



Agnieszka Ciarka, MD, PhD  
Department of Cardiovascular Diseases  
Heart Failure and Heart Transplantation Unit  
Catholic University of Leuven  
Leuven, Belgium

## **Reviews:**

Ambardekar AV, Hunter KS, Babu AN, Tudor RM, Dodson RB, Lindenfeld J. **Changes in Aortic Wall Structure, Composition, and Stiffness With Continuous-Flow Left Ventricular Assist Devices: A Pilot Study.** *Circ Heart Fail.* 2015 Sep;8(5):944-52. doi: 10.1161/CIRCHEARTFAILURE.114.001955. Epub 2015 Jul 1.

The last decade witnessed a big advance in the use of mechanical circulatory support devices. Two Heart Mate II trials have shown a significant survival benefit with continuous flow (CF) left ventricular assist devices (LVADs) over pulsatile devices in patients with advanced heart failure (HF). In addition, the evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure (ADVANCE) trial has demonstrated that the centrifugal-flow HeartWare device was an alternative for Heart Mate II as a bridge to transplantation. After the FDA approved the use of the Heart Mate II as a bridge to transplantation in 2008, and as a destination therapy in 2010, there was an exponential increase in the use of CF LVADs. The function of end organs improved because of a dramatic increase of cardiac output and hemodynamic after LVAD placement. The pathophysiological consequences, however, of chronic exposure to minimally or entirely nonpulsatile flow originating from axial or centrifugal CF LVADs are still unclear. On the cellular and molecular level many patients develop acquired von Willebrand syndrome and there is also growing evidence of maladaptations in neurohumoral stimulation secondary to diminished activation of bareceptors by nonpulsatile flow. Up to now little is known about the effects of nonpulsatile flow on aortic wall structure, although some small studies have observed changes in aortic wall morphology.

Dr. Ambardekar and his colleagues have therefore tested the hypothesis that a lack of pulsatile blood flow with CF LVADs can lead to changes in the structure of the aortic wall with a resultant increase of aortic wall stiffness. Samples of aortic walls were collected from consecutive heart failure patients and a comparison of aortic wall morphometry and composition, as well as arterial stiffness, was performed between three groups of patients: HF patients without CF LAVDs (HF group, n=4, aged 58+/-8 yrs), HF patients with CF LVADs (HF-CF LVAD group, n=7, aged 58+/-6 yrs) and a group of nonfailing donor hearts not used for transplantation because of a non-cardiac reason (control group, n=3, aged 53+/-13 yrs). Morphometry and the composition of the aorta were assessed by measurements of the total wall thickness, as well as the thickness of the arterial adventitia, media and intima. Aortic wall composition was assessed by measuring the volume density of collagen, elastin fibres, smooth muscle cells and mucinous ground substance within the aorta while using an unbiased stereo tactical approach. Stress-strain curves were plotted to assess aortic stiffness. No difference was found in the mean arterial pressure between the three groups, while the brain natriuretic peptide levels and filling

pressures were lower in the HF-CF LVAD group. Aortic wall thickness increased in HF-CF LAVD patients and it was nearly exclusively due to increased adventitia thickness. Collagen contents were higher, while the elastin, smooth muscle and mucinous grand substance content decreased in HF-CF LVAD patients. Finally, morphological and structural changes of the aorta were reflected in increased aortic arterial stiffness in this patient group, which was confirmed by a greater elastic modulus (a measure of an object's elasticity or resistance to deformation). Interestingly, a comparison of samples of patients initially excluded from the analysis because of aortic valve opening on the CF LVAD support, revealed that their aortic stiffness was comparable to the HF group rather than the CF LVAD group.

Dr. Ambardekar and his colleagues, in this pilot study, have demonstrated that nonpulsatile blood flow, in patients with LVADs and no opening of the aortic valve, leads to structural and morphological changes of the aortic wall, such as an increase in collagen content and an increase of the adventitia diameter, while the elastin content decreased. Morphological changes lead to increased arterial wall stiffness in HF patients with CF LVADs when compared to HF patients without mechanical support and age matched healthy control subjects. Interestingly, changes occurring in aortic wall stiffness in CF LVADs patients within 1 year were comparable to those that occur after a time span of several decades in hypertensive heptagenarians. These data suggest that nonpulsatile flow can accelerate the aging of arterial wall vessels, which in turn, together with abnormal neurohumoral control, can contribute to adverse events such as strokes. The mechanism explaining the phenomenon of the stiffening of the arterial wall by exposure to nonpulsatile flow is a matter of speculation. A possible explanation is the diminished stimulation of baroreceptors leading to an increase in neurohumoral stimulation: in in vitro models vasoconstriction promoted vessel wall thickening. This study leaves us with the question what to do in order to prevent aorta stiffening in patients with CF LVADs. Pharmacotherapy with medications known to affect arterial stiffness or automated modulation algorithms in pump speed enhancing pulsatility need to be tested further.

*Imamura T, Kinugawa K, Nitta D, Hatano M, Ono M. [Opening of Aortic Valve During Exercise Is Key to Preventing Development of Aortic Insufficiency During Ventricular Assist Device Treatment](#). ASAIO J. 2015 Sep-Oct;61(5):514-9. doi: 10.1097/MAT.0000000000000247.*

The hypothesis that preserved aortic valve opening after LVAD implantation functions as a defence mechanism against aortic stiffening, presented in the above-mentioned study, is relatively new. However, the effects of preserved aortic valve opening on heart function, and more precisely on the development of aortic regurgitation during the follow up period, have already been investigated. Some studies show that preserved aortic opening at rest protects against aortic regurgitation during follow up in patients with LVADs. Some patients with LVADs, however, present with no opening of the aortic valve at rest, while the aortic valve opens during exercise. Imamura and colleagues have investigated the impact of aortic valve opening during exercise on aortic valve function and myocardial performance, as well as on the readmission rate for cardiovascular events in LVAD patients during follow up.

