increased in patients with diastolic dysfunction (DD).

Design: Prospective observational study.

Setting: University teaching hospital providing primary and tertiary care.

Subjects: 235 consecutive patients undergoing left heart catheterisation were categorised as having definite DD, possible DD or no DD (controls) on the basis of their left ventricular end diastolic pressures and N-terminal brain natriuretic peptide concentrations.

Main outcome measures: LVETI and AP were prospectively assessed non-invasively by radial applanation tonometry. In addition, all patients underwent comprehensive echocardiography, including tissue Doppler imaging of mitral annulus velocity in early diastole (E').

Results: LVETI was longer in patients with definite DD than in patients with possible DD and in controls (433.6 (SD 17.2), 425.9 (17.9) and 414.3 (13.6) ms, respectively, $p < 0.000001$). Arterial wave reflections were higher in definite DD than in possible DD and control groups (AP was 19.4 (SD 8.9), 15.2 (8.0) and 10.7 (6.8) mm Hg, respectively, $p < 0.000001$). In receiver operating characteristic curve analysis, LVETI detected DD as well as echocardiography (E:E'). Area under the curve for LVETI to differentiate patients with definite DD from normal controls was 0.81 (95% CI 0.72 to 0.89, $p < 0.0001$). In multivariable logistic regression analysis, LVETI added significant independent power to clinical and echocardiographic variables for prediction of DD.

Conclusions: Mechanical systole is prolonged and arterial wave reflections are increased in most patients with DD. Rapid non-invasive assessment of these parameters may aid in confirming or excluding DD.

Diastolic dysfunction (DD) and subsequent diastolic heart failure (DHF)¹ are increasingly recognised as major health problems. DD is common in the community and, although it is often not accompanied by recognised heart failure symptoms, it is associated with marked increases in all-cause mortality.² However, in contrast to systolic dysfunction and systolic heart failure, where widely accepted measures of left ventricular (LV) systolic function serve as objective evidence for the disease, current guidelines state that "noninvasive methods that have been developed to assist in the diagnosis of heart failure with normal left ventricular ejection fraction have significant limitations".³

In clinical practice, Doppler echocardiography has become the standard method for identifying and characterising diastolic function, although this approach has been questioned repeatedly.⁴⁻⁵ Unfortunately, prediction of LV filling pressures by mitral inflow velocities appears to be accurate only for patients with systolic dysfunction.⁶ In patients with preserved systolic function, more advanced techniques including tissue Doppler measurement of the velocity of the mitral annulus in early diastole (E') and its ratio with mitral inflow (E:E') can provide information regarding filling pressures in a substantial proportion of patients. However, in a large group of patients, technical limitations or intermediate values preclude exact diagnosis.

Intriguingly, systolic and circulatory abnormalities have been described in patients with "isolated" DD as well.⁷⁻⁸ In particular, aortic distensibility is reduced in patients with heart failure and normal ejection fraction,⁹ and it correlates with exercise intolerance. Many patients with heart failure and preserved ejection fraction had a combination of ventricular systolic and arterial stiffening.¹⁰ The duration of

diastole depends not only on heart rate but also to some extent on the duration of systole, which can be altered with changes in afterload.¹¹ An increase in systolic load prolongs systolic duration, leading to a delayed onset of relaxation. Moreover, with an increase in afterload, relaxation becomes slower and incomplete.¹² In a recently developed animal model, arterial stiffness and systolic duration were increased in dogs with DHF.¹³

In a preliminary retrospective study we used non-invasive pulse waveform analysis (PWA) and observed prolonged mechanical systole as well as increased arterial wave reflections in patients with DD.¹⁴ We therefore designed a prospective study to test the hypothesis that (1) patients with DD have prolonged mechanical systole and increased arterial wave reflections; (2) this can be used for the diagnosis of DD; and (3) measures of systolic duration and of wave reflections add independent diagnostic power to echocardiographic findings.

