The impact of arterial load on left ventricular performance: an invasive haemodynamic study in severe mitral stenosis

Ashwin Venkateshvaran[1,2], Srikanth Sola[2], Satish Chandra Govind[1], Pravat Kumar Dash[2], Banajit Barooah[2], Kambiz Shahgaldi[1], Anders Sahlén[1], Lars Lund[3,4], Reidar Winter[1,3], Anikó Ilona Nagy[5] and Aristomenis Manouras[1,3,4]

[1] *School for Technology and Health, Royal Institute of Technology, Stockholm, Sweden*
[2] *Sri Sathya Sai Institute of Higher Medical Sciences, Bangalore, India*
[3] *Karolinska Institutet, Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden*
[4] *Karolinska Institutet, Department of Medicine, Solna, Sweden*
[5] *Heart and Vascular Centre, Semmelweis University, Budapest, Hungary*

The Journal of Physiology

Key points

- A hallmark of mitral stenosis (MS) is the markedly altered left ventricular (LV) loading.
- As most of the methods used to determine LV performance in MS patients are influenced by loading conditions, previous studies have shown conflicting results.
- The present study calculated LV elastance, which is a robust method to quantify LV function. We demonstrate that LV loading in MS patients is elevated but normalizes after valve repair and might be a result of reflex pathways.
- Additionally, we show that the LV in MS is less compliant than normal due to a combination of right ventricular loading and the valvular disease itself. Immediately after valve dilatation the increase in blood inflow into the LV results in even greater LV stiffness.
- Our findings enrich our understanding of heart function in MS patients and provide a simple reproducible way of assessing LV performance in MS.

Abstract   Left ventricular (LV) function in rheumatic mitral stenosis (MS) remains an issue of controversy, due to load dependency of previously employed assessment methods. We investigated LV performance in MS employing relatively load-independent indices robust to the altered loading state. We studied 106 subjects (32 ± 8 years, 72% female) with severe MS (0.8 ± 0.2 cm^2) and 40 age-matched controls. MS subjects underwent simultaneous bi-ventricular catheterization and transthoracic echocardiography (TTE) before and immediately after percutaneous transvenous mitral commisurotomy (PTMC). Sphygmomanometric brachial artery pressures and TTE recordings were simultaneously acquired in controls. Single-beat LV elastance (E_{es}) was employed for LV contractility measurements. Effective arterial elastance (E_a) and LV diastolic stiffness were measured. MS patients demonstrated significantly elevated afterload (E_a: 3.0 ± 1.3 *vs.* 1.5 ± 0.3 mmHg ml^{-1}; $P < 0.001$) and LV contractility (E_{es}: 4.1 ± 1.6 *vs.* 2.4 ± 0.5 mmHg ml^{-1}; $P < 0.001$) as compared to controls, with higher E_a in subjects with smaller mitral valve area (≤ 0.8 cm^2) and pronounced subvalvular fusion. Stroke volume (49 ± 16 to 57 ± 17 ml; $P < 0.001$) and indexed LV end-diastolic volume (LVEDV$_{index}$: 57 ± 16 to 64 ± 16 ml m^{-2}; $P < 0.001$) increased following PTMC while E_{es} and E_a returned to more normal levels. Elevated LV stiffness was demonstrated at baseline and increased further following PTMC. Our findings provide evidence of elevated LV contractility, increased arterial load and increased diastolic stiffness in severe MS. Following PTMC, both LV contractility and afterload tend to normalize.

Corresponding author Anikó Ilona Nagy: Heart and Vascular Centre, Semmelweis University, Budapest.   Email: anychophora@gmail.com

Abbreviations   BSA, body surface area; CI, cardiac index; CO, cardiac output; E_a, effective arterial elastance; $E_{a\,INV}$, invasive effective arterial elastance; $E_{a\,NI}$, non-invasive effective arterial elastance; E_{es}, LV elastance; $E_{es\,NI}$, non-invasive LV elastance; $E_{es\,INV}$, invasive LV elastance; EF, ejection fraction; E'_{lat}, early diastolic mitral annular velocity of the lateral LV basal wall; E'_{sept}, early diastolic mitral annular velocity of the IV septum; ESPVR, end-systolic pressure–volume relationship; LA, left atrium; LAP, left atrial pressure; LV, left ventricle/ventricular; LVEDP, left ventricular end-diastolic pressure; LVESP, left ventricular end-systolic pressure; $LVEDV_{index}$, left ventricular end-diastolic volume indexed to BSA; $LVESV_{index}$, left ventricular end-systolic volume indexed to BSA; LVOT, left ventricular outflow tract; MS, mitral stenosis; MVA, mitral valve area; MVG, mean transmitral gradient; PAP_d, pulmonary arterial diastolic pressure; PAP_m, pulmonary arterial mean pressure; PAP_s, pulmonary arterial systolic pressure; PCWP, pulmonary capillary wedge pressure; P_d, diastolic systemic arterial pressure; P_m, mean systemic arterial pressure; P_s, systolic systemic arterial pressure; PTMC, percutaneous transvenous mitral commissurotomy; PVR, pulmonary vascular resistance; RAP, right atrial mean pressure; RHC, right heart catheterization; RV, right ventricle/vetricular; RVEDP, right ventricular end-diastolic pressure; RVESP, right ventricular end-systolic pressure; RVP_s, RV systolic pressure; SV, stroke volume; SVi, stroke volume index; SVR, systemic vascular resistance; TTE, transthoracic echocardiography.

Introduction

Despite numerous attempts to characterize left ventricular (LV) systolic function in the setting of mitral stenosis (MS), current evidence remains largely conflicting. Early studies demonstrated impaired LV systolic performance, ascribing this to mechanisms such as myocardial fibrosis (Sunamori *et al.* 1983), impaired inter-ventricular inter-action (Curry *et al.* 1972) and chronic LV under-filling (Kaku *et al.* 1988). However, later investigations challenged this notion, revealing normal LV contractility in pure MS (Gash *et al.* 1983; Liu *et al.* 1992). These discrepancies may at least in part be attributed to the fact that the majority of the conventional methods for LV function assessment are influenced by the considerably altered loading conditions prevailing in the setting of MS. Thus, a more robust approach would comprise the use of indices that are less dependent on changes in LV loading and provide further insight into the ventricular and arterial interaction.

The instantaneous relationship between pressure and volume in the human heart is an expression of the integration of arterial pressure, preload, heart rate and inotropic state of the myocardium. Sunagawa *et al.* (1984) proposed a comprehensive model by which LV energetics, myocardial function and ventricular performance can be investigated taking into account their interaction with the vascular system. Briefly, the framework of arterio-ventricular coupling allows the characterization of heart function in terms of effective arterial elastance (E_a), a 'lumped index' denoting the LV afterload in the time domain, and LV elastance (E_{es}) representing the slope of the end-systolic pressure–volume relationship (ESPVR) and expressing the contractile force of the LV. A number of validating studies have provided evidence that ESPVR is relatively insensitive to afterload alterations, rendering E_{es} the gold standard for LV contractility (Suga *et al.* 1973; Weber *et al.* 1976). As this approach largely overcomes the

limitations associated with haemodynamic loading, it is of particular value in the setting of MS.

