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Working Group Report

How to diagnose diastolic heart failure

European Study Group on Diastolic Heart Failure*

Introduction

Diastolic heart failure has emerged over the last 10 years as a separate clinical entity[1–6]. Diastolic heart failure accounts for approximately one third of all heart failure cases, especially in an elderly population, and its natural history, with an annual mortality rate of 8%, is more benign than other forms of heart failure with an annual mortality of 19%[7–12]. Because of its rising incidence in ageing Western populations and because of its different prognosis[13], specific treatment options for patients suffering from diastolic heart failure are currently being tested in large randomized trials. A need has therefore grown to establish precise criteria for the diagnosis of diastolic heart failure[14,15].

Such diagnostic criteria should: (1) reflect underlying pathophysiological mechanisms; (2) be readily obtainable using modern diagnostic tools; (3) be applicable to different cardiac diseases featuring diastolic heart failure. The present report of the European Study Group on Diastolic Heart Failure proposes a definition of primary diastolic heart failure. Primary diastolic heart failure does not include diastolic left ventricular dysfunction in the presence of systolic cardiac failure[16–19]. Diagnostic criteria satisfying the originally proposed definition of diastolic heart failure will be established for most of the modern cardiac investigations and imaging techniques. Finally, these diagnostic criteria for diastolic heart failure will be applied to diseases frequently characterized by diastolic heart failure. To avoid low specificity of the diagnostic criteria, cut-off values of indices were set at the 95% confidence interval of the mean value of the index observed in a normal population. When age-related changes of an index have been reported, cut-off values are given for different age (y, years) groups (e.g. $\leq$30y; 30–50 y; $\geq$50y) indicated as subscripts to the index.

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How to establish the diagnosis of diastolic heart failure?

A diagnosis of primary diastolic heart failure requires three obligatory conditions to be simultaneously satisfied: (1) presence of signs or symptoms of congestive heart failure; (2) presence of normal or only mildly abnormal left ventricular systolic function; (3) evidence of abnormal left ventricular relaxation, filling, diastolic distensibility or diastolic stiffness (Table 1).

Presence of signs or symptoms of congestive heart failure

Signs or symptoms of congestive heart failure include evidence of raised left atrial pressure, such as exertional dyspnoea, orthopnoea, gallop sounds, lung crepitations and pulmonary oedema. Exercise intolerance caused by exertional dyspnoea related to pulmonary congestion is frequently the earliest event in diastolic heart failure[20]. This form of exercise intolerance does not incorporate exercise-induced muscular fatigue, which results from impaired skeletal muscle metabolism and usually accompanies systolic heart failure[6]. A low peak exercise oxygen consumption (<25 ml . kg^{-1} . min^{-1}), eventually corrected for age and gender[21], on a progressive bicycle ergometer exercise test (20 W + Δ10 W at 1 min intervals[22]) provides objective evidence of reduced exercise tolerance[11] and allows for objective classification of patients in terms of functional impairment[23].

Presence of normal or mildly reduced left ventricular systolic function

Because of the frequent occurrence of diastolic left ventricular dysfunction in patients with systolic left ventricular dysfunction and congestive cardiomyopathy[24–26], a diagnosis of diastolic heart failure requires the presence of normal or only mildly abnormal left ventricular systolic function. A frequently used criterion[7,8,11] is a baseline left ventricular ejection fraction of at least 45%. As left ventricular relaxation depends on end-systolic load and volume[27–30], this criterion needs to be implemented when the left

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Table 1 Diagnostic criteria for diastolic heart failure

Signs or symptoms of congestive heart failure
Exertional dyspnoea [eventually objective evidence by reduced peak exercise oxygen consumption (<25 ml . kg^{-1} . min^{-1})], orthopnea, gallop sounds, lung crepitations, pulmonary oedema.

and
Normal or mildly reduced left ventricular systolic function:
LVEF $\geq 45\%$ and LVEDIDI $<3{\cdot}2$ cm . m^{-2} or LVEDVI <102 ml . m^{-2}

and
Evidence of abnormal left ventricular relaxation, filling, diastolic distensibility and diastolic stiffness:
Slow isovolumic left ventricular relaxation:
$LVdP/dt_{min} < 1100$ mmHg . s^{-1}
and/or $IVRT_{<30y} > 92$ ms, $IVRT_{30–50y} > 100$ ms, $IVRT_{>50y} > 105$ ms
and/or $\tau > 48$ ms
and/or slow early left ventricular filling:
PFR <160 ml . s^{-1} . m^{-2}
and/or $PFR_{<30y} < 2{\cdot}0$ EDV . s^{-1}, $PFR_{30–50y} < 1{\cdot}8$ EDV . s^{-1}, $PFR_{>50y} < 1{\cdot}6$ EDV . s^{-1}
and/or $E/A_{<50y} < 1{\cdot}0$ and $DT_{<50y} > 220$ ms, $E/A_{>50y} < 0{\cdot}5$ and $DT_{>50y} > 280$ ms
and/or $S/D_{<50y} > 1{\cdot}5$, $S/D_{>50y} > 2{\cdot}5$
and/or reduced left ventricular diastolic distensibility:
LVEDP >16 mmHg or mean PCW >12 mmHg
and/or PV A Flow >35 cm . s^{-1}
and/or PV A t $>$ MV A t $+30$ ms
and/or A/H $>0{\cdot}20$
and/or increased left ventricular chamber or muscle stiffness:
b $>0{\cdot}27$
and/or b′ >16

