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ORIGINAL RESEARCH ARTICLE

Modification of ventriculo–arterial coupling by spironolactone in nonischemic dilated cardiomyopathy

Mark A. Lawson, David E. Hansen, Deepak K. Gupta, Susan P. Bell, Douglas W. Adkisson, Ravinder R. Mallugari, Douglas B. Sawyer, Henry Ooi and Marvin W. Kronenberg*

VA Tennessee Valley Health Care System, Vanderbilt University Medical Center, Nashville, TN 37232, USA

Abstract

Aims We sought to clarify the role of ventriculo–arterial (V–A) coupling in the treatment of nonischemic dilated cardiomyopathy (NIDCM) by adding a mineralocorticoid receptor antagonist (MRA) to conventional anti-failure therapy.

Methods and results We employed cardiac magnetic resonance imaging to quantify left ventricular (LV) contractility and V–A coupling in normal subjects at rest (n = 11) and in patients with NIDCM (n = 12) before and after long term anti-failure therapy, in which MRA was added to conventional anti-failure therapy. After ≥6 months' treatment in NIDCM patients, LV volumes and mass decreased, and the LV ejection fraction increased from a median of 24% (17, 27) (interquartile range IQR) to 47 (42, 52) ($P < 0.002$), with a marked reduction in arterial elastance (Ea) from 2.89 mmHg/mL (2.34, 4.0) to 1.50 (1.29, 1.95) ($P < 0.002$), similar to Ea of normal subjects, 1.53 (1.34, 1.67) ($P > 0.05$). The V–A coupling ratio, Ea/end-systolic elastance (single-beat method), decreased by −1.08 (−1.96, −0.55), (P = 0.003), as did Ea/end-systolic pressure/end-systolic pressure ratio, −0.54 (0.35, 0.87), (P = 0.002). The preload recruitable stroke work (PRSW) increased as did PRSW indexed for Ea (both P = 0.002), which reflected 'total circulatory performance'.

Conclusions In NIDCM, adding MRA to conventional anti-failure therapy markedly improved LV ejection fraction and reduced peripheral vascular resistance, due to both improved LV contractility and especially to enhanced V–A coupling, as Ea decreased to normal. Total circulatory performance was a sensitive indicator of both LV pump performance and the arterial loading conditions.

Keywords Nonischemic cardiomyopathy; Ventricular/vascular coupling haemodynamics; Magnetic resonance imaging; Spironolactone

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**Correspondence to: Marvin W. Kronenberg, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Vanderbilt Medical Center East, Ste. 5209, 1215 21st Ave, South, Nashville, TN 37232, USA. Tel: (615) 936-7359; Fax: (615) 936-2437. Email: marvin.w.kronenberg@vumc.org*
From the Division of Cardiovascular Medicine, Vanderbilt University School of Medicine and the Cardiology Section, VA Tennessee Valley Healthcare System, Nashville, TN. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

Introduction

Nonischemic dilated cardiomyopathy (NIDCM) is characterized by depressed left ventricular (LV) contractility with adverse LV remodelling, myocardial fibrosis and heart failure (HF) with reduced ejection fraction (HFrEF).[1] This constellation activates compensatory neurohormonal mechanisms that increase systemic vascular resistance (SVR).[2]

Standard therapy for HFrEF affects both the LV myocardium and the peripheral circulation. Beta-adrenergic blocking drugs (BBs), such as carvedilol, improve myocardial structure and function[3] and reduce SVR.[4] Angiotensin-converting enzyme inhibitors (ACE-I) reduce perivascular collagen[5] and reduce SVR,[2] reducing unfavourable LV remodelling.[6]

Randomized clinical trials in HFrEF patients reduced mortality by treatment with mineralocorticoid receptor antagonist(s) (MRA).[7] Aldosterone causes excess vascular stiffness[8] and stimulates LV interstitial fibrosis,[9] which can be blocked and partly reversed by MRA.[10,11] Relatively little attention has been paid to the role of the peripheral vasculature in improving LV performance in HFrEF.[12,13] However, MRA up-regulate endothelial nitric oxide,[14] causing peripheral vascular dilatation and lower SVR,[15] which may contribute to beneficial LV remodelling.[16,17]

The coupling of LV contractile properties with the peripheral circulation [ventriculo–arterial (V–A) coupling] can be expressed in the pressure–volume plane as the interaction of the LV end-systolic pressure (ESP) volume relationship (ESPVR) and the systemic arterial elastance (Ea).[18] Other methods for estimating LV performance include the ratio of LV end-systolic pressure/end-systolic volume,[19] the single-beat calculation of LV elastance,[20] preload recruitable stroke work (PRSW),[21] and its single-beat calculation.[22]

We sought to clarify the influence of V–A coupling on changes in LV ejection fraction (LVEF) and indices of LV contractility during the treatment of NIDCM. For this, we used serial cardiac magnetic resonance imaging (CMR) and the above-mentioned methods in patients with NIDCM before and after adding MRA to conventional anti-failure therapy with BB and ACE-I and angiotensin receptor blocking (ARB) drugs.[23,24] The CMR method was employed based on its accuracy for quantitating LV mass and volume.[25,26]

