

# A Randomized Pilot Study of Aortic Waveform Guided Therapy in Chronic Heart Failure

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**Background**—Medication treatment decisions in heart failure (HF) are currently informed by measurements of brachial artery pressure, but ventricular afterload is more accurately represented by central aortic pressure, which differs from brachial pressure. We sought to determine whether aggressive titration of vasoactive medicines beyond goal-directed heart failure medical therapy (GDMT) based upon aortic pressure improves exercise capacity and cardiovascular structure-function.

**Methods and Results**—Subjects with chronic HF (n=50) underwent cardiopulmonary exercise testing, echocardiography, and arterial tonometry to measure aortic pressure and augmentation index, and were then randomized to aortic pressure-guided treatment (active, n=23) or conventional therapy (control, n=27). Subjects returned for 6 monthly visits wherein GDMT was first optimized. Additional vasoactive therapies were then sequentially added with the goal to reduce aortic augmentation index to 0% (active) or if brachial pressure remained elevated (control). Subjects randomized to active treatment experienced greater improvement in peak oxygen consumption compared with controls ( $1.37 \pm 3.76$  versus  $-0.65 \pm 2.21$  mL min<sup>-1</sup> kg<sup>-1</sup>,  $P=0.025$ ) though reductions in aortic augmentation index were similar ( $-7 \pm 9\%$  versus  $-5 \pm 6\%$ ,  $P=0.46$ ). Forward stroke volume increased while arterial elastance and left ventricular volumes decreased in all participants, with no between-group difference. Subjects randomized to active treatment were more likely to receive additional vasoactive therapies including nitrates, aldosterone antagonists and hydralazine, with no increased risk of hypotension or worsening renal function.

**Conclusions**—Maximization of goal-directed medical therapy in heart failure patients may enhance afterload reduction and lead to reverse remodeling, while additional medicine titration based upon aortic pressure data improves exercise capacity in patients with heart failure. (*J Am Heart Assoc.* 2014;3:e000745 doi: 10.1161/JAHA.113.000745)

**Key Words:** aortic pressure waveform • exercise • heart failure • vasodilator • ventricular function

Vascular dysfunction and increased arterial load promote left ventricular (LV) remodeling and impair cardiac ejection in patients with heart failure (HF) and reduced ejection fraction (HFrEF), in part due to the heightened afterload-sensitivity of the failing LV.<sup>1–3</sup> Aortic stiffness increases with aging, further augmenting cardiac load.<sup>4</sup> One important repercussion of aortic stiffening is an increase in pulse wave velocity. As the outgoing pressure wave caused by ventricular ejection encounters zones of impedance mismatch, it is partially reflected backward, summing with the incident wave, to increase central aortic blood pressure (cBP).

The magnitude of this systolic pressure wave reflection can be quantified by the aortic augmentation index (AIx).<sup>4</sup> Prior studies have shown that the increases in late-systolic load due to wave reflection impair cardiac ejection and prolong diastolic relaxation,<sup>5–7</sup> effects that would be more poorly tolerated in the failing LV.

Arterial afterload, measured centrally in the ascending aorta, may differ considerably from the brachial cuff-measured pressure, but has historically required invasive assessment. Currently available technologies allow for noninvasive cBP and AIx assessment, but it remains unknown whether strategies to optimize central vascular function in patients with HFrEF using these more precise measures of arterial loading would provide clinical benefit. The objectives of this study were to determine if aggressive titration of HF medications to minimize AIx while maintaining adequate cBP would enhance exercise capacity in subjects with chronic HFrEF. In addition, we sought to determine if vascular-targeted therapy would reduce cBP or improve left ventricular structure or function.

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## Methods

This was a randomized, controlled, single-blind, parallel-group proof of concept study that enrolled patients from 2 trial sites (Mayo Clinic, Rochester, MN and University of Arizona Medical Center, Tucson, AZ). The protocol and amendments were approved by the institutional review boards at each participating center and the study was registered (NCT00588692). Written, informed consent was provided by all patients prior to participation in study-related procedures.

## Study Population

Subjects >18 years of age with chronic HF, NYHA class  $\geq$ II, on stable doses of ACEI/ARB and beta-blockers for at least 3 months were enrolled. Subjects with LV ejection fraction <25% or  $\geq$ 50%, brachial systolic blood pressure <110 mm Hg at most recent clinical assessment, Alx <15%, inability to exercise, irregular heart rhythm, pregnancy, myocardial infarction within 30 days, cardiac surgery within 60 days, significant valvular heart disease (>mild regurgitation or any stenosis), myocarditis, thyroid disease, severe renal disease (creatinine >2.0 mg/dL), or significant competing cause of exercise intolerance (eg, obstructive pulmonary disease, peripheral arterial disease) were excluded. A protocol amendment was later made during the trial to remove the exclusion of subjects with HF and EF  $\geq$ 50%.

