Original Article

Aortic Waveform Analysis to Individualize Treatment in Heart Failure

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Background—Afterload reduction is a cornerstone in the management of patients with heart failure (HF) and reduced ejection fraction. However, arterial load and the effect of HF therapies on afterload might vary between individuals. Tailoring vasoactive medicines to patients with HF based upon better understanding of arterial afterload may enable better individualization of therapy.

Methods and Results—Subjects with HF and reduced ejection fraction underwent aggressive titration of vasoactive HF therapies with assessment of central aortic waveforms analyzed using pulse wave, wave separation, and arterial reservoir models. Clinical response to treatment was assessed using the 6-minute walk test distance, which increased in 25 subjects and decreased or remained unchanged in 13. Subjects with improvement on therapy displayed higher aortic pressure wave pulsatility (central pulse pressure [PP], reflected pressure wave, and reservoir pressure) at study entry compared with subjects without improvement (all $P<0.05$). Parameters derived by the arterial analysis methods were strongly correlated with one another and displayed similar ability to predict improvement. Aortic pressure pulsatility significantly decreased in subjects with functional improvement, whereas no change was observed in patients without functional improvement (P for interaction <0.05). These differences in arterial load at baseline and on therapy were not apparent from conventional brachial artery cuff pressure assessments.

Conclusions—Increased aortic pressure wave pulsatility and greater decrease in pulsatility on treatment are associated with functional improvement in patients with HF and reduced ejection fraction receiving aggressive vasodilator titration. These differences are not identifiable using brachial cuff pressures. Central aortic waveform analysis may enable better individualization of vasoactive therapies in chronic HF and reduced ejection fraction.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00588692.

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Key Words: aorta ■ arterial pressure ■ blood pressure ■ heart failure ■ heart rate

Treatment guidelines in cardiovascular medicine are largely based on the results of randomized, placebo-controlled trials. Although the interventions tested in positive trials may provide benefit to the population studied overall, there are clearly some where the intervention works well, others where it may be ineffective, and still others where it might be harmful. Personalized medicine refers to the science and practice of tailoring treatments to the individual characteristics of each patient.[1,2] In oncology and infectious disease, personalized medicine has enabled major advances in delivering the right intervention to the right patient to improve outcomes. Personalized medicine has yet to be applied to most cardiovascular diseases, including heart failure (HF).

See Clinical Perspective

In patients with HF and reduced ejection fraction (HFrEF), left ventricular (LV) ejection is highly sensitive to arterial load,[3] making afterload reduction a cornerstone in management.[4] In the clinic, afterload is estimated by brachial cuff blood pressure, but the true hydraulic load that is "seen" by the LV is more accurately represented by the central aortic pressure waveform, which can be assessed noninvasively using pulse waveform analysis. Aortic pressure wave reflections impede cardiac ejection and may represent a novel treatment target in patients with HFrEF.

Treatment aimed at reducing aortic pressure wave reflections assessed by the augmentation index (AIx) improves

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exercise capacity in HFrEF.[5] However, AIx has significant limitations,[6,7] and current guidelines recommend the use of alternative methods to assess wave reflections,[8] such as wave separation[9] and arterial reservoir analysis.[10] In the current pilot study, we aimed to identify aortic waveform characteristics that are associated with improvements in exercise capacity on vasodilator therapy added on top of guideline-directed therapy that might serve as targets for personalization of vasodilator therapy in patients with HFrEF.

Methods

Data from subjects participating in a randomized, controlled, single-blind, parallel-group trial testing aortic waveform guided therapy in chronic HF examined in the Mayo Clinic, Rochester, MN, study side with good quality radial pulse wave recording (operator index > 80) were analyzed. Methods and results of this study were previously reported.[5] The protocol and amendments were approved by the institutional review board, and the study was registered (NCT00588692). Written, informed consent was provided by all participants before participation in the study.

Population

Subjects aged >18 years with chronic HFrEF, NYHA class ≥II, on stable doses of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker and β-blockers for at least 3 months were enrolled. Subjects with LV ejection fraction <25% or ≥50%, brachial systolic blood pressure <110 mm Hg at most recent clinical assessment, AIx<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 and peripheral arterial disease) were excluded.

Study Protocol

The study protocol was previously described in detail.[5] In this trial, subjects were randomized to AIx-guided therapy versus sham (central blood pressure and AIx data acquired, but not shared with investigator). Because angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers and specific β-blockers (metoprolol, carvedilol, and bisoprolol) were standard guideline-directed medical therapy in all patients with HFrEF at the time of trial design, medication titrations during the trial were required to be made after these therapies were increased to the maximal tolerated goal doses according to guidelines.[4] The active treatment goal was to reduce central aortic wave reflections, assessed by AIx, to 0% using vasoactive drugs. Additional vasodilator medicines were added as tolerated to maximal guideline-directed medical therapy in the following order: spironolactone, nitrates, hydralazine, and amlodipine. Additional vasodilator therapy was added/dose escalated as long as central blood pressure was maintained in an acceptable range (systolic BP >80 mm Hg with no symptoms of hypotension).

