Changes in Aortic Wall Structure, Composition, and Stiffness With Continuous-Flow Left Ventricular Assist Devices
A Pilot Study

Amrut V. Ambardekar, MD; Kendall S. Hunter, PhD; Ashok N. Babu, MD; Rubin M. Tuder, MD; R. Blair Dodson, PhD*; JoAnn Lindenfeld, MD*

Background—The effects of nonpulsatile flow on the aorta are unknown. Our aim was to examine the structure of the aorta from patients with continuous-flow left ventricular assist devices (LVADs) and directly measure aortic wall composition and stiffness.

Methods and Results—Age-matched aortic wall samples were collected from consecutive patients with heart failure (HF) at the time of transplantation and compared with nonfailing donor hearts. An unbiased stereological approach was used to quantify aortic morphometry and composition, and biomechanical testing was performed to determine the stress–strain relationship of the vessel. Data were obtained from 4 patients without a left ventricular assist device (HF group: mean age, 58.3±8.0 years), 7 patients with a continuous-flow LVAD (HF+LVAD group: mean, 57.7±5.6 years), and 3 nonfailing donors (mean, 53.3±12.9 years). Compared with HF, the aortic walls from HF+LVAD had an increase in wall thickness, collagen, and smooth muscle content accompanied by a reduction in elastin and mucinous ground-substance content. Stress–strain curves from the aortas revealed increased vessel stiffness in HF+LVAD compared with HF and nonfailing. The physiological modulus of the aorta progressively stiffened from 74.3±5.5 kPa in the nonfailing to 134.4±35.0 kPa in the HF to 201.7±36.4 kPa in the HF+LVAD groups (P<0.001).

Conclusions—Among continuous-flow LVAD patients without aortic valve opening, there are changes in the structure and composition of the aorta as well as an increase in aortic wall stiffness compared with age-matched HF patients and nonfailing donors. Further studies examining the role of nonpulsatile blood flow on aortic function and the potential resultant systemic sequelae are needed. *(Circ Heart Fail. 2015;8:944-952. DOI: 10.1161/CIRCHEARTFAILURE.114.001955.)*

Key Words: aorta ■ collagen ■ elastin ■ heart-assist devices ■ heart failure ■ muscle, smooth ■ vascular stiffness
are largely unknown. It was our hypothesis that the lack of pulsatile blood flow with CF-LVADs may result in changes within the structure and composition of the aorta with a resultant increase in aortic wall stiffness—similar to reductions in aortic compliance related to age except occurring over a much shorter time period. This increased aortic wall stiffness could result in an afterload mismatch that may partially explain the low rates of left ventricular recovery seen in HF patients supported with CF-LVADs. Thus, the aim of this study was to examine the histological structure of the aorta from patients supported with CF-LVADs and assess for corresponding changes in direct measures of aortic wall stiffness.

Methods

Patient Selection and Tissue Acquisition

Aortic wall tissue samples were collected from consecutive patients with end-stage HF at the time of cardiac transplantation at the University of Colorado LVAD-Transplant program between May 2013 and May 2014. Tissue was collected from a total of 15 patients during this time period, of which 10 patients were supported with a continuous flow LVAD (HF+LVAD) and 5 patients (HF) were not supported with a LVAD. Of the 10 HF+LVAD patients, 1 patient was excluded because of lack of aortic tissue (history of aortic root replacement with graft) and 2 patients were excluded because of pump malfunction resulting in aortic valve opening on every beat (1 patient with pump thrombosis and 1 patient with LVAD-related severe aortic regurgitation)—leaving at total of 7 patients in the HF+LVAD group for analysis. Of the 5 HF patients, 1 patient with an aortic valve replacement and known aortic dilation was excluded because of the known associated aortopathy in this condition, leaving a total of 4 patients in the HF group for analysis. In addition, age-matched non-failing/control aorta samples were obtained from 3 nonfailing donor hearts that were harvested for transplant but then unused for noncardiac reasons during the same time period.