LVEF = left ventricular ejection fraction; LVEDIDI = left ventricular end-diastolic internal dimension index; LVEDVI = left ventricular end-diastolic volume index; $LVdP/dt_{min}$ = peak negative left ventricular dP/dt; IVRT = isovolumic relaxation time indexed for age groups; τ = time constant of LV pressure decay; PFR = peak LV filling rate indexed for age groups; EDV = end-diastolic volume; E/A = ratio of peak early to peak atrial Doppler flow velocity indexed for age groups; S/D = ratio of pulmonary vein systolic and diastolic flow velocities indexed for age groups; LVEDP = left ventricular end-diastolic pressure; PCW = pulmonary capillary wedge pressure; PV A Flow = pulmonary venous atrial flow velocity; PV A t = pulmonary venous atrial flow velocity duration; MV A t = mitral atrial flow velocity duration; A/H = ratio of atrial wave to total signal excursion on the apexcardiogram; b = constant of LV chamber stiffness; b′ = constant of muscle stiffness.

ventricular end-diastolic internal dimension index (LVEDIDI $<3{\cdot}2$ cm . m^{-2})[31] is normal or when the left ventricular end-diastolic volume index (LVEDVI <102 ml . m^{-2})[32] is normal, in order to exclude diastolic left ventricular dysfunction secondary to high end-systolic load and volume.

Evidence of abnormal left ventricular relaxation, filling, diastolic distensibility and diastolic stiffness

Such evidence can consist of: (1) slow isovolumic left ventricular relaxation and/or (2) slow early left ventricular filling and/or (3) reduced left ventricular diastolic distensibility and/or (4) increased left ventricular chamber stiffness or increased myocardial muscle stiffness. From the viewpoint of cardiac muscle physiology[33], diastole of left ventricular myocardium consists only of diastasis and the atrial contraction phase, and diastolic heart failure can therefore only be inferred from evidence of decreased left ventricular diastolic distensibility or increased left ventricular diastolic stiffness[6]. This theoretical approach is hampered by its limited clinical applicability as it usually requires invasive investigations to establish the diagnosis of diastolic heart failure. Because left ventricular relaxation and filling affect left ventricular diastolic distensibility (= the position on a pressure–volume plot of the left ventricular diastolic pressure–volume relation), diagnostic evidence for diastolic heart failure can also be obtained from analysis of left ventricular relaxation and filling[34], which can be performed more easily in clinical practice using modern non-invasive imaging techniques.

Slow isovolumic left ventricular relaxation

The rate of isovolumic left ventricular pressure decay is intimately coupled to timing, myocardial loading[27–30,35] and segmental coordination[36,37]. Timing refers to the time interval from the Q wave on the ECG to the onset of left ventricular relaxation[6,28]. Commonly used indices are:

(1) *peak negative left ventricular dP/dt* ($LVdP/dt_{min}$): a value of $LVdP/dt_{min} < 1100$ mmHg . s^{-1} is considered indicative of slow isovolumic left ventricular relaxation in man (normal control value: 1864 ± 390 ms; mean $\pm$ SD[40]). A significantly lower value has been reported in hypertrophic cardiomyopathy (998 ± 223 ms) and in congestive cardiomyopathy (1060 ± 334 ms) but not in coronary artery disease or hypertensive heart disease[40].

(2) *isovolumic relaxation time* (IVRT): the time interval between aortic valve closure and mitral valve opening has been measured using transmitral and left

ventricular outflow tract Doppler signals[41], mitral valve opening on the M-mode echocardiogram and aortic valve closure sounds on a simultaneous phonocardiogram[42,43]. IVRT depends on left ventricular relaxation kinetics and on the magnitude of left ventricular pressure at aortic valve closure and mitral valve opening[44]. Control values (mean ± SD) are age-(y, years) dependent: $IVRT_{<30y} = 72 \pm 12$ ms, $IVRT_{30–50y} = 80 \pm 12$ ms, $IVRT_{>50y} = 84 \pm 12$ ms[45]. A prolonged value ($IVRT_{<30y}$ >92 ms, $IVRT_{30–50y}$ >100 ms, $IVRT_{>50y}$ >105 ms) provides evidence of slow isovolumic relaxation, but a normal value fails to exclude it because IVRT returns to control value when elevation of left atrial pressure leads to earlier mitral valve opening[46].

(3) *the time constant of left ventricular pressure decay* (τ = tau): τ is the most widely used index of isovolumic left ventricular relaxation kinetics[47]. In man, normal values of τ, calculated with a zero asymptote pressure, vary from 33 ± 8 ms[40] to 36 ± 6 ms[48] and have recently been shown to be independent of age[49]. A significant prolongation of τ has been reported in numerous clinical conditions including coronary artery disease in the absence of left ventricular dyssynchrony[40] and hypertensive left ventricular hypertrophy[50]. Provided a high quality Doppler flow velocity signal can be obtained, calculation of τ can also be performed on the Doppler flow velocity signal of mitral[51,52] and aortic[53] regurgitation during the isovolumic relaxation period. A recent study also proposes a non-invasive method of calculating τ using a Doppler measure of isovolumic relaxation time and extrapolated values of left ventricular pressures at aortic valve closure and mitral valve opening[41].