Brachial blood pressure, radial pulse wave recording, and 6-minute walk test were performed at baseline and monthly for a total of 6 months. HF medication treatments were adjusted by investigators based on brachial (sham) or aortic pressure data (active treatment) at each of the 7 study visits to optimize brachial BP (in sham controls) or reduce AIx (in active treatment).

To detect changes in the aortic waveform associated with functional improvement on vasoactive HF therapy, subjects were separated by the improvement in 6-minute walk distance during the study. To decrease variability, to provide a longer-term assessment of functional capacity, and to achieve greater precision, the mean value of all 6-minute walk test distances after randomization (on treatment) was compared with the distance before randomization at the baseline visit. Improvement in submaximal exercise capacity was defined by a positive difference between mean postbaseline and baseline walking distance, whereas negative differences marked decrease in walking distance. Subjects with improvement in 6-minute walk distance on treatment were then compared with those with no improvement or deterioration in 6-minute walk distance.

To compare vasoactive medication usage at baseline and on treatment during the trial, ACE inhibitor doses were converted to lisinopril units, angiotensin II receptor blocker to losartan units, and β-blockers to carvedilol units.

Arterial Waveform Measurement and Analysis

Subjects were instructed to refrain from coffee and smoking in the morning of each study visit. After a 5-minute rest in the seated position, brachial blood pressure was measured using an oscillometric device. Arterial waveforms were then measured using a commercially available noninvasive, high-fidelity, hand-held applanation tonometer (SphygmoCor, AtCor Medical Ltd, Sydney, Australia). Built-in, custom software (SphygmoCor Cardiovascular Management Suite) applying a validated general transfer function[11] was used to convert the radial pressure waveform to the central aortic waveform. AIx, augmentation pressure, reflection time, amplitude of the first (P1) and the second (P2) systolic peaks were then calculated using pulse wave analysis by the built-in SphygmoCor software (Figure 1A). Previous studies have shown good to excellent reproducibility of central arterial measures derived from the radial pressure wave using the applanation tonometry.[12–14]

Wave Separation Analysis

Wave separation analysis is a frequency domain method based on the propagation model, which considers both aortic pressure and flow waves. In this analysis, the aortic waveform is decomposed into forward (Pf) and backward (Pb) travelling pressure waves (Figure 1B). The forward pressure wave is explained by ejection of blood from the LV to the aorta, whereas the reflected pressure wave originates from reflection sites of impedance mismatch along the peripheral circulation where part of the incident pressure wave is reflected backward.

Wave separation analysis has been described in detail elsewhere.[15] Briefly, central aortic pressure curves were exported from the SphygmoCor software, and corresponding flow curves were estimated from measured pressure curves based on a 3-element Windkessel model where LV outflow is modeled as a dynamic system of the second order. Windkessel equations were formulated as an isoperimetric problem with a constraint to minimize hydraulic work. Pressure waveform area fitting and a second-order linear delay element were used to estimate the final flow shape. Wave separation was performed in the frequency domain from measured pressure (Pm), modeled aortic flow (Qm), and aortic characteristic impedance (Zc). Zc was calculated using the modulus of the complex input impedance, which was calculated as the ratio of pressure and flow. The forward pressure wave was calculated using the equation $Pf=0.5\times(Pm+Zc\times Qm)$, whereas the reflected pressure wave as $Pb=0.5\times(Pm-Zc\times Qm)$. Analyses were processed in Matlab (Mathworks, Natrick, MA) using algorithms from a commercially available software package validated in non-HF patients[15,16] and in patients with HFrEF.[17]

Arterial Reservoir Analysis

Arterial reservoir analysis was examined as another model to independently characterize the central aortic waveform. This method combines the 2-element Windkessel and wave propagation models. In this model, the aortic waveform is decomposed into the reservoir and excess pressure (Figure 1C). Reservoir pressure accounts for the overall compliance of the arterial system, whereas the excess pressure is determined by local conditions and is the difference between measured pressure wave and reservoir pressure. Custom written Matlab algorithms were applied to calculate reservoir and excess pressures as previously reported.[18]

Six-Minute Walk Test

The test was performed as recommended[19] indoors, along a long, flat, straight, enclosed corridor with a hard surface. The walking course was 30 m in length. The length of the corridor was marked every 3

