



ORIGINAL ARTICLE

Acute effect of clonidine on left ventricular pressure-volume relation in hypertensive patients with diastolic heart dysfunction

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We sought to assess the haemodynamic effects of clonidine on left ventricular (LV) pressure-volume relation in patients with diastolic heart dysfunction due to essential hypertension. Towards this end, simultaneous recordings of LV volume (acoustic quantification) and LV pressure (micromanometer) were obtained in 10 such patients before and after drug administration and compared to baseline findings on 10 matched normal controls. The following measurements and calculations were obtained: maximal positive and negative first derivative of LV pressure (peak +dP/dt and peak -dP/dt, respectively), LV minimal and end-diastolic pressure, peak systolic blood pressure, time constant of relaxation (TAU), LV stroke work and LV stiffness constant. The two invasive indexes, LV stiffness constant and TAU classified 10/10 patients as having abnormal LV diastolic function compared with 7/10 patients so classified by Doppler studies. Central sympathetic suppression by a single oral dose of clonidine 0.125 mg in

these patients resulted within 60 min in a decrease of heart rate and mean arterial pressure as well as a significant improvement of LV diastolic function indexes. Specifically, the LV stiffness constant (ml^{-1}), in normal subjects was 0.0028 vs 0.0152 ($P < 0.001$) in hypertensive subjects at baseline, vs 0.0053 in hypertensive after clonidine ($P < 0.001$ vs baseline). Likewise, the E/A ratio, was 1.08 in normal subjects vs 0.88 ($P < 0.0001$) in hypertensives at baseline, vs 1.28 in hypertensives after clonidine ($P < 0.0001$ vs baseline). With clonidine the diastolic portion of the pressure-volume curve was displaced downward. In conclusion, clonidine can improve diastolic dysfunction without depressing systolic LV performance. The improvement may be attributable in part to withdrawal of direct sympathetic influence on the myocardium and in part to the indirect effect of systemic, pulmonary and coronary artery relaxation.

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Introduction

Our understanding of the pathophysiology of congestive heart failure and our ability to treat this syndrome have improved greatly. The most important pharmacologic advance in recent years is the introduction of the angiotensin-converting enzyme inhibitors and the delineation of their role in the management of congestive heart failure.¹ Another approach is modulation of the sympathetic nervous system by various means. Beta-adrenoreceptor

blockers have been utilised in congestive heart failure patients for more than two decades.²

Modulating the sympathetic nervous system, either by decreasing central sympathetic outflow or decreasing peripheral noradrenaline release, may be advantageous by virtue of blunting rather than blocking catecholamine-mediated responses and by decreasing α -adrenoreceptor-mediated actions, which may have important effects on cell growth and function. Several sympathoinhibitory agents are being evaluated in this respect. Clonidine and related central α_2 -agonists have been used safely in patients with congestive heart failure³ but their effects on diastolic function have not been adequately studied so far.

The proportion of patients carrying the diagnosis of heart failure who are found to have preserved left ventricular (LV) systolic function is estimated to be

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20–40%.^{4–7} In such patients treatment with standard heart failure medications (such as digitalis, diuretics, and vasodilators) is often ineffective and may be detrimental.⁸ The purpose of this study was to assess the haemodynamic effects of central sympathetic inhibition with clonidine in patients with diastolic dysfunction by evaluating changes in the LV pressure–volume relationship.

Materials and methods

Study population

Ten untreated hypertensive patients (six men and four women; mean [±s.d.] age 63 ± 9 years) with concentric LV hypertrophy defined as the presence of ≥ 13 mm wall thickness by two-dimensional or M-Mode criteria, with clinical evidence of limitation of exercise tolerance (nine patients), pulmonary congestion (five patients), or fluid retention (four patients), were studied. The clinical symptomatology was disproportionately severe compared to the objective assessment of systolic cardiac function. Non-cardiac aetiologies for the presenting symptoms and signs, valvular heart disease and coronary artery disease were eliminated. Severe systolic dysfunction was excluded by echocardiographic examination and heart catheterisation (ejection fraction $>45\%$).⁹ The majority of patients demonstrated abnormalities of rapid filling, such as E/A (ratio of transmitral Doppler inflow peak velocities) reversal, in which atrial contribution to ventricular filling was more pronounced than early filling. No patient had atrioventricular or intraventricular conduction disturbances. Ten healthy age- and sex-matched subjects with normal physical examination, and normal two-dimensional and Doppler echocardiographic studies, who were submitted to coronary angiography for evaluation of atypical chest pain and proved to have normal coronary arteries, were used as controls.