Slow early left ventricular filling

Early peak left ventricular filling rate (PFR) derived from left ventricular contrast angiograms in control subjects equals 300 ± 69 ml . s^{-1} . m^{-2}[54]. Left ventricular filling dynamics were also analysed on radionuclide left ventricular angiograms. Because of variations in red cell tagging and in attenuation among different patients, peak left ventricular filling rate derived from radionuclide angiograms is usually normalized to end-diastolic volume (EDV)[55] and expressed as EDV . s^{-1} [normal values for different age (y, years) groups indicated as subscripts to the index: $PFR_{<30y} = 3{\cdot}6 \pm 0{\cdot}8$; $PFR_{30–50y} = 3{\cdot}4 \pm 0{\cdot}8$; $PFR_{>50y} = 3{\cdot}2 \pm 0{\cdot}8$ EDV . s^{-1}[56]]. Further refinement of analysis of global left ventricular filling dynamics, such as appreciation of circumferential–longitudinal shear strain and torsional motion of the myocardium, has recently been achieved using myocardial tagging and magnetic resonance imaging[57–62].

Doppler echocardiographic indices of early left ventricular filling are peak early (E wave) Doppler flow velocity (Normal values: $E_{<30y} = 0{\cdot}69 \pm 0{\cdot}12$ m/s; $E_{30–50y} = 0{\cdot}62 \pm 0{\cdot}14$ m/s; $E_{>50y} = 0{\cdot}59 \pm 0{\cdot}14$ m/s[45]), E/A ratio (A = peak A wave Doppler flow velocity) (normal values: $E/A_{<30y} = 2{\cdot}7 \pm 0{\cdot}7$; $E/A_{30–50y} = 2{\cdot}0 \pm 0{\cdot}6$; $E/A_{>50y} = 1{\cdot}2 \pm 0{\cdot}4$[45]), deceleration time (DT) of E velocity (normal values: $DT_{<50y} = 179 \pm 20$ ms; $DT_{>50y} = 210 \pm 36$ ms[63]) and the ratio of pulmonary vein systolic (S) and diastolic (D) flow velocities (S/D ratio) (normal values: $S/D_{<30y} = 1{\cdot}0 \pm 0{\cdot}3$; $S/D_{>50y} = 1{\cdot}7 \pm 0{\cdot}4$[64]). Slow left ventricular pressure decay, as a result of slow myocardial relaxation or of segmental incoordination related to coronary artery disease[36,65–67] or conduction disturbances[68], reduces the E/A ratio, prolongs DT and increases the S/D ratio[46,64,69] ($E/A_{30–50y}$ <1·0; $DT_{<50y}$ >220 ms; $S/D_{<50y}$ >1·5). A similar pattern has also been observed during hypovolaemia[70]. Elevation of left atrial pressures 'pseudonormalizes' the mitral inflow pattern and reduces the S/D ratio. From a physical point of view, early left ventricular filling is a function not only of the impedance to filling exerted by the mitral valve, subvalvular apparatus and left ventricular structures but also of the atrioventricular pressure gradient[71–73]. Initial invasive observations in patients with aortic stenosis already demonstrated 'pseudonormalization' of early left ventricular filling in the hypertrophied left ventricle when mitral valve opening pressure was elevated. In the presence of pseudonormalization of the mitral inflow pattern, pulmonary venous A wave velocity remains elevated (>35 cm . s^{-1}), exceeding values observed in young adults[69,74,75] and the reversed pulmonary venous A wave outlasts the mitral A wave by 30 ms[76]. A reduction of venous return (e.g. during Valsalva) restores the impaired relaxation pattern of mitral inflow. Color M-mode Doppler of intraventricular filling, measuring flow propagation of the initial velocity[77], filling delay of peak velocity[78] or slope of an aliased velocity contour[79,80] also recognizes pseudonormalization because of maintained slowing of mitral–apical flow propagation. Pseudonormalization has also been observed for segmental left ventricular filling abnormalities: elevation of left atrial pressure reduces the extent of wall motion abnormalities, such as prolonged inward motion in the territory of a stenosed coronary artery or delayed long axis shortening in restrictive left ventricular disease[81] and after successful treatment, a fall in left atrial pressure again unmasks these segmental left ventricular filling abnormalities[82]. A severe decrease in left ventricular compliance causes further restriction to inflow[17], accentuates the pseudonormalization pattern and leads to diastolic mitral regurgitation because of an abnormal elevation of diastolic left ventricular pressure, which exceeds left atrial pressure ($E/A_{30–50y}$ >3·2; $DT_{<50y}$ <140 ms; $S/D_{<50y}$ <0·5). These alterations of left ventricular filling dynamics progressing from normal to slow relaxation, to pseudonormalization and to restriction are paralleled by changes in left atrial function with augmented atrial reservoir function during the slow relaxation phase and augmented atrial conduit function during the restrictive phase[83,84].