Based on the above reasoning, we undertook this study to (1) evaluate LV performance in a large cohort of patients with pure MS using methods that are less susceptible to the altered haemodynamic state, (2) investigate the features of ventricular–arterial interaction in the setting of MS and (3) interrogate the possible alterations in LV diastolic and systolic function following the acute preload increase secondary to valve dilatation.

Methods

Study population

Symptomatic MS patients referred for percutaneous trans-venous mitral commisurotomy (PTMC) to the Sri Sathya Sai Institute were enrolled prospectively between January and June 2012. Subjects were excluded if they presented with more than mild (grade > 1) mitral regurgitation (MR), concomitant aortic valve disease, ischaemic heart disease, atrial fibrillation or hypertension. All patients were on low dose β-blockers (atenolol 25 mg), and a combined regime of diuretics (amiloride + furosemide 40 mg). The control group comprised 40 healthy, age-matched subjects free of any medications. The study conformed to the ethical guidelines of the 1975 *Declaration of Helsinki* and was approved by the institutional review board. All subjects provided written informed consent.

Echocardiographic data

All MS subjects underwent transthoracic echocardiogram (TTE) using a GE Vivid E9 system (GE Ultrasound, Horten, Norway) and a 2.5 MHz matrix array trans-ducer in keeping with current recommendations (Lang

et al. 2005). LV elastance measurements were derived from simultaneously acquired LV volumes by echocardiography and invasive pressures just prior the PTMC. The echocardiographic and invasive recordings were then repeated within 5 min following PTMC.

LV end-systolic volume (LVESV), end-diastolic volume (LVEDV) and ejection fraction (EF) were measured according to current recommendations employing the Simpsons biplane method from two-dimensional TTE four- and two-chamber apical recordings (Lang *et al.* 2005). Stroke volume (SV$_{Doppler}$) was calculated by multiplying the cross-sectional area of the LV outflow tract (LVOT) with the Doppler-derived velocity time integral (VTI$_{LVOT}$). Mitral valve area (MVA) was measured by planimetry and MR was graded semi-quantitatively. Continuous (CW) and pulsed wave (PW) recordings of the inflow mitral velocities (E and A wave) were performed. The mean transmitral gradient (MVG$_{mean}$) was measured using the CW recordings according to current recommendations (Lang *et al.* 2005). Spectral tissue velocities were recorded in the septal and lateral mitral annulus in the patient cohort and in controls using a 5 mm PW sample volume and the early myocardial relaxation velocity (E') as well as the annular tissue velocity during atrial contraction (A') were recorded. The Wilkins score (WS) was employed to assess valve suitability for the procedure (Wilkins *et al.* 1988). All analyses were performed offline (EchoPac PC, GE Ultrasound, Waukesha, WI, USA).

Catheterization data

Right heart catheterization was performed using a 6F Swan-Ganz catheter in all MS patients. Right atrial mean pressure (RAP$_m$), right ventricular systolic pressure (RVP$_s$), pulmonary artery systolic and mean pressure (PAP$_s$; PAP$_m$) and mean pulmonary capillary wedge pressure (PCWP$_m$) were measured under fluoroscopy after careful calibration with the zero level set at the mid-thoracic line. Concurrently, a 6F pigtail catheter was advanced through the femoral artery to measure systolic, mean and diastolic arterial pressures (P_s, P_m, P_d) with subsequent LV end-diastolic pressure (LVEDP) and end-systolic pressure (LVESP) recordings before and after PTMC. Trans-septal puncture was performed with an 8F Mullins sheath, dilator and a Brockenbrough needle. Left atrial pressure (LAP) was subsequently recorded. Pressure tracings were stored (WITT Series III, Witt Biomedical Corp., Melbourne, FL, USA) and analysed off-line.

PTMC was performed using a 24 to 28 mm Accura balloon catheter (Vascular Concepts, Halstead, UK) by experts (P.K.D., B.B.) who have individually performed >4000 procedures. The procedure was considered successful if the resultant MVA was >1.5 cm^2 with less than +1 grade increase in MR. Cardiac output (CO) and vascular resistances were measured before and after PTMC in conjunction with pressure–volume measurements. CO was calculated employing the estimated Fick's method with the oxygen consumption (V_{O_2}) obtained from a standard nomogram.

Measurements of LV and effective arterial elastance

E_a constitutes a 'lumped index' of LV afterload in the time domain and was calculated as

$$E_a = \text{LVESP}/\text{SV}_{Doppler}. \tag{1}$$

For the study's purposes the calculation of E_a was performed based on estimated LVESP values as derived from the equation

$$\text{LVESP} = 0.9 \times P_{s\,fem} \tag{2}$$

as this accurately approximates LVESP in pressure–volume loop measurements and has been widely used to evaluate ventriculo-arterial coupling (Kelly *et al.* 1992). More specifically, in MS patients E_a was calculated invasively ($E_{a\,INV}$) using the P_s recorded from the femoral artery. Additionally, non-invasive estimated E_a ($E_{a\,NI}$) was calculated using the regression equation derived from the validation group in order for the measurement to correspond to the $E_{a\,NI}$ assessment in controls.

E_{es} was calculated using the single-beat approach developed by Chen *et al.* (2001). Importantly, this method does not assume that the volume axis intercept of ESPVR is at the origin of the diagram (0; 0) but can be extrapolated to intersect the volume axis at the point V$_{0;0}$ (Chen *et al.* 2001). Briefly, E_{es} was calculated as:

$$E_{es(sb)} = \left[P_{d\,fem} - \left(E_{Nd(est)} \times \text{LVESP} \right) \right] /$$
$$\left[\text{SV}_{Doppler} \times E_{Nd(est)} \right] \tag{3}$$

where $E_{Nd(est)}$ represents group-averaged normalized E_{es} values as a function of EF and the ratio of diastolic ($P_{d\,fem}$) and systolic ($P_{s\,fem}$) arterial pressure at the level of the femoral artery as described by the equation:

$$E_{Nd\,(est)} = 0.0275 - 0.165 \times \text{EF} + 0.3656 \,\text{x}\, (P_{d\,fem}/P_{s\,fem})$$
$$+ 0.515 \times E_{Nd\,(avg)} \tag{4}$$

In this equation, $E_{Nd\,(avg)}$ is given by a seven-term polynomial function:

$$E_{Nd(avg)} = \sum_{i=0} a_i \times t_{Nd}^i$$

where summation is performed for $i = 0$ to 7, using values for a_i of [0.35695; −7.2266; 74.249; −307.39; 684.54; −856.92; 571.95; −159.1], respectively.

The t_{Nd} value was determined as the ratio of the pre-ejection (R-wave to flow onset) to the total systolic period (R-wave to flow termination), with the time at onset and termination of flow obtained from pulsed Doppler in LVOT. LVESP in eqn (3) was estimated as stated above in eqn (2), i.e. LVESP $= 0.9 \times P_{s\,fem}$.

LV end-diastolic chamber stiffness was estimated from the ratio of LVEDP and LVEDVi as described by Kass (2000). Furthermore, the LV end-diastolic pressure–volume relationship (EDPVR) was investigated employing the single-beat method described by Klotz *et al.* (2006).