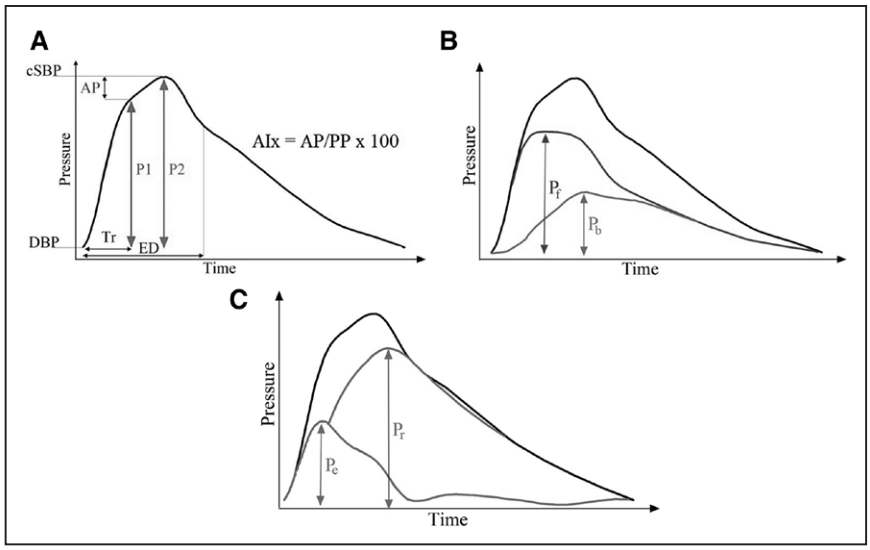

Figure 1. Different aortic pulse models analyzed. **A**, Pulse wave analysis, (**B**) wave separation analysis, and (**C**) arterial reservoir analysis. AIx indicates augmentation index; AP, augmentation pressure; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; ED, ejection duration; P1, amplitude of the first systolic peak; P2, amplitude of the second systolic peak; Pb, reflected pressure wave; Pe, excess pressure; Pf, forward pressure wave; PP, pulse pressure (cSBP–BP); Pr, reservoir pressure; and Tr, time to return of the reflected wave.

m, and the turnaround points were marked with cones. Subjects were instructed to walk as far as possible for 6 minutes. The total distance walked was calculated, rounding to the nearest meter.

Statistical Analysis

Continuous data with normal distribution are presented as mean±SD, non-normally distributed variables as median (quartile 1 to quartile 3). Categorical data are shown as frequencies and percentages. Differences between groups with and without functional improvement at baseline were compared using *t* test, Mann–Whitney *U* test, χ^2 test, or Fisher exact test, as appropriate. To account for correlation on the same patient, generalized mixed models with a random intercept were used to compare differences in hemodynamic parameter changes derived by pulse wave, wave separation and arterial reservoir analyses between patients with and without functional improvement. In this model, group, time and interaction between group and time were analyzed as fixed effects. Gamma regression was used for right skewed data. The model-derived estimated marginal means with 95% confidence interval are reported. Calculations were done using SPSS version 21 (IBM SPSS Statistics, IBM Corporation, Armonk, New York, NY). A 2-sided *P* value of <0.05 was considered statistically significant.

Results

Aortic waveform data from 38 subjects with chronic stable HFrEF participating in a prospective trial[5] were analyzed. Subjects were predominantly male with mild-to-moderate symptoms of HF and depressed exercise capacity (Table 1). As assessed by the change in 6-minute walk distance during the 6-month course of the study, submaximal exercise capacity increased in 25 subjects (6-minute walk distance increased by 48 m, *P*<0.0001), whereas in 13 subjects, there was no improvement or a decrease in functional capacity (6-minute walk distance decreased by 21.9 meters, *P*=0.03). Individual subject data for 6-minute walk tests are shown in the Figure I in the Data Supplement. Maximal exercise capacity (assessed by peak oxygen consumption at study entry and final visit) tended to be greater in subjects with an increase in 6-minute walk distance when compared with participants with no increase in 6-minute walk distance (0.68±2.62 mL/min per kg versus −0.64±2.79 mL/min per kg, *P*=0.16). There were no differences in other clinical characteristics between subjects that did or did not improve functional capacity (Table 1). One subject was hospitalized for HF while participating in the trial. Excluding this participant from the analysis did not affect any of the results.

Higher Aortic Pressure Wave Pulsatility at Baseline Predicts Favorable Response to Treatment

At baseline, subjects with functional improvement had lower heart rate but no difference in brachial cuff-derived blood pressure measurements compared with those with no improvement (Table 1). In contrast to peripheral pressures,

Table 1. Baseline Characteristics

Variable	No Functional Improvement, N=13	Functional Improvement, N=25	*P* Value
Age, y	73.9±7.2	72.4±7.9	0.6
Male sex, n (%)	9 (69)	22 (88)	0.2
Height, cm	173.3±10.1	174.6±7.8	0.7
Weight, kg	90.5±15.7	90.9±14.0	0.9
Body mass index, kg/m^2	30.1±4.7	29.9±4.2	0.9
HF severity and laboratories			
6-min walk distance, m	423±99	396±87	0.4
BNP, pg/mL	441 (378–596)	422 (102–1198)	1.0
Hemoglobin, g/dL	13.4±1.6	13.5±0.9	0.8
Echocardiography			
LV diastolic dimension, mm	59±7	59±5	0.9
Ejection fraction, %	37±9	37±8	0.9
Vital signs			
Heart rate, beats per minute	65.5±4.3	59.9±8.9	0.01
Brachial systolic BP, mm Hg	118.2±14.4	122.1±17.4	0.5
Brachial diastolic BP, mm Hg	71.4±8.6	68.6±8.5	0.3
Brachial pulse pressure, mm Hg	46.8±11.0	53.5±14.3	0.15

BNP indicates B-type natriuretic peptide; BP, blood pressure; HF, heart failure; and LV, left ventricle.

aortic waveform characteristics differed significantly between groups, with greater pressure wave pulsatility in responders compared with nonresponders, assessed by higher central PP, augmented pressure, greater forward and reflected pressure wave amplitudes, and higher reservoir pressure (all $P<0.05$, Table 2). Each of these differences remained significant after adjusting for heart rate (not shown).

