Effects of gradual volume loading on left ventricular diastolic function in dogs: implications for the optimisation of cardiac output

Volume loading and diastolic function

J Fragata, J C Areias

Abstract

Background—Volume loading is commonly used to adjust preload and optimise cardiac output. It is difficult to monitor preload at the bedside because filling affects ventricular diastolic function and consequently end diastolic pressure, which is the variable used to monitor preload.

Objective—To assess the effects of gradual volume loading on the different components of left ventricular diastolic function—filling velocities, relaxation, and chamber compliance—to identify how excessive loading produces diastolic dysfunction.

Methods and results—Eight mongrel dogs, anaesthetised and mechanically ventilated with both the chest and the pericardium closed, were studied during basal conditions (B), during gradual volume loading with physiological saline—5 ml/kg (VL5), 10 ml/kg (VL10), and 15 ml/kg (VL15)—and during infusion of isosorbide dinitrate (10 μg/kg/min) started after the VL15 load was achieved. Dogs were monitored haemodynamically and by transthoracic Doppler echocardiography to assess peak modal velocities of the E and A waves, E/A ratios, and the deceleration time of the E wave. M mode recordings of aligned mitral and aortic valve motion were also obtained to calculate the isovolumic relaxation time. Effects of volume loading on ventricular diastolic function seemed to occur in two phases. Small and moderate volume loads (VL5 and VL10) promoted early ventricular filling, increasing E wave velocities, improving the mean (SD) E/A ratio from 1.95 (0.3) (B) to 2.0 (0.27) (VL5) and 2.6 (0.3) (VL10) (P < 0.00005), prolonging the E wave deceleration time, and only slightly increasing ventricular diastolic pressures. These changes suggest an improvement in ventricular compliance. Extreme volume loads (VL15) produced an abrupt reduction in early ventricular filling, which was transferred to late in diastole, by decreasing E wave velocity, by increasing A wave velocity, and by decreasing E/A ratio from 2.6 (0.3) (VL10) to 0.8 (0.05) (VL15) (P < 0.00005). The E wave deceleration time was shortened and left ventricular diastolic pressures were much increased, all suggesting a deterioration in chamber compliance. All these restrictive changes were promptly reversed by the perfusion of isosorbide dinitrate. The isovolumic relaxation time steadily increased with volume loading.

Conclusions—Small and moderate volume loads improved ventricular diastolic function by promoting early ventricular filling and increasing ventricular compliance. Extreme volume loads promptly induced a diastolic restrictive pattern, transferring filling to the second part of diastole (increasing dependence on atrial contraction) and reducing ventricular compliance. These changes in ventricular diastolic function were independent of simultaneously measured haemodynamic systolic performance and were promptly reversed by isosorbide dinitrate, which after extreme loading promoted early filling, myocardial relaxation, and improved chamber compliance.

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Keywords: diastolic ventricular function; volume loading

Volume loading is the first intervention used to optimise cardiac output in critically ill patients after open heart surgery.

12 Volume loading is aimed to expand ventricular preload to increase stroke volume and cardiac output. This relation, in clinical everyday use, is based on the Frank-Starling law of the heart, that relates fibre distension in diastole (preload) to systolic work—volume displacement, against a given resistance (afterload) for a given level of myocardial contractility.

Ideal myocardial fibre distension induced by volume loading of the ventricles is difficult to monitor in the critically ill. This is particularly true in patients after open heart surgery in whom changes in both the systolic13 and the diastolic4,6 ventricular function are known to take place during the first hours after the operation and to affect ventricular pressure-volume relations to an uncertain extent. Left ventricular filling is complex and known to have multifactorial determinants—moment loading conditions, myocardial relaxation state, ventricular compliance, heart rate, and atrial contraction9;10; these must all be taken into consideration in order to understand both the process and the end result of ventricular filling in response to gradual volume loading.

Optimisation of cardiac output depends firstly on adequate filling of the ventricles.
This is usually obtained by trial and error by assessing filling pressures and the effects produced upon systolic performance. Filling conditions ought to be monitored carefully as overfilling is known to produce deleterious effects on systolic performance of the ventricles.1213 The present study was designed to follow the effects of gradual volume loading on left ventricular diastolic filling patterns, assessed by Doppler-echocardiography, by relating them to simultaneous systolic events, in order to detect early diastolic dysfunctions. The shifting points that occur with extreme loading conditions, even before such shifts could affect systolic performance.