The institutional ethics committee of our hospital approved the study protocol. Written informed consent was obtained from all patients after a detailed description of the procedure.

Echocardiographic studies

A complete study, including M-Mode and two-dimensional echocardiography, Doppler pulsed wave interrogation of the mitral valve and Doppler colour flow imaging was performed according to standard techniques using a Sonos 2500 ultrasonograph (Hewlett-Packard Co. Medical Products Group) with 2.5 MHz transducer. Interventricular septum and posterior wall thickness were measured at end-diastole by M-Mode technique using the standards recommended by the American Society of Echocardiography.¹⁰ After two-dimensional imaging was completed, a spectral Doppler recording of the mitral inflow was made from the apical four-

chamber view with the pulsed wave sample volume positioned at the tips of the mitral valve leaflets. The sample volume was then placed in the LV outflow tract near the aortic valve, so that a recording of both the LV outflow and the mitral inflow were obtained for isovolumetric relaxation time (IVRT) measurements.¹¹

Automated boundary detection (ABD) imaging: All two-dimensional ABD echocardiograms were performed with a Hewlett Packard Sonos 2500 system equipped with a 2.5 MHz imaging transducer having an ABD application. Data were acquired in standard apical four-chamber view.¹² The ABD system displayed a border following the detected cavity-wall interface. A study was considered satisfactory if at least two-thirds of the endocardial contour were correctly tracked by visual assessment.¹³ We automatically proceeded to on-line graphical display of the instantaneous LV volume in ml (Figure 1). A special effort was made to take LV volumes from exactly the same position during repeated measurements. This was achieved by directing the LV volume to the position where the tracing of the regional area of interest (ROI) was kept constant. All measurements were made during quiet respiration.

Left ventricular pressure measurement

LV pressure was recorded by a catheter tip micromanometer simultaneously with instantaneous LV volume measurements derived from ABD two-dimensional echocardiography. After all patients had been premedicated with diazepam (5 mg IM), selective coronary angiography and left ventriculography were performed through the right femoral artery using an 8F sheath. The angiographic studies were evaluated by two observers in a blinded manner and all patients had angiographically normal coronary arteries.

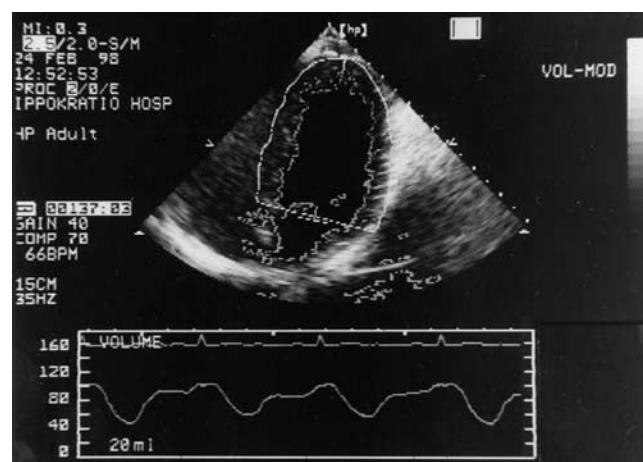


Figure 1 Echocardiographic automatic boundary detection image (top) with the region of interest drawn around the left ventricle and the instantaneous cavity volume displayed simultaneously with the electrocardiogram (ECG, bottom).

All patients received 10000 U of intravenous heparin before catheterisation. A 7 F Millar double-tip micromanometer (Model 804–8169, pigtail), with the sensors 7 cm apart, was used for pressure measurements. The transducers were calibrated electronically against mercury at the beginning of each study. By means of a pigtail catheter a guide wire was advanced into the LV under continuous fluoroscopy. Thereafter, the catheter was withdrawn and the Millar catheter was passed over the guide wire and introduced into the left ventricle. The distal sensor was located in the LV and the proximal sensor in the aorta.