Central PP was strongly correlated with the reflected pressure wave ($r=0.976$, $P<0.001$) and reservoir pressure ($r=0.978$, $P<0.001$), whereas there was also a strong association between the reflected pressure wave and the reservoir pressure ($r=0.985$, $P<0.001$). In the receive operating characteristic (ROC) analysis to predict functional improvement on therapy, baseline central aortic PP >36 mm Hg had 71% sensitivity and 62% specificity (ROC area under the curve=0.763, $P<0.001$), reflected pressure wave (Pb) >15 mm Hg had 75% and 69% specificity (ROC area under the curve=0.779, $P<0.001$), and reservoir pressure >39.0 mm Hg had 88% and 62% specificity (ROC area under the curve=0.760, $P<0.001$). There was no difference in ROC between these parameters (all $P>0.05$).

Reduction in Aortic Pressure Pulsatility Is Coupled With Enhanced Exercise Capacity

There was no difference in traditional brachial cuff pressure measures in subjects with and without functional improvement (Table 3). However, decreases in central aortic pressure wave pulsatility on treatment (central PP derived by pulse wave analysis, Pf and Pb calculated by wave separation analysis, and reservoir pressure by arterial reservoir analysis) were greater in subjects with functional improvement when compared with subjects without functional improvement (interaction P values all <0.05, Table 3; Figure 2). In addition, the reduction in Pb and reservoir pressure on treatment was directly correlated with greater increases in 6-minute walk distance during the trial (Figure 3). Although there was no difference in reflected wave timing (P for interaction=0.9), there was a greater reduction in pulse wave velocity in subjects with functional improvement (P for interaction=0.04), indicating greater reduction in aortic stiffness on treatment in responders, again despite similar brachial BP.

Table 2. Aortic Waveform Characteristics at Baseline

Variable	No Functional Improvement, N=13	Functional Improvement, N=25	*P* Value
Pulse wave analysis			
Central systolic BP, mm Hg	103.8±15.6	114.5±16.7	0.07
Central pulse pressure, mm Hg	33.9±8.9	45.7±14.1	0.01
AIx, %	18.2±6.6	22.0±6.3	0.10
AP, mm Hg	7.9±3.4	13.8±6.1	0.003
Tr, ms	135.2±9.0	135.8±9.6	0.8
ED, ms	282.5±23.1	307.2±37.1	0.02
Wave separation analysis			
Forward pressure wave, mm Hg	23.0±6.6	29.7±9.7	0.04
Reflected pressure wave, mm Hg	13.2±3.7	18.6±5.8	0.005
Reflection magnitude, %	57.9±5.4	63.2±10.2	0.09
PWV, m/s	9.7±1.5	10.0±1.6	0.6
Arterial reservoir analysis			
Excess pressure, mm Hg	11.4±3.6	15.0±6.5	0.08
Reservoir pressure, mm Hg	28.7±8.2	38.6±12.0	0.01

AIx indicates augmentation index; AP, augmentation pressure; BP, blood pressure; ED, ejection duration; PWV, pulse wave velocity; and Tr, time to return of the reflected wave.

Individual Aortic Waveform Responses to Vasodilator Therapy Differ Widely

Medication changes (additions or titrations) were performed during the trial in all 38 participants. New medicines were added in 27 subjects. The average number of medication adjustments was 3.2. Despite the significant differences in aortic pressure waveforms in responders and nonresponders, there was no difference in vasodilator therapy at baseline or vasodilator therapies added (medicine type or dosage) during the trial between groups (Table 4). This suggests that it is the individual participant's hemodynamic response to vasodilator therapy that is more important in explaining the relation to exercise improvement, rather than the absolute dose of vasodilator medicine provided. It also indicates that individual patients respond differently to vasoactive medicines in terms of central aortic waveforms, and that these differences are not evident from analysis of conventional cuff arterial pressures. These points are illustrated by examining the individual subject response to addition of hydralazine during the trial (Figure 4). Subjects with improved exercise capacity had higher aortic pulsatility at baseline and greater reduction on treatment when compared with nonresponders. These differences were not apparent from examination of baseline or changes in brachial BP.

Discussion

In this pilot study among patients with HFrEF, there was a large interindividual variability in the effect of HF therapy on functional status that could not be identified by changes in conventional brachial cuff blood pressure. In contrast, increased central aortic pressure wave pulsatility at baseline and greater decrease in pressure wave pulsatility on treatment were found to be associated with improvement in submaximal exercise capacity, an association that was consistently observed across the different methods to assess central aortic waveforms. There were no differences in medical therapy in responders and nonresponders, but differences in the aortic waveforms on treatment, suggesting that it is the individual patient response to vasoactive therapy that may be more important than the dose achieved for a given medicine. These data support the hypothesis that assessment of arterial waveform characteristics may allow for tailoring and personalization of vasoactive therapies in patients with HFrEF.