Methods

ANIMAL PREPARATION

Eight mongrel dogs (12·0 (2·7) kg) were used for the study. Their care complied with the Principles of Laboratory Animal Care, formulated by the National Society for Medical Research, and the Guide for the Care and Use of Laboratory Animals, prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH Publication No 86–23, revised 1985).

Dogs lay supine on a heating pad and were anaesthetised with intravenous pentobarbitone (30 mg/kg). They were mechanically ventilated with room air using a Palm animal ventilator (tidal volume of 12 ml/kg at a rate of 20/minute to keep arterial PCO2 between 30 and 40 mm Hg). The electrocardiogram was continuously monitored, a 6F pigtail catheter was advanced retrogradely from the femoral artery into the left ventricle, a double lumen 7F Swan–Ganz thermodilution catheter was introduced through the femoral vein and placed in the pulmonary artery and a 6F pressure line was placed in the descending aorta, through the femoral artery. Pressures were measured in the aorta, the left ventricle, and the pulmonary artery, by using fluid filled catheters and Gold transducers zeroed at mid chest level and a Datasonic 2000A cardiac monitor.

Cardiac output was evaluated by thermodilution using an Arrow A1 thermodilution computer and a Swan–Ganz thermodilution catheter. Values were automatically computed from dilution curves obtained with triplicate injections of 5 ml physiological saline, kept in ice and delivered by hand and at a temperature of 4°C, into the right atrium. Haemodynamic data were recorded in absolute values and then related to the dog’s body surface area where appropriate. Body surface area was calculated by the formula:

\[ \text{BSA} = 0.112 \times \text{weight}^{0.37} \text{(kg)} \]

and left ventricular stroke work index was calculated according to the formula:

\[ \text{LVSWI} = \left( \text{MAP} - \text{PCW pressure} \right) \times \text{SVI} \times 0.0136 \]

Doppler echocardiograms were obtained using a 5 MHz probe and an Aloka SSD-720 echo machine and recorded for future reading in VHS videotapes (50 mm/s speed). Pulsed cross sectional echo-Doppler recordings of mitral inflow were obtained with the transducer aligned with the long axis of the ventricle and the sample volume was placed at the valve ring level. Transthoracic recordings of five consecutive cycles were made during short periods of apnoea and after the dogs were momentarily positioned in the left lateral decubitus position, in order to improve the echocardiographic window and to ensure accurate echo recordings. The echocardiographic signal was continuously recorded and M mode recordings of the aligned mitral and aortic valve motion were obtained for calculation of the isovolumic relaxation time (IRT).

Although M mode measurements of ventricular dimensions were taken during volume loading they were not systematically registered because the unpredictable variation in the chamber shape suggested they would be of little use for judging volume changes from linear dimensions.

The tapes were read blindly. Peak modal velocities of the E wave and A wave of the Doppler mitral flow profile were measured in cm/s. The E/A ratio was calculated and the deceleration time of the E wave was measured in ms from the peak of E wave to its nadir on the baseline. Occasionally, when the A wave started before the E wave had reached the zero line, the E wave deceleration time had to be measured by extrapolating its descent and estimating its nadir on the baseline.

Means and standard deviations of the mean were compared by Student's paired r test and linear regression analysis was performed where appropriate. Values of P < 0·05 were regarded as statistically significant.

EXPERIMENTAL DESIGN

Dogs were studied during basal conditions (B) and during gradual volume loading with physiological saline, 5 ml/kg (VL5), 10 ml/kg (VL10), and 15 ml/kg (VL15). Saline loads were infused for up to 5 minutes and measurements were made after allowing 10 minutes for haemodynamic stabilisation. After the 15 ml/kg volume load (VL15) an intravenous infusion of isosorbide dinitrate (10 g/kg/min (IDN)) was given and measurements were repeated after 10 minutes of haemodynamic stabilisation.

Dogs were killed by a bolus injection of potassium chloride, and the placement of all intracardiac lines was checked.