METHODS

Study population

This study was conducted in a high-volume cardiac catheterisation centre in a tertiary referral hospital in Austria. We prospectively enrolled 271 unselected patients undergoing

Abbreviations: Alx, augmentation index; Alx@75, augmentation index normalised for heart rate of 75 beats/min; AP, augmented pressure; AUC, area under the curve; CAD, coronary artery disease; DD, diastolic dysfunction; DHF, diastolic heart failure; DT, deceleration time; E', mitral annulus velocity in early diastole; IVRT, isovolumetric relaxation time; LV, left ventricular; LVEDP, left ventricular end diastolic pressure; LVETI, left ventricular ejection time index; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; PWA, pulse waveform analysis; ROC, receiver operating characteristic

cardiac catheterisation for suspected coronary artery disease (CAD). Inclusion criteria were preserved systolic function (ejection fraction $> 50\%$), stable clinical condition and the presence of sinus rhythm. Exclusion criteria were the presence of more than mild valvular dysfunction and pericardial or congenital heart disease. Patients were studied while taking their regular drugs. All patients gave written informed consent, and the study was approved by our local ethics committee.

Hypertension was present with repeated measurements ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic blood pressure or with permanent hypertension drug treatment. Diabetes mellitus was defined as a fasting blood glucose concentration ≥ 6.99 mmol/l or hyperglycaemia drug treatment. Creatinine clearance was estimated by the Cockcroft–Gault formula. For this study, we defined significant CAD as at least one $\geq 50\%$ diameter stenosis in at least one coronary vessel, or prior percutaneous or surgical coronary revascularisation.

Definition of diastolic dysfunction

A hallmark of DD is the finding of a raised LV end diastolic pressure (LVEDP) in patients with normal LV volumes and contractility.^{3 15 16} Our main criterion for DD therefore was raised LVEDP (> 16 mm Hg) in the presence of a normal end diastolic volume index (< 102 ml/m²)¹⁵ and normal ejection fraction ($> 50\%$). LVEDP was measured during cardiac catheterisation with digitised coronary angiography equipment (Cathcor; Siemens, Munich, Germany) by standard techniques and fluid-filled catheters, and was defined as the pressure after atrial contraction just before LV systolic pressure rise. All pressure tracings were checked manually by one experienced senior angiographer (CP), who was blinded to all other clinical, haemodynamic and laboratory data. Owing to poor-quality tracings, 36 patients had to be excluded from the study. Reproducibility of LVEDP measurements was fair. According to the Bland–Altman method, the mean difference between consecutive LVEDP measurements was 1.0 mm Hg and 95% limits of agreement were 2.7 mm Hg. To improve our diagnostic accuracy, and in line with previous work relating concentrations of brain natriuretic peptide and N-terminal pro-brain natriuretic peptide (NT-proBNP) to the presence and severity of DD,¹⁷ we added raised NT-proBNP (> 125 pg/ml) to our definition of DD. This cut-off level is in good agreement with a recently published study,¹⁷ where mean NT-proBNP concentrations were 189 pg/ml in patients with DD and 52 pg/ml in controls. Technicians not involved in the design and conduct of the study measured NT-proBNP with the commercially available electrochemiluminescence immunoassay ECLIA on the Elecsys 1020 analyser (Roche Diagnostics GmbH, Mannheim, Germany). In addition to definite DD, being present in patients with raised LVEDP as well as raised NT-proBNP, we categorised patients as having possible DD with either raised LVEDP or raised NT-proBNP and as normal controls with both normal LVEDP and normal NT-proBNP.