This study is the first longitudinal trial in subjects with HFrEF, where changes in central hemodynamics were tracked and related to serial changes in submaximal exercise capacity. We used three different methods of central pressure wave analysis that are currently in use—pulse wave

Table 3. Changes During the Course of the Study by Functional Improvement Group

	No Functional Improvement, N=13		Functional Improvement, N=25		
	Δ	*P* Value	Δ	*P* Value	*P* for Interaction
Brachial blood pressure					
Brachial systolic BP, mm Hg	−4.6 (−12.3 to 3.0)	0.2	−8.8 (−14.3 to −3.3)	0.002	0.40
Brachial diastolic BP mm Hg	−5.0 (−9.2 to −0.7)	0.02	−6.2 (−9.2 to −3.2)	0.001	0.60
Brachial pulse pressure, mm Hg	0.3 (−4.9 to 5.5)	0.9	−2.6 (−6.3 to 1.2)	0.18	0.40
Heart rate, beats per minute	−0.1 (−3.0 to 2.8)	0.9	0.4 (−1.7 to 2.5)	0.7	0.80
Pulse wave analysis					
Central systolic BP, mm Hg	−1.6 (−9.6 to 6.4)	0.7	−11.6 (−17.5 to −5.7)	0.001	0.048
Central pulse pressure, mm Hg	1.5 (−3.5 to 6.6)	0.6	−4.9 (−8.6 to −1.2)	0.01	0.04
Augmentation index, %	−2.6 (−6.6 to 1.4)	0.2	−4.5 (−7.9 to −1.1)	0.01	0.60
Augmentation pressure, mm Hg	0.1 (−2.6 to 2.8)	0.9	−3.0 (−5.0 to −1.1)	0.003	0.06
Tr, ms	2.8 (−3.3 to 8.9)	0.4	4.2 (−0.3 to 8.7)	0.07	0.70
ED, ms	−0.02 (−12.2 to 12.1)	1.0	−3.9 (−12.9 to 5.1)	0.4	0.60
Wave separation analysis					
Forward pressure wave, mm Hg	1.2 (−2.0 to 4.4)	0.5	−2.8 (−5.1 to −0.5)	0.02	0.047
Reflected pressure wave, mm Hg	0.6 (−1.7 to 2.8)	0.6	−2.5 (−4.2 to −0.9)	0.003	0.03
Reflection magnitude, %	−0.01 (−0.06 to 0.04)	0.7	−0.03 (−0.06 to 0.01)	0.12	0.50
PWV, m/s	0.1 (−0.3 to 0.4)	0.8	−0.4 (−0.6 to −0.1)	0.002	0.04
Arterial reservoir analysis					
Excess pressure, mm Hg	1.1 (−0.6 to 2.8)	0.2	−0.04 (−1.6 to 1.5)	0.9	0.30
Reservoir pressure, mm Hg	1.4 (−3.0 to 5.9)	0.5	−5.1 (−8.3 to −1.8)	0.002	0.02

Δ indicates difference between mean on-treatment and baseline value; BP, blood pressure; ED, ejection duration; PWV, pulse wave velocity; and Tr, time to return of the reflected wave.

analysis, wave separation, and arterial reservoir analysis. In each method, increased parameters of pressure wave pulsatility at trial entry and greater decrease in pulsatility with vasodilator therapy were associated with functional improvement. Although the assumptions underlying the 3 different methods to assess central pressure waveform differ greatly, each of the methods was correlated with the others and revealed similar value in identifying responders on treatment. While this study cannot identify the mechanism underlying the decrease in central pressure pulsatility, these data suggest that targeting aortic waveform indices may be useful to improve clinical status in HFrEF.

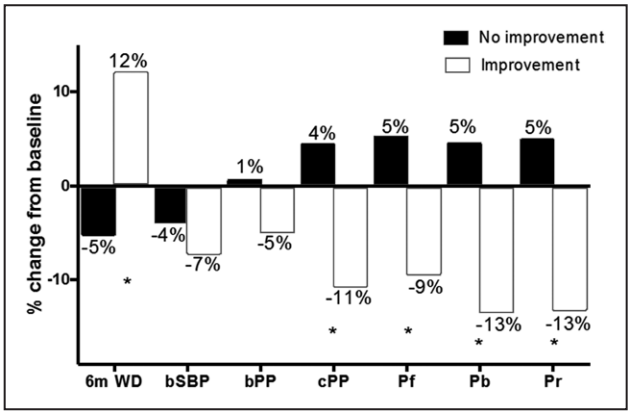

Figure 2. Changes in the 6-minute walk distance in relation to changes in peripheral and aortic waveforms. 6m WD indicates 6-minute walking distance; bPP, brachial pulse pressure; bSBP, brachial systolic blood pressure; cPP, central pulse pressure; Pb, reflected pressure wave; Pf, forward pressure wave; Pr, reservoir pressure; *P<0.05 for the difference between groups.