Based on these observations, diagnostic evidence of slow early left ventricular filling consists of at least one of the following criteria:

(1) PFR <160 ml . s^{-1} . m^{-2} on a contrast left ventricular angiogram;

(2) $PFR_{<30y}$ $<2{\cdot}0$ EDV . s^{-1} or $PFR_{30–50y}$ $<1{\cdot}8$ EDV . s^{-1} or $PFR_{>50y}$ $<1{\cdot}6$ EDV . s^{-1} on a radionuclide left ventricular angiogram;
(3) $E/A_{<50y}$ $<1{\cdot}0$ and $DT_{<50y}$ >220 ms or $E/A_{>50y}$ $<0{\cdot}5$ and $DT_{>50y}$ >280 ms on the mitral Doppler flow velocity signal;
(4) $S/D_{<50y}$ $>1{\cdot}5$ or $S/D_{>50y}$ $>2{\cdot}5$ on the pulmonary vein Doppler flow velocity signal.

Reduced left ventricular diastolic distensibility

Left ventricular diastolic distensibility refers to the position on a pressure–volume plot of the left ventricular diastolic pressure–volume relation[85] and a reduction in left ventricular diastolic distensibility refers to an upward shift of the left ventricular pressure–volume relation on the pressure–volume plot, irrespective of a simultaneous change in slope. Using progressive balloon caval occlusion, multiple end-diastolic pressure–volume points can be obtained and a diastolic left ventricular pressure–volume relation can be constructed, which is composed of multiple static end-diastolic left ventricular pressure–volume points[86–89]. This relation does not reflect the instantaneous operating relation of the left ventricle but offers the advantage of avoiding early dynamic effects of left ventricular relaxation[90] and of myocardial viscous forces[91] related to left ventricular filling.

A reduction in left ventricular diastolic distensibility provides diagnostic evidence for diastolic left ventricular dysfunction. Left ventricular end-diastolic distensibility is reduced when left ventricular end-diastolic pressure (>16 mmHg)[49] or mean pulmonary venous pressure (>12 mmHg)[15] are elevated in the presence of a normal left ventricular end-diastolic volume index (<102 ml . m^{-2}) or normal left ventricular end-diastolic internal dimension index ($<3{\cdot}2$ cm . m^{-2}). Similar diagnostic information on decreased left ventricular end-diastolic distensibility can also be derived from a shortened Doppler mitral A wave deceleration time[92], from the Doppler pulmonary vein flow signal when it reveals reverse pulmonary venous A wave flow velocity >35 cm . s^{-1}[69,74,75] or from the pulmonary venous A wave duration, when it exceeds mitral A wave duration[76,93]. Pulmonary venous A wave duration exceeding the duration of the mitral A wave by more than 30 ms indeed predicts a left ventricular end-diastolic pressure >15 mmHg with a $0{\cdot}85$ sensitivity and a $0{\cdot}79$ specificity[76]. Diagnostic evidence of decreased left ventricular end-diastolic distensibility can also be inferred from the apexcardiogram at rest when the magnitude of the A wave $>0{\cdot}20$ of the total excursion[94–97].

Increased left ventricular chamber or myocardial muscle stiffness

Left ventricular stiffness refers to a change in diastolic left ventricular pressure relative to diastolic left ventricular volume (dP/dV) and equals the slope of the diastolic pressure–volume relation. Its inverse is left ventricular diastolic compliance (dV/dP). Because the slope of the diastolic left ventricular pressure–volume relation varies along the left ventricular pressure–volume curve, left ventricular stiffness is often compared at a common level of left ventricular filling pressures[98]. A relation was demonstrated between Doppler mitral inflow deceleration time and left ventricular chamber stiffness[99]. Mean value and upper range of the constant of chamber stiffness (b) in control subjects are $0{\cdot}21$ and $0{\cdot}27$[100]. A b value $>0{\cdot}27$ therefore provides diagnostic evidence for diastolic left ventricular dysfunction.

Muscle stiffness is the slope of the myocardial stress–strain relation and represents the resistance to stretch when the myocardium is subjected to stress. The mean value of the constant of muscle stiffness (b′) observed in a control group equals $9{\cdot}9 \pm 3{\cdot}3$[101]. A b′ value >16 provides diagnostic evidence for diastolic left ventricular dysfunction.

Diagnostic criteria for evidence of abnormal left ventricular relaxation, filling, diastolic distensibility and diastolic stiffness in cardiac diseases

This chapter reviews the previous use of the currently proposed indices for evidence of abnormal left ventricular relaxation, filling, diastolic distensibility and diastolic stiffness in coronary artery disease, hypertrophic cardiomyopathy, cardiac amyloidosis, hypertensive heart disease, valvular heart disease, diabetes and cardiac transplantation (Table 2).

Coronary artery disease

Evidence for abnormal left ventricular relaxation filling, diastolic distensibility and diastolic stiffness can be present in coronary artery disease: (1) at rest without previous myocardial infarction; (2) at rest in the presence of previous myocardial infarction; (3) during acute ischaemia (exercise, pacing, coronary occlusion).