Methods

Study design

We enrolled patients with newly diagnosed NIDCM who were recruited from the Vanderbilt University Medical Center and the Veterans Affairs Tennessee Valley Medical Center. Eligible participants were 18–80 years old, of any ethnic background and either sex, New York Heart Association Functional Class II–IV, with an echocardiographic LVEF of ≤35% and serum potassium level less than 5.0 mmol/L (5 mEq/dL) while on medical therapy for HF (including stable BB and ACE-I/ARB for ≥3 months). Exclusion criteria were the need for an implantable cardioverter-defibrillator, evidence of prior myocardial infarction on electrocardiogram, a positive stress test or coronary artery disease with ≥50% stenosis in a major epicardial artery at angiography, severe chronic obstructive airway disease precluding adenosine use, creatinine >220 μmol/L (2.5 mg/dL), glomerular filtration rate <30 mL/min/1.73m^2, uncontrolled atrial fibrillation, current spironolactone therapy, and physician preference. Of 590 screened clinic visits, 16 patients who met the inclusion and exclusion criteria were recruited. Among these, four did not complete the study due to erroneous inclusion of one patient, bronchoconstriction from adenosine used for CMR (n = 1), implantation of implantable cardioverter-defibrillator (n = 1), and patient withdrawal (n = 1), leaving a total of 12 patients who completed the study protocol. Significant coronary atherosclerosis was excluded by coronary angiography (n = 10) or the absence of ischemia or infarction on nuclear stress perfusion imaging (n = 2).

The NIDCM patients underwent a 5 day trial of spironolactone to assess tolerability. After this drug was discontinued, the patients underwent CMR at baseline and after ≥6 months of spironolactone therapy added to ACE-I/ARB and BB anti-failure treatment. The CMR protocol is described later. The patients took spironolactone 25 mg daily for ≥6 months, up-titrated to 50 mg daily if possible. The doses of ACE-I/ARB and BB drugs remained constant. Eleven normal subjects were recruited by advertisement and had no history of hypertension, diabetes mellitus, or heart disease. They were studied at rest at a single time point using similar CMR technique.

This investigation conforms with the principles outlined in the Declaration of Helsinki. The NIDCM study was approved by both the Vanderbilt and Nashville Veterans Affairs Institutional Review Boards. The normal subject study was approved by the Vanderbilt Institutional Review Board. All patients provided written informed consent.

Cardiac magnetic resonance imaging acquisition and analysis

Cardiac magnetic resonance imaging was performed using a commercially available 1.5-T Siemens Magnetom Avanto scanner (Erlangen, Germany) using methods previously published.[23] During CMR, the blood pressure was measured using an magnetic resonance imaging compatible automated cuff sphygmomanometer, and heart rate was recorded from telemetry.

Data analysis

Cardiac magnetic resonance imaging

The end-diastolic and end-systolic endocardial borders on CMR were outlined using system software (Argus software Version B17, Siemens, Erlangen, Germany) (NIDCM patients) or Medis software (normal subjects) and adjusted manually as needed to calculate LVEF. The end-diastolic volume (EDV), end-systolic volume (ESV) and stroke volume (SV), were divided by body surface area, yielding these indices (mL/m^2). Simplified pressure–volume diagrams were constructed from CMR data and the noninvasive blood pressure values for each patient.

Echocardiography acquisition and analysis

All subjects underwent standard two-dimensional, M-mode, and Doppler transthoracic echocardiography according to American Society of Echocardiography guidelines. Imaging was performed using Phillips IE33 echocardiographs using standard transducers. For calculation of $E_{Nd(est)}$, the ratio of the pre-ejection period (PEP) to the total systolic period (Q-S2 interval) was determined using Doppler tracings of the LV outflow tract. Among normal subjects, SV was calculated using the LV outflow tract diameter and velocity time integral.[27]

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Indices of contractility

End-systolic pressure The ESP (Pes) was calculated as 0.9 × systolic blood pressure (SBP).[28]

End-systolic elastance (single-beat method) A single-point estimate of the LV contractile state was calculated as

$E_{es\ (sb)} = [P_d - (E_{Nd\ (est)} \times P_s \times 0.9)]/[SV \times E_{Nd\ (est)}]$,[20]

in which $E_{es(sb)}$ = end-systolic elastance using a single-beat method (SBM) (mmHg/mL), P_d = systemic arterial diastolic pressure (mmHg), P_s = systolic arterial pressure (mmHg), SV = stroke volume (mL), and $E_{Nd(est)}$ = group averaged LV elastance at the onset of ejection. To calculate $E_{Nd(est)}$, the ratio of the PEP to the total systolic period (Q-S2 interval) was determined using Doppler tracings of the LV outflow tract on echocardiograms obtained as baseline or follow-up studies. These data were available in 10 of 12 HF patients at baseline and for five patients who had echocardiograms within 1.5 years after completing the study. The mean values for PEP and Q-S2 were applied to the remaining HF patients. All normal subjects had echocardiograms within 6 hours of their CMR study.

Magnetic resonance imaging was employed to calculate SV instead of echocardiography as performed previously.[20] To evaluate our CMR adaptation, in 10 normal subjects, echocardiography was employed for estimating PEP, Q-S2, and SV, and results were compared with end-systolic elastance (single-beat method) [Ees (sb)] using CMR SV.