## Study Protocol

Subjects underwent echocardiogram, brachial and cBP assessment, 6-minute walk test, and cardiopulmonary exercise stress testing on an upright cycle ergometer to quantify exercise performance. Subjects were then randomized (1:1) to Alx-guided therapy (termed “active treatment”) versus sham (cBP and Alx data acquired, but not shared with investigator, “control”). All subjects remained masked to their randomization assignment throughout the trial and had no knowledge of whether the investigator was basing treatment decisions on Alx/cBP or standard brachial cuff pressures. cBP data was obtained at monthly follow-up visits for a total of 6 months. At each visit, investigators made medication adjustments based upon conventional bBP cuff data or cBP and Alx (described below).

Because ACEI/ARBs and specific beta-blockers (metoprolol, carvedilol, bisoprolol) are standard guideline-directed medical therapy (GDMT) in all patients with HFrEF, medication titrations during the trial were required to be made after these therapies were increased to the maximal tolerated goal doses (Table 1).<sup>1</sup> At the time of trial initiation, aldosterone antagonists were indicated only for more advanced HF (NYHA III and IV), but given prior evidence of vascular protective actions

**Table 1.** Goal Doses of ACE Inhibitors/ARB/Beta-Blockers

Name	Target Dose
Lisinopril	20 mg daily
Enalapril	20 mg BID
Captopril	50 mg TID
Quinapril	20 mg BID
Ramipril	5 mg BID
Trandolapril	4 mg daily
Fosinopril	20 mg daily
Valsartan	160 mg BID
Candesartan	32 mg daily
Losartan	150 mg daily
Carvedilol	25 mg BID
Carvedilol phosphate	80 mg daily
Metoprolol succinate	200 mg daily
Bisoprolol	10 mg daily

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BID, twice a day; TID, thrice a day.

and benefit for select HFrEF populations, aldosterone antagonists and the combination of nitrates and hydralazine were favored next-line additions.<sup>8–11</sup> The active treatment goal was to reduce Alx to 0%, provided that cBP was maintained in an acceptable range (suggested systolic cBP >85 to 100 mm Hg). Based upon HF treatment guidelines and documented efficacy to reduce wave reflections, cBP and Alx,<sup>12–14</sup> the following suggested algorithm for study medication changes/additions was employed at each visit, provided that Alx was >0%:

1. Maximize ACEI or ARB and beta blockade to guideline-recommended dose
2. Add spironolactone if no contraindications (creatinine <2.0, K<5.0)
3. Add nitrate and up-titrate
4. Add hydralazine and up-titrate
5. Add amlodipine and up-titrate
6. If Alx still >0%, change metoprolol or bisoprolol to carvedilol

Decisions regarding medication adjustment were made by board-certified cardiologists with experience in caring for HF patients, factoring in all subject-specific factors as in standard clinical practice (along with Alx/cBP data if randomized to active treatment). Reasons motivating investigators to prescribe different drugs and dosages at each visit were not documented. In patients randomized to sham (controls), GDMT was first maximized exactly as in the active treatment arm, but additional vasoactive therapies were then added only if brachial systolic BP remained elevated (>130 mm Hg).

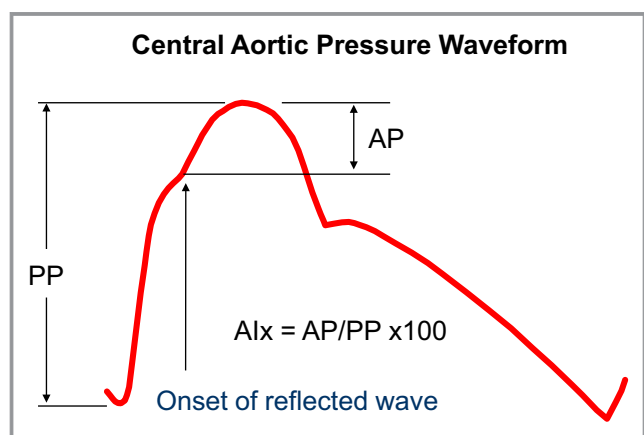
During each monthly study visit, vital signs and history were obtained to assess for symptoms of hypotension, fatigue, worsening heart failure or orthostatic intolerance. Laboratory evidence of electrolyte disturbance or worsening renal function was sought with additions or change in dosage of ACEI/ARB or aldosterone antagonists or otherwise at investigator's discretion. At the final (6-month) study visit, subjects underwent repeat arterial tonometry, echocardiography, and cardiopulmonary exercise testing.

## Study End Points

The co-primary endpoints were the change in peak oxygen uptake ( $\text{VO}_2$ ) during exercise testing and the change in Alx after 6 months of active therapy or sham relative to baseline. Secondary endpoints were the number of medication changes and HF medications added to regimen, measures of left ventricular structure and function, and changes in blood pressure and arterial load.