Assessment of ejection time and arterial wave reflections: PWA

Pulse waveforms were analysed non-invasively with the commercially available SphygmoCor system (AtCor Medical, Sydney, Australia) as previously described.¹⁸ In brief, peripheral pressure waveforms were recorded from the radial artery at the wrist, by using applanation tonometry with a high-fidelity micromanometer (Millar Instruments, Houston, Texas, USA). LV ejection time was derived from the radial waveform by measuring the time interval from the foot of the pressure waveform to the beginning of the incisura caused by aortic valve closure; this delay was then normalised to heart rate according to Weissler *et al.*¹⁹ A validated²⁰ generalised

transfer function was used to generate the corresponding central aortic pressure waveform. Pressure augmentation due to wave reflection (augmented pressure (AP)) was the maximum systolic pressure minus pressure at the merging point between the primary and reflected waves. The augmentation index (AIx) was defined as the AP divided by pulse pressure and expressed as a percentage. In addition, as AIx is influenced by heart rate, an index normalised for heart rate 75 beats/min (AIx@75) was used. Nurses not involved in the recording or interpretation of the angiograms took all PWA measurements with the patient in the sitting position in a quiet, temperature-controlled room (22 (1) °C) after a brief period (at least 5 min) of rest, most often on the day after cardiac catheterisation. Repeatability of PWA with respect to AP and AIx was good, as previously reported.¹⁸ With respect to LV ejection time index (LVETI) and according to the Bland–Altman method, the mean difference between consecutive LVETI measurements was 5.8 ms and 95% limits of agreement were 14.6 ms. Blood pressure during PWA was measured with a validated, automated wrist blood pressure monitor (Omron R3; Omron Healthcare, Tokyo, Japan) with the radial artery kept at heart level during measurement.

Doppler echocardiography

One single experienced observer (TW) obtained a detailed two-dimensional and Doppler echocardiogram for all patients with a Philips Sonos 7500 machine (Philips, Eindhoven, The Netherlands). Peak velocities of E and A diastolic filling, deceleration time (DT) and isovolumetric relaxation time (IVRT) were measured according to the guidelines of the American Society of Echocardiography.²¹ LV mass was calculated according to a validated formula²² and indexed to body surface area (LV mass index (LVMI)). For Doppler tissue imaging recordings, the sample volume was located at the septal side of the mitral annulus in the four-chamber view, where we obtained E'. Combining the mitral inflow velocity with the mitral annular velocity into a ratio (E:E') can predict LV filling pressure²³ and has been recently recommended as the primary echocardiographic measure in the assessment of diastolic function in patients with preserved ejection fraction.⁶

Statistics

All parametric values were expressed as mean (SD). Baseline characteristics, echocardiographic data and PWA parameters were compared between diagnostic groups by Kruskal–Wallis analysis of variance or χ^2 test for continuous or categorical variables, as appropriate. Numerical correlations were established by Spearman correlation. To account for multiple testing, Bonferroni's correction was applied.

Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic utility of LVETI, AP, E:A, E' and E:E' in separating patients with definite DD from normal controls and was summarised by the area under the curve (AUC). We also report the sensitivity, specificity and accuracy of LVETI, AP and E:E' at the optimal point on the ROC curve as the point nearest the corner of the ROC curve where sensitivity and specificity would be 100%. Lastly, the incremental value of LVETI over clinical data and echocardiographic variables was assessed by a logistic regression model. Sex, age, body height, presence of hypertension, presence of CAD, creatinine clearance, brachial systolic, diastolic or mean blood pressure or brachial pulse pressure, heart rate, AIx, AP, left atrial diameter, LVMI, ejection fraction, E:A, DT, E:E' and LVETI were entered into the multivariable model for the prediction of definite DD, as compared with normal controls. A value of $p < 0.05$ was considered to indicate significance.

Data were statistically analysed with the Statistica V.6.0 (StatSoft Inc, Tulsa, Oklahoma, USA) and BiAS for Windows

Table 1 Baseline characteristics and haemodynamic variables of patients with definite and possible DD and of normal controls