The tissue collected was a circumferential ring of the aorta ≈1 cm long above the aortic valve that is removed with the failing heart by necessity at the time of organ transplant. The aortic tissue was placed in calcium-free phosphate buffered saline solution and stored at 4°C until mechanical testing. An additional small piece was also placed in formalin for histological sectioning and analysis. The Colorado Multicenter Institutional Review Board approved the protocol for the collection, storage, and analysis of human tissue.

Medical records were retrospectively reviewed by a trained physician to obtain demographic and clinical data. Echocardiographic and hemodynamic data were obtained from the medical record at the time closest to cardiac transplantation. The mean arterial blood pressure for any portion of the aorta multiplied by 100%.

Aortic Wall Mechanical Testing

Aortic samples were mechanically tested with uniaxial tests performed within 72 hours of surgery using an MTS Insight II (MTS Systems, Eden Prairie, MN) equipped with a 25-N load cell and environmental chamber filled with calcium- and magnesium-free phosphate buffered saline (pH 7.4, 37°C) to ensure no smooth muscle contribution to the mechanics as previously described. Uniaxial extension was applied at a constant crosshead speed of 0.5 mm/s, executing 5 successive preconditioning cycles to a prescribed elastin and collagen activation strain. The tensile force and specimen length were continuously recorded (10 Hz, Testworks 4 software). The final loading cycle of the uniaxial preconditioned sample was analyzed. From the recorded data, the Cauchy stress (\( \sigma \)) was calculated to allow direct comparison of samples by dividing the measured force (\( F \)) by the unstressed area (\( A = \text{initial width} \times \text{initial thickness} \times \lambda \)) and the stretch ratio (\( \lambda \)).

\[ \sigma = \frac{F}{A} = \frac{F}{w_0 l_0 \lambda} \]  

where the stretch ratio (\( \lambda \)) is the current length (\( l \)) divided by the initial length (\( l_0 \)). Percent strain of the aorta was calculated by change in length divided by initial length (\( (l - l_0)/l_0 \)). Stress–strain curves were plotted to provide an assessment of aortic stiffness. Curves with a more steep increase in stress at lower strains (a left shifted curve) reflect a vessel with greater stiffness. The physiological modulus was obtained at the patients’ mean blood pressure to assess stiffness at physiological stress. The stress–strain curve composition was further analyzed to provide information relating stiffness mechanics to the content of the aorta. The initial linear slope (or low-strain modulus) was measured as this is related to elastin fibers, mucinous ground-substance, and cellular content of the vessel. Similarly, the second linear slope (or high-strain modulus) was also measured as this is related to the collagen content of the vessel.

Aortic samples underwent elastic mechanical loading with repeatable stress–strain curves following the cyclic preconditioning and hysteresis. However, 2 of the HF+LVAD samples rippled, and therefore mechanical data were only available in 5 of the HF+LVAD samples. Because of the tears in these aortic samples during testing, the stress–strain data were not included in our analysis. To provide additional insights about the relevance of aortic mechanical testing to other disease conditions, we also tested aortic samples from the HF patient with known aortopathy with aortic root dilation as well as the 2 HF+LVAD patients whose aortic valves opened on every beat because of pump malfunction.

Aortic Morphometry and Composition

Aortic wall samples were placed in histological cassettes in the operating room oriented such that the adventitial to intimal side made the longitudinal axis. Samples were fixed using 10% buffered formalin, dehydrated by ethanol, and embedded in paraffin. The arteries were randomly sectioned perpendicular to the longitudinal axis at 4 μm in thickness, stained with Movat’s Pentachrome, and coded to allow for blinded analysis. Slides were scanned with the Aperio ImageScope system (Vista). Quantitative analysis of aortic morphometry and composition was performed at 2 levels. First, planimetry was used for general morphometric analysis, including measurements of total wall thickness as well as thickness of the arterial adventitia, media, and intima. Second, aortic wall composition was assessed by measuring the volume density of collagen, elastin fibers, smooth muscle cells, and mucinous ground-substance within the aorta.