Validation study

As provided above, E_{es} measurements in MS patients were based on invasive pressure measurements at the femoral artery level. However, invasive pressure measurements were not performed in controls and the E_{es} in that group was calculated based on non-invasive sphygmomanometric measurements in the brachial artery. To investigate the relationship between the two different approaches we performed a validation study on 14 MS patients referred for PTMC in whom simultaneous pressure measurements were performed sphygmonanometrically in the brachial artery and invasively in the femoral artery.

Stratification of subjects by severity of MS

MS subjects were dichotomized *post-hoc* based on MVA of ≤ 0.8 and > 0.8 cm^2. Additionally, the MS group was stratified based upon WS (low: ≤ 9; high: > 9).

Echocardiographic and haemodynamic measurements in controls

The 40 subjects constituting the control arm of the study underwent TTE and simultaneous sphygmomanometric measurements for pressure recordings at the left arm. Systolic ($P_{s\,brach}$) and diastolic brachial artery pressures ($P_{d\,brach}$) were recorded. With regard to echocardiographic data, volumetric and quantitative two-dimensional and Doppler measurements were performed and analysed as assessed in the patient cohort. For measurements of E_a and E_{es}, LVESP was estimated using the systolic brachial artery pressure as recorded sphygmomanometrically and derived from the equation: LVESP $= 0.9 \times P_{s\,brach}$. Similarly, for E_{es} measurements eqns (3) and (4) were modified for controls using the non-invasive brachial artery pressures, i.e.:

$$E_{es(sb)} = \left[P_{d\,brach} - \left(E_{Nd(est)} \times \text{LVESP} \right) \right] /$$
$$\left[\text{SV}_{Doppler} \times E_{Nd(est)} \right] \quad (3a)$$

and

$$E_{Nd\,(est)} = 0.0275 - 0.165 \times$$
$$+ 0.3656 \, x \left(P_{d\,brach} / P_{s\,brach} \right) + 0.515 \times E_{Nd\,(avg)} \quad (4a)$$

In controls, PCWP was calculated according to the equation PCWP $= 1.24\,[E/E'] + 1.9$, as proposed by Nagueh *et al.* (1997). In this equation, E denotes the peak early transmitral inflow velocity (E wave) and the E' is the early myocardial tissue Doppler velocity at the lateral mitral annulus (Nagueh *et al.* 1997).

Based on the assumption that PCWP equals LVEDP in healthy individuals, LV end-diastolic chamber stiffness was estimated in controls using the two aforementioned methods, i.e. the end diastolic pressure–volume ratio (Kass, 2000) and the single beat approach (Klotz *et al.* 2006).

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean $\pm$ SD and categorical variables in absolute values and percentage. The Shapiro–Wilk test was used to check normality. Continuous variables were compared using the paired Student t test or the Wilcoxon test. Controls were compared with study subjects using the Mann–Whitney test. Correlations between variables were tested by the Pearson two-tailed correlation. Multiple regression analysis was used to identify independent confounders of end-diastolic LV stiffness. All tests were performed at 95% confidence intervals, and a *P*-value of < 0.05 was considered statistically significant. Mann–Whitney U test was performed for analysis of the difference between the predicted elastance values derived from the validation study and the corresponding non-invasive values for controls. Analysis of inter- and intraobserver variability was performed for E_{es} in 10 patients by two observers. Methodological error (Err) in a single measurement estimated from double measurements was calculated according to formula: Err $= (\text{SD}_{diff} \times 100\%)/(\text{total mean} \times \sqrt{2})$, where SD_{diff} is the SD of the difference between the measurements (Dahlberg, 1940)

Results

Study population

Of the 120 patients enrolled, 14 were excluded due to severe MR following leaflet tear during PTMC ($n = 6$), tamponade ($n = 2$), unsuccessful PTMC ($n = 1$) and incomplete oximetry data ($n = 5$). In effect, 106 subjects

Table 1. Baseline and echocardiographic characteristics of the study population

Variable	Controls ($n = 40$)	MS ($n = 106$)	P
Female	28 (70%)	77 (72%)	
BSA (m^2)	1.5 ± 0.1	1.4 ± 0.1	
HR (beats min^{-1})	76 ± 10	75 ± 10	
SBP (mmHg)	116 ± 9	108 ± 10	<0.001
NYHA Class			
II		59 (56%)	
III		47 (44%)	
Prior PTMC		34 (32%)	
Medication (%)			
Atenolol 25 mg		100%	
Amiloride + furosemide 40 mg		100%	
MR severity			
No MR		34 (32%)	
Grade I		72 (68%)	
Wilkins score			
≤8		47 (44%)	
>8		59 (56%)	
MVA (cm^2)	4.7 ± 0.9	0.8 ± 0.2	<0.001
MVG_{mean} (mmHg)	1 ± 0.3	19 ± 9	<0.001
LVEDV (ml)	88 ± 18	82 ± 24	n.s.
$LVEDV_{index}$ (ml m^{-2})	57 ± 9	57 ± 16	n.s.
LVESV (ml)	28 ± 7	34 ± 12	<0.05
$LVESV_{index}$ (ml m^{-2})	19 ± 4	23 ± 9	<0.001
$SV_{Doppler}$ (ml)	71 ± 13	49 ± 16	<0.001
EF (%)	66 ± 5	60 ± 8	<0.001

PTMC, percutaneous transvenous mitral commisurotomy; BSA, body surface area; HR, heart rate; MR, mitral regurgitation; LVID, left ventricular internal diameter; d, diastolic; s, systolic; LVEDV, end-diastolic volume; LVESV, end-systolic volume; $SV_{Doppler}$, Doppler-derived stroke volume; EF, ejection fraction; MVA, mitral valve area; MVG_{mean}, mean mitral valve gradient; RVSP, right ventricular systolic pressure.

(age 32 ± 8 years, 72% female) were analysed. Table 1 summarizes the population characteristics. In total, 46% demonstrated markedly narrowed MVA (≤ 0.8 cm^2). Despite lower EF as compared to controls, LV contractility was significantly higher in MS patients (E_{es}: 4.1 ± 1.6 *vs.* 2.4 ± 0.6 mmHg ml^{-1}; $P < 0.001$).

LV and arterial elastance in MS

E_{es} was inversely associated with SV in the MS group ($r = -0.66$; $P < 0.001$). LVEDV did not differ significantly, but LVESV was larger among MS subjects as was afterload (E_a: 3.0 ± 1.3 *vs.* 1.5 ± 0.3 mmHg ml^{-1}; $P < 0.001$). Figure 1 illustrates ESPVR in controls and MS subjects. Controls demonstrated a positive association between E_a and LVEDV ($r = 0.60$; $P < 0.001$), whereas an inverse relationship was seen in the MS group ($r = -0.73$; $P < 0.001$) with a strong positive correlation between E_a and E_{es} ($r = 0.74$; $P < 0.001$). E_a in the MS group was inversely related to EF ($r = -0.54$; $P < 0.001$), exhibiting a weak association with heart rate ($r = 0.34$; $P = 0.005$).