	Definite DD	Possible DD	Normal controls	p Value*
Number	44	109	82	
Age (years)	65.7 (10.1)	61.7 (10.6)	55.6 (8.9)	<0.000001†
Men	50%	55.9%	71.9%	0.02
Hypertension	81.8%	75.2%	45.1%	<0.000001†
Diabetes	22.7%	15.6%	11.0%	0.22
Dyspnoea	65.9%	55.0%	35.4%	0.002
Pulmonary disease	11.3%	13.8%	14.6%	0.88
Coronary artery disease	54.5%	42.2%	31.7%	0.04
Ejection fraction (%)	72.2 (8.2)	72.8 (8.4)	70.9 (8.9)	0.50
Angiographic EDV (ml)	131.3 (38.3)	136.3 (40.0)	133.9 (32.0)	0.85
EDV/BSA (ml/m ²)	70.0 (17.1)	69.9 (18.5)	67.1 (14.9)	0.85
Angiographic ESV (ml)	40.3 (24.7)	37.5 (20.1)	39.3 (17.6)	0.76
Total cholesterol (mmol/l)	5.40 (1.18)	5.43 (1.18)	5.48 (1.19)	0.86
LDL cholesterol (mmol/l)	3.13 (1.10)	3.18 (1.01)	3.29 (1.07)	0.72
HDL cholesterol (mmol/l)	1.39 (0.40)	1.45 (0.44)	1.35 (0.42)	0.33
Triglycerides (mmol/l)	1.96 (0.03)	1.84 (0.99)	2.09 (1.58)	0.62
Creatinine clearance (ml/s)	1.17 (0.39)	1.37 (0.51)	1.57 (0.47)	0.000009†
Body height (cm)	166.8 (9.1)	168.8 (8.8)	171.4 (8.1)	0.007
SBP brachial (mm Hg)	142.9 (21.4)	140.8 (20.7)	130.5 (17.6)	0.0002†
DBP brachial (mm Hg)	78.4 (11.5)	83.3 (13.6)	80.1 (11.7)	0.10
PP brachial (mm Hg)	65.5 (15.8)	57.9 (15.3)	50.5 (13.9)	0.000003†
SBP aortic (mm Hg)	134.2 (21.2)	131.3 (20.3)	120.1 (17.0)	0.00002†
DBP aortic (mm Hg)	79.3 (11.7)	84.1 (13.7)	80.9 (11.8)	0.10
PP aortic (mm Hg)	54.9 (15.5)	47.6 (14.5)	39.5 (13.2)	<0.000001†
Aspirin	88.6%	75.2%	73.2%	0.12
β blockers	72.7%	56.9%	46.3%	0.02
Calcium channel blockers	25%	17.4%	8.5%	0.04
ACE inhibitor/ARB	50%	51.4%	35.4%	0.07
Nitrates	22.7%	11.9%	14.6%	0.24
Statins	34.1%	29.4%	34.1%	0.74
Diuretics	31.8%	25.7%	18.3%	0.22

Data are mean (SD) or percentage.

*Kruskal–Wallis analysis of variance for comparison between all three groups; †Bonferroni correction ($p < 0.0017$ indicates significance).

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BSA, body surface area; DBP, diastolic blood pressure; DD, diastolic dysfunction; EDV, end diastolic volume; ESV, end systolic volume; HDL, high density lipoprotein; LDL, low density lipoprotein; PP, pulse pressure; SBP, systolic blood pressure.

V.7.05 (Hanns Ackermann, Frankfurt/Main, Germany) software packages.

RESULTS

Table 1 presents baseline characteristics of our patients, subdivided into three groups with respect to diastolic

function. Patients with definite DD were older and slightly smaller, and more of them were women, had hypertension, exertional dyspnoea and impaired renal function, and were taking hypertension drugs than in the other groups.

Table 2 shows selected echocardiographic parameters, LVETI and measures of wave reflections in the three groups.