Results

Progressive volume loading simultaneously affected haemodynamics and ventricular filling and relaxation. It eventually induced a restrictive filling pattern that was reversed by IDN. These complex changes are analysed separately:

HAEMODYNAMIC VARIATION (Table I)

Heart rate showed no significant variation from baseline to maximal volume loading. Left ventricular systolic pressure increased gradu-
ally with volume loading, from 121-4 (24-9) (VL7) to 129-7 (20-8) (VL5) to 138-7 (26-3) (VL10) and to 144-6 (18-3) mm Hg (VL15); these changes did not reach statistical significance. Left ventricular diastolic pressure increased gradually, from 1-5 (3-2) (B) to 4-2 (3-5) (VL5) mm Hg (P = 0-02) and to 7-4 (5-9) (VL10) (P = 0-003); it increased dramatically with extreme volume loading, from 7-4 (5-9) (VL10) to 14-6 (6-0) mm Hg (VL15) (P = 0-0005).

Cardiac index increased steadily for all levels of volume loading, from 1-9 (0-6) (B) to 2-6 (1-1) (VL5) to 3-4 (0-7) (VL10) and to 4-0 (0-5) l/min/m² (VL15); these changes did not reach statistical significance. Left ventricular stroke work index increased from 1-2 (4-2) (B) to 2-2 (9-8) (VL5) (P = 0-01) to 3-0 (8-6) (VL10) (P = 0-006) and to 3-8 (13-2) g/min/m² (VL15) (P = 0-025).

EARLY FILLING WAVE (E WAVE) (TABLE 2)

During volume loading peak modal E wave velocity increased from 76 (6-3) (B) to 84-2 (9-7) (VL5) (NS) and to 99-2 (9-2) cm/s (VL10) (P = 0-01). Then it decreased to 72-7 (8-1) cm/s during the extremely high volume loading (VL15) (P = 0-00).

LATE FILLING WAVE (A WAVE) (TABLE 2)

Peak modal A wave velocities did not vary significantly for the first two volume loads, changing from 41-5 (6-1) (B) to 41-7 (8-0) (VL5) (NS) to 38-8 (5-7) (VL10) (NS). Then it increased significantly from 38-8 (5-7) (VL10) to 85-8 (8-0) cm/s (VL15) (P = 0-0005).

E/A RATIO (TABLE 2)

The E/A ratio increased from 1-95 (0-3) (B) to 2-0 (0-27) (VL5) and 2-6 (0-3) (VL10) (P < 0-00005), to decrease to 0-8 (0-05) (P < 0-00005) with extreme volume loading (VL15). E/A ratio, as a global index of the filling conditions, correlated well with left ventricular diastolic pressure, r = 0-61 (P < 0-001, n = 24) and with IRT, r = 0-70 (P < 0-001, n = 24).

E WAVE DECCELERATION TIME (EWD T) (TABLE 2)

Variation in EWD T during volume loading paralleled E wave velocity variation, increasing from 101-8 (14-9) (B) to 104-8 (8-7) (VL5) to 132-0 (26-3) (VL10) (P = 0-04) and decreasing to 86-2 (14-7) ms (P = 0-003) with extreme volume loading (VL15). EWD T correlated well with left ventricular diastolic pressure (r = 0-54 (P < 0-01, n = 24).

ISOVOLUMIC RELAXATION TIME (IRT) (TABLE 2)

IRT increased significantly from 75-4 (6-6) (B) to 86-4 (5-2) (VL5) (P = 0-005) to 100-6 (6-0) ms (VL10) (P = 0-022) during gradual volume loading. Left ventricular systolic pressure increased along with each volume load and correlated with IRT (r = 0-56, P < 0-01, n = 30), while the heart rate slowed down, though not significantly, from 157-4 (23-8) (B) to 139-4 (19-3) beats/min (VL15).

