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Clinical Research

The Effect of Artificial Pulsatility on the Peripheral Vasculature in Patients With Continuous-Flow Ventricular Assist Devices

Peter Ivak, MD, PhD,[a,b,c] Ivan Netuka, MD, PhD,[a,c] Zuzana Tucanova, MD,[a] Peter Wohlfahrt, MD, PhD,[d] Miroslav Konarik, MD,[a,e] Ondrej Szarszoi, MD, PhD,[a] Sarka Novakova,[d] Milos Kubanek, MD, PhD,[f] Vera Lanska, DSc,[g] and Jan Pitha, MD[b]

[a] *Department of Cardiovascular Surgery, Institute for Clinical and Experimental Medicine, Prague, Czech Republic*

[b] *Department of Physiology, Third Faculty of Medicine, Charles University, Prague, Czech Republic*

[c] *Second Department of Surgery, Department of Cardiovascular Surgery, First Faculty of Medicine, Charles University, Prague, Czech Republic*

[d] *Laboratory for Atherosclerosis Research, Institute for Clinical and Experimental Medicine, Prague, Czech Republic*

[e] *Institute of Physiology, First Faculty of Medicine, Charles University, Prague, Czech Republic*

[f] *Department of Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic*

[g] *Medical Statistics Unit, Institute for Clinical and Experimental Medicine, Prague, Czech Republic*

ABSTRACT

Background: Implantation of left-ventricular assist systems (LVASs) has become the standard of care for advanced heart failure (HF). The absence of pulsatility in previous devices contributes to vascular and endothelial dysfunction related to atherosclerotic or vascular complications. We hypothesized that the artificial pulsatility provided by the HeartMate 3 (HM3) (Abbott, Chicago, IL) LVAS would exert a favourable effect on the vasculature.

Methods: In 32 patients implanted with HM3 (5 female patients, mean age 55 ± 13.6 years), the reactive hyperemia index (RHI) and peripheral augmentation index (AI), markers of endothelial function and arterial stiffness, were measured with an EndoPAT2000 before and in the third and sixth month after implantation. RHI and AI data from 30 HeartMate II (HM II) (Abbott) recipients in the third and sixth month after implantation, from 15 patients with advanced HF without LVASs and from 13 healthy volunteers were also analyzed.

Results: In HM3 recipients, the mean RHI significantly decreased at 3 and 6 months after implantation. The RHI was substantially lower at

RÉSUMÉ

Contexte : L'implantation de dispositifs d'assistance ventriculaire gauche (DAVG) est devenue un standard des soins pour une insuffisance cardiaque (IC) avancée. L'absence de pulsatilité dans les dispositifs précédents contribue à la dysfonction vasculaire et endothéliale liée aux complications athérosclérotiques ou vasculaires. Nous avons émis l'hypothèse que la pulsatilité artificielle fournie par le DAVG HeartMate 3 (HM3) (Abbott, Chicago, IL) entraînerait un effet bénéfique sur le système vasculaire.

Méthodes : Chez 32 patients implantés avec le HM3 (5 femmes, âge moyen 55 ± 13,6 ans), l'indice d'hyperémie réactive (IHR) et l'indice d'amplification périphérique (IAP), marqueurs de la fonction endothéliale et de la rigidité artérielle, ont été mesurés par un EndoPAT2000 avant puis trois et six mois après implantation. Les données IHR et IAP de 30 patients porteurs de HeartMate II (HM II) (Abbott) au troisième et sixième mois post-implantation, de 15 patients atteints d'une IC avancée sans DAVG et de 13 volontaires sains ont également été analysées.

Implantation of left-ventricular assist systems (LVASs) has become a part of the standard of care for advanced heart failure.[1,2] The nearly complete transition to continuous-flow LVASs has enabled both reduced size and improved durability of the devices but at the cost of attenuated pulsatility, with a potential for negative impact on end-organ function and vasculature. The nonpulsatile flow produced by these systems could contribute to the compromise of vascular functional properties.[3-5] Mechanistically, unfavourable vascular effects could occur through dysfunction of the endothelium exposed to a diminished pulsatile pattern. The endothelial dysfunction aggravates thrombotic, proinflammatory, and proliferative mechanisms, resulting in vasospasm, thrombosis, and atherosclerosis, in general.[6,7] Therefore, endothelial dysfunction potentiated by continuous flow could contribute to LVAS-associated clinical complications such as gastrointestinal bleeding, hypertension and stroke.[3,7-9] To mitigate these unfavourable effects, rotor-speed modulation to provide more normal pulsatile perfusion has been introduced.[10-13]

The HeartMate 3 (HM3) (Abbott, Chicago, IL) LVAS is a recent compact, fully magnetically levitated centrifugal-flow

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Corresponding author: Dr Peter Ivak, Institute of Clinical and Experimental Medicine, Videnska 1958/9, 140 21 Prague, Czech Republic. Tel.: +420261365016.

E-mail: peter.ivak@ikem.cz

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baseline than that of healthy or the HF reference group. Increasing AI values, indicating worsening arterial stiffness, were also observed. Similar trends were observed in HM II recipients between the third and sixth months but with higher absolute values of RHI and AI.

Conclusions: We detected impaired vascular function in HM3 patients and provided additional evidence on the negative effect of low pulsatility on vascular function after LVAS implantation. The results suggest that the artificial pulsatility of the HM3 does not avert the progression of endothelial dysfunction.

Résultats : Chez les receveurs du HM3, l'IHR moyen a significativement diminué trois et six mois après implantation. L'IHR basal était sensiblement plus faible que celui des personnes en bonne santé ou du groupe IC de référence. Des valeurs croissantes de l'IAP, indiquant une exacerbation de la rigidité artérielle, ont également été observées. Des tendances similaires ont été constatées chez les receveurs du HM II entre le troisième et le sixième mois, mais avec des valeurs absolues de l'IHR et de l'IAP plus élevées.