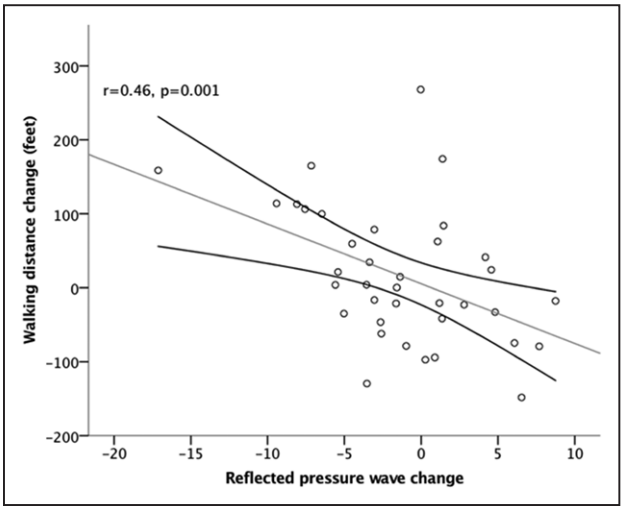

Figure 3. Association between reflected pressure change and 6-minute walk distance change.

Table 4. Pharmacotherapy at Baseline and Final Visit

	No Functional Improvement, N=13	Functional Improvement, N=25	*P* Value
Baseline			
ACEi, n (%)	9 (69%)	15 (60%)	0.73
ACEi dose, mg of lisinopril	12.5±6.1	18.0±10.7	0.17
ARB, n (%)	3 (23%)	7 (28%)	1.00
ARB dose, mg of losartan	66.7±28.9	66.1±34.4	0.98
β-blockers, n (%)	12 (92%)	23 (92%)	1.00
β-blockers dose, mg of carvedilol	26.0±13.5	38.9±25.5	0.06
Loop diuretics, n (%)	4 (31%)	12 (48%)	0.49
Loop diuretics dose, mg of furosemide	32.5±22.2	40.0±28.2	0.60
Calcium blockers, n (%)	1 (8%)	3 (12%)	1.00
Calcium blockers dose, mg of amlodipine	5.0±0.0	8.3±2.9	0.42
Aldosterone antagonist, n (%)	4 (31%)	5 (20%)	0.69
Aldosterone antagonist dose, mg of spironolactone	25.0±0.0	32.5±24.4	0.56
Hydralazine, n (%)	0 (0%)	5 (20%)	0.14
Hydralazine dose, mg		98.0±71.2	NA
Nitrate, n (%)	1 (8%)	5 (20%)	0.64
Nitrate dose, mg	120.0±0	38.0±31.1	0.07
Final visit			
ACEi or ARB, n (%)	13 (100%)	22 (88%)	0.50
ACEi dose, mg of lisinopril	22.0±13.4	24.3±12.9	0.66
ARB dose, mg of losartan	100±0	91.1±58.1	0.80
β-blockers, n (%)	13 (100%)	25 (100%)	1.00
β-blockers dose, mg of carvedilol	26.9±12.3	39.3±23.4	0.09
Loop diuretics, n (%)	8 (62%)	15 (60%)	1.00
Loop diuretics dose, mg of furosemide	30.0±26.8	47.7±30.0	0.24
Calcium blockers, n (%)	1 (8%)	5 (20%)	0.64
Calcium blockers dose, mg of amlodipine	5.0±0	8.0±2.7	NA
Aldosterone antagonist, n (%)	7 (54%)	7 (28%)	0.16
Aldosterone dose, mg	21.4±6.1	26.8±22.2	0.55
Hydralazine, n (%)	5 (39%)	11 (44%)	1.00
Hydralazine dose, mg	36.0±13.4	98.2±100.4	0.07
Nitrate, n (%)	5 (39%)	14 (56%)	0.50
Nitrate dose, mg	60.0±43.0	42.1±21.5	0.42

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; and NA, not applicable.

In previous studies, both augmented pressure and AIx have been shown to predict cardiovascular outcomes.[20–22] However, in this study among patients with HFrEF, only the decrease in augmentation pressure was associated with functional improvement, whereas there was no difference in baseline AIx, or AIx change between subjects with and without functional improvement. This finding is in line with the results of the study by Chirinos et al[20] and suggests that the prognostic information of augmentation pressure and PP cannot be fully contained in the AIx. These data further reinforce recent consensus recommendations to not rely on AIx alone to quantify wave reflections in pharmacological and physiological studies.[8]

Blood pressure assessed at the brachial artery is used clinically to guide decision-making in HFrEF but was not helpful to identify responders to treatment in this study, suggesting that it may be too crude to gauge treatment effects or identify potentially responsive patients. Brachial PP, a less sensitive index of pulsatile load, tended to be higher in responders (P=0.15). Although this difference might have been significant in a larger sample, it seems evident that the sensitivity for brachial cuff indices is limited compared with central pulse wave analysis. The current data support the concept that people with higher central pulsatile load may stand to benefit more from vasodilator therapy, and should, thus, be treated more aggressively. There may be other patients that may fair poorer with more aggressive therapy, and in this population, aortic waveform analysis may enable greater avoidance of adverse effects. These questions merit future study.