EFFECTS OF IDN ON DIASTOLIC FUNCTION INDICES AFTER EXTREME VOLUME LOADING (TABLES 1 AND 2)

IDN was given after the extreme 15 ml/kg volume load was reached. It reduced IRT from 122-6 (14-6) (VL15) to 55-7 (6-0) ms (IDN) (P = 0-023). It also decreased left ventricular diastolic pressure from 158 (6-0) (VL15) to 10-3 (4-7) mm Hg (IDN) (P = 0-0005) and

Table 1 Haemodynamic data

<table>
<thead>
<tr>
<th>Variables</th>
<th>Basal</th>
<th>VL5 (ml/kg)</th>
<th>VL10 (ml/kg)</th>
<th>VL15 (ml/kg)</th>
<th>DNI</th>
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<td>150-0 (21-4)</td>
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<td>LV SP (mm Hg)</td>
<td>121-4 (24-9)</td>
<td>129-7 (20-8)</td>
<td>138-7 (26-3)</td>
<td>144-6 (18-3)</td>
<td>161-0 (22-0)</td>
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<td>LV DP (mm Hg)</td>
<td>1-5 (3-2)</td>
<td>4-2 (3-5)</td>
<td>7-8 (5-9)</td>
<td>15-8 (6-0)</td>
<td>10-3 (4-7)</td>
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<td>Cardiac index (l/min/m²)</td>
<td>1-9 (0-6)</td>
<td>2-6 (1-1)</td>
<td>3-4 (0-7)</td>
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<td>LV stroke work (g/min/m²)</td>
<td>12-7 (4-2)</td>
<td>22-9 (9-8)</td>
<td>30-2 (8-6)</td>
<td>38-5 (13-2)</td>
<td>41-0 (14-4)</td>
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</table>

Values are means (SD).
*Compared with basal; †compared with VL5; ‡compared with VL10; §compared with VL15.
LV SP, left ventricular systolic pressure; LV DP, left ventricular diastolic pressure.

Table 2 Doppler echocardiographic data

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<th>Basal</th>
<th>VL5 (ml/kg)</th>
<th>VL10 (ml/kg)</th>
<th>VL15 (ml/kg)</th>
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<td>E/A ratio</td>
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<td>4-3 (2-2)</td>
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<tr>
<td>EWD T (ms)</td>
<td>101-8 (14-9)</td>
<td>104-8 (8-7)</td>
<td>132-0 (26-3)</td>
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<td>119-0 (3-6)</td>
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<td>IRT (ms)</td>
<td>75-4 (6-6)</td>
<td>86-4 (5-2)</td>
<td>100-6 (6-6)</td>
<td>122-6 (14-6)</td>
<td>55-7 (6-0)</td>
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<td>(P = 0-005)$</td>
<td>(P = 0-005)$</td>
<td>(P = 0-022)$</td>
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</table>

Values are means (SD).
*Compared with basal; †compared with VL5; ‡compared with VL10; §compared with VL15.
increased left ventricular systolic pressure from the VL15 value of 144.6 (18.3) to 161.0 (22.0) mm Hg (IDN) (P = 0.001). EwDT increased from 86.2 (14.7) (VL15) to 119.0 (3.6) ms (IDN) (P = 0.022) and E/A filling ratio from 0.8 (0.05) (VL15) to 2.2 (0.02) (IDN) (P = 0.0007).

IDN reversed the restrictive filling pattern imposed by extreme volume loading, by improving both relaxation and chamber compliance and by promoting early ventricular filling.

Discussion
Our study demonstrates the effects of gradual volume loading upon different components of left ventricular diastolic function—filling velocities, relaxation, and chamber compliance—and the simultaneously produced haemodynamic variation. The effects of volume loading seemed to be biphasic: small and moderate volume loads promoted early ventricular filling, improved ventricular compliance, and exerted no effect on ventricular diastolic pressures. Extreme volume loads abruptly reduced early filling, transferring it to late in diastole, and to dependance on atrial contraction. Volume loading also decreased chamber compliance and increased ventricular diastolic pressure. At the same time isovolumic relaxation was steadily prolonged for all levels of volume loading. These changes in diastolic function took place at the same time as haemodynamic systolic variables, such as the cardiac index and ventricular stroke work, increased steadily with additional volume loading.

When we assessed the effects of IDN, a commonly used vasodilator, on extreme loading conditions we found that it reversed the pattern of restrictive diastolic dysfunction induced by excessive loading, promoting early filling, chamber compliance, and myocardial relaxation.