MS severity and elastance

Patients with MVA ≤ 0.8 cm^2 ($n = 47$) displayed similar LV contractility (E_{es}: 4.3 ± 1.6 *vs.* 3.8 ± 1.7 mmHg ml^{-1}; $P > 0.05$) but considerably higher E_a (3.3 ± 1.3 *vs.* 2.8 ± 1.3 mmHg ml^{-1}; $P = 0.03$) compared to the rest of the MS group. Subjects with high WS ($n = 17$) had elevated arterial load compared to those with low WS ($n = 85$) (E_a: 3.7 ± 1.7 *vs.* 3.0 ± 1.2 mmHg ml^{-1}; $P = 0.04$), while E_{es} between the two groups did not differ significantly (E_{es}: 4.0 ± 1.5 *vs.* 4.6 ± 2.2 mmHg ml^{-1}; $P > 0.05$).

Normal *vs.* reduced EF

Twenty-five MS patients (24%) exhibited reduced EF (≤ 55%). They showed significantly higher E_{es} (5.5 ± 2.9 *vs.* 3.9 ± 1.4 mmHg ml^{-1}; $P = 0.01$) and E_a (5.1 ± 2.3 *vs.* 2.9 ± 1 mmHg ml^{-1}; $P < 0.001$) as well as more extensive subvalvular fusion (SVF: 3 ± 0.4 *vs.* 3.4 ± 0.4, $P < 0.05$) compared to those with normal EF ($n = 81$).

Invasive measurements

As shown in Table 2, all MS subjects demonstrated elevated intracardiac pressures and reduced CO. Immediately after commissurotomy, LVEDP (12 ± 4 to 16 ± 4 mmHg; $P < 0.001$) and cardiac index (CI; 2.5 ± 0.6 to 3.2 ± 0.8 l min m^{-2}; $P < 0.001$) rose significantly, with concomitant SVR (27 ± 8 to 21 ± 8 Wood Units; $P < 0.001$) and PVR reduction (4.5 ± 4 to 3.4 ± 3 Wood Units; $P < 0.001$); no significant changes in arterial pressures were noted.

Diastolic changes

In MS patients, LVEDP correlated significantly with RVEDP ($r = 0.43$, $P < 0.001$) and CI ($r = 0.24$, $P < 0.05$) and was elevated (>16 mmHg) in 24 cases (23%). Following PTMC, LVEDP further increased (>16 mmHg in 52% of the cases). LV stiffness was significantly higher in the MS group compared to controls both when using the EDPVR of the operant LV stiffness and when estimating the beta value derived from the single beat approach (Fig. 2). In the patient cohort, a reduction in LV stiffness occurred in only 11 patients. When comparing the two groups, patients with a reduction in chamber stiffness following PTMC had lower MVG$_{mean}$ prior to PTMC as compared to the corresponding group with increased LV stiffness (MVG$_{mean}$ 15.7 ± 10.8 vs. 20.8 ± 9.1 mmHg) and lower RVP$_s$ (44 ± 10.1 vs. 63.5 ± 24 mmHg). Multiple regression analysis identified RVEDP, E_a and MVAi as constituting the only independent predictors of LV stiffness both before and after PTMC as described by the regression equation: LV stiffness $= 0.165 + 0.1 \times$ RVEDP $+ 0.03 \times E_a$ $-0.147 \times$ MVAi, with an overall model fit of $r^2 = 0.41$, $F_{1,94} = 21$, $P < 0.001$. Furthermore, RVEDP at baseline acted as the sole independent predictor of the magnitude of augmentation of the beta value following dilatation of the MV ($r = 0.41$, $P < 0.001$). On the other hand, no correlation between LV stiffness and WS, SVF or age was found.

Haemodynamic alterations following PTMC

MVA increased in all cases following PTMC (0.8 ± 0.2 to 1.6 ± 0.2 cm^2; $P < 0.001$) with a corresponding reduction in the transmitral gradient (19 ± 9 to 5 ± 2 mmHg; $P < 0.001$) (Table 3). Immediately after PTMC, both E_{es} (4.1 ± 1.6 to 3.5 ± 1.3 mmHg ml^{-1}; $P < 0.001$) and E_a (3.0 ± 1.6 to 2.6 ± 1.1 mmHg ml^{-1}; $P < 0.001$) returned to more normal values with a concomitant increase in preload (LVEDV: 82 ± 2 to 90 ± 24 ml; $P < 0.001$), EF (60 ± 8 to $64 \pm 8\%$; $P < 0.001$) and SV$_{Doppler}$ (49 ± 16 to 57 ± 17 ml; $P < 0.001$). Importantly, both methods for assessing LV stiffness revealed a significant reduction in chamber compliance following PTMC, with higher beta and lower alpha values following PTMC, indicating right and upward change in EDPVR following intervention.

Validation measurements

In the validation group comprising 14 MS patients, simultaneous pressures were acquired sphygmomanometrically at the brachial artery level and invasively at the femoral artery level (Table 4). The non-invasive E_{es} measurements ($E_{es\,NI}$) were highly correlated to the invasively derived E_{es} ($E_{es\,INV}$) ($r^2 = 0.94$, $E_{es\,NI} = 0.16 + 0.86 \times E_{es\,INV}$) although significantly lower ($P = 0.005$). Using the regression equation derived from the validation study, we calculated the predicted $E_{es\,NI}$ in our patient cohort to verify that the observed difference between the $E_{es\,INV}$ and non-invasive
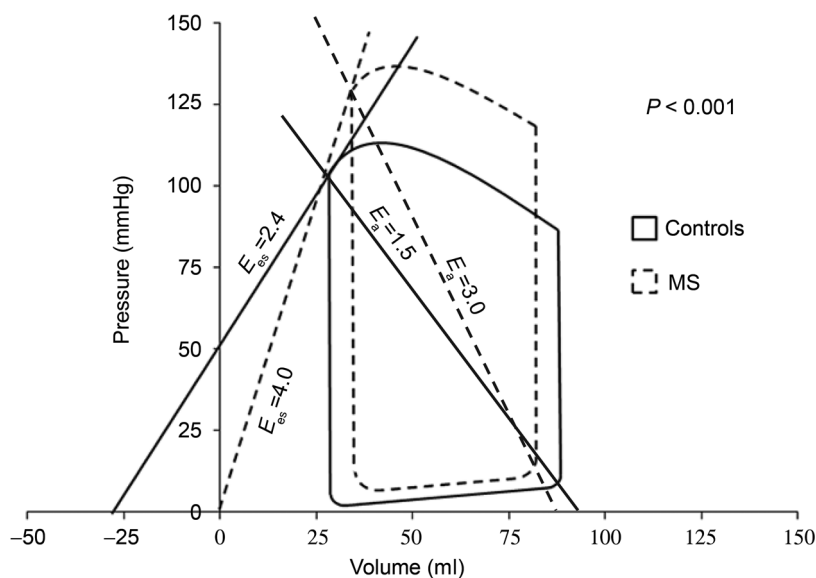

Figure 1. Left ventricular end-systolic elastance (E_{es}) and arterial elastance (E_a) in severe rheumatic mitral stenosis (MS) as compared to normal subjects
MS patients demonstrated significantly elevated E_{es} and E_a as compared to controls. Values shown here represent the mean for the two study groups.