Given the limitations in terms of where we could sample aortic tissue (we could only sample aortic tissue from the portion of the vessel removed by necessity at the time of cardiac transplantation), we used an unbiased stereological approach for the measurement of volume densities. This method allows for quantitative assessment of structures without the need to determine total vessel volume or deal with potential artifacts related to tissue shrinkage during histological processing. The free stereological software StepAnizer (http://www.stepanizer.com/), with a 64-point grid (ap: 13689 px, 9426.063 um2) was used for point count measurements of desired structures. In preliminary studies, we determined that 30 vessel fields that were acquired at ×20 magnification would be needed to have at least 100 points hitting on desired structures using this 64-point grid. Images (40.4 μm²/field) were acquired at a ×20 magnification (field area=0.61 cm²) using the Aperio ImageScope system, with a random start. Total sampling fields were determined by total section area/image area, with a sampling fraction of 1:total sampling fields/30. Then the volume density percentages of collagen, elastin fibers, smooth muscle cells, and mucinous ground-substance were determined based on the sum of point hits for these structures divided by the sum of point hits for any portion of the aorta multiplied by 100%.
Statistical Analysis
Results are expressed as mean± SD. A 1-way ANOVA test that used a Bartlett’s test and corrected for unequal variances was used to compare differences between the 3 groups (HF, HF+LVAD, and nonfailing) and t tests were used to compare differences between 2 individual groups. Statistical significance of the biomechanical characteristics were found using a mixed-model ANOVA with terms for treatment (HF, HF+LVAD, and nonfailing) to account for repeated stress and strain measurements made in the same aorta test sample. P values were adjusted using the Tukey–Kramer method to account for multiple comparisons. Statistical significance was defined as a 2-tailed P value of <0.05. All statistics were performed using Graphpad Prism Software Version 6 (La Jolla, CA).

Results
Patients were similar in age among the cohorts, with an average age of 58.3±8.0 years in the HF group, 57.7±5.6 years in the HF+LVAD group, and 53.3±12.9 years in the nonfailing group, P=0.88 (Table). As expected, HF and HF+LVAD patients had lower ejection fractions compared with nonfailing. Brain natriuretic peptide levels and filling pressures were lower in HF+LV AD patients; however, there were no differences in mean arterial pressure between the groups. Among the HF+LV AD group, 4 patients were supported with the HeartMate II LVAD (Thoratec, Pleasanton, CA) and 3 patients were supported with the HeartWare HVAD (HeartWare, Framingham, MA). The mean duration of LVAD support was 230 days (range of 44–595 days). All of the HF+LVAD patients had no evidence of aortic valve opening on echocardiography and no palpable pulse.

Aortic Vessel Morphometry
Representative histological cross-sections of the aortas from a patient with HF and HF+LVAD are shown in Figure 1. The mean aortic wall thickness from HF+LVAD patients was significantly greater than HF patients (2014±294 versus 1566±119 μm; P=0.007), but not significantly different than nonfailing patients (1730±454 μm; P=0.26) as shown in Figure 2. This difference in total wall thickness seemed largely related to changes in the adventitial layer of the aorta, where there was a trend for greater adventitial thickness in HF+LV AD versus HF (446±301 versus 179±88 μm, P=0.062) and significantly greater adventitial thickness compared with nonfailing patients (157±15 μm, P=0.044). The intimal and medial layers of the aorta did not seem to be significantly different between the groups.

Aortic Vessel Composition
Volume density measurements of aortic wall composition are presented in Figure 3. The mean volume density of

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<th>Table. Baseline Patient Characteristics</th>
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<td><strong>Heart Failure: With LVAD</strong> (n=7)</td>
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<td><strong>Nonfailing</strong> (n=3)</td>
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<td>Phosphodiesterase inhibitor</td>
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<td>Loop diuretic</td>
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ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; and NA, not available.
*P<0.05 for comparison of nonfailing vs HF and nonfailing vs HF+LVAD.
†P<0.05 for comparison of HF vs HF+LVAD.
‡It was not possible to measure systolic and diastolic blood pressure in these patients.
elastin was significantly lower in HF+LVAD compared with HF (18.9±4.3% versus 34.0±5.4%; \(P=0.001\)) and nonfailing (34.6±12.4%; \(P<0.001\)). Similarly, the volume density of mucinous ground substance was lower in HF+LVAD compared with HF (2.5±1.8% versus 12.2±8.0%; \(P=0.019\)) with a trend for also be lower than nonfailing (6.6±4.4%; \(P=0.075\)).
Conversely, the mean volume density of collagen was significantly higher in HF+LV AD compared with HF (38.9±3.7% versus 26.7±11.7%; \( P =0.039 \)) and nonfailing (22.5±7.3%, \( P =0.002 \)). Smooth muscle volume density was significantly lower in HF patients compared with HF+LV AD (27.1±1.6% versus 39.7±3.2%; \( P <0.001 \)) and nonfailing (36.3±6.2%; \( P =0.033 \)).