## Arterial Tonometry Assessment

Brachial and aortic pressures were assessed in the seated position after 5 minutes of quiet rest as previously described.<sup>15,16</sup> Aortic pulse waveform analysis was performed using a noninvasive, high-fidelity, hand-held tonometer (Millar Instruments) placed over the radial artery. Built-in, custom software (SphygmoCor CVMS, Atcor Medical) applying a mathematical transfer function was then used to convert radial pressure waveforms to central aortic waveforms, which more accurately reflect LV afterload. The reflected wave arrival creates an inflection point or "shoulder" on the cBP tracing (Figure 1). The ratio of this augmented pressure to



**Figure 1.** Central aortic pressure waveform. The return of aortic wave reflections is identified by an inflection point in the aortic pressure waveform. The ratio of the augmented pressure (AP) from this point to the total aortic pulse pressure (PP) defines the augmentation index (Alx).

aortic pulse pressure is defined as the augmentation index (Alx), which served as the principal therapeutic target for titration of vasodilator therapy in the trial. Because Alx varies inversely with heart rate, it was normalized to an HR of 75 beats per minute.<sup>16</sup>

## Exercise Testing

Subjects underwent maximal-effort upright cycle exercise testing at study entry and after 6 months. Oxygen consumed ( $\text{VO}_2$ ), carbon dioxide produced ( $\text{VCO}_2$ ), and minute ventilation ( $\text{V}_E$ ) were measured (MedGraphics) throughout exercise, with peak values taken as the average over the final 30 seconds of exercise. Respiratory exchange ratio (RER) was calculated as  $\text{VCO}_2/\text{VO}_2$ .  $\text{V}_E/\text{VCO}_2$  slope was calculated by linear regression from baseline to peak. Heart rate (HR) was continuously recorded by 12-lead electrocardiography. Exercise physiologists administering the cardiopulmonary stress testing were blinded to treatment assignment, and all expired gas analysis was performed offline by a single experienced exercise physiologist (TPO) blinded to both randomization assignment and study visit (initial or final).

## Echocardiography

Echocardiography was performed by experienced sonographers who were masked to treatment assignment. All echocardiograms were interpreted according to ASE guidelines by experienced cardiologists (GL and SA) in the Mayo core echocardiographic laboratory without knowledge of subject randomization or sequence of study (initial or final exam). LV end diastolic volume, end systolic volumes, and EF were determined from Simpson's biplane method.<sup>17</sup> Forward stroke volume (SV) was determined from pulse-wave Doppler in the LV outflow tract. Transmitral flow velocities (E and A) and E-wave deceleration time were measured to assess diastolic function. Integrated arterial afterload was measured by effective arterial elastance ( $\text{Ea}=0.9 \times \text{systolic cBP}/\text{SV}$ ).

## Sample Size Considerations

Prior studies have shown that mean Alx in HFrEF patients is 21%,<sup>18</sup> and that Alx is reduced (in absolute units) by 8% with enalapril,<sup>12</sup> 20% with nitrates,<sup>13</sup> and 9% with spironolactone.<sup>14</sup> The goal in the active treatment arm was to reduce Alx to 0%. Assuming a standard deviation of 20%, 58 subjects (29 in each group) would provide 80% power to detect a placebo-corrected reduction in Alx of 15% in the active treatment arm with  $\alpha=0.05$ . Prior data examining effects of HF medical therapies on exercise capacity in HFrEF with enalapril, losartan, or their combination has shown increases in peak

VO<sub>2</sub> of 2±2, 2±2, and 4±3 mL kg<sup>-1</sup> min<sup>-1</sup>, respectively.<sup>19</sup> Assuming a standard deviation of 3 mL kg<sup>-1</sup> min<sup>-1</sup>, 58 subjects would allow for 80% power to detect a placebo-corrected improvement in peak VO<sub>2</sub> of 2.2 mL kg<sup>-1</sup> min<sup>-1</sup> with α=0.05.

## Statistical Analysis

Data are expressed as mean with standard deviation, median (IQR), or number (percentage). Categorical variables were compared by chi-square or Fisher's exact test and continuous variables were compared using 2-way repeated measures ANOVA or Wilcoxon Rank Sum (between groups) or paired *t* test (within groups). Significance for the co-primary endpoints in this proof of concept study was judged at *P*<0.05. Analyses were performed with JMP version 8.0 (SAS Institute).

## Results

### Patient Population

A total of 60 subjects were enrolled (30 controls, 30 active). Six subjects (2 controls, 4 active) withdrew because of inability or unwillingness to return for follow-up visits, and 3 subjects (1 control, 2 active) withdrew because of noncardiac medical conditions that developed during the study period (cancer, severe peptic ulcer disease, hip surgery). One subject in the active treatment arm died during the study. The remaining 50 subjects (27 controls, 23 active) completed the study.

Baseline characteristics were not different between treatment groups (Table 2). Subjects were predominantly male, displayed mild-to-moderate symptoms of HF, depressed exercise capacity, elevated natriuretic peptide levels and typical comorbidities associated with HF including hypertension, diabetes, obesity, and renal disease. One subject in the control group and none in the active arm had normal EF. Use of GDMT including ACEI/ARB and beta-blockers was frequent (≥90%) with no group differences at baseline.