Table 2 Echocardiographic parameters, wave reflections and duration of mechanical systole in patients with definite and possible DD and in normal controls

	Definite DD	Possible DD	Normal controls	p Value*
LVEDP (mm Hg)	20.2 (2.5)	16.2 (3.9)	12.8 (2.2)	
NT-proBNP (pg/ml)	395.3 (304.7)	355.1 (1365)	58.8 (36.6)	
LA diameter (mm)	39.3 (6.5)	39.2 (5.8)	36.5 (6.1)	0.003†
LVMI (g/m ²)	120.2 (30.3)	106.4 (27.2)	104.4 (54.9)	0.001†
E (cm/s)	66.4 (15.8)	62.9 (18.9)	59.4 (13.3)	0.08
A (cm/s)	75.8 (17.8)	74.9 (17.8)	68.7 (16.0)	0.01
E:A ratio	0.94 (0.40)	0.88 (0.42)	0.91 (0.28)	0.48
DT (ms)	198.9 (46.3)	197.8 (50.9)	190.1 (49.1)	0.39
IVRT (ms)	110.4 (24.2)	107.4 (28.4)	103.0 (21.7)	0.27
E' (cm/s)	5.1 (1.5)	5.3 (1.6)	6.2 (1.8)	0.00007†
E:E' ratio	13.6 (3.4)	12.6 (4.9)	10.1 (3.0)	<0.000001†
Heart rate (beats/min)	59.4 (8.5)	62.8 (11.8)	64.4 (10.4)	0.04
Alx	33.9 (8.6)	30.8 (11.1)	25.7 (11.1)	0.0001†
Alx@75	26.4 (8.9)	25.1 (9.8)	20.7 (10.5)	0.003†
AP (mm Hg)	19.4 (8.9)	15.2 (8.0)	10.7 (6.8)	<0.000001†
LVETI (ms)	433.6 (17.2)	425.9 (17.9)	414.3 (13.6)	<0.000001†

Data are mean (SD).

*Kruskal–Wallis analysis of variance for comparison between all three groups; †Bonferroni correction ($p < 0.004$ indicates significance).

Alx, augmentation index; Alx@75, augmentation index normalised for heart rate of 75 beats/min; AP, augmented pressure; DD, diastolic dysfunction; DT, deceleration time; E', mitral annulus velocity in early diastole; IVRT, isovolumetric relaxation time; LA, left atrial; LVEDP, left ventricular end diastolic pressure; LVETI, left ventricular ejection time index; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Figure 1 Radial (left) and calculated aortic (right) pressure waveforms. (Top) Prolonged systolic duration (315 ms) and increased wave reflections (augmentation index (AIx) 29%) in a patient with diastolic dysfunction (left ventricular end diastolic pressure (LVEDP) 27 mm Hg, N-terminal pro-brain natriuretic peptide (NT-proBNP) 193 pg/ml). (Bottom) Normal systolic duration (284 ms) and normal wave reflections (AIx 3%) in a control group patient (LVEDP 9 mm Hg, NT-proBNP 15 pg/ml). Heart rate was 77 beats/min in both patients. DP, diastolic pressure; MP, mean pressure; PP, pulse pressure; SP, systolic pressure.

LVETI was longest in patients with definite DD, intermediate in patients with possible DD, and normal in controls (419 (10) ms for men, 418 (10) ms for women according to Weissler *et al*¹⁹) (figs 1 and 2). Patients with definite and possible DD had increased wave reflections, expressed as AP, AIx and AIx@75, as compared to normal controls (fig 2). With respect to echocardiographic findings, patients with definite DD had larger left atrial dimensions, higher LVMI, lower E' and higher A and E:E' than the other groups. More conventional Doppler echocardiographic parameters (E, E:A, IVRT, DT) were not different between the groups.

We observed a significant positive association between the duration of mechanical systole (LVETI) and the extent of wave reflections, expressed as AP (Spearman R = 0.39, $p < 0.0001$). E' and E:E', echocardiographic measures known to be related to the time constant of LV pressure decay (τ) and to filling pressures, were correlated significantly with AP (Spearman R = -0.25 and 0.27, respectively, $p < 0.001$ for both). Lastly, the degree of prolongation of systole (LVETI) was correlated positively and significantly to the degree of rise of LVEDP (Spearman R = 0.44, $p < 0.0001$).

Multivariable predictors of DD

In logistic regression analysis, including a large number of clinical, echocardiographic and PWA variables (statistics section), LVETI provided additional and independent diagnostic information for the discrimination between patients with definite DD and normal controls (table 3). Other independent predictors of definite DD were a higher E:E' ratio, higher LVMI, lower creatinine clearance and the presence of hypertension.

