Tremendous advances in mechanical circulatory support have occurred during the past decade. The HeartMate II trials demonstrated that second-generation, continuous-flow (CF) left ventricular assist devices (LVADs) led to greater survival rates than first-generation, pulsatile devices for patients with advanced heart failure (HF). After Food and Drug Administration approval of the HeartMate II LVAD in 2008 as a bridge to transplant and in 2010 as destination therapy, axial CF-LVADs quickly replaced the HeartMate XVE, and the era of nonpulsatility was born. After publication of the Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure (ADVANCE) trial, the centrifugal-flow HeartWare VAD was introduced as an alternative to the HeartMate II trial for the bridge to transplant population, and now >10,000 patients with HF have been implanted.

Although patients benefit from improvements in functional capacity and HF symptoms after CF-LVAD insertion, there is growing awareness of the risks associated with chronic exposure to minimally or entirely nonpulsatile blood flow. On a cellular and molecular level, nearly all CF-LVAD patients develop an acquired von Willebrand syndrome, which may increase the risk of nonsurgical, and more particularly, gastrointestinal bleeding. Indeed, the risk of bleeding seems to be inversely proportional to the degree of pulsatility in the system. Reductions in pulsatility also lead to maladaptations in neurohumoral pathways. For example, CF-LVADs are associated with a hyperadrenergic environment characterized by marked increases in sympathetic neural activity, which likely results from reductions in pulsatile distortion of the arterial baroreceptors. In addition, renin and aldosterone levels are higher than those observed in patients with pulsatile LVADs. Although it is not yet clear whether such neurohumoral abnormalities have adverse clinical consequences in this setting, it is certainly plausible that they could contribute to elevated blood pressure, which itself has been shown to increase the risk of pump thrombosis.

Perhaps an overlooked but nonetheless important consequence of reduced pulsatility relates to alterations in vascular biology, which could also influence blood pressure and end-organ function. It has previously been shown that peripheral vascular reactivity (as determined by flow-mediated dilatation) is blunted in patients with CF-LVADs but improves as pulsatility is increased. Given the severity of HF and comorbidities present in LVAD patients, it is not unexpected that impairments in peripheral reactivity are present in patients with HF after implantation of a CF-LVAD. However, it is noteworthy that peripheral vasoreactivity normalizes in patients implanted with pulsatile devices, finding that suggests that pulsatility, or lack thereof, may be influential to normal function of the vasculature. Given that endothelial dysfunction is a marker of future adverse cardiovascular events, this abnormality is not to be dismissed and raises the possibility that CF-LVAD therapy may lead to other abnormalities in vascular biology as well.

Differences in peripheral vasoreactivity between pulsatile and CF-LVADs have been attributed to reductions in nitric oxide bioavailability among CF-LVAD patients. Vessel wall shear stress promotes nitric oxide production by vascular endothelial cells. Because these shearing forces are proportional to the degree of pulsatility in the system, the reduction in vascular shear stress during CF circulatory support likely contributes to the reduction in nitric oxide bioavailability in CF-LVAD patients. However, it is also important to consider whether structural adaptations of the blood vessels occur as a result of CF-LVAD support—adaptations that could contribute to reductions in peripheral vascular reactivity and alterations in end-organ function.

In this regard, Ambardekar et al have provided important insights into the effect of CF-LVADs on vascular biology in this issue of Circulation: Heart Failure. Tissue samples of the ascending aorta were taken from CF-LVAD patients and compared with those of HF patients without LVADs and with healthy controls. The CF-LVAD patients were found to have a greater aortic wall thickness than the patients with HF, primarily due to collagen deposition in the adventitia. In addition, the aortas from patients with CF-LVADs had less elastin and mucinous ground substance than the other groups. These changes in wall structure were associated with a leftward shift in the stress–strain curves, implying that patients with CF-LVADs have stiffer aortas. This finding was confirmed through demonstration of a greater elastic modulus (a measure of an object’s elasticity or resistance to deformation) among CF-LVAD patients than patients with HF and controls.

As noted by the authors, it is interesting that these changes in wall structure and function occurred after a relatively short...
time of CF-LVAD support (mean of 230 days). Indeed, the changes observed in aortic wall composition after <1 year of mechanical support were similar to age-related changes in vessel composition that occur over a timespan of several decades in patients not supported with CF-LVADs. For example, the CF-LVAD cohort (age, 58±6 years) had a modulus of 201.7±36.4 kPa, which is in line with values expected from hypertensive septuagenarians,16 whereas the HF group (age, 58±8 years), whose demographics and past history were similar to the CF-LVAD cohort, had a modulus of only 134.4±35.0 kPa, which is near values that are expected based on these patients’ age and past history. Together, these data suggest that CF circulatory support accelerates the aging process of the blood vessels, adding to the list of concerns associated with chronic exposure to minimally or entirely nonpulsatile flow. Given that the increase in elastic modulus occurs within the first year of support, it is likely that this abnormality, combined with a hyperadrenergic environment, all work together to increase the risk of adverse events, such as stroke, which affects >10% of patients in the first year of CF-LVAD support.17

The question still remains, why would nonpulsatile flow accelerate aging of the blood vessels? Traditionally, it has been taught that with age, there is a reduction in arterial distensibility as vessel walls thicken, in turn increasing pulse pressure over time.18 As aortic pressure waves (generated by ventricular contraction) approach branches in the arterial tree, wave reflections are transmitted back to the ascending aorta. In young subjects with a low pulse wave velocity, these reflections augment diastolic blood pressure. With stiffening of the central arteries, however, pulse wave velocity increases, and as a result, wave reflections are transmitted back at higher velocities, causing systolic blood pressure (and consequently, pulse pressure) to rise. Thus, arterial stiffening precedes the changes in blood pressure that occur with aging.