Evidence for abnormal left ventricular relaxation, filling, diastolic distensibility and diastolic stiffness at rest without previous myocardial infarction

In patients with coronary artery disease and no detectable asynergy, a prolonged value of τ (53 ± 16 ms) was first reported by Hirota[40]. In a group of patients with triple vessel coronary artery disease and no previous myocardial infarction a similar value was observed (49 ± 5 ms)[102] but in patients with single vessel coronary artery disease of the proximal left anterior descending artery no prolongation of τ was observed (37 ± 10 ms)[103]. In patients with coronary artery disease, early left ventricular filling assessed by radionuclide angiograms was abnormal irrespective of impairment of systolic function or history of previous myocardial infarction[104]. In a series of patients with single-vessel coronary artery disease and no evidence of

Table 2 Evidence of abnormal left ventricular relaxation, filling, diastolic distensibility and diastolic stiffness in cardiac diseases

	LV isovolumic relaxation	LV filling	LV distensibility	LV muscle stiffness
Cor art disease				
No previous MI	$\tau = 49 \pm 5$ ms[102]			
Previous MI	$\tau = 57 \pm 13$ ms[40] IVRT = 200 ms[106]	E/A = 0·77 ± 0·46[109]		
Pacing ischaemia	$\tau = 58 \pm 7$ ms[102]	E/A = 0·68 ± 0·15[114]	LVEDP = 24 ± 7 mmHg at LVEDVI = 88 ± 17 ml . m^{-2}[103]	b′ = 79 ± 47[102]
Balloon cor occl	$\tau = 60 \pm 14$ ms[103]	E/A = 0·91 ± 0·20[118]		
Hypertrophic CMP	$\tau = 63 \pm 20$ ms[43] IVRT = 112 ± 26 ms[43] $LVdP/dt_{min}$ = 998 ± 223 mmHg . s^{-1}[40]	PFR = 1·3 EDV . s^{-1}[129]	LVEDP = 22 ± 8 mmHg at LVEDID = 39·4 ± 8·6 mm[43]	
Restrictive CMP			LVEDP = 25 ± 6 mmHg at normal LVEDVI[138]	
Hypertensive hypertrophy	$\tau = 56 \pm 5$ ms[50]		LVEDP = 23 ± 6 mmHg at LVEDVI = 86 ± 24 ml . m^{-2}[50]	b = 0·32 ± 0·04[175]
Valvular heart disease				
Aortic valve disease	$\tau = 97 \pm 23$ ms[161]		LVEDP = 23 ± 8 mmHg at LVEDVI = 77 ± 29 ml . m^{-2}[189]	b′ = 21 ± 6[161]
Diabetes mellitus				b = 0·86 ± 0·26[175]
Cardiac allograft	IVRT = 107 ± 20 ms[184]			

Cor art disease = coronary artery disease; MI = myocardial infarction; τ = time constant of LV pressure decay; IVRT = isovolumic relaxation time; PFR = peak LV filling rate; E/A = ratio of peak early to peak a wave Doppler flow velocity; LVEDP = left ventricular end-diastolic pressure; LVEDVI = left ventricular end-diastolic volume index; LVEDID = left ventricular end-diastolic internal dimension; b′ = constant of muscle stiffness; b = constant of LV chamber stiffness.

prior myocardial infarction, two thirds of patients had decreased peak filling rate and/or prolonged time to peak filling rate, both of which improved following angioplasty[105]. These abnormalities could relate to subclinical ischaemia, to altered myocardial mechanical loading because of reduced early diastolic coronary engorgement or to modified endothelial release of mediators because of lower endothelial shear stress.

Evidence for abnormal left ventricular relaxation, filling, diastolic distensibility and diastolic stiffness at rest in the presence of previous myocardial infarction

In patients with coronary artery disease and previous myocardial infarction, τ was significantly longer than in controls (57 ± 13 ms vs 33 ± 8 ms)[40]. Frame-by-frame analysis of contrast left ventricular angiograms revealed inward regional wall motion during isovolumic relaxation in the region of the affected coronary artery[36], which resulted in marked prolongation (200 ms) of the isovolumic relaxation time on the M-mode echocardiogram[106]. Early diastolic left ventricular filling assessed by radionuclide angiogams is abnormal in the presence of previous myocardial infarction[104]. Peak early diastolic left ventricular filling rate derived from contrast LV angiograms is similarly reduced[107,108]. Following myocardial infarction, studies analysing the mitral Doppler inflow signal reported both a slow relaxation pattern with $E/A \leq 1$[109] and a short deceleration time of early filling[110,111], probably because of variable increases in left atrial pressure.

Evidence for abnormal left ventricular relaxation, filling, diastolic distensibility and diastolic stiffness during acute ischaemia

During pacing-induced ischaemia in patients with multivessel coronary artery disease and no previous myocardial infarction, there is further prolongation of τ (58 ± 7 ms[102]; 59 ± 7 ms[112]). Exercise-induced ischaemia results in a significantly smaller reduction in τ than that which occurs in patients without ischaemia[113]. Because of higher left atrial pressures, angiographic left ventricular peak filling rates remained either unaltered or increased during pacing or exercise-induced ischaemia[112,113]. Probably because of variable increases in left atrial pressure, the Doppler mitral inflow signal shifted to a delayed relaxation pattern with $E/A = 0{\cdot}68 \pm 0{\cdot}15$[114] or to a pseudonormalization pattern[115,116]. During balloon coronary occlusion, τ prolongs (60 ± 14 ms[103]) and the Doppler mitral inflow signal displays a slow relaxation pattern ($E/A = 0{\cdot}91 \pm 0{\cdot}20$)[117,118]. During pacing-induced ischaemia, left ventricular end-diastolic distensibility is reduced[102,103,119,120] as evident from the rise in left ventricular end-diastolic pressure from 13 ± 4 to 24 ± 7 mmHg at a comparable left ventricular end-diastolic volume index (control: 83 ± 19 ml . m^{-2}; post-pacing: 88 ± 17 ml . m^{-2})[103]. During pacing-induced ischaemia, a radial myocardial stiffness modulus of the ischaemic segment is also significantly increased from 38 ± 12 to 79 ± 47[102]. A similar reduction in left ventricular diastolic distensibility was observed during