Value of LVETI, AP and selected echocardiographic measures for the detection of definite DD

The efficiency of LVETI, AP, E:A, E' and E:E' to differentiate patients with definite DD from normal controls was assessed with ROC curve analysis in the total group and in subgroups of patients with and without CAD (table 4). The AUC for LVETI to differentiate patients with definite DD from normal controls was 0.81 (95% confidence interval (CI) 0.72 to 0.89, $p < 0.0001$) in the total group and 0.88 (95% CI 0.81 to 0.95, $p < 0.0001$) in patients without CAD. An optimal LVETI cut-off value of 427.1 ms had a sensitivity of 70%, a specificity of 82% and an accuracy of 76% for separating patients with definite DD from normal controls. For this differentiation, LVETI was as accurate as E:E' (accuracy at the optimal cut-off value of 11.2 was 73%, sensitivity was 73% and specificity was 73%), the single best echocardiographic parameter in our as well as in other populations with normal systolic function.⁶ An optimal AP cut-off value of 14.5 mm Hg had a sensitivity of 73%, a specificity of 73% and an accuracy of 73% for differentiating patients with definite DD from normal controls. Whereas LVETI, AP and E:E' provided acceptable AUCs for detection of definite DD (table 4), E' was less useful, and E:A, E, A, DT and IVRT did not detect definite DD at all (data presented in part only). With regard to subgroups, LVETI and AP detected definite DD best in patients without CAD, whereas E:E' had advantages in patients with CAD.

Lastly, we evaluated the usefulness of LVETI and E:E' in the group of patients with dyspnoea. LVETI differentiated patients with definite DD (and, therefore, patients with symptomatic DHF) from control group patients with an AUC of 0.89 (95% CI 0.78 to 0.96, $p < 0.0001$) and, therefore, was at least as accurate as E:E' ($p = 0.052$ for comparison

Figure 2 Duration of mechanical systole, expressed as left ventricular ejection time index (LVETI; left), and wave reflections, expressed as augmented pressure (AP; middle) or augmentation index (Alx; right), in patients with definite or possible diastolic dysfunction (DD) and in normal controls. CI, confidence interval.

between the AUCs) in this patient group. (The AUC for E:E' was 0.75, 95% CI 0.62 to 0.86, $p < 0.0001$.)

DISCUSSION

The major novel finding of our study is that increased filling pressures and NT-proBNP concentrations in patients with normal ejection fraction, normal ventricular volumes and no evidence of valvular or pericardial disease, and therefore patients usually considered to have isolated DD, are accompanied by a pronounced increase in the duration of ventricular ejection. Although this has been shown before in animal experiments,^{11, 13} to the best of our knowledge we are the first to describe this finding in a large series of human patients. Moreover, and closely coupled with this finding, arterial wave reflections in these patients were premature or increased.

Table 3 Multivariable predictors of definite diastolic dysfunction compared with normal controls

Variable	OR	95% CI	p Value
Hypertension present	6.90	1.61 to 29.5	0.009
LVMi	1.01	1.001 to 1.02	0.03
Creatinine clearance	0.98	0.95 to 0.99	0.04
E:E'	1.24	1.01 to 1.52	0.03
LVETI	1.09	1.05 to 1.14	<0.0001

$\chi^2 = 63.7$, $p < 0.0001$.

Other parameters entered into the model were age, sex, body height, heart rate, presence of coronary artery disease, brachial systolic, diastolic or mean blood pressure or pulse pressure, left atrial diameter, ejection fraction, E:A ratio, deceleration time and augmented pressure did not reach significance.

CI, confidence interval; LVETI, left ventricular ejection time index; LVMi, left ventricular mass index; OR, odds ratio.