Table 2. Invasive haemodynamic variables in the study population before and immediately after PTMC

Variable	Controls (n)	Pre-PTMC (n)	Post-PTMC (n)	P
RAP_m (mmHg)	6 ± 3		5.7 ± 3	n.s.
PAP_s (mmHg)		58 ± 24 (105)	49 ± 17 (105)	<0.001
PAP_m (mmHg)		39 ± 14 (105)	32 ± 11 (105)	<0.001
$PCWP_m$ (mmHg)	9.5 ± 1.2 (40)	25 ± 7 (104)	18 ± 5 (104)	<0.001
LAP_m (mmHg)		26 ± 7 (104)	18 ± 5 (104)	<0.001
LVESP (mmHg)		135 ± 18 (104)	132 ± 18 (104)	n.s.
LVEDP (mmHg)		12 ± 4 (104)	16 ± 4 (104)	<0.001
RVEDP (mmHg)		7.8 ± 4.2 (104)	7.6 ± 4.1 (104)	n.s.
Arterial systolic pressure (mmHg)		134 ± 22 (98)	131 ± 19 (98)	n.s.
Arterial mean pressure (mmHg)		97 ± 13 (98)	97 ± 14 (98)	n.s.
Arterial diastolic pressure (mmHg)		74 ± 12 (98)	75 ± 12 (98)	n.s.
Arterial pulse pressure (mmHg)		59 ± 17 (98)	56 ± 15 (98)	n.s.
CI (l min^{-1} m^{-2})		2.5 ± 0.6 (104)	3.2 ± 0.8 (104)	<0.001
PVR (Wood Units)		4.5 ± 4 (103)	3.4 ± 3 (103)	<0.001
SVR (Wood Units)		27 ± 8 (99)	21 ± 8 (99)	<0.001
$E_{es\ INV}$ (mmHg ml^{-1})		$4.1 \pm 1.6^*$ (95)	$3.5 \pm 1.3^*$ (91)	<0.001
$E_{es\ NI}$ (mmHg ml^{-1})	2.4 ± 0.6 (40)	$3.7 \pm 1.4^*$ (95)	$3.2 \pm 1.2^*$ (91)	<0.001
$E_{a\ INV}$ (mmHg ml^{-1})		$3.1 \pm 1.3^*$ (101)	$2.6 \pm 1.1^*$ (102)	<0.001
$E_{a\ NI}$ (mmHg ml^{-1})	1.5 ± 0.3 (40)	$2.7 \pm 1.2^*$ (101)	$2.3 \pm 1.0^*$ (102)	<0.001
LV stiffness (mmHg ml^{-1})	0.17 ± 0.04 (40)	$0.23 \pm 0.1^*$ (99)	$0.26 \pm 0.1^*$ (99)	<0.001
Beta (EDPVR)	5.84 ± 0.03 (40)	$5.95 \pm 0.17^*$ (99)	$6.2 \pm 0.52^*$ (99)	<0.001
Alpha (EDPVR) $\times 10^{-11}$ (mmHg)	7.6 ± 7.7 (40)	35.2 ± 143 (99)	$9.1 \pm 2.52^*$ (99)	<0.001

PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure, LAP_m, left atrial mean pressure; LVEDP, left ventricular end diastolic pressure; LVESP; left ventricular end systolic pressure; RVEDP, right ventricular end diastolic pressure CI, cardiac index; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; $E_{es\ INV}$, invasively derived LV elastance; $E_{es\ NI}$, non-invasively derived estimated LV elastance; $E_{a\ INV}$, invasively derived arterial elastance; $E_{a\ NI}$, non-invasively derived estimated arterial elastance; EDPVR, end diastolic pressure–volume relation. *P* values indicate the significance of differences between pre- and post-PTMC data in the MS group. Significant differences between the control and pre- or post PTMC MS group values are indicated by asterisks.

measurements in controls was valid. As shown in Table 4, the predicted $E_{es\ NI}$ values in MS patients both before ($E_{es\ NI\ pre} = 3.7 \pm 1.4$ mm Hg ml^{-1}) and after PTMC ($E_{es\ NI\ post} = 3.2 \pm 1.1$ mm Hg ml^{-1}) were higher as compared to the controls ($E_{es\ NI\ controls} = 2.4 \pm 0.6$) ($z = -4.4$ and $z = -2.2$, respectively) with the mean $E_{es\ NI\ pre}$ and $E_{es\ NI\ post}$ being 38 and 28% higher than the corresponding values in controls.

Similarly, we calculated the predicted E_a values based on the validation study. An excellent correlation between invasive ($E_{a\ INV}$) and non-invasively derived $E_{a\ NI}$ ($r^2 = 0.97$, $P < 0.001$) was found in the validation group. As shown in Table 4, the $E_{a\ NI}$ was lower as compared to $E_{a\ INV}$ ($E_{a\ NI} = 0.04 + 0.87 \times E_{a\ INV}$, $P < 0.001$). Based on that equation, the predicted $E_{a\ NI}$ was calculated in our patient group both before and following PTMC (Table 3). We also inferred that MS patients showed significantly higher E_a values compared to controls, and this was valid for the measurements both before and after PTMC.

Inter- and intraobserver variability analysis showed relatively low error for repeated measurements of E_{es} (7.7 and 12.8% for intra- and interobserver measurements, respectively).

Discussion

To our knowledge, this is the largest invasive study evaluating LV performance in patients with pure rheumatic MS. Contrary to some previous reports, we demonstrate augmented LV contractility along with reduced LV compliance in severe MS. Our data indicate that EF poorly describes the inherent LV performance in this patient population. The elevated arterial load is strongly associated with LV stiffness and MS severity. Finally, the elevated LV contractility and afterload at baseline returned to more normal levels immediately following PTMC, along with a further increase in LV stiffness.

LV performance in rheumatic MS has been an issue of debate with conflicting observations that might partly be attributed to the load susceptibility of the various measurements employed for the quantification of LV function (Ahmed *et al.* 1977; Kaku *et al.* 1988). Indeed, based on the analysis of indices such as EF, stroke work as well as ESPVR and wall motion scoring, earlier studies reported evidence of impaired LV function in MS patients (Heller & Carleton 1970; Curry *et al.* 1972; Hildner *et al.* 1972). Reduced SV in relation to LV

end-diastolic pressures at rest and during exercise as well as depressed EF have been previously interpreted as indicative of impaired LV function in these patients (Horwitz *et al.* 1973). Regardless, given the limited pre-load recruitment secondary to MS, lower LV output *per se* may not imply impaired ventricular performance. Similarly, circumferential fibre shortening rate (Vcf) was found to be reduced, thus arguing for myocardial dysfunction in this patient population (Holzer *et al.* 1973). However, experimental studies demonstrated that Vcf varies inversely with afterload alterations (Covell *et al.* 1966; Urschel *et al.* 1968). In contrast, Ahmed and colleagues (Ahmed *et al.* 1977) assessed $dP/dt/P_{max}$ and reported preserved LV contractile function in MS patients, although later studies have shown that even this approach is subjected to load dependency, thus providing unreliable results in the setting of MS (Schmidt and Scheer, 1981).

