The role of renin-angiotensin system in patients with left ventricular assist devices

Alexandros Briasoulis1*, Ernesto Ruiz Duque1*, Dimitrios Mouselimis2, Anastasios Tsarouchas2, Constantinos Bakogiannis1 and Paulino Alvarez1

Abstract
End-stage heart failure is a condition in which the up-regulation of the systemic and local renin-angiotensin-aldosterone system (RAAS) leads to end-organ damage and is largely irreversible despite optimal medication. Left ventricular assist devices (LVADs) can downregulate RAAS activation by unloading the left ventricle and increasing the cardiac output translating into a better end-organ perfusion improving survival. However, the absence of pulsatility brought about by continuous-flow devices may variably trigger RAAS activation depending on left ventricular (LV) intrinsic contractility, the design and speed of the pump device. Moreover, the concept of myocardial recovery is being tested in clinical trials and in this setting LVAD support combined with intense RAAS inhibition can promote recovery and ensure maintenance of LV function after explantation. Blood pressure control on LVAD recipients is key to avoiding complications as gastrointestinal bleeding, pump thrombosis and stroke. Furthermore, emerging data highlight the role of RAAS antagonists as prevention of arteriovenous malformations that lead to gastrointestinal bleeds. Future studies should focus on the role of angiotensin receptor inhibitors in preventing myocardial fibrosis in patients with LVADs and examine in greater details the target blood pressure for these patients.

Keywords
Heart failure, LVAD, renin angiotensin system, hypertension

Introduction
Despite advances in cardiac therapy, heart failure (HF) remains a progressive, highly symptomatic and deadly disease affecting more than 18 per 1000 United States citizens.1 Hospitalization for HF, apart from being an important marker for poor prognosis, raise the global cost of care for HF patients up to 108 million dollars per year.2 Heart failure with reduced ejection fraction (HFrEF) represents approximately 50% of all patients with HF and about 5% of HFrEF patients progress to end-stage HF,3 which is a stage of disease refractory to guideline-directed medical and device therapy.4 Specialized strategies for patients with refractory HFrEF include intravenous vasodilator and inotropic therapy, ultrafiltration, mechanical circulatory support, surgery including cardiac transplantation, and palliative care.4

Mechanical circulatory support devices
Mechanical circulatory support (MCS) devices were initially designed to support patients in hemodynamic instability.5 Currently, they are used in patients...
undergoing cardiac surgery, in cases of cardiogenic shock and also as durable long-term support devices either in patients awaiting cardiac transplantation (bridge to transplantation, BTT), or as permanent mechanical assistance (destination therapy, DT) in selected patients, who are not eligible for cardiac transplantation. The majority of long-term mechanical circulatory support devices implanted are left ventricular assist devices (LVADs). In less than 15% of patients, particularly those with biventricular failure, refractory ventricular arrhythmias or congenital heart disease, biventricular support as a bridge to transplantation, either with biventricular assist devices or a total artificial heart, is preferable. LVADs have evolved since the publication of the REMATCH trial in 2001 by Rose et al. and are still rapidly shifted to the point that 1-year survival has increased from 52% to approximately 90% in the latest randomized controlled trials. LVADs are divided into first, second, and third generation devices, with sizable differences in the mechanism of operation between each generation. The first generation LVADs were pulsatile positive displacement pumps, which include the HeartMate I, the Thoratec Paracorporeal Ventricular Assist Device (PVAD) and the Novacor. These pulsatile devices provided excellent hemodynamic support and improved survival but came with several limitations, such as limited long-term device durability, the need for extensive surgical dissection to implant, the presence of a large external lead prone to infection, an audible pump, and the need for medium-large body habitus. Therefore, LVAD designs quickly shifted to continuous flow, leading to the second-generation devices (axial flow pumps such as HeartMate II, Jarvik2000) and third generation devices (centrifugal flow pumps such as HeartWare HVAD and HeartMate 3).