End-systolic pressure/end-systolic volume ratio The ESP/end-systolic volume (P/V) ratio was calculated as Pes/Ves.[4]

End-systolic volume pressure of 100 mmHg The ESV at a pressure of 100 mmHg (End-systolic volume at pressure 100 mmHg) was calculated as an expression of contractility, needing minimal extrapolation, if any, from measured values, similar to the work of others.[29]

Stroke work This was calculated as stroke work (SW) = SV × MAP,[21] where MAP = mean systemic arterial pressure (mmHg).

Preload recruitable stroke work This was expressed as M_w = SW/EDV − Vw, where Vw is the *X*-axis intercept of this slope and M_w is the slope of the relation,[21] employing a single beat method (SBM), SBM_w.[22]

Systemic arterial properties

Total systemic vascular resistance This was calculated as total systemic vascular resistance (TVR) = 80 × MAP/CO (dyn s cm^{-5}), where CO = cardiac output (L/min), converted to Wood units (mmHg-min/L).

Arterial elastance The Ea was expressed as Pes/SV.[18]

Ventriculo–arterial coupling

Arterial elastance/end-systolic elastance (single-beat method) The V–A coupling ratio expressed as the relation of Ea and LV contractility expressed as Ees (sb),[18] Ea/Ees(sb).

Arterial elastance/end-systolic pressure/end-systolic volume ratio The V–A coupling ratio expressed as the relation of Ea and LV contractility using the end-systolic Pes/Ves ratio[4] Ea/[P/V].

Total circulatory performance To evaluate the hypothesis that Ea is incorporated in PRSW,[30,31] we compared its main component, SW/EDV, with SBM_w and then indexed the result for Ea by comparing the relation of [(SW/EDV)/Ea] to SBM_w. Incorporating Ea was considered an index of total circulatory performance (TCP) that reflected both LV contractility and arterial loading conditions.

Statistical analysis

Descriptive statistics are presented as median (25th to 75th percentile) or counts (percentages). Either the Wilcoxon rank-sum or Fisher's exact test was used for comparisons between normal subjects and patients with NIDCM. For paired data examining changes in parameters of cardiac structure and function before and after spironolactone, the Wilcoxon signed-rank test was used. Comparisons of the slopes of the relationships between SW/EDV (or [SW/EDV]/Ea) and SBM_w before and after MRA therapy were performed using linear regression with an interaction term with robust adjustment. Differences between the slopes of SW/EDV to SBM_w and [SW/EDV]/Ea to SBM_w were assessed using the 'suest' package in Stata. Analyses were performed using Stata v15.0 (Stata Corp., Austin, TX, USA).

Results

Baseline characteristics

Selected baseline data of each patient group are listed in *Tables 1* and *2*. Other details of the NIDCM patients were published previously.[23] The NIDCM and normal subjects were of similar ages. Before study entry, the median duration of taking a BB and either an ACE-I or ARB drug was 21 weeks, and the median duration on stable doses of BB was 16 weeks. The baseline CMR study was at a median of 10 weeks (IQR 6–16) after the screening echocardiogram that met inclusion criteria. There was a strong correlation between Ees (sb) determined by echocardiography alone compared with Ees (sb) using CMR for SV (R^2 = 0.79, P = 0.0006).

Table 1 Characteristics at time of baseline CMR

	NIDCM $N = 12$	Normal $N = 11$	P
Age (years)	52 (45, 55)	55 (52, 58)	0.039
Male	8 (67%)	3 (27%)	0.10
Medications			
Beta blocker	12 (100%)	0 (0%)	
ACE-I or ARB	12 (100%)	0 (0%)	
Diuretic	7 (58%)	0 (0%)	
BMI (kg/m^2)	30.0 (25.7, 34.3)	24.7 (21.0, 27.8)	0.023
BSA (m^2)	2.07 (1.85, 2.33)	1.63 (1.56, 2.01)	0.019
NYHA class			
1	0 (0%)	7 (100%)	
2	5 (42%)	0 (0%)	
3	7 (58%)	0 (0%)	
Heart rate (bpm)	67 (58, 71)	62 (57, 68)	0.48
Systolic BP (mmHg)	121 (115, 125)	120 (113, 125)	0.62
Diastolic BP (mmHg)	67 (63, 73)	72 (67, 82)	0.25
MAP (mmHg)	84 (80, 90)	87 (82, 95)	0.39

Median (interquartile range). ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocking drug; BMI, body mass index; BP, blood pressure; bpm, beats per minute; BSA, body surface area; CMR, cardiac magnetic resonance imaging; MAP, mean arterial pressure; mmHg, millimetres Mercury; NIDCM, nonischemic dilated cardiomyopathy; NYHA, New York Heart Association.