Aortic Arterial Stiffness

Mechanical testing of aortic wall stiffness was performed in all 4 of the HF patients, all 3 of the nonfailing samples, and 5 of the 7 HF+LV AD patients. For unknown reasons, 2 of the HF+LV AD samples ripped during mechanical testing and thus were not included in the analysis. It is possible that these 2 samples had substantial changes in stiffness that may have resulted in them tearing during mechanical stretching; however, it is not possible to definitely test this possibility with our currently available mechanical testing methods, so these samples were excluded from the mechanical testing analysis.

Stress–strain curves from the aortic wall samples revealed significant differences in aortic stiffness between nonfailing, HF, and HF+LVAD samples (Figure 4, \( P<0.001 \)). The aortic wall samples from HF and HF+LVAD samples had significantly increased stiffness compared with nonfailing samples (\( P<0.001 \) for both comparisons). In addition, there was a trend for increased stiffening in the HF+LV AD compared with HF (\( P=0.10 \)). The physiological modulus of the aorta was measured at the patients’ mean blood pressure as a physiological measure of aortic stiffness. The aortic stiffness at these physiological pressures progressively increased from 74.3±5.5 kPa in the nonfailing to 134.4±35.0 kPa in the HF to 201.7±36.4 kPa in the HF+LVAD groups (\( P<0.001 \), Figure 5).

Figure 3. Aortic wall composition analysis revealed a reduction in the volume density of elastin fibers and mucinous ground-substance in patients with HF+LVAD compared with heart failure (HF) and nonfailing. Conversely, there was an increase in the aortic wall volume density of collagen in patients with HF+LVAD aorta compared with HF and nonfailing. LVAD indicates left ventricular assist device.

Figure 4. Stress–strain curves from the aortic wall samples revealed increased vessel stiffness in comparisons of nonfailing, heart failure (HF), and HF+LVAD aortic samples. An upward-left shift of these curves represents a stiffer (or less compliant) vessel. LVAD indicates left ventricular assist device.
Further analysis of the initial linear slope of the stress–strain curve—which is directly related to elastin fiber and mucinous ground-substance content—revealed a decreasing trend in the low modulus for HF+LV AD compared with HF and nonfailing (Figure 6A). Furthermore, analysis of the second linear slope of the stress–strain curve—directly related to collagen content—revealed a significant increase in the high modulus for HF+LV AD compared with HF and nonfailing (Figure 6B, \( P = 0.01 \)) corroborating with the histomorphology results.

Stress–strain testing curves from the single patient with a history of aortic valve replacement and aortic dilation did reveal that this arterial wall appeared to be qualitatively less stiff compared with HF+LV AD and HF groups (Figure 7A). Furthermore, biomechanical data from the 2 HF+LV AD patients with aortic valve opening on every beat because of pump malfunction revealed that the aortic stiffness from these samples were significantly different compared with HF+LV AD samples without aortic valve opening, and more in line with the values obtain from patients with HF (Figure 7B).

**Discussion**

The main finding of this study is that among patients supported with CF-LVADs and no aortic valve opening, there are changes in the structure and composition of the aortic wall compared with age-matched HF patients and nonfailing donors. In addition, these changes are associated with an increase in the physiological stiffness of the aortic vessel itself. The potential clinical consequences of such changes within the aortic wall for patients chronically supported with CF-LVADs are unknown. Furthermore, the implications of aortic wall changes and the contribution of an afterload mismatch toward the low rates of myocardial recovery after CF-LVAD implantation deserve further study.