exercise-induced ischaemia[113,121]. The changes in left ventricular diastolic distensibility during balloon coronary occlusion are controversial: some studies reported a decrease in diastolic left ventricular distensibility[87,88,122] but other studies, which excluded the presence of coronary collaterals, observed an increase in diastolic left ventricular distensibility[103,123,124]. Decreased diastolic left ventricular distensibility has also been deduced from the apexcardiogram during handgrip exercise in patients with coronary artery disease[125–127]. In 60% of patients without prior infarction and normal ejection fraction, a doubling of the apexcardiographic A wave/total excursion ratio was observed[128].

Hypertrophic cardiomyopathy

Indices of left ventricular relaxation have been shown to be abnormal in patients with hypertrophic cardiomyopathy using several techniques[129]. A prolongation of isovolumic relaxation time has been reported by numerous investigators[42,43,129–131] (e.g. 112 ± 26 ms[43]) using M-mode echocardiograms and aortic valve closure sound and a similar prolongation of τ was observed on microtip left ventricular pressure recordings[43,132] (e.g. 63 ± 20 ms[43]). M-mode echocardiographic and mitral inflow Doppler examinations of hypertrophic cardiomyopathy patients revealed reduced posterior wall thinning rates[133,134], prominent A waves (E/A ratio: $1{\cdot}4 \pm 0{\cdot}8$)[45] and prolonged deceleration times (244 ± 55 ms)[45]. Nuclear angiograms showed asynchrony of regional lengthening leading to impairment of global filling[129,135] (e.g. 1·3 EDV . s^{-1}[129]). Asynchrony induced by atrioventricular pacing caused further slowing of isovolumic relaxation and early left ventricular filling[136]. In patients with increased chamber stiffness superimposed on slow relaxation the nuclear peak filling rate pseudonormalized and its value (4·9 EDV . s^{-1}) even exceeded the normal value (3·2 EDV . s^{-1}[129]). End-diastolic left ventricular distensibility is clearly reduced in patients with hypertrophic cardiomyopathy, as evident from elevated end-diastolic pressures (22 ± 8 mmHg[43]) in the presence of small end-diastolic cavity volumes and from a high A wave/total excursion ratio (>0·35) on the apexcardiogram[97]. Because of prolonged left ventricular pressure decay into the filling phase, the diastolic left ventricular pressure–volume relation is often shifted upward and flat and the calculated constant of chamber stiffness underestimates the real stiffness[89].

Cardiac amyloidosis

Amyloidosis is the classical example of infiltrative restrictive cardiomyopathy. In this condition, end-diastolic left ventricular internal dimension appears to be normal and systolic function mildly reduced on echocardiographic examination[137]. Left ventricular end-diastolic distensibility is reduced as evident from elevated left ventricular end-diastolic pressure in the presence of normal or mildly enlarged end-diastolic volume[137,138]. When wall thickness is moderately increased (12–15 mm), IVRT is prolonged (87 ± 15 ms), the Doppler inflow signal reveals a slow relaxation pattern with $E/A = 1{\cdot}2 \pm 0{\cdot}6$ and $DT = 181 \pm 43$ ms and the pulmonary vein signal shows in some patients an increased S wave, decreased D wave and reverse atrial flow velocity greater than normal (21 cm . s^{-1})[139]. For further increases in wall thickness, pseudonormalization of the Doppler inflow signals occur and prognosis becomes worse for patients with DT < 150 ms[140,141].

Hypertensive heart disease — role of neurohormones and extracellular matrix

A prolongation of IVRT[142–144] and of τ[50,145] (e.g. $\tau = 56 \pm 6$ ms[50]) has been observed in hypertensive left ventricular hypertrophy, especially in more severe left ventricular hypertrophy. This prolongation reacts favourably to an acute intracoronary administration of angiotensin converting enzyme inhibitors[50] and this reaction supports a determinant role of the cardiac renin–angiotensin system in diastolic left ventricular dysfunction of hypertensive left ventricular hypertrophy[146]. Acute effects on diastolic left ventricular function have also been reported for other neurohormones such as brain natriuretic peptide[147] and C-type natriuretic peptide[148]. Neurohormones affect diastolic left ventricular function not only acutely but also chronically through altered composition of the left ventricular wall (i.e. increased interstitial fibrosis or fibrous content)[149] and through altered activity of myofibroblasts[150]. Indices of slow left ventricular relaxation return towards normal values following antihypertensive therapy induced regression of left ventricular hypertrophy[151]. Early left ventricular filling is impaired, as evident from reduced left ventricular peak filling rate on radionuclide angiograms[152,153], depressed E/A ratio and blunted E waves on the mitral Doppler inflow signal[154–157]. This impairment of left ventricular filling is related to left ventricular mass index and leads to inadequate augmentation of left ventricular end-diastolic volume during exercise to maintain systolic function[158]. Finally, left ventricular diastolic distensibility[50] and compliance are reduced in hypertensive left ventricular hypertrophy[145].