In the present report, LV function was assessed by ESPVR, a relatively load-independent approach well suited for MS (Suga *et al.* 1973; Suga and Sagawa, 1974). Our findings refute the notion of impaired LV contractile performance in severe MS advocated in previous studies. Instead, they indicate a state of elevated LV contractility, as demonstrated by a roughly 40% higher E_{es} in MS patients compared to that of age-matched controls. A direct comparison of the single beat E_{es} with other than EF LV performance indices was not performed in the current study, and thus a detailed physiological explanation of the discrepancy compared to previous

findings is not appropriate. However, in an attempt to approach a constructive appreciation of the current results we suggest that they might reflect a less pronounced load sensitivity of E_{es} as compared to other previously employed LV function measurements. Increased sympathetic activity has been demonstrated in patients with MS and has been ascribed to the decreased SV secondary to the reduced space of the mitral valve (Ashino *et al.* 1997). The depressed LV ventricular output would yield a reduction in afferent activity of the baroreceptors, which has been considered as a possible cause of sympathetic activation in these patients (Ashino *et al.* 1997). Apart from the elevated E_{es}, we demonstrate increased arterial load and systemic peripheral vascular resistance in MS patients as compared to controls, a constellation of findings that might advocate increased sympathetic activity in our patient cohort. A significant association between sympathetic activity and systemic vascular resistance has been previously demonstrated (Ashino *et al.* 1997). The elevated LV elastance in MS patients as compared to controls in the present study stands in contrast to the findings of Liu *et al.* (1992) showing similar E_{es} values in MS patients compared to controls. A plausible explanation for this disparity might lie in the discrepancy of haemodynamic findings between the two cohorts; in our study, MS subjects demonstrated lower CO (3.0 ± 1.0 *vs.* 3.7 ± 0.9 l min^{-1}), higher LAP (26 ± 7 *vs.* 18 ± 7 mmHg) and higher PAP$_m$ (58 ± 24 *vs.* 41 ± 13 mmHg). These haemodynamic discrepancies suggest lower baroreceptor sensitivity (Ferguson *et al.* 1990) and increased atrial stretch (Koizumi *et al.* 1977; Ashino *et al.*
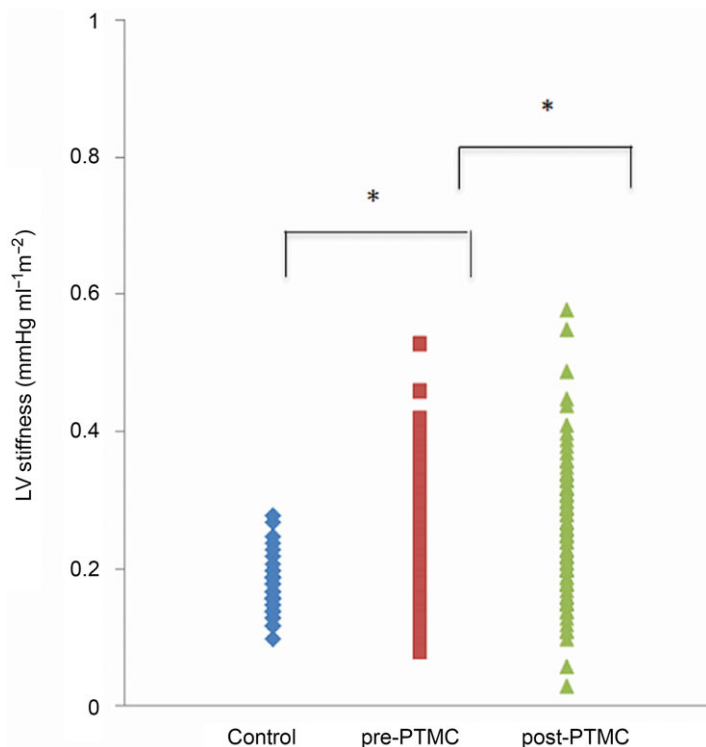

Figure 2. Left ventricular (LV) diastolic stiffness as expressed by the ratio of LV end-diastolic pressure to LV end-diastolic volume
Patients with MS demonstrated elevated LV stiffness compared to controls. Following percutaneous transvenous mitral commissurotomy (PTMC), a further significant increase in LV stiffness was documented.

Table 3. Echocardiographic variables in the study population before and immediately after PTMC

Variable	Pre-PTMC	Post-PTMC	*P*
HR (beats min^{-1})	75 ± 10	77 ± 15	n.s.
LVEDV (ml)	82 ± 24	90 ± 24	<0.001
LVEDV$_{index}$ (ml/m^2)	57 ± 16	64 ± 16	<0.001
LVESV (ml)	34 ± 12	33 ± 12	n.s.
LVESV$_{index}$ (ml/m^2)	23 ± 9	23 ± 9	n.s.
SV$_{Doppler}$ (ml)	49 ± 16	57 ± 17	<0.001
EF (%)	60 ± 8	64 ± 8	<0.001
MVA (cm^2)	0.8 ± 0.2	1.6 ± 0.2	<0.001
MVG$_{mean}$ (mmHg)	19 ± 9	5 ± 2	<0.001

HR, heart rate; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; SV$_{Doppler}$, Doppler-derived stroke volume; EF, ejection fraction; MVA, mitral valve area; MVG, mitral valve gradient.

1997), which in turn imply increased sympathetic tone and hence elevated contractility.

LV systolic function and arterial load

Consistent with previous results, our MS patients demonstrated significantly increased afterload (Liu *et al.* 1992) with 24% of them showing reduced EF (< 55%) (Kennedy *et al.* 1970; Gash *et al.* 1983). E_{es}, however, was not significantly different in these patients, whereas arterial load was higher (E_a: 4.1 ± 1.9 *vs.* 2.8 ± 0.9, $P < 0.001$) compared to those with preserved EF. The concept of ventriculo-arterial coupling posits that EF is determined by the interaction between LV contractility and afterload (Sunagawa *et al.* 1985). Providing there are no alterations in contractility, PV loop analysis suggests that a 33% afterload reduction (representing the measured difference between mean E_a in the two MS groups) yields an EF increase of roughly 20%, consistent with our results (Kass *et al.* 1990). Furthermore, with the reduction of E_a observed following PTMC (from 4.1 ± 1.9 to 3.5 ± 1.7 mmHg ml^{-1}), EF normalized (EF: 60±9%) in all cases with depressed LV performance at baseline. This, together with the significant inverse correlation between E_a and EF, suggests that employing EF to describe LV performance in severe MS can be misleading.

MS subjects demonstrated significantly higher LVESV, but not LVEDV, suggesting afterload mismatch (E_a *vs.* LVEDV, $r = -0.75$; $P < 0.001$) only partially compensated for by an increase in contractility (E_{es} *vs.* LVEDV, $r = 0.61$; $P < 0.001$). In normal hearts, afterload elevation is countered by preload increase to prevent SV reduction. However, MS hinders adequate preload recruitment (MVA *vs.* LVEDV, $r = 0.4$; $P < 0.001$), thereby limiting preload reserve. Hence, despite elevated E_{es}, the raised arterial load cannot be overcome owing to a hampered Frank–Starling mechanism, yielding lower SV. Although in normal hearts increased LVESV often indicates reduced inotropy, a more

applicable explanation in MS could be a state of exhausted contractile reserve, or the LV's inability to further increase E_{es}. This 'ceiling effect' in contractility may also be attributed to the inhibiting impact of β-blockers, partially preventing further increases in LV contractility.