Continuous-flow LVADs account for 100% of patients receiving DT since 2010 and more than 95% of patients receiving primary MCS implants. In contrast to the pulsatile LVADs, the continuous-flow LVADs have only one moving part, the rotor, and hence are much more durable, they are smaller, quieter with smaller drivelines and lower rates of reoperation for device malfunction. Third generation VADs are centrifugal pumps designed for longer durations of reoperation for device malfunction. Continuous-flow LVAD implantation frequently leads to improvement in myocardial structure and function manifesting as improved left ventricular (LV) ejection function, decreased end-systolic and end-diastolic LV volumes and LV mass as early as 30 days after implantation. Interestingly, a small number of patients supported with LVADs exhibit significant improvement in their myocardial function and prolonged unloading of the left ventricle may lead to a degree of functional improvement enough to allow explantation of the device. Despite improvements in durability, quality of life and mortality, continuous-flow LVADs are associated with high rates of gastrointestinal bleeding, which is likely related to the continuous flow, the absence of pulsatility and enhanced proteolysis of large von Willebrand factor polymers. Furthermore, due to the non-pulsatile flow, continuous-flow LVADs may be associated with poor microcirculation perfusion and reduced end-organ function.

Continuous-flow LVADs are preload dependent and afterload sensitive (note the relationship between blood flow and head pressure in Figure 2(b)), which translates into a need for strict blood pressure control. The role of the renin-angiotensin-aldosterone system (RAAS) is important to all these key processes and aspects of care related to the use of continuous-flow LVADs, from LV unloading to myocardial recovery, from lack of pulsatility to higher risk of bleeding, and necessity for strict BP control. Nonetheless, there is a paucity of data in preclinical and clinical level regarding the activation and inhibition of RAAS in the setting of LVADs. In this narrative review, we sought to summarize current evidence on the interplay of RAAS and important aspects of management of LVAD patients (Figure 1).

**Renin-angiotensin-aldosterone system in advanced HF**

The renin-angiotensin aldosterone system (RAAS) plays a crucial role in the regulation of renal, cardiac, and vascular physiology, and its activation is involved in many common pathologic conditions including heart failure. The classic and simplified view of the RAAS pathway begins with renin, an enzyme excreted by renal afferent arterioles cleaving its substrate, the hepatic derived angiotensinogen, to produce an inactive peptide, angiotensin I, which is then converted to angiotensin II by endothelial angiotensin-converting enzyme (ACE). Increased beta-adrenergic activity, reduced delivery of chloride to macula densa and constriction of the afferent arteriole all stimulate renin release. In turn, ACE activation of angiotensin II occurs mainly in the lungs. Active Angiotensin II binds to two types receptors, angiotensin receptor type 1 (AT1) and angiotensin receptor type 2 (AT2). Angiotensin
II mediates, mainly via AT1, vasoconstriction as well as aldosterone release from the adrenal gland, resulting in sodium retention and increased blood pressure.\textsuperscript{21,22,24} Interestingly, there are also several localized RAAS pathways in various human tissues including the heart, that function independently of each other and of the systemic RAAS.\textsuperscript{21,22}

In patients with HF the sympathetic nervous system (SNS), the RAAS, and antidiuretic hormone are upregulated.\textsuperscript{21,22,24,25} That said, the generation of angiotensin II at the tissue level is as important as circulating angiotensin II.\textsuperscript{22} These local RAAS exert autocrine (cell-to-same cell) and paracrine (cell-to-different cell) effects.\textsuperscript{24} As a result, the RAAS is more complex than a simple pathway controlling blood volume and blood pressure.\textsuperscript{22} The local activation of AT1 mediates target-organ damage including remodeling, endothelial dysfunction, and collagen deposition resulting in fibrosis.\textsuperscript{24} Moreover, angiotensin II is also synthesized locally, and local angiotensin II production is increased proportionally to the severity of HF.\textsuperscript{25} In HF patients, local and systemic angiotensin II production leads to increased sodium reabsorption, systemic and renal vasoconstriction, myocardial hypertrophy, apoptosis and alterations in the interstitium.\textsuperscript{24}

Blocking the RAAS constitutes the basis of HF pharmaceutical treatment in HF patients with reduced ejection
fraction (HFrEF). Angiotensin converting enzyme inhibitors (ACEi) and AT1 blockers have been proven to benefit HFrEF patients, significantly improving their morbidity and mortality rates. Antagonizing the action of aldosterone on the mineralocorticoid is also an important step in the optimal treatment of HFrEF. Aldosterone antagonists such as spironolactone and eplerenone have been proven to significantly improve outcomes in the disease. Last but not least, the addition of sacubitril, a nephrilisin inhibitor, to valsartan, an AT1 blocker, has been established since the PARADIGM-HF trial as the mainstay treatment for HF patients with advanced disease status.