Table 2 Baseline parameters of LV performance and ventriculo–arterial coupling

	NIDCM $N = 12$	Normal $N = 11$	P
LVEF (%)	24 (17, 27)	66 (62, 67)	<0.001
LVEDVI (mL/m^2)	82 (74, 91)	63 (55, 75)	0.002
LVESVI (mL/m^2)	63 (56, 78)	19 (17, 28)	<0.001
LVSVI (mL/m^2)	19 (14, 21)	41 (37, 47)	<0.001
LV mass (g)	169 (154, 203)	69 (49, 77)	<0.001
TVR (Wood units)	2.69 (2.23, 3.85)	1.48 (1.38, 1.75)	<0.001
Ea	2.89 (2.34, 4.00)	1.53 (1.34, 1.67)	<0.001
E_{es} (sb)	0.96 (0.75, 1.43)	1.44 (1.26, 1.64)	0.016
Ea/Ees (sb)	3.08 (2.54, 3.78)	0.95 (0.91, 1.11)	<0.001
P_{es}/Ves	0.83 (0.65, 0.95)	3.04 (2.63, 3.49)	<0.001
V_0	16 (−14, 38)	−38 (−39, −24)	0.001
ESV-100	121 (104, 148)	30 (27, 37)	<0.001
SBM_w	35 (24, 45)	113 (101, 119)	<0.001
TCP	7.4 (3.4, 11.4)	40.2 (35.2, 43.8)	<0.001
Ea/[Pes/Ves]	3.24 (2.65, 4.83)	0.51 (0.49, 0.60)	<0.001
Vw	71.3 (60.2, 90.2)	51.1 (49.2, 56.4)	0.012

Median (interquartile range). Pairwise comparisons between groups using Wilcoxon rank sum test, with Bonferroni corrected threshold $P < 0.0166$ for significance. Ea, arterial elastance (mmHg/mL); Ea/[Pes/Ves], arterial elastance/end-systolic pressure/end-systolic volume ratio; Ees (sb), end-systolic elastance (single-beat method) (mmHg/mL); ESV-100, end-systolic volume at 100 mmHg (mL); LV, left ventricular; LVEDVI, LV end-diastolic volume index; LVEF, LV ejection fraction; LVESVI, LV end-systolic volume index; LVSVI, LV stroke volume index; Pes/Ves, end-systolic pressure/end-systolic volume ratio; SBM_w, slope of preload recruitable stroke work relation (single-beat method) ($erg.cm^{-3}\ 10^3$); TCP, total circulatory performance (stroke work/end-diastolic volume/Ea); TVR, total vascular resistance; V_0, end-systolic volume at SBP 0 mmHg (mL); Vw, LV volume at Stroke Work 0.

Left ventricular remodelling in nonischemic dilated cardiomyopathy

Following ≥6 months of spironolactone therapy (median 45 weeks, IQR 27–74) CMR showed evidence for beneficial remodelling, with significant reductions in LV EDVI and ESVI, associated with an increase in SVI and LVEF (*Figure 1*, *Table 3*).

Indices of contractility

There were significant changes in the P/V ratio, ESV-100, SW/EDV, and SBM_w, all consistent with improved contractility, except for Ees (sb) (*Figure 2*, *Table 3*). At baseline, Ees (sb) was 0.96 (0.75, 1.43) mmHg/mL, which was less than in our normal subjects and normal values in the literature,[20,32] and was 0.79 (0.69, 1.11) at follow-up ($P = 0.12$). With a decrease in ESV, the calculated V_0 shifted leftward.

Peripheral circulation

There was a strong correlation between Ea and TVR in NIDCM patients ($R^2 = 0.85$, $P < 0.0001$). The Ea of NIDCM patients was 2.89 (2.34, 4.00) mmHg/mL at baseline, and as SV increased, Ea declined sharply to 1.50 (1.29, 1.95) at follow-up ($P = 0.002$).

Figure 1 Pressure–volume relations of patients with nonischemic dilated cardiomyopathy before (red) and after anti-failure therapy (blue). Dashed lines show Ees (sb) and calculated V_0. ESV-100, end-systolic volume pressure of 100 mmHg; LVEF, left ventricular ejection fraction; P/V, end-systolic pressure/end-systolic volume; SBM, single-beat method.