The potential importance of aortic waveform analysis to personalized medicine in HFrEF is further underscored by the absence of differences in the usage of HF medical therapy in responders and nonresponders (Table 4). For example, addition of hydralazine, a vasodilator to which many subjects were naïve at trial entry, produced dramatic improvements on the aortic waveform in responders, with little or no effect in nonresponders (Figure 4). Treatment guidelines clearly stress the importance of prescribing established medical therapies in HFrEF with escalation to the doses used in previous trials. However, the question of "how low to go" with BP reduction once guideline-directed medical therapy has been optimized remains unclear. Aortic waveform analysis may offer a means to determine which patients may benefit from more aggressive vasodilation, and how far to push the regimen. Collectively, the current data provide strong rationale to pursue further prospective trials testing personalized medicine strategies based on aortic waveform analysis in HFrEF.

Limitations

The sample size of this trial is small and the split between responders and nonresponders is uneven. Therefore, precision of estimates and power to detect group differences are reduced, and there may have been other (small to moderate magnitude) differences between groups that were not detected. However, assessing variables at several time points allowed us to decrease variability and to achieve greater precision of point estimates. The aortic pressure waveforms used were transformed from radial recording using the generalized transfer function. This reconstructed aortic pressure curve may lack characteristics of

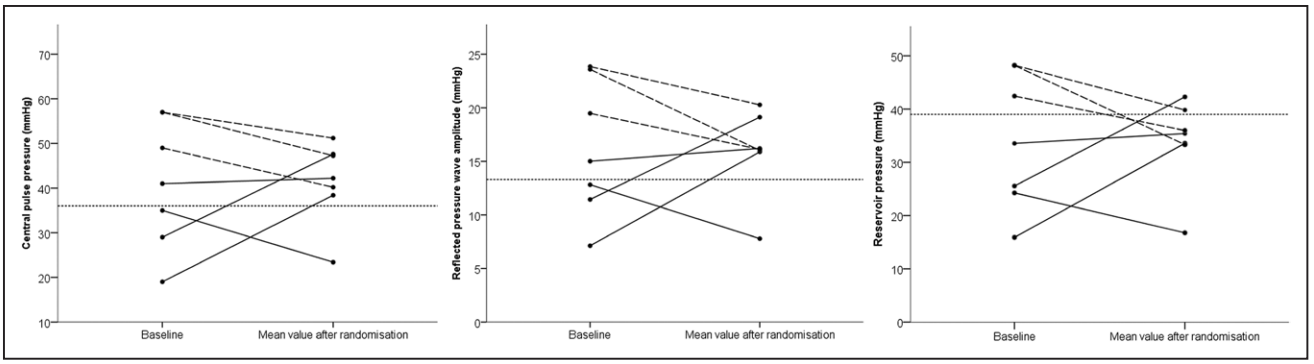

Figure 4. Solid lines represent subjects without functional improvement, dashed lines patients with functional improvement, dotted lines cut-off values of baseline value for functional improvement calculated by the receive operating characteristic analysis. The functional status change associated with hydralazine therapy is dependent on baseline value and change in parameters of pressure wave pulsatility.

directly measured aortic tracings, but this method has been used extensively in previous studies and clinical trials. Aortic flow was not directly measured but derived from pressure waveforms as previously described. While this method requires a greater number of assumptions, it shows similar ability to characterize arterial load.[17] Furthermore, the consistency of results across the 3 models strongly supports the veracity of our conclusions. We used the 6-minute walk test that assess the submaximal exercise performance, rather than peak oxygen consumption because this test was performed more frequently during the trial and because it provides a better evaluation of capacity in the activities of daily life than true maximal aerobic capacity which is rarely achieved in HFrEF. Peak exercise capacity tended to improve more in responders, but this difference was not statistically significant, possibly related to greater variability in the assessment of peak oxygen consumption. There might have been a "ceiling effect" that affected the results, whereby further improvement in 6-minute walk distance might not have been possible, and we cannot discount this possibility. Because the assignment to groups was not random, we cannot exclude the effect of residual confounding. Because of large variability in the individual response to vasoactive therapy, our data do not allow to identify a single specific drug responsible for functional capacity improvement. Patients with severe LV dysfunction and hypotension were excluded from this trial; therefore, these results may not apply to patients with more advanced HFrEF, particularly patients with lower arterial pressures. There was a trend toward higher dose of β-blockers in responders at study entry, and although the differences in pressure pulsatility between responders and nonresponders remained significant after adjusting for heart rate, we cannot discount the possibility that greater tolerance of β-blocker dosage at study entry might have also helped identify a group more likely to respond to more aggressive vasodilator therapy. As the study population consisted predominantly from older men, future studies evaluating the effect of vasoactive therapy in younger patients and women with HFrEF are needed. While radial tonometry has good reproducibility,[12–14] it is not well described how aortic indices change during the course of the day in patients with HF, which would be important to understand to properly apply this technique in practice. This trial was not powered to examine harder end points, such as hospitalization burden or survival, and future study is needed in this regard.