Left ventricular assist device physiology, pulsatility and renin-angiotensin-aldosterone system

Under normal conditions, LV ventricular filling and contractility is represented by the pressure-volume loop (PVL) which has a trapezoidal shape and a rounded top. In the presence of an LVAD the PVL will change into a triangular shape which reflects the loss of normal isovolumic periods (Figure 2(a)). Systemic blood flow depends on the LVAD speed under static loading conditions. Thus, increasing the speed will cause a progressive leftward shift of the PVL increasing the systemic arterial pressures, and decreasing peak LV pressure generation, LV end diastolic pressure, left atrial pressure and pulmonary capillary wedge pressure. In addition to being directly proportional to the rotor speed, flow is inversely proportional to the pressure differential between LV and aorta also known as the pressure across the inlet and outlet called “pump Delta P”, “head pressure” or “H” (Figure 2(b)). The blood flow through the device is described as Q and is directly proportional to the pump speed at a given head pressure. Continuous-flow LVADs are preload dependent and sensitive to the gradient across the inflow and outflow cannula. At a given pump speed the flow will decrease if head pressure increases. Left ventricle-aorta intrinsic properties also play an additional role in flow determination. Regarding the cardiac hemodynamics in general an LVAD implantation leads to a significant increase in cardiac output which extenuates the workload of the right ventricle via lowering the pulmonary arterial pressure. As a result, tricuspid regurgitation subsides, while functional mitral regurgitation has been reported in a study conducted by Goodwin et al. to be alleviated regardless of its severity level.

It is worth mentioning that there are important differences in the HQ curves between the currently available LVADs which are classified as axial devices, such as the HeartMate II (Abbott, Abbott Park, IL) and centrifugal devices, consisting of the HVAD (Medtronic, Minneapolis, Minnesota) and HeartMate 3 (Abbott, Abbott Park, IL). These differences reflect the differing engineered characteristics and the response to speed changes. Axial LVADs have much steeper HQ curves, with an inverse linear relationship in flow with pump pressure differential. This translates in lower flow pulsatility than the centrifugal
devices and higher likelihood of high-pressure differential in the setting of low flows, which can cause suction events within the left ventricular cavity. On the other hand, centrifugal devices operate over a wide range of flows with little change in pressure differential across the pump, translating into higher pulsatility and smaller change in pressure differentials. Within low flow conditions such as hypovolemia and right ventricular failure centrifugal devices will have less common suction events. For any of the current LVADs, the interaction between LVAD and each patient is unique due to factors inherent to the patient as body-size, gender, mean arterial pressure, volume status, intrinsic myocardial contractility, RV function, vasoactive and neuro-hormonal medications. In any case, the continuous flow exerts unique effects on the sympathetic and RAAS.

Sympathetic nerve activity plays an important role in the arterial blood pressure regulation via baro-receptors. Arterial baroreceptors in the aortic arch and carotid sinus respond to fluctuation of the pulsatility and stimulate the afferent fibers from baroreceptors to the brainstem modulating a negative feedback over the sympathetic nerve activity. A previous animal study on canines shown that at the same arterial mean pressure, pulsatile flow has greater carotid baroreceptor afferent response and suppression of SNS compared with continuous flow. Continuous flow does not stimulate arterial baroreceptors to a similar degree as pulsatile flow leading to desensitization of the receptors. Measurement of muscle sympathetic nerve activity represents an integrated sympathetic outflow from carotid and cardiopulmonary baroreceptors. Ambulatory patients with continuous-flow devices have shown markedly elevated levels of muscle sympathetic nerve activity compared with patients with pulsatile devices and healthy controls. However, the degree of pulsatility does not always depend on the device in fact. LV intrinsic contractility can contribute to maintain a wide pulse pressure which might stimulate enough baroreceptors. Moreover, a study with ambulatory patients with HeartMate II devices, reduction of LVAD speed leads to augmentation of pulse pressure, carotid distension, baroreceptor stimulation and reduction in the sympathetic neural activity. Decreased pulse pressure may lead to minimal baroreceptor stimulation and increased SNS activity which in turn activates the RAAS and predisposes to higher blood pressure, increased risk of stroke and chronic kidney disease and lower probability of myocardial recovery. For these patients the use of beta blockers has been associated with significantly lower brain natriuretic peptide levels and appears to be safe even in patients with right ventricular dysfunction.