Brachial and central BP were similar and well controlled by conventional standards in both groups at baseline (Table 3), with no group differences in Alx, cBP, or Ea. LV volumes were similarly enlarged, and both groups showed similar degrees of LV systolic and diastolic dysfunction (Table 3). Exercise capacity (peak VO<sub>2</sub>) was markedly impaired in both groups and tended to be worse in the active treatment group (*P*=0.07, Table 2), with adequate objective effort achieved (average peak RER >1.05 in both) and significant ventilatory inefficiency (elevated V<sub>E</sub>/VCO<sub>2</sub> slope). Peak VO<sub>2</sub> was severely depressed (<14 mL min<sup>-1</sup> kg<sup>-1</sup>) in 64% of subjects, and ventilatory efficiency was abnormal (>35) in 78% of subjects.

**Table 2.** Baseline Characteristics

	Controls (n=27)	Active (n=23)	<i>P</i> Value
Age, y	72±8	74±8	0.5
Male, n (%)	23 (85)	16 (70)	0.3
White race, n (%)	27 (100)	22 (96)	0.5
Body mass index, kg/m <sup>2</sup>	29.9±4.6	29.2±4.6	0.6
HF severity			
NYHA class II/III	23/4	20/3	1.0
Enrolling LVEF, %	39 (34, 45)	38 (33, 43)	0.3
6 minute walk distance, m	410±100	380±91	0.3
Past medical history			
Hypertension, n (%)	26 (96)	20 (87)	0.2
Diabetes, n (%)	12 (44)	12 (52)	0.6
Obesity, n (%)	14 (56)	10 (43)	0.4
Chronic kidney disease, n (%)	5 (19)	4 (17)	0.9
Laboratories			
Sodium, mmol/L	140±3	140±4	0.98
Creatinine, mg/dL	1.1 (1.0, 1.3)	1.2 (0.9, 1.5)	0.8
BNP, pg/mL	432 (887, 1380)	533 (355, 1739)	0.3
Hemoglobin, g/dL	13.4±1.3	13.0±1.5	0.3
Medications			
ACEI, n (%)	18 (67)	13 (57)	0.6
ARB, n (%)	6 (22)	8 (35)	0.4
ACEI or ARB, n (%)	24 (89)	21 (91)	1.0
Beta-blocker, n (%)	26 (96)	21 (91)	0.6
Aldosterone antagonist, n (%)	4 (15)	4 (17)	1.0
Hydralazine, n (%)	5 (19)	1 (4)	0.2
Nitrate, n (%)	8 (30)	3 (13)	0.19

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

### Primary Endpoints

Subjects randomized to active therapy experienced a greater improvement in peak VO<sub>2</sub> relative to baseline than controls (Figure 2A), displaying a sham-corrected increase in peak VO<sub>2</sub> of 2.0 mL min<sup>-1</sup> kg<sup>-1</sup>. There was no difference between active treatment and controls in objective effort at the final exercise test (peak RER 1.10±0.09 versus 1.08±0.08, *P*=0.5). Alx decreased significantly within active treatment and control subjects at 6 months (−7±9% and −5±6%, *P*<0.01 compared to baseline within each group). However, there was no between-group difference in the magnitude of

**Table 3.** Baseline Ventricular-Vascular Function and Exercise Capacity

	Controls (n=27)	Active (n=23)	P Value
<b>Arterial properties</b>			
Brachial systolic BP, mm Hg	120 (106, 135)	114 (103, 125)	0.2
Brachial diastolic BP, mm Hg	71 (60, 77)	66 (62, 78)	0.8
Central systolic BP, mm Hg	110 (97, 123)	107 (93, 115)	0.2
Central diastolic BP, mm Hg	70 (61, 76)	66 (62, 78)	0.7
Augmentation index, %	22 (17, 26)	23 (20, 26)	0.5
Arterial elastance, mm Hg/mL	1.3 (1.1, 1.7)	1.1 (1.0, 1.5)	0.14
<b>Ventricular structure and function</b>			
Heart rate, bpm	63 (56, 69)	61 (60, 68)	0.9
LV end diastolic volume, mL	166 (135, 208)	166 (155, 208)	0.7
LV end systolic volume, mL	91 (75, 136)	116 (86, 142)	0.5
LV ejection fraction, %	41 (34, 46)	36 (30, 42)	0.13
Forward stroke volume, mL	73 (65, 88)	83 (63, 99)	0.6
Mitral E velocity, cm/s	0.6 (0.5, 0.7)	0.6 (0.5, 0.8)	0.7
Mitral E/A ratio	0.8 (0.7, 1.3)	0.7 (0.6, 1.0)	0.6
Mitral E wave deceleration time, ms	290 (259, 321)	282 (240, 344)	0.9
<b>Exercise capacity</b>			
Peak VO <sub>2</sub> , mL min <sup>-1</sup> kg <sup>-1</sup>	13.5 (10.8, 18.6)	10.8 (9.4, 14.7)	0.07
Peak respiratory exchange ratio	1.07 (1.03, 1.10)	1.06 (1.02, 1.10)	0.7
V <sub>E</sub> /VCO <sub>2</sub> slope	40 (36, 44)	42 (36, 47)	0.4

BP indicates blood pressure; LV, left ventricle; VCO<sub>2</sub>, carbon dioxide produced; V<sub>E</sub>, minute ventilation; VO<sub>2</sub>, oxygen consumed.

reduction in Alx (Figure 2B). Aortic Alx was inversely correlated with peak VO<sub>2</sub> at the baseline test ( $r=-0.29$ ,  $P=0.04$ ) and at the final test ( $r=-0.33$ ,  $P=0.02$ ), but the change in Alx during the study was not correlated with the change in peak VO<sub>2</sub> ( $P=0.4$ ). In a sensitivity analysis restricted to HF subjects with EF 25% to 49% and EF 35% to 49%, similar results were observed regarding the primary endpoints (Table 4).