Valvular heart disease

Structural intramyocardial abnormalities and impairment of myocardial relaxation represent a major cause of diastolic heart failure in patients with valvular heart disease[1]. The enhanced susceptibility of hypertrophied myocardium to ischaemia[159] and the frequent elevation of right atrial pressure with concomitant engorgement of the coronary veins[160] further contribute to the reduction of left ventricular diastolic distensibility in valvular heart disease. In aortic valve disease, 50% of patients with aortic stenosis and 90% of patients with aortic regurgitation have signs of diastolic left ventricular dysfunction in the presence of normal systolic function[161] as evident from a prolongation of τ (97 ± 23 ms) and an increase of the myocardial stiffness modulus (b′) ($b' = 21 \pm 6$). This increase in the myocardial stiffness modulus progresses ($b' = 30 \pm 7$) in the early

post-operative period because of slower regression of fibrosis than of muscular hypertrophy. In aortic stenosis, diastolic left ventricular dysfunction is dependent on both gender and age, being more common in male patients ($b' = 31 \pm 14$)[162] and in the elderly ($b' = 36 \pm 12$)[163] and improves following intracoronary infusion of an angiotensin converting enzyme inhibitor[164], possibly through increased myocardial action of bradykinin and nitric oxide[165]. In patients with isolated aortic stenosis, Doppler left ventricular filling indices are not different from age-matched normal subjects[166].

Diabetes mellitus

The incidence of heart failure is increased in diabetes mellitus[167] and especially following myocardial infarction, diastolic heart failure seems to be a major contributing factor[168]. Possible mechanisms for diastolic heart failure include excessive myocardial fibrosis[169], interstitial accumulation of glycoproteins[170], slow sarcoplasmic calcium reuptake[171] or altered release from a dysfunctional coronary endothelium of mediators such as nitric oxide and endothelin, which exert paracrine myocardial effects on diastolic properties[172,173]. To investigate whether diabetes mellitus results in primary myocardial abnormalities unrelated to ischaemic heart disease, hypertension or obesity, several studies investigated left ventricular function in early insulin dependent diabetes with normal coronary angiograms. Invasive studies revealed a large increase in left ventricular chamber stiffness[174,175] especially in the obese (diabetic lean: $b = 0{\cdot}86 \pm 0{\cdot}26$; diabetic obese: $b = 1{\cdot}44 \pm 0{\cdot}26$[175,176]) which was related to plasma glucose and not to plasma insulin or left ventricular mass, and which exceeded the increase in chamber stiffness observed in the same study in hypertensives (hypertensives lean: $b = 0{\cdot}32 \pm 0{\cdot}04$; hypertensive obese: $b = 0{\cdot}39 \pm 0{\cdot}06$). Non-invasive studies further confirmed a decrease in diastolic left ventricular distensibility in children with type 1 diabetes, as evident from smaller end-diastolic cavity dimensions[177] and an increased A wave on the mitral inflow signal, especially during a cold pressor test[178]. Following administration of nitroglycerin, adults with uncomplicated type 1 diabetes showed a reduced E/A ratio and prolonged deceleration time on the Doppler mitral inflow signal consistent with unmasking of a slow left ventricular relaxation pattern through left ventricular preload reduction[179].

Cardiac allograft

Diastolic heart failure contributes to the reduced exercise tolerance of allograft recipients[180]. Allograft recipients show evidence of slow isovolumic relaxation ($\tau = 43 \pm 6$ ms)[48] and an increased diastolic left ventricular chamber stiffness modulus[181] because of a steeper than normal diastolic left ventricular pressure–volume relation, which was variably attributed to donor–recipient heart size mismatch[182], ischaemic injury at the time of graft retrieval, repetitive episodes of rejection, or cardiac hypertrophy because of cyclosporine-induced arterial hypertension. During episodes of rejection, restrictive physiology of the allograft becomes more prominent[183] with abbreviation of isovolumic relaxation time from 107 ± 20 ms to 65 ± 19 ms[184]. Even at the time of routine annual cardiac follow-up[185], some patients ($\pm 15\%$) show signs of persistent restrictive physiology with a sharp early diastolic dip on the left ventricular pressure recording, a shorter isovolumic relaxation time (65 ± 16 ms) and a shorter deceleration time of mitral and tricuspid inflow. These patients were characterized by a significantly higher rejection incidence.

Conclusion

The present study proposes guidelines for the diagnosis of diastolic heart failure using well defined cut-off values of indices of left ventricular function obtainable during cardiac catheterization or during non-invasive cardiac imaging and summarizes existing evidence for abnormal left ventricular relaxation, filling, diastolic distensibility and diastolic stiffness in different cardiac diseases frequently characterized by diastolic heart failure. A correct diagnosis of diastolic heart failure has become relevant to daily practice because diastolic heart failure features a more benign prognosis and requires specific forms of treatment, some of which are currently under investigation in large randomized clinical trials.