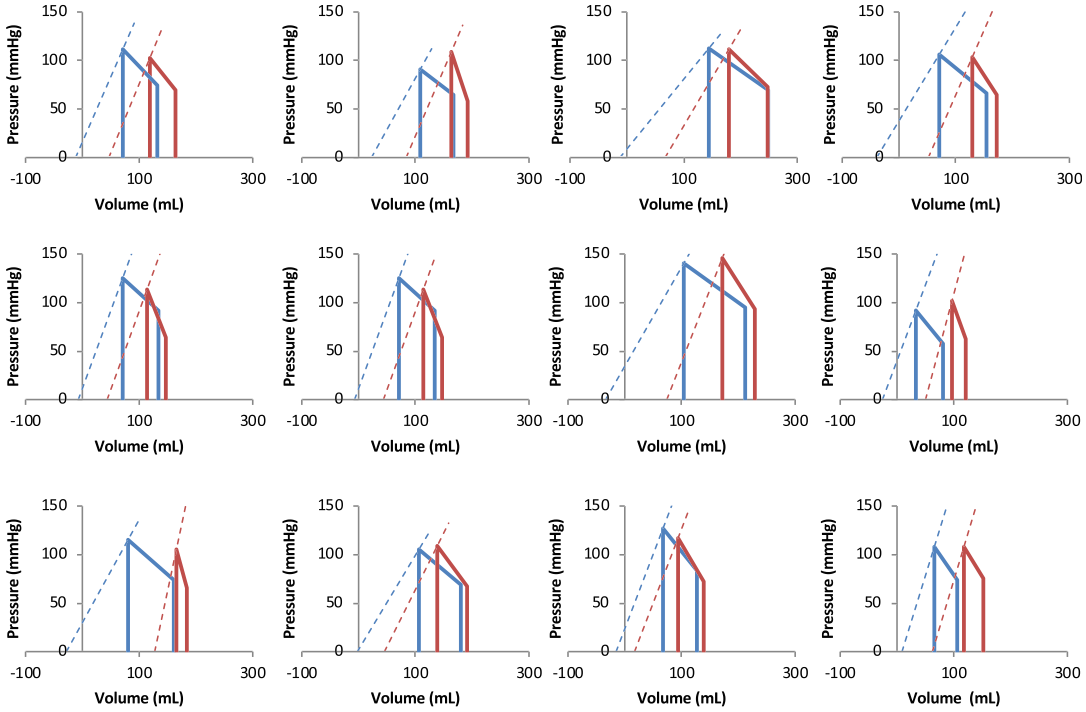
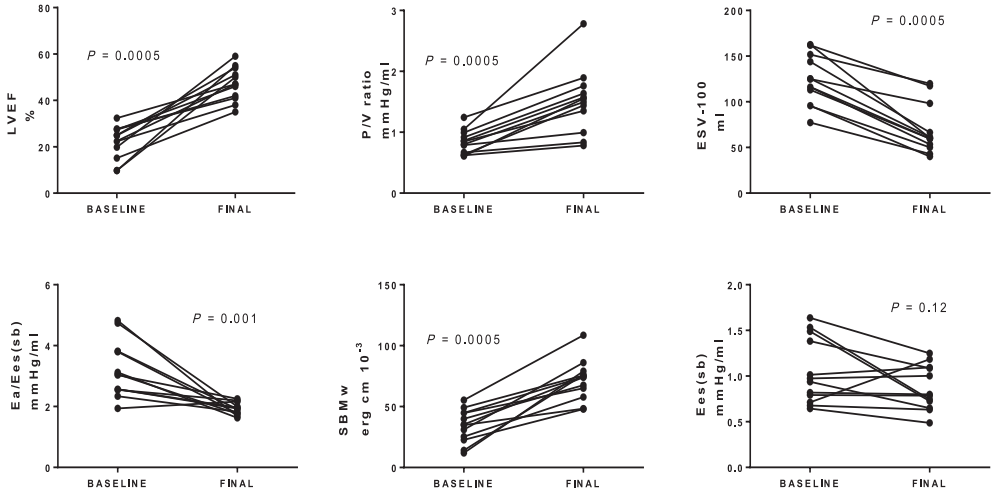


Table 3 LV performance and ventriculo–arterial coupling at baseline and after adding mineralocorticoid receptor antagonist in NIDCM patients

	Baseline	Follow-up	Change	*P*
Heart rate (bpm)	67 (58, 71)	72 (65, 76)	5 (3, 12)	0.021
Systolic BP (mmHg)	121 (115, 125)	122 (112, 134)	2 (−5, 11)	0.46
Diastolic BP (mmHg)	67 (63, 73)	72 (65, 79)	4 (−1, 10)	0.059
MAP (mmHg)	84 (80, 90)	89 (81, 97)	1 (−1, 10)	0.21
LVEF (%)	24 (17, 27)	47 (42, 52)	22 (15, 34)	0.002
LVEDVI (mL/m^2)	82 (74, 91)	74 (59, 82)	−8 (−14, −5)	0.003
LVESVI (mL/m^2)	63 (56, 78)	36 (31, 46)	−24 (−32, −19)	0.002
LVSVI (mL/m^2)	19 (14, 21)	36 (28, 40)	15 (9, 19)	0.002
LV mass (g)	169 (154, 203)	151 (138, 190)	−12 (−21, −6)	0.008
TVR (Wood units)	2.69 (2.23, 3.85)	1.34 (1.15, 1.87)	−1.17 (−2.06, −0.73)	0.002
Ea	2.89 (2.34, 4.00)	1.50 (1.29, 1.95)	−1.19 (−2.26, 0.53)	0.002
Ees (sb)	0.96 (0.75, 1.43)	0.79 (0.69, 1.11)	−0.10 (−0.35, 0.02)	0.12
Vo ml	16 (−14, 38)	−56 (−73, −37)	−70 (−102, −34)	0.003
Vw	71.3 (60.2, 90.2)	61.7 (47.0, 79.0)	−11.9 (−18.1, −4.4)	0.004
ESV-100	121 (104, 148)	60 (52, 82)	−54 (−63, −39)	0.002
Ea/Ees (sb)	3.08 (2.55, 3.78)	1.89 (1.75, 2.07)	−1.08 (−1.96, −0.55)	0.003
Pes/Ves	0.83 (0.65, 0.95)	1.52 (1.17, 1.70)	0.70 (0.35, 0.79)	0.002
SBM_w	35.1 (24.0, 44.7)	74.1 (61.5, 77.5)	31.0 (25.8, 54.2)	0.002
TCP	7.4 (3.4, 11.4)	25.0 (22.7, 33.9)	19.3 (13.0, 28.9)	0.002
Ea/[Pes/Ves]	3.24 (2.65, 4.83)	1.12 (0.91, 1.4)	0.54 (0.35, 0.87)	0.002