In the study 37 patients were involved who were diagnosed with a closed native aortic valve 3 months after LVAD implantation. During cardiopulmonary exercise testing at 3 months after LVAD implantation seven patients (19%) presented with aortic valve opening. These patients showed a better left ventricular contractility and had a higher exercise tolerance level in comparison to those patients whose aortic valve remained closed during exercise. Patients with an opening of the aortic valve during exercise at a baseline, in comparison to those whose aortic valve remained closed, had no aortic regurgitation at 6 months. 43% of the subjects with a closed aortic valve during the exercise test

developed aortic regurgitation within 6 months after LVAD implantation. Patients with an opening of the aortic valve during exercise had a lower admission rate because of cardiovascular events during the 2 years follow up period (56% vs. 100%,  $p=0.005$ ). Among the patients with a closed aortic valve, those with centrifugal pumps had a lower rate of aortic regurgitation in the follow up.

In the modern era of mechanical circulatory support devices with improved reliability, we have observed an exponential use of LVADs. This is partly due to FDA approval of the Heart Mate II as a destination therapy for heart failure patients who are not candidates for heart transplantation. For patients who lack further therapeutic options, a LVAD is the ultimate solution and the mechanical circulatory device uneventful pump function is of crucial importance. However, the quality of life of these patients also depends on the status of the native heart and aortic regurgitation is a marker of a poor prognosis after LVAD implantation. This is mainly due to decreased exercise capacity and an increased risk of congestion, as well as the enhancement of the risk of thrombosis, which relate to aortic regurgitation. During follow up studies, a closed aortic valve after LVAD implantation has been demonstrated to contribute to the development of aortic regurgitation. This is probably due to the facilitation of the fusion of the immobile cusps of the aortic valve. The study of Imamura and colleagues offers a possible explanation as to why some patients with a closed aortic valve at rest do not present with aortic regurgitation during follow up. Those who have an opening of the aortic valve during exercise, even though they have a closed aortic valve at rest, are possibly protected against developing aortic regurgitation, and have a better exercise tolerance and LV contractility. These circumstances impact patients' quality of life, especially because they had a lower readmission rate because of cardiovascular events. The current study thus leaves us with the question as to possible interventions that could facilitate the opening of the native aortic valve. Interventions such as the lowering of rotation speed and aggressive rehabilitation are possible strategies, which need further evaluation.

## **ASAIO Journal**

*Halaweish I, Cole A, Cooley Elaine, Lynch WR, Haft JW. Roller and Centrifugal Pumps: A Retrospective Comparison of Bleeding Complications in Extracorporeal Membrane Oxygenation. ASAIO Journal. 61(5):496-501, September/October 2015.*

*Sieg Adam, Mardis BA, Mardis CR, Huber MR, New JP, Meadows HB, Cook JL, Toole JM, Uber E. Developing an Anti-Xa-Based Anticoagulation Protocol for Patients with Percutaneous Ventricular Assist Devices. ASAIO Journal. 61(5):502-508, September/October 2015*

*Bradford CD, Stahovich MJ, Dembitsky WP, Adamson RM, Engelbert JJ, Perreiter AS. Safety of Prothombin Complex Concentrate to Control Excess Bleeding During Continuous Flow LVAD Insertion. ASAIO Journal. 61(5):509-513, September/October 2015.*

*Taghavi S, Jayarajan SN, Mangi AA, Hollenbach K, Dauer E, Sjolholm LO, Pathak A, Santora TA, Goldberg AJ, Rappold JF. Examining Noncardiac Surgical Procedures in Patients on Extracorporeal Membrane Oxygenation. ASAIO Journal. 61(5):520-525, September/October 2015.*

*Imamura T, Kinugawa K, Nitta D, Hatano M, Ono M. Opening of Aortic Valve During Exercise Is Key to Preventing Development of Aortic Insufficiency During Ventricular Assist Device Treatment. ASAIO Journal. 61(5):514-519, September/October 2015.*

## **Journal of Cardiac Failure**

None

## **Circulation Heart Failure**

*Cornwell WK III, Urey M, Drazner MH, Levine BD. Continuous-Flow Circulatory Support: The Achilles Heel of Current-Generation Left Ventricular Assist Devices? Circ Heart Fail. 2015;8:850-852, doi:10.1161/CIRCHEARTFAILURE.115.002472*

*Ambardekar AV, Hunter KS, Babu AN, Tudor RM, Dodson RB, Lindenfeld J. Changes in Aortic Wall Structure, Composition, and Stiffness With Continuous-Flow Left Ventricular Assist Devices: A Pilot Study. Circ Heart Fail. 2015;8:944-952, published online before print July 1 2015, doi:10.1161/CIRCHEARTFAILURE.114.001955*

*Loyaga-Rendon RY, Acharya D, Pamboukian SV, Tallaj JA, Cantor R, Starling RC, Naftel DC, Kirklin JK. Duration of Heart Failure Is an Important Predictor of Outcomes After Mechanical Circulatory Support. Circ Heart Fail. 2015;8:953-959, published online before print August 6 2015, doi:10.1161/CIRCHEARTFAILURE.115.002321*

## **European Journal of Heart Failure**

None

## **Journal of Thoracic and Cardiovascular Surgery**

None

## **Journal of American College of Cardiology**

None