Endothelial function is affected by pulsatility, which maintains a balance between vascular smooth muscle cell proliferation and apoptosis. In a canine model of HF study with use of continuous-flow LVAD the blood pressure and systemic vascular resistance decrease with higher pulse pressures along with increased plasma nitrite/nitrate concentration. A recent study suggested impaired endothelial function with continuous-flow devices, a phenomenon which was clinically significant as it was associated with higher rates of cardiovascular events. Finally, non-pulsatile kidney perfusion can lead to activation of RAAS with elevated plasma renin and aldosterone activity. It has been reported by Welp et al. that renin and aldosterone activity were greater in patients with non-pulsatile compared with pulsatile LVADs early after implantation whereas these hormones return close to normal range 1 month after implantation of pulsatile LVADs.

Renal cortical artery hypertrophy and inflammatory cell infiltration of the renal cortex have been reported in preclinical studies of continuous-flow LVADs. Severe periarteritis in kidneys and pulmonary arteries occurred after continuous-flow support in calves with LVAD and RVAD respectively. The significant hemodynamic differences were lower pulsatility and pulse pressure with no difference in mean blood pressure. Also, the deformation of carotid baro-receptors tends to be reduced in patients with continuous-flow devices which lead to higher levels of angiotensin II activity.

Hypertension in LVAD patients

Poorly controlled blood pressure can have detrimental effects on outcomes of LVAD recipients. Firstly, continuous-flow devices are afterload sensitive, meaning that increased blood pressure caused by systemic vascular resistance decreases LVAD flow, predisposing to pump thrombosis. Furthermore, uncontrolled blood pressure impairs LV unloading which in turn increases left atrial and pulmonary pressures and the latter translates into worsening symptoms of HF, hospitalizations and eventually right ventricular failure. Also, elevated filling pressures may cause subendocardial ischemia and ventricular arrhythmias. Moreover, uncontrolled blood pressure can promote de novo aortic insufficiency as the increased afterload prevents aortic valve opening and causes commissural fusion of the aortic leaflets. Finally, poorly controlled blood pressure increases substantially the risk of ischemic and hemorrhagic stroke, but also any risk of major bleeding especially in the setting of anticoagulation.

Although, the importance of blood pressure control is well recognized for patients with continuous-flow LVADs, the treatment targets are defined based on expert panel consensus rather that data from appropriately designed studies. Previous studies have proposed treatment targets of mean arterial pressure (MAP) of 70 to 80 mmHg, 70 to 90 mmHg, or according to the International Society for Heart and Lung Transplantation guidelines a target MAP <80 mmHg (Class IIb recommendation, level of evidence C). An analysis of 220 HeartMate II patients with serial outpatient blood pressure measurements, conducted by
Pinsino et al., suggested that high MAP >90 and systolic blood pressure >100 mmHg was associated with higher risk of stroke. MAP had higher predictive value for the composite endpoint of pump thrombosis and stroke than systolic blood pressure, and the combination of systolic blood pressure and low pulse pressure <22 mmHg were associated with the highest risk of stroke. Maltais et al. in the PREVENTion of HeartMate II Pump Thrombosis Through Clinical Management (PREVENT) trial protocol demonstrated a low rate of pump thrombosis with standardized implant and perioperative management including MAP <90 mmHg. However, BP levels were similar in patients with and without pump thrombosis in this analysis.