In contrast, there seems to be a unique mechanism at play among the CF-LVAD population, whereby reduced pulsatility is a precursor to vascular stiffening. This is a novel concept that has not been previously described in humans. Although a mechanism explaining this phenomenon is not entirely clear, it is likely related, at least in part, to the aforementioned changes in the neurohumoral axis. For example, in vitro models have previously shown that vasconstrictors promote vessel wall thickening and that nitric oxide inhibits cell growth.19 Therefore, reductions in pulsatility may indirectly lead to alterations in vascular wall morphology through baroreceptor-mediated increases in sympathetic activity and possibly by reductions in nitric oxide bioavailability.

Another major consequence of CF circulatory support on vascular biology is the loss of a Windkessel effect.20 In normal humans, the aorta stores about half of the blood ejected from the left ventricle. During diastole, the elastic recoil of the aorta forces this blood into the peripheral vasculature, which reduces ventricular afterload and ensures that coronary and peripheral circulation are maintained throughout the cardiac cycle. Ventriculoarterial coupling thus depends on rhythmic, pulsatile flow generated by the heart. Pulsatile distension and recoil of the aorta requires the presence of elastin in the arterial wall—as such, it is interesting (and perhaps, not surprising) that Ambardekar et al15 have found that there is less elastin in the aortas of CF-LVAD patients than the other groups. This finding suggests that elastin production is downregulated as a result of chronic exposure to nonpulsatile flow.

The next question is, what, if anything can be done to remedy this problem? The answer may be a multiform approach involving pharmacotherapy for patients with current-generation devices and advances in engineering of next-generation LVADs. Regarding pharmacotherapy, it is notable that in this study, the CF-LVAD patients were largely treated with a combination of medications, including aldosterone antagonists, hydralazine, and loop diuretics, to control their blood pressure, and only a minority received angiotensin-converting enzyme inhibitors and β-blockers. Although β-blockers reduce sympathetic neural activity,21 direct vasodilators, such as hydralazine, increase it.22 Similarly, angiotensin-converting enzyme inhibition has been associated with dose-dependent reductions in arterial stiffness independent of blood pressure effects, and the renin–angiotensin aldosterone axis has been considered the primary therapeutic target for management of arterial stiffening in non-LVAD populations.23,24 Therefore, a higher utilization of β-blockers and angiotensin-converting enzyme inhibitors may have blunted the adverse vascular remodeling seen in this study.

Regarding refinements in device design, efforts are underway to incorporate automated flow-modulation algorithms in pump speed of CF LVADs, in hopes of enhancing arterial pulsatility.25 Interestingly, Ambardekar et al15 found that among the 2 CF-LVAD patients whose aortic valve opened every beat, there was a rightward shift in the stress–strain curve compared with the remaining CF-LVAD patients whose aortic valves never opened, providing some preliminary evidence that enhanced pulsatility may counteract the arterial stiffening that otherwise results from nonpulsatile flow. This hypothesis can be more rigorously tested as more patients are implanted with devices that augment pulsatility through modulations in pump speed.

Ambardekar et al15 are to be congratulated for advancing the field. Their study has provided important insights into alterations in vascular biology associated with CF-LVAD technology. They have elegantly demonstrated that nonpulsatile flow accelerates arterial stiffening, which adds to the list of concerns associated with CF circulatory support. Their work also suggests that enhancements in pulsatility may counteract or prevent this response. Future work is necessary to determine the extent to which these alterations in vascular biology influence end-organ function, the mechanism by which this occurs and whether next-generation devices, which will theoretically increase pulsatility in the system, will in fact delay or prevent arterial stiffening.

It is foreseeable that CF-LVAD technology could one day replace orthotopic heart transplantation as the gold standard therapy for patients with advanced HF. However, we must first identify solutions to resolve the physiological maladaptations resulting from CF circulatory support, which are currently preventing our patients from otherwise enjoying improvements in functional status that follow restoration of a normal cardiac output.
Disclosures

Dr. Levine has received research funding from Thoratec Corp. The other authors report no conflicts.

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Key Words: Editorials  ●  blood pressure  ●  heart failure  ●  pulsatile flow  ●  vascular stiffness
Continuous-Flow Circulatory Support: The Achilles Heel of Current-Generation Left Ventricular Assist Devices?
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Circ Heart Fail. 2015;8:850-852
doi: 10.1161/CIRCHEARTFAILURE.115.002472
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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