## Secondary Endpoints

Compared with baseline, there were significant reductions in both brachial and central systolic BP and Ea in subjects randomized to active treatment (all  $P<0.05$ ; Table 5). However, changes in each of these arterial parameters were numerically similar in controls, with no between-group differences in the magnitude reduction.

Left ventricular end diastolic and end systolic volumes significantly decreased during the study in both groups (each  $P<0.05$ , Table 5), consistent with reverse remodeling, but as with the arterial effects, the magnitude of reduction in LV volumes was similar in active treatment and controls. Reductions in arterial afterload were coupled with significant increases in forward stroke volume in each group ( $P<0.05$ ), though again, the magnitude of change was not different in active treatment compared with controls. There were no changes in left ventricular EF or diastolic function within or between the groups.

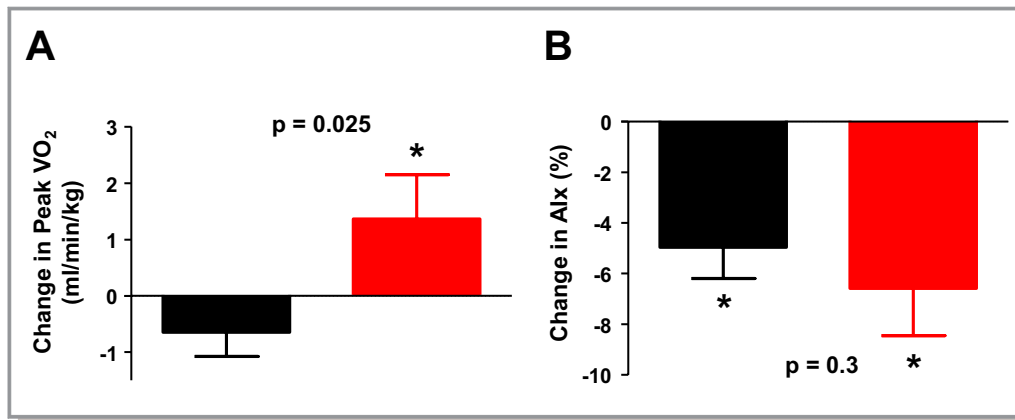
Medication changes during the study were common in both groups, but were over 2-fold more frequent in the active treatment arm (Figure 3A). There were 0.9 and 0.4 medication changes per study visit in active treatment and controls ( $P<0.0001$ ). An average of 4.4 adjustments were made in active treatment subjects compared with 2.2 changes over the study period in controls ( $P<0.0001$ ). Accordingly, active treatment subjects were more likely to be initiated and maintained on aldosterone antagonists, nitrates, or hydralazine compared with controls by study conclusion (Figure 3B). Among subjects receiving these medications at study conclusion, dosages were similar in active treatment and controls for aldosterone antagonists ( $33\pm 20$  mg versus  $22\pm 6$  mg,  $P=0.3$ ), nitrates ( $54\pm 38$  mg versus  $56\pm 41$  mg,  $P=0.9$ ), and hydralazine ( $118\pm 120$  mg versus  $60\pm 57$  mg,  $P=0.15$ ), indicating that the group differences in additional HF medication use were driven by the number of agents prescribed, rather than by dosage achieved. Aldosterone antagonists were initiated but stopped because of hyperkalemia in 1 control and 2 active treatment subjects.

## Safety Endpoints

Active treatment subjects were more likely to report dizziness at the 1-month visit (17% versus 0%,  $P=0.03$ ), but there were no differences at subsequent monthly visits or over the entire course of the study compared with controls (Table 6). There were no episodes of syncope and no differences in mortality, HF hospitalizations, or worsening renal function between the groups.

## Discussion

This is the first randomized, controlled trial to test the strategy of making treatment decisions in heart failure



**Figure 2.** A, Exercise capacity (peak oxygen consumption, VO<sub>2</sub>) improved significantly more relative to baseline in subjects randomized to active treatment (red) compared with controls (black). B, While augmentation index (Alx) decreased significantly in both active treatment and controls, there was no between-group difference in the magnitude of change. P-values represent 2-way repeated measures analysis of variance (ANOVA). \*P<0.05 relative to baseline within each group.