Application of uniform and standardized guidelines for the diagnosis of diastolic heart failure is a prerequisite for establishing a database on patients with diastolic heart failure. Such a database could provide a more precise insight into the incidence of diastolic heart failure in different patient populations and help to oversee the health care management problem imposed by diastolic heart failure. In the currently proposed guidelines, diagnostic evidence for diastolic heart failure is obtainable using several techniques and indices. The application of several techniques and the determination of several indices in the same patient population with diastolic heart failure will allow for future assessment of the independent predictive value of each technique and each index for the diagnosis of diastolic heart failure. The currently proposed guidelines for the diagnosis of diastolic heart failure will therefore require continuous updating as new insights into the predictive value of techniques and indices emerge.

Appendix 1

Indices of left ventricular relaxation, filling, diastolic distensibility and diastolic stiffness: methodological aspects

Peak negative left ventricular dP/dt (LV dP/dt_{min}): a valid measurement of this index requires a high fidelity tip micromanometer left ventricular pressure signal and adequate signal processing (high-cut filter >100 Hz).

Time constant of left ventricular pressure decay (τ = tau): τ is derived from a high fidelity tip micromanometer left ventricular pressure recording using the following formula:

$$P_t = P_0 e^{-t/\tau} + P_\infty$$

where P_t equals left ventricular pressure at time t, P_0 equals pressure at dP/dt_{min} and P_∞ the asymptote pressure or final pressure to which pressure would decay in the absence of filling. Curve fits to the digitized (5 ms interval) pressure data points have used monoexponential[47], two sequential monoexponentials[186], polynomial[43] or logistic[187] models. Other investigators derived τ from a linear curve fit to a dP/dt vs P plot[188]. A monoexponential fit yields a satisfactory correlation coefficient ($r > 0{\cdot}99$) except in an occasional patient with hypertrophic cardiomyopathy[188,189], aortic regurgitation[190] or acute myocardial ischaemia[103]. In these patients, a non-exponential decay of isovolumic left ventricular relaxation pressure can easily be appreciated from the convex downward morphology of the dP/dt signal during isovolumic relaxation[188,189]. The curve fit is applied to the isovolumic left ventricular pressure data points. It starts from left ventricular pressure at peak dP/dt_{min}, which coincides with aortic valve closure, and ends at a left ventricular pressure corresponding to mitral valve opening (usually set equal to the following left ventricular end-diastolic pressure +5 mmHg). Because of a slight deviation of left ventricular pressure decay from an exponential decline, a higher starting point or a higher end point will erroneously prolong τ[191]. Under conditions of drastically different left ventricular loads, this can easily be corrected for by calculation of all time constants with an equal starting point (= the lowest pressure at which left ventricular dP/dt_{min} occurred) and equal end point (= the highest mitral valve opening pressure)[189]. P_∞ (= asymptote pressure) is the final pressure to which left ventricular pressure would decay in the absence of filling. It has experimentally been determined in the non-filling dog heart using a metal occluder and amounted to −7 mmHg[192]. In another non-filling dog heart preparation with preserved mitral apparatus[193] and in patients with mitral stenosis[194] during occlusion of the mitral valve with the self-positioning Inoue balloon at the time of percutaneous balloon mitral valvuloplasty, these sub-atmospheric pressures were not observed and P_∞ equalled +2 mmHg. In both experimental[192] and clinical[194] non-filling beats, it has been demonstrated that the value of P_∞ derived from a curve fit procedure had no relation to the directly measured value of P_∞. The use of a zero asymptote ($P_\infty = 0$) therefore seems adequate as evidence of abnormal left ventricular relaxation in an individual patient. The use of a variable asymptote is recommended for a more refined analysis such as evaluation of effects of treatment on isovolumic relaxation kinetics.

Peak early left ventricular filling rate (PFR): Estimates of peak early left ventricular filling rate have been obtained from frame-by-frame analysis of left ventricular contrast angiograms measuring instantaneous filling volumes (V) at 20 ms intervals (filming rate 50 frames . s^{-1}) and calculating instantaneous filling rate (FR) as $FR = V(t + 0{\cdot}02) - V(t - 0{\cdot}02)/0{\cdot}04$, where t = time[195].

Increased left ventricular chamber or myocardial muscle stiffness: Determination of left ventricular chamber stiffness requires an exponential curve fit to the diastolic left ventricular pressure (P)-volume (V) relation constructed from a frame-by-frame analysis (every 20 ms) of a left ventricular angiogram and a simultaneously recorded high-fidelity tip micromanometer left ventricular pressure recording. Although the mathematical validity of such an exponential curve fit has been challenged[196], this is usually achieved through logarithmic transformation of the exponential diastolic left ventricular pressure–volume relation into a linear equation[197–199],

$$\ln(P - c) = \ln a + bV$$

where b = constant of chamber stiffness and a,c = intercept and asymptote of the relation.

Muscle stiffness is the slope of the myocardial stress–strain relation. Calculation of stress requires a geometric model of the left ventricle and calculation of strain an assumption of the unstressed left ventricular volume, which cannot be measured in vivo and is therefore usually replaced by left ventricular dimension at a wall stress of lg . cm^{-2}. Determination of muscle stiffness requires a mathematical curve fit to the diastolic left ventricular wall stress (S)–strain (E) relation, which can be transformed into a linear equation[197–199]

$$\ln(S - c') = \ln a' + b'E$$

where b′ = constant of muscle stiffness and a′,c′ = intercept and asymptote of the relation.

Appendix 2

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