Study protocol

In all patients, baseline measurements were recorded at rest during a steady state period, 30 min after the last infusion of contrast medium. Then, a single dose of 0.125 mg of clonidine was administered orally. Haemodynamic parameters (Swan-Ganz thermodilution catheter and pressure-volume relation) were measured both before and 60 min after clonidine administration.

Reproducibility of the method

To test the reproducibility of this method, we investigated the control group at two separate times 1 h apart. The reproducibility coefficient was calculated as defined by the British Standard Institution.¹⁴

Data collection

Millar micromanometer and electrocardiogram (ECG) cables were connected to a VF-1 mainframe (Crystal Biotech). Signals of LV and aortic pressures, as well as signals of LV volume and ECG were fed into a personal computer (IBM Pentium 100 MHz) and simultaneously displayed in real-time mode in the monitor of the computer using a multichannel 12-bit analog-to-digital converter (Data Translation Inc.) and commercially available data acquisition software (Dataflow, Crystal Biotech), as we have previously reported.¹⁵ The sampling rate was 3 msec. Plots of simultaneous pressure and volume were obtained using a commercially available software (Microsoft Excel for Windows, Figure 2).

Data analysis

Waveform analysis: The following measurements were made from the mitral inflow tracings: peak early (E) and, peak late (A) diastolic velocities, E/A ratio, pressure half-time of early mitral flow,¹⁶ and isovolumetric relaxation time measured as the time interval from the closure click of the aortic valve to the opening click of the mitral valve. The mean value \pm s.d. of the studied parameters of the normal group defined the normal range for diastolic Doppler and invasive indexes. A method was considered to

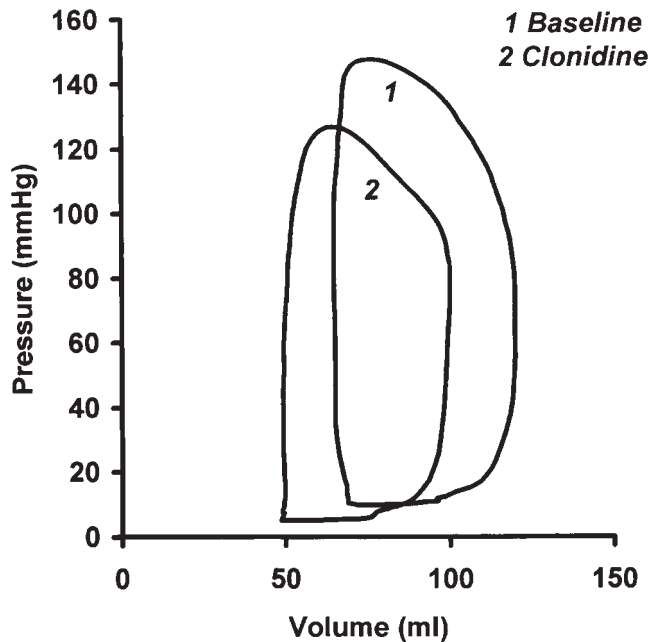


Figure 2 Examples of pressure–volume loops in a patient receiving clonidine 0.125 mg. Loops are shown at baseline and after 1 h of p.o. administration. The dominant effect was on the diastolic portion of the pressure–volume loop with substantial decline in stiffness constant.

indicate abnormal relaxation in an individual patient if at least two of its indexes were abnormal.

Pressure–volume analysis: The stored digitised data were analysed by the Excel for Windows computer software. For LV pressure and volume values and subsequent calculations of derivative parameters, analyses were performed on 10 consecutive cycles and results were averaged. The LV pressure–volume curve was obtained at baseline and after clonidine administration (Figure 2).

The ABD processing for calculation of echocardiographic volume introduced a time delay into the analog volume signal, compared with the instantaneous pressure signal derived from the Millar catheter. To correct this delay, which varied among patients, the volume signal was aligned by matching the minimum volume time point and the peak of the R wave of the simultaneously recorded electrocardiogram.