LV performance and MS severity

Previous studies have demonstrated a rapid rise in tension in the subvalvular apparatus (Salisbury *et al.* 1963; Semafuko & Bowie, 1975) during isovolumetric LV contraction, and a considerable reduction in E_{es} when the chordae were severed (Hansen *et al.* 1986). To investigate the influence of mitral apparatus on LV performance, we sub-grouped our patients based on WS, degree of chordal fusion and length separately. Although LV contractility did not differ between these groups, subjects with EF < 55% displayed a significantly higher degree of subvalvular fusion. Our results also suggest that LV afterload is related to the degree of valvular deformation, as reflected by increased E_a in patients with higher valve scores.

LV diastolic function in MS

Previous studies have shown reduced LV compliance in MS patients (Liu *et al.* 1992; Mayer *et al.* 1999). A number of possible mechanisms for this observation have been proposed, including a mechanically mediated increase in LV stiffness by the rigid mitral apparatus (Heller & Carleton 1970; Curry *et al.* 1972), inherent myocardial alterations due to rheumatic disease, as well as altered RV loading and inter-ventricular interaction with this condition (Mayer *et al.* 1999). Our results provide important details regarding the possible underlying mechanisms of the reduced end-diastolic LV compliance in MS patients. First, we show that the degree of MV stenosis could independently predict the

Table 4. Simultaneous invasive and non-invasive pressure and elastance measurements in the validation group

Variable	Invasive	Non-invasive PTMC	P
Systolic arterial pressure (mmHg)	123 ± 18 (14)	107 ± 11 (14)	<0.001
Diastolic arterial pressure (mmHg)	68 ± 9 (14)	62 ± 7 (14)	0.047
E_{es} (mmHg ml^{-1})	4.15 ± 1.8 (14)	3.74 ± 1.6 (14)	<0.001
E_a (mmHg ml^{-1})	3.1 ± 1.4 (14)	2.7 ± 1.2 (14)	<0.001

E_{es}, LV elastance; E_a, effective arterial elastance.

degree of LV compliance. In that sense a more rigid and immobile valvular apparatus could act in a constraining manner reducing the distensibility of the LV during diastolic filling, as suggested by Liu *et al.* (1992). More importantly, RVEDP was identified as a strong predictor of end-diastolic LV stiffness. The role of inter-ventricular interaction in the setting of EDPVR has been suggested by Curry *et al.* (1972). In their study, MS patients with enlarged RV, reflecting increased RV preload, displayed impaired anterolateral wall motion and LV function; this observation was ascribed to the mechanical influence of the RV. Another group of investigators showed that RVEDP was associated with LV diastolic conditions in MS patients (Mayer *et al.* 1999). It has been suggested that a right to left interaction in MS might be secondary to alterations in anterolateral wall motion due to RV pressure overload (Nagel *et al.* 1996).

Acute haemodynamic alterations following PTMC

Following PTMC, SV and LVEDV rose significantly, while E_{es} returned to more normal values. SV elevation was directly related to the effect of the Frank–Starling mechanism (ΔLVEDV *vs.* ΔSV; $r = 0.73$, $P < 0.001$), suggesting that following MV dilatation, the LV counteracts afterload mismatch by recruiting preload reserve. Hence, the fall of LV elastance following PTMC can be assigned partly to SV increase after the intervention (ΔSV *vs.* ΔE_{es}; $r = -0.37$, $P < 0.001$) as the increased SV is expected to yield afferent parasympathetic baroreceptor stimulation. This in turn would inhibit sympathetic systemic output, resulting in lower arterial tonus (E_a reduction) and less pronounced LV contractility. Normalization of the baroreceptor reflex function has been attributed to CI increase and occurs within 1 week following PTMC (Ashino *et al.* 1997). Our findings imply that the arterial pressor reflexes may be reactivated immediately following valve dilatation, supporting the notion that their function is impaired due to haemodynamic rather than structural alterations (Ferguson *et al.* 1989). An intriguing finding of the present study is that LV end-diastolic stiffness showed a statistically significant albeit slight increase immediately after dilatation of the MV when employing two separate

non-invasive measurements of chamber stiffness. In fact, an elevation of chamber stiffness was noted in roughly 90% of the patients. Our data provide a plausible explanation for this finding as we have identified RV preload as the only independent predictor of the increases in EDPVR slope following PTMC. The presence of a non-distensible pericardium surrounding the two ventricles and the common septal wall shared by the two chambers contribute to the haemodynamic interaction between the two ventricles. In particular, the diastolic interaction between the two chambers has been increasingly recognized recently. In the setting of MS, the increased RVEDP occurring in MS due to pulmonary hypertension might be a plausible explanation for the increased LV stiffness. The observation that RVEDP did not change significantly following intervention, despite a significant fall in systolic RV pressures, adds weight to this hypothesis as after opening of the MV the LV has to accommodate larger volumes (increase in LVEDV). This would add a further constraint and thus lead to elevated LV stiffness. Although the present study did not investigate possible changes in myocardial stiffness following PTMC, it appears not to provide a plausible explanation for the altered LV chamber stiffness observed after MV dilatation.

Clinical implications

EF is misleading when studying LV performance in patients with MS as a result of the elevated LV afterload. The single-beat approach to measuring E_{es} provides a feasible, more comprehensive evaluation of LV function. Optimal pharmacological inhibition of the adrenergic activation might have a beneficial effect in MS patients.

Limitations

In the present study, non-invasive indices of LV and arterial function were used. LV end-diastolic stiffness and LV elastance as well as arterial elastance are optimally recorded using conductance catheters. However, all the aforementioned non-invasive measurements are validated against gold standard invasive methods (Kelly *et al.* 1992; Kass, 2000; Chen *et al.* 2001). Additionally, in our study, we calculated E_{es} and E_a using the invasively

derived pressures, whereas in the controls non-invasive pressure measurements were performed for the same reason. This limitation of the study was addressed by a validation study. The predicted values for the patient cohort, although different from the invasive data, did not alter the results of the study. Furthermore, in controls LV chamber stiffness was measured using PCWP values estimated using a previously proposed equation (Nagueh *et al.* 1997). As the authors in that study reported a standard error of approximately 4 mmHg, this would result in overlap in LV stiffness between MS patients and controls. To resolve this concern we proceeded by using a PCWP value of 11 mmHg for all healthy controls (the generally accepted upper normal value in young healthy subjects). Measurements of LV stiffness thus revealed that even in that extreme case LV stiffness in controls was significantly lower (0.2 ± 0.03 mmHg ml^{-1}) as compared to MS patients ($P < 0.001$). Doppler and two-dimensional echocardiographic measurements entail an inherently larger variability compared to invasive measurements. On the other hand, measurements of intra- and interobserver variation performed for E_{es} show a rather low variation for repeated single measurements. Finally, patients in our study had advanced rheumatic MS (WS > 8 in 56% of cases) and may not represent the haemodynamic state in less severe degrees of stenosis. However, the study adds important physiological insight into severe rheumatic MS.

Conclusion

Subjects with severe MS exhibit a hypercontractile LV, most probably reflecting an increased sympathetic tone. With preload recruitment immediately following PTMC, LV afterload and contractility tend to normalize in most patients. Finally, we demonstrate that heightened arterial load is associated with MS severity.

References

Ahmed SS, Regan TJ, Fiore JJ, Levinson GE (1977). The state of the left ventricular myocardium in mital stenosis. *Am Heart J* **94**, 28–36.