Discussion of Methods
We used anaesthetised mechanically ventilated, closed chest dogs under stable homeostatic conditions. The effects of the anaesthetic, pentobarbitone, on ventricular function are well established and the possible effects of ventilation on ventricular filling were abolished by taking measurements only during post-expiratory apnoea.

Doppler echocardiography is an established non-invasive method of assessing ventricular diastolic function but because many factors interact simultaneously to influence ventricular relaxation, Doppler filling patterns must be interpreted cautiously and considered, as we have done, in the light of simultaneous haemodynamic variation.

Heart rate was allowed to fluctuate in our experiments, although it is known to affect both relaxation and ventricular filling. Heart rate variation in our series was small and so unlikely to have affected relaxation conditions. In our experimental group, and like others, we did not find any correlation between heart rate and either IRT or filling velocities.

For haemodynamic monitoring of the filling conditions, we preferred to use the mid-diastolic left ventricular pressure plateau that is related to the equalisation of both the left atrial and the left ventricular diastolic pressure at the end of the early filling phase of diastole, although we know that it relates more to the end result of early filling rather than to the early part of diastole. This choice may be open to criticism but it was made because left atrial pressure could not be measured directly and so an accurate measurement of the transmitral haemodynamic gradient was not available. Also, we did not think that pulmonary wedge pressure would have been an accurate method to estimate left atrial pressure and indirectly to assess left ventricular filling conditions.

Gradual volume loading, as used in our series, allows for a better understanding of the progressive changes that occur simultaneously in diastolic and systolic ventricular function while volume expansion is taking place in conditions that mimic the clinical situation.

VOLUME LOADING EFFECTS ON VENTRICULAR RELAXATION
Relaxation is affected by moment loading conditions. Loads applied early in diastole are called relaxation loads and are known to accelerate the relaxation process, while loads applied late in diastole are called contraction loads and are known to delay relaxation (directly if they are pressure loads or indirectly if they are volume loads, and they secondarily affect the afterload conditions). This is the case for in vivo models such as the one we used.

Sequential volume infusion in our series is an example of a combined direct distension load and an indirect tension load acting in sequence during both the contraction and relaxation phases of the cardiac cycle. These loads determine the increases and decreases in relaxation time respectively and contribute to the so-called auxotonic regulation of the relaxation process. The prolongation of IRT, which reflects the relaxation delay, that we found for all levels of volume loading in our series, sums the effects of these different loading factors on relaxation. This is borne out by the positive correlation found between IRT and left ventricular peak systolic pressure (contraction load) and by the negative correlation found between IRT and systemic vascular resistance (relaxation load) in our series.

VOLUME LOADING EFFECTS ON VENTRICULAR FILLING
Left ventricular filling is a complex phenomenon that takes place during an early (85% of the filling volume) and a late filling phase (15% of the filling volume), which are separated by the diastasis pause. Filling is known to be a multifactorial process determined by moment loading conditions, myocardial relaxation state, ventricular compliance, heart rate, and atrial contraction.

Several groups have assessed the effects of
volume loading and the effects of volume unloading upon diastolic function indices. Our results show, for the first time, a biphasic pattern of diastolic function, characterized initially by improved filling conditions with small to moderate volume loading, followed by a restrictive filling pattern induced by extreme loading that was detected even before systolic function started to deteriorate as a consequence of "overfilling"—that is, even before the start of the decline in the Starling curve.

Small and moderate volume loads (5 and 10 ml/kg) increased the early filling velocity (E wave) and kept the late filling velocity (A wave) constant because they increased the left atrial to left ventricular pressure gradient that initiates early ventricular filling. This haemodynamic effect was bigger than the simultaneously induced prolongation of IRT that we and others observed, which tends to reduce early filling velocity. EwDT, a variable related to ventricular compliance, became longer as loading increased. An indication that ventricular compliance increased in parallel is the increase in diastolic volume with only a small increase in diastolic pressure. Our results are similar to those of Nishimura et al. in moderately volume loaded patients, except that they found that EwDT was reduced. The reason for this important difference may lie in the fact that they studied coronary patients, in whom ventricular compliance is reduced, and that in their study filling pressures were increased by 20%, which corresponds only to our extreme loading conditions.