LV function: The following measurements and calculations were obtained: maximal positive and negative first derivative of LV pressure (peak +dP/dt and peak –dP/dt, respectively), LV minimal and end-diastolic pressure, peak systolic blood pressure, time constant of relaxation (TAU), LV stroke work and LV stiffness constant. End-diastole was defined as the time that the LV dP/dt first exceeded 200 mm Hg/sec. End-systole was defined as the point where the ratio between LV pressure and volume was maximal.

LV ejection indices: We measured LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV). The LV stroke volume was calculated as LVEDV – LVESV, and LV ejection fraction as EF = (LVEDV – LVESV)/LVEDV.

LV relaxation: TAU was calculated by the semilogarithmic method allowing the pressure to decay to a zero asymptote P_B : $P(t) = P_0 e^{-t/TAU}$. A nonlinear^{11,14,16} least squares technique was used to estimate the TAU. For the high-fidelity pressure curve, the nonlinear least squares fit begun at minimum dP/dt and ended at 5 mm Hg above the LV end-diastolic pressure.

LV work: LV stroke work was calculated as the area of the pressure-area loop (Figure 2).

LV stiffness: LV stiffness constant, β , was determined by using the equation $P = \alpha e^{\beta V}$, where P = pressure (mm Hg), V = LV volume (ml), β = volume stiffness constant (ml^{-1}), and α = the factor characterising the position of the pressure–area relation.¹⁷ LV pressure and volume data derived from the minimal LV diastolic pressure to the peak of the A wave.¹⁸ Points less than a LV pressure of 5 mm Hg were excluded from analysis because the LV diastolic pressure–volume relation is not monoexponential at extremely low pressures and volumes.¹⁹ This analysis integrates the viscous effects of early rapid filling and atrial contraction with passive chamber properties and, therefore, may not purely reflect passive chamber stiffness. In addition, it assumes a monoexponential relation between pressure and area that may not exist throughout the entire range of values studied. However it provides a commonly used index of LV diastolic chamber stiffness.²⁰

Cardiac output: This was calculated according to the Fick principle by thermodilution and was indexed by the body surface area. Measurements were repeated twice and their mean values were accepted if they varied by less than 10%.

Statistical analysis

Continuous variables from the patients and controls were compared by Student's unpaired *t*-test. Qualitative data were compared using the chi-square test. Comparisons within patients under different conditions were performed by the paired *t*-test. Prediction of TAU and LV stiffness constant was obtained by stepwise forward multiple linear regression analysis (SPSS 8.0 release, for Windows). Statistical significance was defined as $P < 0.05$.

Results

Reproducibility of the method

Reproducibility coefficient values for intraobserver repeatability (comparison of two determinations

obtained at 1 h intervals representing repeated measurements by the same observer) concerning LV end-diastolic and end-systolic volumes were 9.1 and 4.2 ml, respectively. These values were small compared with the mean values of LV volumes in the control group (Table 1). The same procedure was applied for peak and end-diastolic LV pressure, stroke work, TAU, and stiffness constant. Reproducibility coefficient values were 10.3 mm Hg, 1.0 mm Hg, 823 mm Hg per ml, and 0.001 ml^{-1} , respectively. These values were small compared with the mean values of peak and end-diastolic LV pressure, stroke work, TAU, and stiffness constant in this group (Tables 1 and 2).

Hypertensive patients vs normal subjects

Demographic characteristics are shown in Table 3. A significant difference was found between patients and controls for most invasive and non-invasive parameters. Notably, indexes of systolic LV function, such as ESV and EDV, ejection fraction, minimal pressure, maximal positive dP/dt, stroke work and cardiac index were similar in the two groups (Table 1). Stepwise multiple linear regression analysis showed that time constant of relaxation was independently associated only with increased LV mass index (Multiple $R = 0.86$, $F = 23.23$, $\beta = 4.5 \times 10^{-4}$, $P = 0.001$). Furthermore, LV stiffness constant was independently associated with age ($\beta U = -5.83 \times 10^{-4}$, $P = 0.003$) and cardiac index ($\beta = -0.004$, $P = 0.02$). Although as a group patients were significantly different from normal subjects the peak E and peak A velocities were similar between the two groups ($P = \text{NS}$, Table 2).