Ashino K, Gotoh E, Sumita S, Moriya A, Ishii M (1997). Percutaneous transluminal mitral valvuloplasty normalizes baroreflex sensitivity and sympathetic activity in patients with mitral stenosis. *Circulation* **96**, 3443–3449.

Chen CH, Fetics B, Nevo E, Rochitte CE, Chiou KR, Ding PA, Kawaguchi M, Kass DA (2001). Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. *J Am Coll Cardiol* **38**, 2028–2034.

Covell JW, Ross J Jr, Sonnenblick EH, Braunwald E (1966). Comparison of the force–velocity relation and the ventricular function curve as measures of the contractile state of the intact heart. *Circ Res* **19**, 364–372.

Curry GC, Elliott LP, Ramsey HW (1972). Quantitative left ventricular angiocardiographic findings in mitral stenosis. Detailed analysis of the anterolateral wall of the left ventricle. *Am J Cardiol* **29**, 621–627.

Dahlberg G (1940). *Statistical Methods for Medical and Biological Students.* G. Allen & Unwin, London.

Ferguson DW, Berg WJ, Sanders JS (1990). Clinical and hemodynamic correlates of sympathetic nerve activity in normal humans and patients with heart failure: evidence from direct microneurographic recordings. *J Am Coll Cardiol* **16**, 1125–1134.

Ferguson DW, Berg WJ, Sanders JS, Roach PJ, Kempf JS, Kienzle MG (1989). Sympathoinhibitory responses to digitalis glycosides in heart failure patients. Direct evidence from sympathetic neural recordings. *Circulation* **80**, 65–77.

Gash AK, Carabello BA, Cepin D, Spann JF (1983). Left ventricular ejection performance and systolic muscle function in patients with mitral stenosis. *Circulation* **67**, 148–154.

Hansen DE, Cahill PD, DeCampli WM, Harrison DC, Derby GC, Mitchell RS, Miller DC (1986). Valvular–ventricular interaction: importance of the mitral apparatus in canine left ventricular systolic performance. *Circulation* **73**, 1310–1320.

Heller SJ & Carleton RA (1970). Abnormal left ventricular contraction in patients with mitral stenosis. *Circulation* **42**, 1099–1110.

Hildner FJ, Javier RP, Cohen LS, Samet P, Nathan MJ, Yahr WZ, Greenberg JJ (1972). Myocardial dysfunction associated with valvular heart disease. *Am J Cardiol* **30**, 319–326.

Holzer JA, Karliner JS, O'Rourke RA, Peterson KL (1973). Quantitative angiographic analysis of the left ventricle in patients with isolated rheumatic mitral stenosis. *Br Heart J* **35**, 497–502.

Horwitz LD, Mullins CB, Payne RM, Curry GC (1973). Left ventricular function in mitral stenosis. *Chest* **64**, 609–614.

Kaku K, Hirota Y, Shimizu G, Kita Y, Saito T, Kawamura K (1988). Depressed myocardial contractility in mitral stenosis–an analysis by force–length and stress-shortening relationships. *Jpn Circ J* **52**, 35–43.

Kass DA (2000). Assessment of diastolic dysfunction. Invasive modalities. *Cardiol Clin* **18**, 571–586.

Kass DA, Grayson R, Marino P (1990). Pressure–volume analysis as a method for quantifying simultaneous drug (amrinone) effects on arterial load and contractile state *in vivo*. *J Am Coll Cardiol* **16**, 726–732.

Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, Kass DA (1992). Effective arterial elastance as index of arterial vascular load in humans. *Circulation* **86**, 513–521.

Kennedy JW, Yarnall SR, Murray JA, Figley MM (1970). Quantitative angiocardiography. IV. Relationships of left atrial and ventricular pressure and volume in mitral valve disease. *Circulation* **41**, 817–824.

Klotz S, Hay I, Dickstein ML, Yi GH, Wang J, Maurer MS, Kass DA, Burkhoff D (2006). Single-beat estimation of end-diastolic pressure–volume relationship: a novel method with potential for noninvasive application. *Am J Physiol Heart Circ Physiol* **291**, H403–412.

Koizumi K, Nishino H, Brooks CM (1977). Centers involved in the autonomic reflex reactions originating from stretching of the atria. *Proc Natl Acad Sci U S A* **74**, 2177–2181.

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

Liu CP, Ting CT, Yang TM, Chen JW, Chang MS, Maughan WL, Lawrence W, Kass DA (1992). Reduced left ventricular compliance in human mitral stenosis. Role of reversible internal constraint. *Circulation* **85**, 1447–1456.

Mayer IV, Fischer A, Jakob M, Mandinov L, Hug R, Vassalli G, Hess OM (1999). Reversal of increased diastolic stiffness in mitral stenosis after successful balloon valvuloplasty. *J Heart Valve Dis* **8**, 47–56.

Nagel E, Stuber M, Hess OM (1996). Importance of the right ventricle in valvular heart disease. *Eur Heart J* **17**, 829–836.

Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA (1997). Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* **30**, 1527–1533.

Salisbury PF, Cross CE, Rieben PA (1963). Chorda tendinea tension. *Am J Physiol* **205**, 385–392.

Schmidt HD & Scheer RD (1981). Quantitative data on the afterload dependence of left ventricular dp/dtmax in isolated canine hearts. *Basic Res Cardiol* **76**, 89–105.

Semafuko WE & Bowie WC (1975). Papillary muscle dynamics: *in situ* function and responses of the papillary muscle. *Am J Physiol* **228**, 1800–1807.

Suga H & Sagawa K (1974). Instantaneous pressure–volume relationships and their ratio in the excised, supported canine left ventricle. *Circ Res* **35**, 117–126.

Suga H, Sagawa K, Shoukas AA (1973). Load independence of the instantaneous pressure–volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ Res* **32**, 314–322.

Sunagawa K, Maughan WL, Sagawa K (1985). Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. *Circ Res* **56**, 586–595.

Sunagawa K, Sagawa K, Maughan WL (1984). Ventricular interaction with the loading system. *Ann Biomed Eng* **12**, 163–189.

Sunamori M, Suzuki A, Harrison CE (1983). Relationship between left ventricular morphology and postoperative cardiac function following valve replacement for mitral stenosis. *J Thorac Cardiovasc Surg* **85**, 727–732.

Urschel CW, Covell JW, Sonnenblick EH, Ross J Jr, Braunwald E (1968). Effects of decreased aortic compliance on performance of the left ventricle. *Am J Physiol* **214**, 298–304.

Weber KT, Janicki JS, Hefner LL (1976). Left ventricular force–length relations of isovolumic and ejecting contractions. *Am J Physiol* **231**, 337–343.

Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF (1988). Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. *Br Heart J* **60**, 299–308.

Additional information

Competing interests

No extramural funding was used to support this work. None of the authors have any conflict of interest to disclose. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Author contributions

A.M., A.V., A.I.N., S.S. and R.W. designed the study; A.V., A.M., B.B. and P.K.D. performed invasive and echocardiographic measurements; A.V., A.M., A.I.N., K.S., S.C.G., A.S., R.W., B.B. and P.K.D. contributed to analysis and interpretation of the data; A.V., A.M. and A.I.N. wrote the manuscript. K.S., S.C.G., A.S., R.W., B.B. and P.K.D. revised the manuscript critically. All authors have read and approved the final manuscript.