Conclusions

Elevated aortic pulsatile load and greater decrease in pulsatile load using vasodilator therapy is associated with improvement in submaximal exercise capacity in patients with chronic HFrEF, even when guideline directed medical therapy has been maximized. Patients with increased pulsatile load that may benefit from aggressive therapy are not identifiable from conventional brachial blood pressure assessments, and changes in aortic pulsatile load on treatment are similarly not evident from cuff pressure assessment. These data suggest that there may be a role for individualized, precision medicine in the tailoring of vasoactive therapies in HFrEF, and prospective trials testing this concept are warranted.

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Disclosures

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CLINICAL PERSPECTIVE

Afterload reduction with vasodilators is central to the management of patients with heart failure and reduced ejection fraction. However, arterial load and the effect of heart failure therapies on afterload might vary substantially between individuals in ways that affect clinical response. Currently, treatment decisions about vasoactive medicines are made based on brachial cuff blood pressure, but analysis of central aortic waveforms may allow for more robust and sensitive assessment of cardiac load, including pulsatile load components that may have more deleterious effects on left ventricular performance. We demonstrate that heart failure and reduced ejection fraction patients with higher central aortic pulsatile pressure load respond more favorably to aggressive vasodilation, and that greater reductions in aortic pressure load were directly correlated with greater improvement in submaximal exercise test performance, assessed by 6-minute walk distance. Importantly, these aortic pressure differences associated with favorable responses were not apparent based on conventional brachial cuff measures. These data show that greater aortic pressure pulsatility may be a viable treatment end point to help guide management decisions and allow for better individualization of vasoactive therapies in patients with chronic heart failure and reduced ejection fraction.

Circulation
Heart Failure

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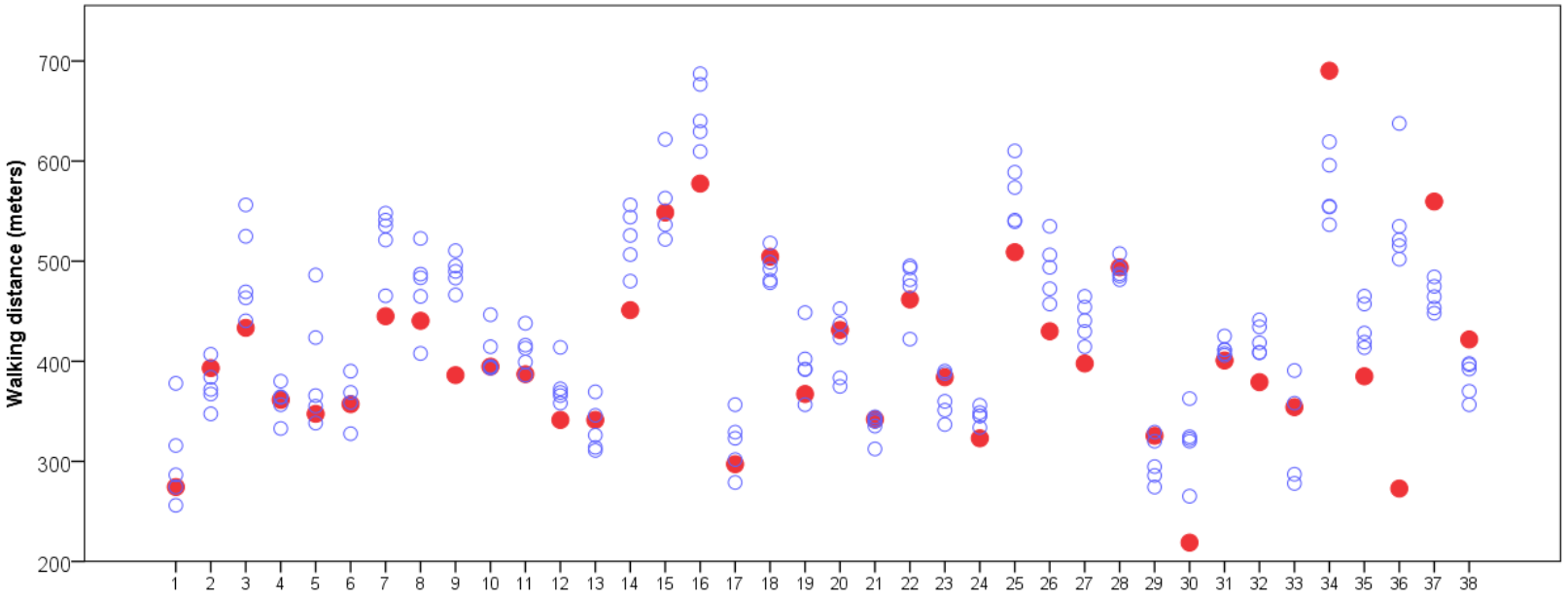
SUPPLEMENTAL MATERIAL



Supplementary Figure: Results of the 6 minute walk test distances for the baseline test at study entry (red) and the tests performed after study entry on treatment for each subject (numbered 1-38, abscissa).