The two invasive indexes, LV stiffness constant and TAU classified 10/10 patients as having abnormal LV diastolic function compared with 7/10 patients as classified by Doppler studies.

Effects of clonidine administration

Systolic, diastolic and mean arterial pressure as well as heart rate significantly decreased after clonidine administration ($P < 0.001$, Table 1). Stroke volume, ejection fraction LV stroke work and cardiac index were not significantly affected. Max +dP/dt was slightly decreased reflecting diminished LV systolic pressure rather than decreased contractility. Calculated total peripheral and pulmonary resistance, were significantly decreased ($P < 0.001$). LV stiffness constant showed a significant decrease in the whole group ($P < 0.001$). TAU was normalised in five patients but in the whole group it did not show a significant difference. The mean IVRT remained unchanged while the E/A ratio and the PHT were significantly different after clonidine administration ($P < 0.001$). These Doppler indexes suggested normalisation of LV filling in 6/10 patients.

Table 1 Haemodynamic data at baseline in controls and in patients and after clonidine administration in patients

	Controls		Patients			
	Baseline	P ₁	Baseline	Clonidine	Δ%	P ₂
Heart rate (bpm)	70.24 ± 6.81	0.001	82.15 ± 7.25	71.93 ± 6.71	-12.45	0.001
Systolic blood pressure (mm Hg)	110.02 ± 11.40	0.000	160.20 ± 7.51	126.21 ± 18.96	-23.71	0.000
Diastolic blood pressure (mm Hg)	65.29 ± 9.50	0.000	94.00 ± 4.18	69.27 ± 10.06	-26.08	0.000
Mean arterial pressure (mm Hg)	80.20 ± 10.70	0.000	116.07 ± 4.70	86.92 ± 12.98	-25.02	0.000
End-diastolic volume (ml)	124.71 ± 8.50	NS	120.92 ± 9.40	115.31 ± 9.59	5.04	NS
End-systolic volume (ml)	53.25 ± 8.10	NS	59.42 ± 8.64	56.12 ± 8.80	9.02	NS
Stroke volume (ml)	71.46 ± 11.80	NS	61.50 ± 6.46	59.19 ± 9.69	4.41	NS
Ejection fraction	0.57 ± 0.07	NS	0.51 ± 0.05	0.51 ± 0.06	0.12	NS
LV peak systolic pressure (mm Hg)	112.99 ± 12.70	0.000	162.46 ± 8.21	128.20 ± 18.94	-21.13	0.000
LV minimal pressure (mm Hg)	4.69 ± 1.10	NS	4.98 ± 1.01	4.96 ± 1.01	-0.27	NS
End-diastolic pressure (mm Hg)	5.74 ± 1.30	0.000	11.95 ± 1.00	6.72 ± 1.19	-44.14	0.000
Maximal +dP/dt (mm Hg/s)	1195.18 ± 89.00	NS	1237.67 ± 78.24	1096.62 ± 88.59	-10.96	0.01
Minimal -dP/dt (mm Hg/s)	-1190.65 ± 189.64	0.005	-1157.57 ± 110.63	-1040.02 ± 200.64	-10.37	0.050
LV stroke work (mm Hg/ml)	7664.16 ± 2002.0	NS	8918.87 ± 1158.04	7594.60 ± 2058.00	-14.17	NS
Cardiac index (1 min ⁻¹ m ⁻²)	2.79 ± 0.38	NS	2.70 ± 0.41	2.45 ± 0.41	-8.67	NS
SVR (dyn s ⁻¹ cm ⁻⁵)	1198.57 ± 201.30	0.000	1852.06 ± 205.40	1498.36 ± 188.40	-19.12	0.000
PAR (dyn s ⁻¹ cm ⁻⁵)	131.40 ± 48.40	0.000	331.54 ± 77.39	216.21 ± 52.55	-33.84	0.000

P₁, Unpaired *t*-test between controls and patients at baseline; P₂, paired *t*-test before and after clonidine administration in patients; Δ%, per cent changes; LV, left ventricular; SVR, systemic vascular resistance; PAR, pulmonary artery resistance.