Data from the ENDURANCE Supplemental cohort analysis by Milano et al. demonstrated that target MAP <85 mmHg or Doppler opening pressure ≤90 mmHg with home BP measurements, successfully reduced stroke rates in patients implanted with an HVAD compared to the original trial results that suggested higher risk of stroke with this device. This finding is attributed to better BP control. However, there was no difference in incident stroke between HVAD and HeartMate II study groups. A recent very interesting analysis of the INTERMACS registry, showed a bimodal association between blood pressure and survival, as survival was lower among patients with MAP <75 mmHg Dopplers ≤80 mmHg, and systolic blood pressures <90 mmHg than those with normal or high blood pressures. Patients with MAPs >100 mmHg, Doppler ≥105 mmHg, and systolic blood pressures ≥120 mmHg had higher adjusted risk of death than those with normal pressures.

However, accurate non-invasive measurement of blood pressure is challenging because of diminished pulsatile flow. Currently, the gold-standard for BP measurement in LVAD patients is an arterial line, which obviously is not feasible in the outpatient. Automated BP devices obtain a BP measurement successfully obtain a BP measurement approximately 50% of the time due to reduced pulse pressure. Doppler ultrasound with sphygmomanometer is most frequently used and its measurements closely reflect arterial-line MAP but they also reflect systolic blood pressure in cases of high pulse pressure. Overall, Doppler opening blood pressure has good correlation with MAP even with higher pulse pressures. The main issue with Doppler-derived BP measurements is that it is impractical for home blood pressure monitoring. An alternative method the Terumo Elemano BP Monitor is a slow cuff deflation device and provides a valid measurement device for blood pressure measurement in LVAD patients with arterial line MAP and systolic blood pressure. In the presence of palpable arterial pulse, automatic blood pressure devices can be used, and several measurements should be obtained to confirm the accuracy of the measurements. Also, this measurement should be correlated with the Doppler method which is the approach of choice in the absence or palpable pulse. This approach has not been validated yet in the HeartMate 3 devices which generate an artificial pulse. These devices decrease the rotor speed every 2 s by 2000 rpm for 0.15 s, then increases by 4000 rpm for 0.20 s before returning to the preset speed. Therefore, in HeartMate 3 recipient the pulsatility is not only determined by the native heart residual contractility but also by the artificial device-generated pulsatility which is not synchronous with the cardiac cycle. The measurement of blood pressure in these patients can be more challenging as it will require monitoring over serial cardiac cycles to determine MAP and systolic blood pressure.

Regarding blood pressure management in patients who are not reaching the targets, the optimal first-line drugs and combinations have not been determined. Antihypertensive requirements tend to increase in the long-term after device implantation and by 2 years, LVAD recipients require on average approximately two antihypertensives according to an INTERMACS analysis. Beta blockers were the most frequently used AHs, followed by ACE inhibitors and aldosterone antagonists. Approximately, 50% of patients were on ACE inhibitors or ARBs. RAAS antagonists may exert effects beyond blood pressure lowering in this setting, promoting reverse LV remodeling and preventing progression of underlying renal disease. Further applications of these medications include prevention of gastrointestinal bleeding and utilization as part of myocardial recovery protocols and these will be discussed below.

The combination of angiotensin receptor neprilysin inhibitor maybe a superior antihypertensive medication compared with equivalent doses of ACE or ARBs and the adoption of these medications in the LVAD population should be studied further. Neprilysin levels tend to decrease after LVAD implantation and their levels postoperatively have been associated with adverse events.

**Gastrointestinal bleeding in LVAD patients and the role of RAAS inhibition**

It is noteworthy that a common complication of patients with LVAD support is gastrointestinal bleeding (GIB). GIB occurs after LVAD implantation and is a common adverse event. Proposed mechanisms of gastrointestinal bleeding (GIB) during LVAD support include acquired von Willebrand disease, impaired platelet aggregation and enhanced angiogenesis causing arterial-venous-malformation (AVM). Increased sympathetic tone can lead to smooth muscle relaxation and development of angiodysplasias. Also, low pulse pressure during continuous-flow support leads to intestinal hypoperfusion, vascular dilation and stimulation of angiogenesis.