Extreme volume loading (15 ml/kg) reduced early filling velocity, increased late filling velocity (A wave velocity), and reduced EwDT whereas left ventricular diastolic pressure was significantly increased, suggesting deterioration in ventricular compliance. This corresponds to a restrictive filling pattern of diastolic dysfunction in which filling was transferred to the second half of diastole and which depended on atrial contraction, but which still maintained the filling volumes and an entirely normal systolic performance, with increases in cardiac index and ventricular stroke work. These results accord with those of Ishida et al. and Nishimura et al. in dogs in which extreme volume loading induced similar restrictive diastolic filling patterns.

Alternatively we might infer that this biphasic response of the early filling velocity to volume loading is related to changes in the preceding isovolumic relaxation phase, which is a well known determinant of ventricular filling. The response of isovolumic relaxation velocity to increases in load was also recently shown to be biphasic in a recent study by Leite-Moreira and Gillebert. They showed that the biphasic response was related to the relative load, assessed as a percentage of the peak isovolumic pressure. Our failure to show a biphasic pattern of variation for the isovolumic relaxation time too is probably due to the large variation imposed by different volume loading conditions on aortic valve closing and mitral valve opening times.

VOLUME LOADING EFFECTS ON VENTRICULAR COMPLIANCE

Chamber compliance is known to depend on myocardial modular elasticity, diastolic volume, ventricular mass, shape of the cavity, and diastolic interdependence mechanisms mediated by the closed pericardium. EwDT relates to ventricular compliance and varied in our series with volume loading, increasing with small and moderate loads, in favour of early filling, and decreasing with extreme loads. The reason for these changes, confirmed by others but only for extreme loads, lies not only in the increase in diastolic volume but also in changes of cavity shape mediated by diastolic interdependence mechanisms with the right ventricle, septum, and pericardium that occur because the right ventricle is being simultaneously loaded while other determinants remain constant. Because of the curvilinear shape of the pressure-volume curve, extreme volume loading produced a sudden leftward shift on the curve, accounting for the dramatic increase in ventricular diastolic pressures, which were found to correlate negatively with EwDT.

EFFECTS OF IDN ON FILLING CONDITIONS AFTER EXTREME VOLUME LOADING

The effects of IDN on the restrictive filling pattern induced by extreme loading were dramatic and characterised by improved relaxation (IRT decrease), improved ventricular pressure-volume relations (prolongation of EwDT and reduction in ventricular diastolic pressures), and reversal of the restrictive filling pattern and the E/A ratio. These actions contrast with the apparently negative effects of nitrates on diastolic ventricular function, which are similar to pure haemodynamic preload reduction and are characterised by reduction in early filling velocity and decreases in EwDT. In our series the clearly favourable effect of IDN on diastolic function has to do with the fact that, unlike other studies, nitrates were used only when extreme loading conditions were achieved and not when haemodynamic variables were normal. The mechanisms responsible may have been primarily a preload reduction effect that induced a favourable ventricular pressure-volume curve shift and eventually a direct myocardial effect with improved relaxation (IRT decreased). This effect could either be direct or depend on induced myocardial vasodilation that could act as an intrinsic load to enhance relaxation or even correspond to a vasodilator effect that would favour sub-endocardial perfusion in a volume loaded, distended ventricle with sub-endocardial ischaemia and improve relaxation compliance and filling.

CLINICAL IMPLICATIONS

Our study allowed for a better understanding of the gradual volume loading process, as used to optimise cardiac performance in critically ill patients. Transition from normal diastolic function to abnormal relaxation and filling was demonstrated and proved to be sudden and to occur with high filling pressures, even before...
any haemodynamic systolic deterioration could occur. The true restrictive filling pattern that was induced by extreme loading was easily reversed by nitrate therapy, allowing for new pressure-volume relation and more room for volume optimisation.

Correlation between Doppler derived data and haemodynamic measurements was poor in our series as in others, but was present between the E/A ratio and ventricular diastolic pressures.

Combination of both diastolic ventricular function data assessed by Doppler echocardiography (namely transoesophageal) and traditional haemodynamic data might be useful to monitor changing filling conditions (for example, after open heart surgery) and to optimise systolic function in relation to volume loading as well as to guide fluid therapy in any critically ill patient.

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