Table 2 Diastolic function data at baseline in controls and in patients and after clonidine administration in patients

	Controls		Patients			
	Baseline	P ₁	Baseline	Clonidine	Δ%	P ₂
LV stiffness constant (ml ⁻¹)	0.0028 ± 0.0022	0.000	0.0152 ± 0.0027	0.0053 ± 0.0026	-66.11	0.000
Time constant of relaxation (ms)	0.0301 ± 0.0023	0.000	0.0391 ± 0.0028	0.0368 ± 0.0043	-5.68	NS
Isovolumetric relaxation time (ms)	86.00 ± 10.29	0.000	111.66 ± 8.10	105.25 ± 12.29	-5.68	NS
E(cm/s)	52.81 ± 8.40	NS	47.96 ± 9.54	60.58 ± 7.66	29.34	0.005
A(cm/s)	48.91 ± 3.96	NS	54.37 ± 8.40	47.14 ± 2.45	-11.54	0.05
E/A	1.08 ± 0.09	0.000	0.88 ± 0.09	1.28 ± 0.13	46.40	0.000
Pressure half time (ms)	49.87 ± 11.03	0.000	71.55 ± 12.77	54.98 ± 12.23	-66.11	0.000

P₁, Unpaired *t*-test between controls and patients at baseline; P₂, paired *t*-test before and after clonidine administration in patients; Δ%, per cent changes; LV, left ventricular; E and A, peak early and late transmitral Doppler flow velocities, respectively.

Table 3 Demographic characteristics of the study population

	Controls	Patients	P
Age (years)	63 ± 9	63 ± 9	NS
Sex (M/F)	6/4	6/4	NS
IST (mm)	8.9 ± 1.2	14.1 ± 1.1	0.001
LVMI (g/m ²)	68.9 ± 5.9	122.9 ± 5.5	0.001
N.Y.H.A.			
I	10	0	0.001
II	0	5	0.001
III	0	5	0.001

IST, Intraventricular septum thickness; LVMI, left ventricular mass index; N.Y.H.A., functional classification according to the New York Heart Association.

Discussion

The main finding of this study was that clonidine administration in patients with diastolic dysfunction resulted in a decrease of heart rate and mean

arterial pressure as well as improvement of LV diastolic function indexes. These beneficial haemodynamic effects may result in symptomatic improvement of these patients.

Manifestation of diastolic dysfunction in hypertensive patients

As expected, mean group values of Doppler indexes were significantly different between normal subjects and patients and were consistent with a relaxation abnormality in the latter group. However, the ventricular filling patterns provided by these Doppler recordings are strongly influenced by several factors, including volume status, left atrial pressure and previous treatment with diuretics.²¹ In the present study all 10 hypertensive patients had LV hypertrophy, a known precursor of diastolic dysfunction. The assumption that diastolic dysfunction was present was tested by catheterisation. Using the LV

stiffness constant and the TAU, we found that all patients had diastolic abnormalities, as these indexes were significantly different at baseline from the values obtained in the normal subjects.

Not surprisingly, the time constant of relaxation was independently associated with LV mass index. A relative myocardial ischaemia may be partially accounted for this relationship. The correlation between LV hypertrophy and abnormal myocardial status, including diminished perfusion and electrical instability, has been repeatedly demonstrated in the past.²²

The LV stiffness constant was also significantly and independently associated with age. Diastolic function in elderly hypertensive patients may be characterised by a shift to the right and a steep change in the pressure–volume curve due to a marked increase in myocardial stiffness.^{23,24} The change enables the heart to handle large stroke volumes at low pressures over a wide range of volumes. When a certain volume is exceeded, a sharp, large rise in ventricular pressure occurs. Extensive alterations in the functional and structural composition of the elastic network of contractile and noncontractile components are reflected in corresponding changes in diastolic function.²⁵ Isovolumic relaxation time was significantly longer in patients compared to normal controls. Abnormal prolongation of the isovolumic relaxation time represents a wasted period in the cardiac cycle when the ventricle is neither ejecting nor filling. Dysfunction of the left ventricle in hypertension is at first diastolic and later systolic.