**Table 4.** Sensitivity Analysis According to Ejection Fraction

EF Subgroup (%)	Change in Alx (%)		Change in Peak VO <sub>2</sub> (mL min <sup>-1</sup> kg <sup>-1</sup> )	
	Control	Active	Control	Active
25 to 49	-4.9±6.3	-6.9±8.8	-0.5±2.5	1.5±3.8*
35 to 49	-5.5±6.0	-8.3±8.7	-1.0±1.9	2.0±5.4*

Alx indicates augmentation index; EF, ejection fraction; VO<sub>2</sub>, oxygen consumed. \*P<0.05 vs control.

patients based upon aortic pressure waveform analysis as compared with conventional clinical assessment. All subjects received close (monthly) clinical follow-up. As the first step, guideline-directed medical therapy (GDMT) was maximized in all subjects. Additional therapies targeting vascular function were then sequentially added in the active treatment group based upon aortic pressure waveform data and in the control group if arm cuff blood pressure was not adequately controlled. Subjects randomized to active treatment experienced greater improvement in exercise capacity, but the magnitude of arterial afterload reduction measured at rest was not different between active treatment and controls. Reductions in arterial afterload during the study were coupled with improvements in forward stroke volume and reverse left ventricular remodeling compared with baseline, with no differences between active treatment and controls in the extent of improvement. Subjects randomized to active treatment received more medication changes and were more likely to be initiated on additional HF medications (aldosterone antagonists, nitrates, and/or hydralazine). Aortic waveform-guided therapy was well tolerated, with no excess of dizziness, worsening renal function, syncope, hospitalization,

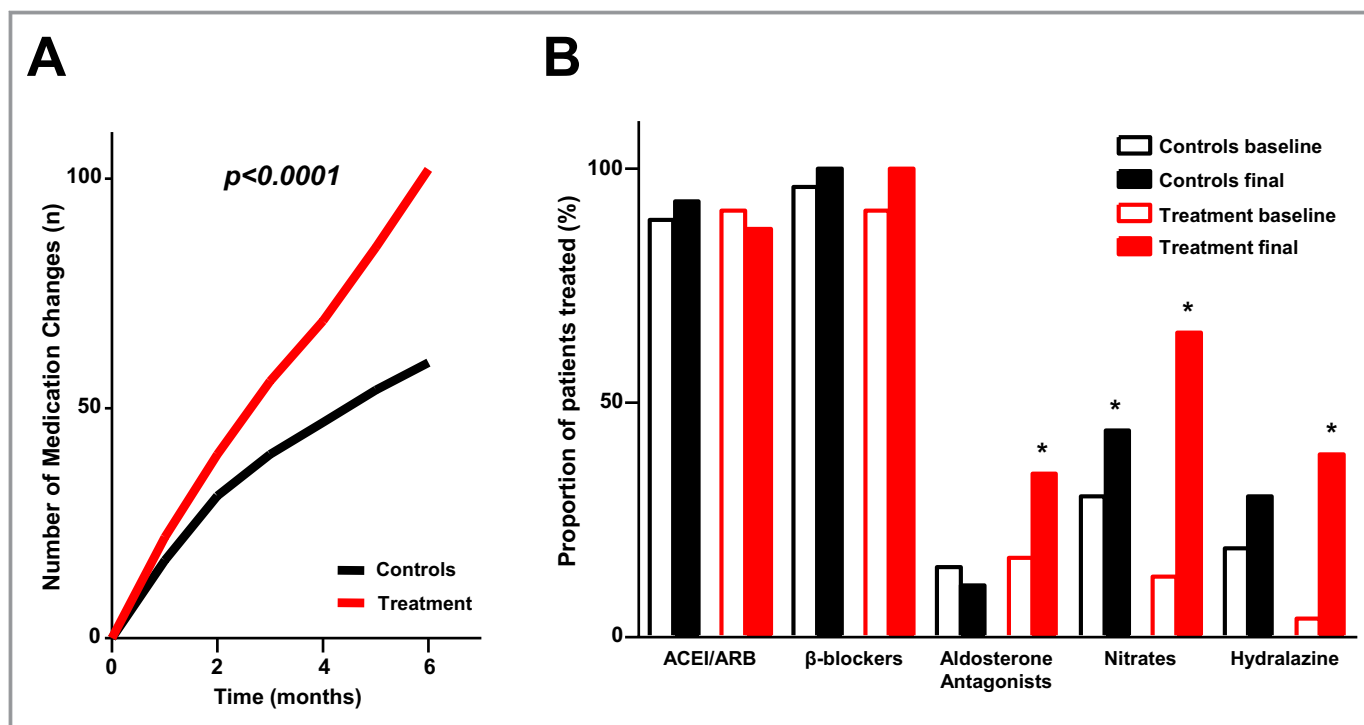
**Table 5.** Changes in Ventricular-Vascular Function

	Controls (n=27)	Active (n=23)	P Value
<b>Changes in arterial properties</b>			
Brachial systolic BP, mm Hg	-9±24	-9±17*	0.9
Brachial diastolic BP, mm Hg	-4±14	-2±8	0.6
Central systolic BP, mm Hg	-9±18*	-8±19*	0.9
Central diastolic BP, mm Hg	-3±9	-7±10*	0.11
Augmentation index, %	-5±6*	-7±9*	0.4
Arterial elastance, mm Hg/mL	-0.3±0.4*	-0.3±0.4*	0.9
<b>Changes in ventricular structure and function</b>			
Heart rate, bpm	-1±10	3±7	0.06
LV end diastolic volume, mL	-17±32*	-24±30*	0.5
LV end systolic volume, mL	-11±20*	-18±18*	0.26
LV ejection fraction, %	-0±2	2±2	0.4
Stroke volume, mL	10±21*	10±21*	0.9
Mitral E velocity, cm/s	4±12	5±15	0.9
Mitral E/A ratio	-0.1±0.3	-0.1±0.3	0.9
Mitral E wave deceleration time, ms	-5±43	-25±58	0.3