Pathophysiological background

Whereas active relaxation may be regarded in the strictest sense as an early diastolic event, the time of onset of this process depends, at least in part, on systolic events such as the duration of contraction.¹¹ Increases in loading during the contraction phase induce compensatory increases in systolic duration (LVETI)¹¹ and, in turn, delayed onset of relaxation. In a recently developed large-animal model, duration of systole was longer in DHF than in young controls, and was as

Table 4 AUCs discriminating between patients with definite diastolic dysfunction and normal controls for the duration of mechanical systole, wave reflections and selected Doppler echocardiographic parameters

Patient group	AUC	95% CI	p Value
Total group (n = 126)			
LVETI	0.81	0.72 to 0.89	<0.0001
AP	0.78	0.69 to 0.87	<0.0001
E:A	0.50	0.40 to 0.61	0.95
E'	0.69	0.59 to 0.79	<0.01
E:E'	0.78	0.69 to 0.87	<0.0001
No CAD (n = 76)			
LVETI	0.88	0.81 to 0.95	<0.0001
AP	0.84	0.76 to 0.92	<0.0001
E'	0.59	0.48 to 0.69	0.26
E:E'	0.74	0.64 to 0.83	<0.01
CAD (n = 50)			
LVETI	0.71	0.61 to 0.81	<0.01
AP	0.67	0.57 to 0.77	<0.05
E'	0.76	0.67 to 0.85	<0.01
E:E'	0.84	0.76 to 0.92	<0.0001

AP, augmented pressure; CAD, coronary artery disease; AUC, area under the receiver operating characteristic curve; E', mitral annulus velocity in early diastole; LVETI, left ventricular ejection duration index.

long in DHF as in older controls despite a higher heart rate in the DHF group.¹³ What is a possible cause of this increase in systolic load? Clinical studies indicate that arterial stiffness is increased in clinical DHF,^{9, 10} and recently Munagala *et al*¹³ observed increases in arterial elastance in dogs with DHF. Aortic stiffening increases aortic pulse wave velocity so that wave reflection returns earlier, augmenting aortic pressure in late systole and increasing late systolic load.²⁴ In addition to these effects on the onset of relaxation, the influence of the systolic pressure waveform on relaxation rate has been well described.²⁵ Recently, Yano *et al*²⁶ investigated the influence of timing and magnitude of arterial wave reflections on LV relaxation in dogs and in eight elderly patients. Femoral compression in the patients and constriction of the aorta in the dogs induced an earlier return of arterial wave reflections (that is, in late systole) and in turn a prolongation of the LV pressure decay (τ). Moreover, Iketani *et al*²⁷ found inter-related, proportional changes of τ and AIx during administration of angiotensin and glyceryl trinitrate and concluded that late systolic pressure augmentation (that is, wave reflections) in the ascending aorta is one important factor that influences the rate of isovolumic LV pressure decline in humans. Consequently, we observed that the extent of systolic pressure augmentation (AP) due to wave reflections correlated significantly with echocardiographic measures of relaxation (E' , $E:E'$).

Our results differed slightly, whether or not ischaemia contributed to DD. Interestingly, it has been shown in dogs that ischaemia can lead to a shortened ejection time.²⁸ However, in patients with CAD, other mechanisms, such as hypertension and increased wave reflections, in addition to ischaemia may contribute to DD, and therefore LVETI and AP were still able to discriminate patients with DD from controls, although their discriminative power was greater in patients without CAD (table 4).

Diagnostic considerations

In clinical practice, Doppler echocardiography has become the primary tool for the assessment of diastolic function and ventricular filling pressures.⁶ In patients with impaired systolic function, mitral inflow parameters are predictive of filling pressures. However, in patients with preserved ejection fraction, transmitral parameters have important limitations in the prediction of filling pressures. Even the $E:E'$ ratio, the preferred parameter for the diagnosis of DD in these patients, is not useful when its value is intermediate (8–15) as in 66% of our patients. These limitations suggest the need for additional measures for DD. Consequently, and according to our results, LVETI as well as AP should complement the haemodynamic assessment of patients with suspected DD. This is in good agreement with the aforementioned pathophysiological considerations and the recommendations from physiologists¹¹ and may provide diagnostic accuracy superior to either method alone. Moreover, the linear correlation between filling pressures and LVETI suggests a possible role not only for diagnosis but also for the monitoring of therapeutic interventions in patients with DD.