The RAAS may significantly contribute to this process via Angiotensin II. Angiotensin II receptor activation results theoretically in abnormal angiogenesis through two
pathways: the augmentation of TGF-β which upregulates vascular endothelial growth factor (VEGF) and angiopoietin-2. Increased levels of transforming growth factor-β (TGF-B) after LVAD implantation leads to increased vascular endothelial growth factor (VEGF) expression which might play an important role in the pathogenesis of angiodyplasias as well. Indeed, antagonists of angiotensin II pathway have been shown to reduce signaling through the TGF-β pathway and the expression of VEGF, angiopoietin-2, hence inhibiting angiogenesis. Houston et al. performed a retrospective analysis of patients with HeartMate II and HeartWare with over 100 days with LVAD support and examine the role of ACEi or angiotensin receptor blockers (ARBs) therapy in prevention of GIB caused by AVM. Patients receiving ACEi or ARB therapy during VAD support had significantly lower rates of GIB and AVM related bleeding in the unadjusted analysis, but the association became non-significant after adjustment of clinical variables. Converse et al. found significantly lower GIB and AVM related bleeding patients who received ACEi or ARBs within 30 days after LVAD implantation. The effect was dose dependent as doses of lisinopril ≥5 mg were related with a 74% reduction in risk of GIB. Unlike, ACE inhibitors or ARBs, beta-blockers have not been associated with reduced rates of GIB in this setting.

**Myocardial recovery**

LVAD unloading of the LV can promote recovery of myocardial function. Occasionally, myocardial recovery can be sufficient to allow device removal without cardiac transplantation and allow the patient to have good functional capacity and quality of life. This strategy is known as “bridge to recovery” and combines mechanical unloading with LVAD support and specific pharmacologic interventions to maximize the likelihood of myocardial recovery and improve the durability of recovery after LVAD explantation. In an analysis of 14,138 INTERMACS patients, with total rate of recovery 1.3%, independent predictors of this phenomenon included: age <50 years, non-ischemic cardiomyopathy, and time from cardiac diagnosis <2 years, absence of ICD, creatinine ≤1.2 mg/dl, and LVEDD <6.5 cm and these parameters were incorporated in a weighted score (I-CARS) with overall good performance to predict recovery. The pharmacologic interventions in studies of myocardial recovery included ACE inhibitors and ARBs, beta blockers, and aldosterone antagonists, which were given at very high doses, doses that these patients would not have tolerated before pump insertion because of hypotension and/or renal dysfunction, in order to achieve reverse remodeling. Moreover, in a noninvasive study, conducted by Yousefzai et al., ACE inhibitors and ARBs were the only regimens that significantly reduced the risk of mortality in LVAD patients almost by half (47%). The study population consisted of 307 LVAD patients from two large centers in the United States and the follow-up period lasted 24 months. The validity of the assumed beneficial effect of blocking the RAAS with ARBs and ACE inhibitors is enhanced by the 24-month reported survival rate of the study of 73%, which is in agreement with the survival rate of the INTERMACS report.

The role of RAAS modulation in achieving myocardial recovery may be substantial. ACEi have been found to decrease AngII levels and cross-linked collagen in myocardial tissue. Thus, even the “holy grail” of LVAD-mediated myocardial recovery may depend on intimate knowledge of the RAAS.

**Conclusion**

End-stage heart failure is a condition in which the up-regulation of the systemic and local RAAS leads to end organ damage and the reversibility is beyond medication use only. LVADs can downregulate RAAS activation by unloading the left ventricle and increasing the cardiac output which translate into a better end organ perfusion improving survival. However, in the setting of continuous-flow devices the absence of pulsatility may trigger the RAAS activation depending on LV intrinsic contractility, axial or centrifugal pump device and LVAD speed. Blood pressure control on LVAD recipient is a key to avoid complications as gastrointestinal bleeding, pump thrombosis and stroke. Furthermore, we have emerging data on the role of RAAS antagonist as prevention of AVM-related GIBs. Finally, the concept of myocardial recovery is being tested in clinical trials and in this setting LVAD support combined with intense RAAS inhibition can promote recovery and ensure maintenance of LV function after explantation. Future studies should focus on the role of angiotensin receptor nephrilysin inhibitors in patients with LVADs and examine in greater details the target blood pressure for these patients.

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**ORCID iD**

Alexandros Briasoulis https://orcid.org/0000-0002-5740-9670

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