BP indicates blood pressure; LV, left ventricle. \*P<0.05 for within group change compared to baseline (paired t test).

or death. These results suggest that maximization of GDMT may enhance afterload reduction and lead to reverse remodeling, while additional medicine titration based upon aortic waveform analysis is further associated with improvements in aerobic capacity in patients with chronic heart failure.

Ejection properties in the failing ventricle are much more afterload-sensitive than in the normal heart.<sup>2</sup> For any given



**Figure 3.** A, Total number of cumulative medication changes made in active treatment (red) and controls (black) throughout the study. B, Proportion of subjects receiving classes of HF medications at study entry (open bars) and conclusion (solid bars). \**P* < 0.05 compared with baseline.

**Table 6.** Adverse Events

	Controls (n=27)	Active (n=24)	P Value
Death, n (%)	0 (0)	1 (4)	0.5
Self-reported dizziness, n (%)	5 (19)	8 (35)	0.3
Worsening renal function, n (%)	0 (0)	2 (8)	0.2
Heart failure hospitalization, n (%)	2 (7)	2 (8)	1.0

decrease in arterial afterload, there is greater enhancement in forward stroke volume and less reduction in arterial BP in HF with reduced EF as compared with healthy volunteers or compared with HF with preserved EF.<sup>3</sup> These observations have formed the hemodynamic basis for the use of vasodilator therapies in HF for the past 4 decades.<sup>20</sup> However, it remains unclear how aggressively patients with HF should be treated with vasoactive therapies, or how best to titrate medication adjustments in practice.<sup>21</sup>

Precise, detailed characterization of the central aortic pressure waveform, which more accurately represents the load that is “seen” by the left ventricle compared with brachial pressures,<sup>22</sup> would seem to be a plausible candidate to better inform clinical decision making. Aortic and brachial pressures

importantly differ because of the phenomenon of peripheral pulse amplification, where reflected pressure waves add with incident (outgoing) waves to increase arterial pressure.<sup>4</sup> However, these reflected pressure waves also interfere destructively with forward traveling flow waves, impairing cardiac ejection. The ventricle must then perform more hydraulic work to sustain ejection in the setting of pressure wave reflections, increasing “wasted” effort while elevating myocardial oxygen demands, decreasing ventricular efficiency and impairing systolic and diastolic function.<sup>5–7</sup> In patients with normal EF, increases in late systolic load may prolong relaxation,<sup>6</sup> while in patients with reduced EF there is enhanced sensitivity to peak and early systolic wall stress as well.<sup>7</sup> These deleterious effects are of greater relevance in the failing ventricle where systolic reserve is already compromised.<sup>2</sup> It is now well established that many antihypertensive medicines have diverging effects on central and peripheral BP,<sup>15</sup> and that central pressure may better predict outcome.<sup>23</sup> Collectively, these observations served as the rationale for this trial, to test whether a strategy to aggressively reduce arterial load aided by central aortic waveform analysis would be associated with improvements in exercise capacity, a clinically relevant measures of short-term outcome in HF.

Subjects randomized to active treatment displayed a significant, placebo-corrected increase in peak VO<sub>2</sub> of

$\approx 2 \text{ mL min}^{-1} \text{ kg}^{-1}$ , a change exceeding the threshold that is generally considered clinically meaningful and one that is on par with improvements in exercise capacity noted with other HF therapies such as cardiac resynchronization.<sup>24</sup> This improvement in aerobic capacity was coupled with increased use of HF therapies including nitrates, hydralazine, and aldosterone antagonists, but while measures of central arterial load were significantly reduced within subjects, there was no difference in the magnitude of change in Alx or cBP in the active treatment arm as compared with controls.

The reasons underlying the differences between changes in arterial load and exercise capacity are not clear. First, the mean reduction Alx achieved in the current study ( $-6\%$ ) was much lower than what has previously been published with use of HF medications ( $-8\%$  to  $-20\%$ ),<sup>12-14</sup> attenuating the power to observe a significant Alx reduction with active treatment. While medication titrations were more common in the active group than sham, there was still an average of  $>2$  medication additions/adjustments in control subjects, reducing afterload in controls and further diluting potential between-group differences. It is possible that single-time point assessments of aortic pressure waveforms lack sensitivity (Type II error), and 24-hour ambulatory assessments might have provided greater precision to detect a treatment effect. Central pressures were measured only at rest, and it is possible that there may have been greater reduction in Alx during exercise in the active treatment group compared with controls, which could contribute to the greater improvement in peak  $\text{VO}_2$ .