Therapeutic implications

If an earlier return or an increase in arterial wave reflections plays a part in the pathogenesis of DD, either directly by raising late systolic pressure and, therefore, delaying the onset and prolonging the course of relaxation or indirectly by causing LV hypertrophy and ischaemia, then it should be relieved by reducing or delaying wave reflections. Of note, it has been shown that drugs that block the renin–angiotensin system²⁹ and nitric oxide donors or drugs that enhance nitric oxide release³⁰ improve diastolic function in humans. Typically, these drugs also decrease arterial wave reflections.

In a recent study, verapamil was shown to be particularly effective in reducing indices of arterial stiffness (carotid augmentation and aortic pulse wave velocity) for improving ventricular–vascular interaction and for increasing the capacity for exercise in older people with diastolic LV dysfunction.³¹

Possible limitations

Firstly, owing to the observational nature of our study, the positive correlations we observed between LVEDP, duration of contraction (LVETI) and wave reflections (AP) probably reflect a close relationship between those measures (and the severity of DD), but this does not necessarily imply cause and effect. Cause and effect can only be determined by independent manipulation of those parameters in an experimental setting. Secondly, delayed or prolonged contraction alone may not be sufficient to shift diastolic pressure–volume relations upward¹¹ and to lead to DD and DHF. A recently published computer model simulated the influence of abnormal relaxation and prolonged systole on end diastolic pressure rise.³² With prolonged relaxation being present, the increase in filling pressures at higher heart rates was attributed to incomplete relaxation. In addition, prolonged systolic intervals augmented the effects of τ on filling pressures. In other words, when the start of relaxation is delayed by prolonged systole and the progress of relaxation is retarded by intrinsic abnormalities, the relaxation process can easily extend late into diastole, resulting in an upward shift of the pressure–volume relation, and hence DD. These mechanisms may well explain the observed exertional dyspnoea (with higher heart rates) in our patients. Thirdly, owing to study design (including heart catheterisation), our patients were highly selected. However, our patients with definite DD shared many of the typical characteristics (elderly, women, hypertension) with patients who have DHF from previous series. Fourthly, the trend towards even better discrimination with LVETI than with $E:E'$ between DD and controls in symptomatic patients should be interpreted with caution (subgroup analysis, small patient number) and requires confirmation. Lastly, as patients with atrial fibrillation were excluded, our findings cannot be generalised to that patient group, although an inadequately high heart rate (an important contributor to DD, see above) may be very relevant in many of these patients.

Conclusions

The current data show that the ejection period is prolonged in most patients traditionally viewed as having isolated DD. This is closely related to—and perhaps caused by—premature or increased arterial wave reflections, at least in patients without CAD. Both parameters can be measured easily and non-invasively and may complement echocardiographic assessment of LV filling. From a therapeutic point of view, reduction of wave reflections seems to be a logical goal in patients with DD and DHF. However, this has to be tested in a prospective trial.

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IMAGES IN CARDIOLOGY

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Angiographic presentation of sinus of Valsalva aneurysm

Angiography of the aorta in a right anterior oblique view.

A 75-year-old patient was admitted because of dyspnoea, and a coronary angiography was performed due to slightly elevated troponin concentration. The coronary arteries were unremarkable. The angiography of the aorta revealed an aneurysm of the right sinus of Valsalva with massive contrast enhancement (see panel and video 1; to view video footage visit the *Heart* website—<http://www.heartjnl.com/supplemental>). Transoesophageal echocardiography showed spontaneous echo contrast in the area of the aneurysm (video 2). The troponin elevation was thus possibly due to microembolisation from the aneurysm. The aneurysm was successfully resected, and the postoperative course was uneventful.

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There are no competing interests.

To view video footage visit the
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