Median (interquartile range). Ea, arterial elastance (mmHg/mL); Ea/[Pes/Ves], arterial elastance/end-systolic pressure/end-systolic volume ratio; Ees (sb), end-systolic elastance (single-beat method) (mmHg/mL); ESV-100, end-systolic volume at 100 mmHg (mL); LV, left ventricular; LVEDVI, LV end-diastolic volume index; LVEF, LV ejection fraction; LVESVI, LV end-systolic volume index; LVSVI, LV stroke volume index; Pes/Ves, end-systolic pressure/end-systolic volume ratio; SBM_w, slope of preload recruitable stroke work relation (single-beat method) (erg.cm^{-3} 10^3); TCP, total circulatory performance (stroke work/end-diastolic volume/Ea); TVR, total vascular resistance; V_0, end-systolic volume at SBP 0 mmHg (mL); Vw, LV volume at Stroke Work 0.

Figure 2 Estimates of left ventricular contractility before and after anti-failure therapy. Please see text for abbreviations.



Ventriculo–arterial coupling

Arterial elastance/end-systolic elastance (single-beat method)

At baseline, patients with NIDCM, compared with normal subjects, had a greater V–A coupling ratio, Ea/Ees (sb), due to greater Ea and lower Ees (sb). At follow-up, Ea declined sharply to a value similar to normal subjects ($P > 0.05$) (*Tables 2* and *3*) because of the increase in SV. However, the V–A coupling ratio, Ea/Ees (sb), was still greater than in normal subjects ($P < 0.001$) (*Tables 2* and *3*).

Arterial elastance/end-systolic pressure/end-systolic volume ratio

At baseline, patients with NIDCM had a similarly greater V–A coupling ratio compared with normal subjects (*Table 2*). There was a marked decrease in in this value at follow-up (*Table 3*, *Figure 3*), although this measure of V–A coupling remained greater than normal ($P < 0.001$).

Total circulatory performance

At baseline, TCP was markedly different between NIDCM and normal subjects, but lay along the same regression line (*Figure 4*). At baseline, in the NIDCM patients, the slope of the relation between [SW/EDV] and M_w was similar to the slope of the relation when indexed for Ea (*Figure 5*, Panel A vs. C) ($P = 0.61$). After MRA, the values of [SW/EDV] increased

Figure 4 Relation between preload recruitable stroke work as SBM_w vs. [SW/EDV]/Ea in patients with nonischemic dilated cardiomyopathy and normal subjects. The values are markedly different between the two groups but the relations are similar. Closed circles: nonischemic dilated cardiomyopathy. Open circles: normal. ESV, end-systolic volume; SBM, single-beat method.

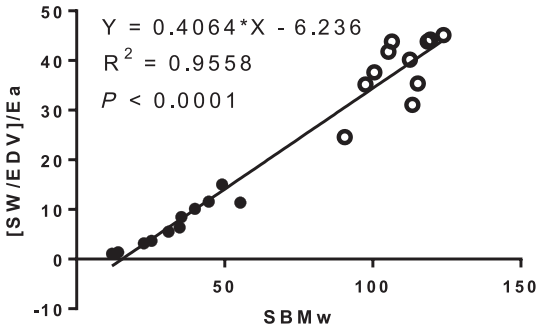


Figure 3 Changes in ventriculo–arterial coupling using two definitions of left ventricular contractility. (A). Arterial elastance/end-systolic elastance (single-beat method) [Ea/Ees (sb)]. (B). Arterial elastance/end-systolic pressure/end-systolic volume ratio (Ea/[Pes/Ves]). ESV, end-systolic volume; SBM, single-beat method.

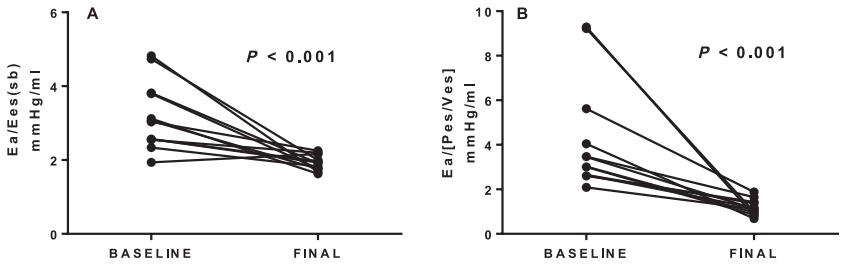
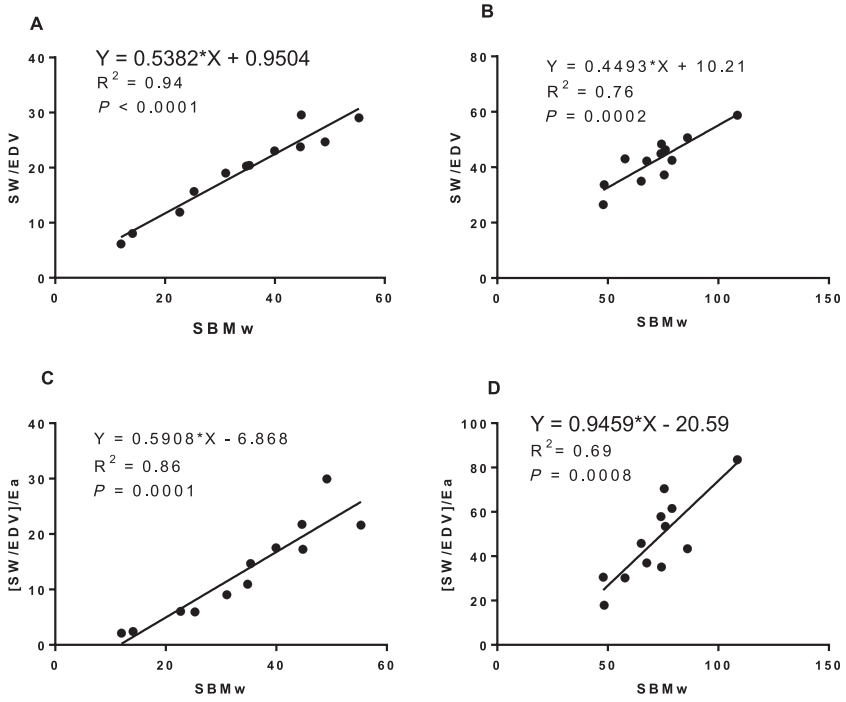