The measurements of aortic stiffness from our study do corroborate with previously published reports assessing the influence of age and disease on aortic properties. For example, among healthy individuals, there is a progressive increase in the thoracic aortic elastic modulus with increasing age from reported values of 23 kPa in early adolescents to 52 to 76 kPa in 30- to 40-year olds to 123 kPa in 60- to 70-year olds.\(^9\) In addition, there is an additive increase in thoracic aortic elastic modulus with aging among individuals with concomitant disease with reported values of 98 to 107 kPa in hypertensive 30- to 40-year olds to 212 kPa in hypertensive 60- to 70-year olds with coronary artery disease.\(^9\) Thus, the measured physiological modulus values from our study of 74 kPa in the nonfailing cohort and 134 kPa in the HF cohort are in line with what would be expected given the age and condition of these patients. However, the measured aortic modulus value of 201 kPa in the HF+LV AD cohort is more in line with what would be expected with the combination of aging and disease. These findings support the concept of an aortic afterload mismatch potentially impeding left ventricular recovery during CF-LVAD support.

We found that the total wall thickness of the aorta from HF+LVAD patients was greater than HF or nonfailing. Most of this difference was related to increased thickness of the adventitial wall of the aorta—thus it is not surprising that we found that the collagen content, the main component of the adventitial layer, was also more abundant in HF+LVAD.
patients. In addition to these changes, there was also a significant reduction in elastin content in HF+LV AD patients compared with HF or nonfailing. Two other studies have also noted depletion in the number of elastin fibers after LVAD support.3,4 Alterations of collagen and elastin are known to directly affect vessel compliance,10,11 and the histological findings of this study are likely reflected in the mechanical changes of differences in vessel compliance.

A prior study of patients implanted with a different model of a CF-LVAD with an outflow graft to the descending aorta noted a decrease in medial thickness after device placement.3 We did not observe such a change in our study of patients implanted with a CF-LVAD with an outflow graft to the ascending aorta, but there were differences in the composition and components of the medial layer including collagen and elastin as noted above. In addition, there was a significant reduction in mucinous-ground substance content in HF+LV AD suggesting that cellular processes within the extracellular matrix may have differing responses in aortas exposed to nonpulsatile blood flow. Further investigation into the implications of this finding is needed.

There was a reduction in smooth muscle content in the aorta from HF patients compared with HF+LV AD patients or nonfailing donors. The reasons for these changes are unknown, but may be related to known alterations in the neurohormonal milieu that are seen in end-stage HF. It is known that vasoactive mediators, such as nitric oxide and angiotensin II, can influence arterial vessel smooth muscle growth,12 and it is possible that the reversal of neurohormonal activation after LVAD placement resulted in these changes.

Our study is in contrast to another study of patients with LVADs where investigators found no differences in end-organ arterial pathology after an average of 263 days of CF-LVAD support.2 The duration of CF-LVAD support was similar in our study, but we focused on alterations within the aorta—the arterial vessel that is normally exposed to the greatest magnitude of pulsatility from left ventricular contraction. It is unknown if distal arterial vessels may be susceptible to the changes we observed in the aorta if exposed to nonpulsatile flow for a longer period of time. As the number of patients supported with CF-LVADs and duration of LVAD support increases,13 the potential clinical implications of changes in end-organ pathology, such as the potential for arterial changes in the cerebrovascular system to alter the risk of stroke, merit further investigation.

Indeed a recent physiological study of cerebral autonomic autoregulation found that patients with nonpulsatile blood flow from CF-LVADs had a lower magnitude of oscillation of mean arterial blood pressure and cerebral blood flow velocity during a sit–stand maneuver compared with patients with pulsatile LVADs, but that dynamic cerebral autoregulation was preserved among patients with both pulsatile and nonpulsatile LVADs.14 The structural changes within the aorta noted in our study may partly explain the baseline physiological changes in cerebral perfusion noted by these investigators. Additional studies are needed to determine the potential physiological compensatory responses to such structural changes within the vessels in the cerebral and other vascular beds.