Effects of clonidine on myocardial function

In addition to lowering heart rate and systemic, pulmonary and intracardiac pressures, as expected, clonidine altered significantly a number of indexes of abnormal myocardial relaxation in the hypertensive patients. Specifically, the LV stiffness constant, which was about five-fold higher in patients at baseline compared to normal controls, was diminished by 66% after clonidine. The E/A ratio, which indicates diastolic dysfunction when <1 , increased by 46% after clonidine, from an average 0.88 at baseline to 1.28 after clonidine. These results may be partly due to a direct effect of sympathetic withdrawal on the myocardium²⁶ and partly to withdrawal of sympathetically mediated coronary constriction.²⁷ Furthermore, clonidine may also be efficacious indirectly by slowing heart rate (allowing more complete left atrial emptying), by reducing myocardial oxygen demand,²⁸ and by controlling blood pressure. In the long run, regression of LV hypertrophy has been reported with chronic therapy with clonidine.^{29,30} If this occurs, then presumably the intrinsic abnormality in LV diastolic function may also improve, although long-term data are lacking in this regard.³¹

Effects of clonidine on LV chamber stiffness

The period of passive ventricular stiffness is that during which pressure and volume increase together. There is no theoretic reason why the pressure–volume curve should be exponential. In many patients, particularly those with ventricular disease, this is not the case. Even the undemanding criterion that stiffness should increase continuously rather than linearly with pressure was met in only one-fourth of subjects.³² The stiffness constant, whose existence depends on assuming an exponential pressure–volume relation, cannot be a direct measure of stiffness, either from its derivation or from its units. Rather, it states how cavity stiffness depends on pressure. The physical significance of measurements of cavity stiffness is thus not clear.³³

With clonidine the diastolic portion of the pressure–volume curve was displaced downward. This parallel shift was accompanied by a decrease in the slope of the curve, indicating decreased cavity stiffness. This effect is of clinical importance as it is associated with alterations in ventricular filling rate and TAU. The underlying mechanism remains uncertain, although disturbances in the rate or extent of relaxation have been invoked.³⁴ Other possibilities include pericardial restraint associated with a change in right ventricular volume.³⁵ Clonidine resulted in a significant decrease in right ventricular pressure and pulmonary arterial resistance. A decrease in right ventricular pressure, whether by decreasing loading or resistance to ejection, may be associated with downward displacement of the LV pressure–volume curve. These effects are mediated via the epicardium or the interventricular septum. Furthermore, intrinsic changes in LV properties are possible. Although their mechanism is not clear, these shifts in the pressure–volume relation go some way to explain therapeutically significant effects of clonidine on ventricular diastolic pressure in patients with diastolic heart failure.⁸

Systolic function

Withdrawal of sympathetic drive might be *a priori* expected to diminish myocardial contractility. However, recent experience with the use of β -adrenergic blockers and clonidine in the treatment of congestive heart failure^{2,3,36,37} has shown that this is not the case. Lowering of heart rate and systemic arterial pressure decreases haemodynamic burden and improves myocardial efficiency. Indeed, the slight decrease in max +dp/dt is commensurate to the decreased LV systolic pressure and does not indicate adverse effect on myocardial performance.³ Furthermore, the significant reduction in heart rate is also beneficial in this respect, because peak contractile force in the failing myocardium was shown to occur at much lower heart rates than in normal myocardium.³⁸

Specific comments

The technique of ABD two-dimensional echocardiography for assessing LV or left atrial volumes has been previously well validated that has a satisfactory accuracy if specific instructions are taken into account.^{12,15,17} Regarding the reproducibility of our measurements, we have not obtained data for inter-observer variability since some controls were studied on two occasions 1 h apart by the same observer. However, we had to balance against the different degree of experience of the method and the further increase of the duration of this invasive protocol, particular in clinical healthy subjects.

Conclusion

Clonidine is safe and effective in decreasing LV stiffness and improving diastolic dysfunction without depressing LV performance. The suppression of sympathetic activity in diastolic heart failure is likely to be a successful therapeutic approach, complementary to the benefits already afforded by angiotensin-converting enzyme inhibitors. Long-term follow-up studies are necessary to further confirm the haemodynamic benefits of sympathetic suppression in the treatment of diastolic dysfunction in patients with heart failure due to cardiac hypertrophy.

Acknowledgements

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