Figure 5 Preload recruitable stroke work (SW) (PRSW) as SBM_w in patients with nonischemic dilated cardiomyopathy. Comparison of SBM_w and SW/EDV before (A) and after adding mineralocorticoid receptor antagonist (MRA) (B). Comparison of SBM_w and SW/EDV adjusted for peripheral vascular elastance (Ea) (TCP) before (C) and after adding MRA (D). PRSW increased markedly after adding MRA (Panel A vs. B). Increased slope of the [(SW/EDV)/Ea]-SBM_w relation after MRA demonstrated both increase in PRSW and sensitivity to Ea (Panel B vs. D). Please refer to the text for details. EDV, end diastolic volume; SBM, single-beat method.



markedly, but the slope of the [SW/EDV] relation to M_w remained similar to baseline (Panel A vs. B) (P = 0.254). In contrast, however, after MRA, the slope of the relation of [SW/EDV]/Ea to M_w was significantly greater than without this adjustment (Panel B vs. D) (P = 0.003) and significantly greater than its baseline value (Panel D vs. C) (P = 0.033).

Discussion

Among patients with NIDCM, the addition of MRA to BB and ACE-I/ARB produced beneficial LV remodelling,[23] greater LV contractility, and normalization of Ea, indicating strongly enhanced V–A coupling, all leading to a marked improvement in LVEF.

Aldosterone and ventriculo–arterial coupling in heart failure

Randomized clinical trials in HFrEF patients have demonstrated reductions in mortality rates with MRA,[7] likely due to reducing the effects of circulating aldosterone. The serum aldosterone and the aldosterone/renin ratio are significant factors in peripheral vascular stiffness,[8] and spironolactone can improve this by up-regulating arterial nitric oxide synthase[33] and reducing endothelial dysfunction.[14,34]

The V–A coupling has been studied in untreated patients with NIDCM and normal subjects, with greater Ea/Ees in NIDCM (2.02 vs. 0.46).[32] At baseline, our results were similar. Three prior studies examined V–A coupling after long-term anti-failure therapy including MRA. These found 18–42% decreases in the V–A coupling ratio, but with variability in the estimates of LV contractility.[4,12,13] In the present study, we found a sharp decrease in Ea, but no change in Ees (sb), producing an average 32% decrease in Ea/Ees (sb).

Beneficial left ventricular remodelling compared with peripheral vascular effects

Anti-failure therapy has direct myocardial effects. BB drugs benefit myocardial metabolism.[3] ACE-I reduce myocardial inflammation, vascular remodelling,[5] and the rate of adverse LV remodelling.[6] Spironolactone inhibits myocardial collagen synthesis.[11]

However, even lacking myocardial effects, drugs such as nitroprusside can reduce SVR,[35] increase SV, and decrease ESV, thus increasing LVEF.[21] Similarly, spironolactone enhances

peripheral vascular dilatation both in animal models and in patients.[14,34] Thus, LVEF could, in theory, improve by reducing SVR, as seen here, without improving LV contractility. In fact, however, there was both a decrease in SVR and an increase in contractility.

Classic experiments in the isolated supported heart show that ESPVR is affected little by the arterial characteristics[18] but LV performance, as judged by SV and SW, increases with lower SVR,[18] which is also supported by an analytical model.[36] 'Optimal' LV performance depends on the clinical context. Thus, greater SV might be the goal in treating HFrEF, rather than SW, although greater SW is associated with greater LV mechanical efficiency.[36,37]

Parameters of contractility in NIDCM

Several parameters of contractility (P/V, ESV-100, V_0, and PRSW), suggested an increase in contractility, except for Ees (sb). All these indices depend on SV, which increased greatly as the SVR decreased. The equation for Ees (sb) (refer to Methods) shows the marked influence of SV on this, because SBP did not change significantly (median difference 1 mmHg) but SVI increased markedly, yielding no increase in Ees (sb). Thus, it is likely that Ees (sb) is inadequate to estimate LV contractility in this situation. Similar to the present study, Maurer *et al*.[4] analysed the effects of carvedilol on patients with HFrEF and found an increase in Pes/Ves, an increase in SV, and a significant decrease in Ea/[Pes/Ves] in responders to carvedilol. Dekleva *et al*. analysed elderly patients in the CIBIS study and found similar results to ours, including no change in Ees (sb), which they termed Elv.[38]