This study has several unique strengths compared with prior studies. Despite the small number of patients, the groups were relatively well age-matched given the known relationship between age and vessel compliance. In addition, we chose to not only compare aortic vessel properties from LVAD patients to nonfailing donor samples but also compare them with patients with HF without a LVAD. It would not be surprising to find differences in aortic properties between a group of patients with HF compared with nonfailing donors given the high concomitant rates of hypertension in the HF population and the known relationship of hypertension with vascular stiffening. The differences in aortic structure and function between patients with HF with and without a LVAD suggest that the properties of the LVAD itself or the resultant changes in systemic circulating factors after LVAD placement have roles in these changes. Furthermore, we used a quantitative, unbiased stereological method for analysis of the content of the vessel. This approach allows for a more accurate
estimation of vessel content free of errors related to tissue processing and sectioning. Finally, we were able to perform mechanical stress–strain testing on the majority of arterial samples to provide direct functional data to corroborate histological changes. Larger studies and possibly alternate techniques are needed to clarify whether the 2 HF+LVAD samples that rippled were the result of dramatically increased stiffness and resultant tearing during mechanical testing.

Limitations
This was a small single-center study so an institution-specific effect cannot be excluded. However, we were careful to select a homogeneous, age-matched population. We specifically acknowledge that there were only 3 nonfailing donor samples for comparison, but would note the difficulties in trying to age match a donor organ population with a HF population. We did test other nonfailing samples from donors that were younger in age, and not surprisingly these vessels were more compliant. We also acknowledge that with our small number of samples from LVAD patients, we were unable to determine if there was a change in aortic vessel vascular stiffness based on the duration of LVAD support. Certainly, one could hypothesize that there would be a greater degree vessel stiffening with a longer duration of unloading, and future studies in this area are needed. Similarly, we do not know the effects of partial LVAD unloading or intermittent aortic valve opening on aortic vessel properties. However, based on a small comparison of 2 patients whose aortic valves opened on every beat because of pump malfunction, there is certainly a suggestion of differential effects of aortic properties based on the degree of LV unloading from the LVAD.

In addition, we note that only the most proximal portion of the aorta was used for the analyses of this study as this is the portion of the aorta that is removed by necessity at the time of transplant. The effect of nonpulsatile flow on the descending aorta or other vascular beds warrants further investigation, but will be more challenging because of constraints of tissue availability. Finally, further cellular and molecular studies are need to provide a mechanistic basis for the observed structural and functional findings of this study.

Conclusions
There are changes in the structure and composition of the aortic wall after CF-LVAD support including an increase in collagen and reduction in elastin content. These changes are accompanied by changes in the physiological stiffness of the aortic wall. As the number of patients with chronic CF-LVADs increase, further studies examining the role of nonpulsatile blood flow on aortic vascular function and the potential resultant system sequelae are needed.

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Disclosures
None.

References
CLINICAL PERSPECTIVE
The effects of nonpulsatile blood flow that results from the current generation of continuous-flow left ventricular assist devices (CF-LVADs) on the structure, composition, and stiffness of the aorta are largely unknown. In this study, we evaluated the histological structure of the aortic wall and directly measured aortic composition and stiffness from tissue samples obtained at the time of cardiac transplantation from patients with heart failure (HF) with and without CF-LVAD support. Comparisons were also made with aortic tissue samples obtained from nonfailing donors. When compared with HF patients without a CF-LVAD and nonfailing donors, the aortas from HF patients supported with a CF-LVAD had an increase in wall thickness, collagen content, and smooth muscle content accompanied by a reduction in elastin content and mucinous ground-substance content. The direct effects of these changes in aortic structure and composition on wall stiffness were assessed by performing biomechanical stress–strain testing. This testing revealed a progressive increase in the physiologic aortic stiffness in comparing tissue samples from nonfailing donors with HF patients without a CF-LVAD to HF patients with a CF-LVAD. The potential implications of this aortic stiffening in regards to creating an afterload mismatch and impeding left ventricular recovery during CF-LVAD support—and ultimately CF-LVAD explantation—remain unknown. In addition, the effects of nonpulsatile blood flow on other vascular beds and the potential systemic sequelae during CF-LVAD support, such as changes in the cerebral vasculature and risk of stroke or intestinal vasculature and risk of gastrointestinal bleeding, warrant further investigation.
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