Another possibility is that the beneficial effects of more aggressive HF therapy are independent of the BP lowering. Indeed, in elegant analyses from the A-HeFT and Val-HeFT trials, Anand and colleagues have shown that HFrEF patients with the lowest BP at study entry have little to no reduction in BP from addition of nitrates/hydralazine or valsartan, yet these groups derived just as much benefit compared with subjects with higher baseline BP.<sup>25,26</sup> This may be related to neurohormonal, nonhemodynamic effects, nitric oxide availability, or simply to vasodilation-induced enhancements in stroke volume that offset any BP-lowering effects caused by reductions in arteriolar resistance.<sup>2</sup> Enhancement in forward stroke volume was similar in active treatment and controls, but because exercise capacity at baseline tended to be more impaired in the active group ( $P=0.07$ ), it is conceivable that these patients were better poised to benefit from more aggressive vasodilation, and this may partly explain the greater improvement in exercise capacity in the active group despite similar changes in Alx and cBP.

Improvements in exercise capacity noted in the active treatment arm were coupled with greater utilization of nitrates and hydralazine, consistent with previously published data showing increase in peak  $\text{VO}_2$  with this combination<sup>27,28</sup> or

with nitrates alone.<sup>29,30</sup> This may be related, in part, to venodilator effects of nitrates, which may mitigate the increase in filling pressures and pulmonary artery pressures during exercise in HF.<sup>31,32</sup> Importantly, the current study revealed benefit for exercise capacity in the active treatment group that was coupled with greater nitrates/hydralazine use in the background of GDMT.<sup>1</sup> Current guidelines recommend addition of nitrates and hydralazine in self-reported African Americans,<sup>1,10</sup> but it is also notable in the current study that beneficial effects upon exercise capacity were observed in a population that was almost exclusively white.

Despite clear demonstration of efficacy, aldosterone antagonists and the combination of nitrates and hydralazine continue to be underutilized in HFrEF.<sup>33,34</sup> The reasons for this are likely manifold and may include “therapeutic inertia,” lack of appreciation of benefit, and fear of precipitating hypotension or worsening renal function. The current study shows that even in a well-compensated chronic HFrEF population where blood pressure is adequately controlled by conventional criteria (mean brachial systolic BP 119 mm Hg), additional vasoactive HF therapies can be safely added with demonstrable improvements in exercise capacity and no excess of dizziness, syncope, azotemia, death or hospitalization. Indeed, these data support more aggressive intensification of HF therapy in apparently stable outpatients, though further study is required in this regard.

Both groups showed evidence of reverse remodeling after 6 months, and it is tempting to speculate that this might have been related to greater use of GDMT and other HF medications in both study arms. However, we cannot make any conclusions regarding the causality of the observed reduction in LV volumes, since there was no attention-control population in whom no medication changes were made. A sensitivity analysis revealed similar results when restricting the sample to subjects with EF 25% to 49% or 35% to 49%, though the magnitude of reduction in Alx tended to increase with higher EF (Table 4). It is conceivable that interventions to reduce wave reflections may be more effective in patients with HFpEF or even HF and very low EF ( $<25\%$ ) and study of a more homogenous HF cohort might help resolve this question more definitively.

## Limitations

The sample size was small and the subjects did not have advanced HF (mostly NYHA class II), which limit the generalizability of these results. Almost all (98%) subjects had HFrEF, but the degree of systolic dysfunction was modest, and we cannot determine how patients with more severe systolic dysfunction might have responded. This trial was not powered to assess clinical endpoints such as hospitalizations or mortality. The “control arm” subjects in this study still



received fairly aggressive intervention, including monthly clinic visits and forced titration of GDMT as tolerated with addition of other vascular therapies if BP remained elevated. An alternative control group might have included only the initial and final visits, which might have allowed greater insight into the effect of GDMT optimization on afterload and remodeling, and with this control we may have observed a greater improvement in Alx in the active treatment arm. This study was predominantly conducted prior to changes in the HF treatment guidelines broadening the use of aldosterone antagonists in HF.<sup>1</sup> While aldosterone antagonists were still recommended as the first addition to therapy, their utilization remained low (35% and 11% of active treatment and controls at study end). This is partly explained by development of hyperkalemia, but this does not fully account for the low utilization. The investigator's rationale behind medication choices for subjects was not recorded. Wave reflection and amplification can be assessed at the carotid artery rather than the radial,<sup>35</sup> and while technically more challenging this may offer advantages in some circumstances. While Alx was used to assess wave reflection in the current study, recent data has demonstrated that the reflection magnitude (ratio of reflected/forward wave amplitude) is superior to Alx in the prediction of incident HF.<sup>36</sup>

## Conclusions

Aggressive afterload reduction guided by aortic pressure waveform assessment was associated with improved exercise capacity and greater utilization of established HF therapies, even in the setting of maximal guideline-directed medical therapy. These beneficial effects were observed even among patients with excellent blood pressure control at study entry, suggesting that clinically relevant improvements in exercise capacity, arterial loading, and potentially ventricular remodeling can be achieved with more liberal use of vasoactive therapies in HF.

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## Disclosures

None.

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