There may be other influences on the Ees (sb) result. Possibly, the myocardial mechanism of 'shortening deactivation' is responsible for the Ees (sb) result, based on experiments finding lower ESPVR with reduced afterload[29] and lower ESP as SV increased.[39] Others found lower ESP on ejecting beats than isovolumic beats,[40,41] and that LV pressure is reduced at greater flow rates, termed 'flow-induced deactivation'.[42] The Ees (sb) might be affected by these LV mechanical properties or also by reflex feedback.[43] Consistent with our results using Ees (sb), afterload reduction with nitroprusside had no effect on another single-beat estimate of contractility.[44]

Incorporation of peripheral vascular resistance into analysis of left ventricular contractility

Preload recruitable stroke work

The PRSW, expressed as SBM_w, increased sharply with MRA, consistent with an increase in LV contractility (*Table 3*, *Figure 4A,B*) but with no significant difference in the slopes of the relations between SW/EDV and SBM_w after treatment. PRSW is a highly linear index of LV contractility in the intact dog model with autonomic blockade,[21] not affected by phenylephrine or nitroprusside infusions. Its linearity is thought due to incorporating Ea into PRSW,[30,31] where, mathematically, a linear SW–EDV relation could only exist if there is autoregulation in which Ea changes with ED volume.[30] McClain *et al*. concluded that PRSW was a descriptor of TCP, rather than only intrinsic myocardial performance.[31] The mechanism of such autoregulation is unclear because beta-adrenergic blockade and atropine were employed in these studies.[21,31]

Total circulatory performance

In this study, we intentionally incorporated Ea into the analysis of SW/EDV vs. SBM_w, and there was a much steeper slope of the [SW/EDV]/Ea relation to SBM_w following anti-failure therapy (which we termed total circulatory performance, TCP) (*Figure 4C* vs. *Figure 4D*). This is likely due to both greater SV and reduced Ea and contrasts with the lack of change in the slope of SBM_w (*Figure 5A* vs. *Figure 5B*), in spite of the marked decrease in Ea. This direct incorporation of Ea into the [SW/EDV] relation demonstrated both increased contractility and the importance of Ea in TCP. The results of PRSW and TCP in the treatment of actual patients with HFrEF are a step beyond prior analyses in animal models.

Possible effects of fibrosis on left ventricular performance

The large increase in LVEF in our patients with NIDCM was greater than in other studies of HFrEF using MRA.[12,13] This may be a specific attribute of our study population, compared with chronic NIDCM.[1] Our patients had a relatively short duration of HF symptoms, no replacement fibrosis, and little interstitial fibrosis.[45] Other studies of MRA in HFrEF have not documented the duration of HF symptoms or the amount of interstitial fibrosis.[45]

Limitations

The fewer echocardiograms carried out after the follow-up CMR study were a potential limitation for not having paired PEP and the total duration of systole (QS2 interval) when calculating Ees (sb) for all patients. However, this was of minimal importance, because the main determinants of Ees (sb) are SBP, SV, and the complex regression equation that specifies E_{nd}, as shown in the formula (Methods). The total duration of systole is similar in normal and HF patients, while PEP is longer and LVET is shorter (the latter consistent with reduced SV in HF).[46] The mean difference between PEP in HF patients and normal subjects is 42 ms, which is 30% greater than normal.[46] We calculated the effect of PEP on Ees (sb), using our results for SBP and SV at follow-up. Even including a very

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significant 10% decrease in PEP, concordant with much improved contractility, would change Ees (sb) by only 0.1 mmHg/mL, a minimal difference. These factors support our Ees (sb) results.

The calculation of Ees (sb) led to a decrease in V_0 to negative values in most patients. While this shift is consistent with improved contractility, we did not emphasize this because the LV ESPVR is likely curvilinear at non-physiological low pressures.[29]

Others have studied V–A coupling in HF by measuring pulsatile arterial loading.[47] But nevertheless, even with simpler methods, the present study showed highly significant changes in V–A coupling. We studied a relatively small group of patients, but CMR is very accurate for defining LV volume[25] and shows significant changes using fewer subjects.[48]

Conclusions

Adding MRA to anti-failure therapy with BB and ACE-I/ARB drugs, produced a marked improvement in LVEF due primarily to reduced peripheral vascular resistance, reflected by Ea, with contributions from beneficial LV remodelling and improved LV contractility. It is important to judge the effects treating HFrEF in patients with NIDCM by using indices such as Ea/Ees (sb), PRSW and TCP that reflect V–A coupling. The parameter, TCP, best expressed both the improvement in LV pump performance and the reduction in arterial load. Future studies of the treatment of NIDCM prior to replacement fibrosis may allow similar results.

Clinical trials registration

https://register.clinicaltrials.gov/Clinical Trials. Gov ID NCT00574119.

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Conflict of interest

None declared.

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