Conclusions : Nous avons décelé une fonction vasculaire altérée chez les patients porteurs du HM3 et fourni des éléments supplémentaires de l'effet négatif d'une faible pulsatilité sur la fonction vasculaire après l'implantation d'un DAVG. Les résultats suggèrent que la pulsatilité artificielle du HM3 n'empêche pas la progression de la dysfonction endothéliale.

continuous ventricular-assist device. The key novel features of the device—including a magnetically levitated rotor, wide blood-flow path gaps, and artificial pulsatility that allows periodic washout of the device—may lead to decreased rates of major adverse events. Indeed, in a large clinical study, a favourable clinical effect of HM3 was observed compared with a completely nonpulsatile device.[14] The pathophysiological mechanisms responsible for these findings are not fully understood. Hence, the programmed fixed artificial pulsatility in HM3 generated by rapid rotor-speed modulation has attracted additional interest as a potential modifier of the pump flow−microvasculature interaction. Therefore, we hypothesized that the detrimental impact of deficiency of pulsatility on the vasculature might potentially be mitigated by the artificial pulsatility provided by the HM3. To analyze endothelial function, peripheral arterial tonometry was performed with an operator-independent proprietary analyzer EndoPAT2000 (Itamar Medical Ltd, Caesarea, Israel) to evaluate pulsatile arterial volume changes.[15,16]

Materials and Methods

The study was a single-centre prospective observational study. Institutional ethics committee approval of the protocol was obtained before initiation of the study. All patients provided written informed consent before enrollment in the study.

Study group

The study was designed to assess peripheral vascular function in the HeartMate 3 LVAS recipients before implantation and in the third and sixth month after the procedure. Consecutive patients eligible for long-term LVAS support between April 2016 and January 2018 were assessed for participation in the study. The exclusion criteria included age < 18 or > 75 years and acute hemodynamic instability requiring high doses of inotropes or short-term mechanical circulatory support before LVAS implantation.

Baseline characteristics, medical history, laboratory assessments, and medications were collected before and at prespecified time points after implantation. Laboratory parameters were assessed by standard certified institutional laboratory methods.

After implantation, heparin was continuously administered intravenously as a bridge until the target anticoagulation range was reached with warfarin. The aim of anticoagulation therapy was to reach an international normalized ratio (INR) of 2 to 2.5 for the HeartMate II (HM II) (Abbott) and 2.0 to 2.7 for the HM3. Acetylsalicylic acid was administered at a dose of 100 mg per day as a part of an antithrombotic regimen in patients implanted with HM3.

Reference groups

For reference groups, we included patients implanted with the HeartMate II and examined at the third and sixth month after implantation (HM II reference group); patients with advanced HF (New York Heart Association [NYHA] III-IV) who were not (yet) indicated for implantation of LVAS (HF reference group) and group of healthy subjects without any clinically manifested disease (healthy reference group). All participants were examined by an identical protocol, described as follows; advanced HF and healthy reference groups were examined once each.

Examination of vascular function

For the assessment of vascular function, peripheral arterial tonometry was performed with a proprietary analyzer-peripheral arterial tonometry (EndoPAT2000) that evaluated pulsatile arterial volume changes.[15,16] This is an operator-independent, FDA-approved device designed to assess endothelial function by examining the reactive hyperemia index (RHI, a measure of endothelial responsiveness) and peripheral augmentation index (AI, a measure of arterial stiffness).[17-19] RHI and AI were assessed before LVAS implantation and in the third and sixth month after the procedure ($\pm$ 15 days). The third month for the first follow-up visit was chosen to avoid the effect of complex hemodynamic changes present immediately after implantation.[20] The method has been described in detail previously.[15,16] Briefly, the system uses a finger probe to assess digital volume changes accompanying pulse waves. The examination was performed in all patients in the morning hours in a quiet, temperature-controlled room. All subjects were examined after 5 minutes of rest in the supine position. The baseline pulse amplitude was recorded over a period of 5 minutes before the induction of ischemia. Ischemia was induced by placing a blood-pressure cuff on the upper arm, whereas the opposite arm served as a control. The peripheral arterial tone probes were placed on 1 finger of each hand. After 5 minutes, the blood pressure cuff was inflated to

200 mm Hg for 5 minutes and then deflated to induce reactive hyperemia. RHI and AI were calculated using a computerized automated algorithm (software version 3.1.2) provided with the device. RHI is the ratio of postocclusion to preocclusion PAT signals on the occluded side, normalized to the control side and further corrected for baseline vascular tone. AI is calculated from PAT pulses recorded during the baseline period. Lower AI values (including values below zero) reflect better arterial elasticity.[19]

Statistical analysis

Continuous data with a normal distribution are presented as the mean ± standard deviation, and non-normally distributed variables are presented as the median (interquartile range [IQR]). Categorical data are presented as frequencies (percent). The Spearman correlation coefficient was used to evaluate the association among variables. Differences among groups were tested using the Mann-Whitney test. To account for correlation in the same patients, we used generalized linear mixed models to study the longitudinal trajectories of study variables. In these models, time, age group, and the interaction between time and age group were analyzed as fixed effects, whereas the intercept was treated as a random effect. Gamma regression was used for right-skewed data. The model-derived estimated marginal means with 95% confidence intervals (CIs) are reported, whereas the estimated marginal means and standard error of the mean are shown in graphs. The Bonferroni correction was applied for multiple comparisons. A 2-sided P value < 0.05 was considered statistically significant. Calculations were performed using SPSS version 21 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

Results

Patients

Fifty-one LVAD candidates were assessed for study enrollment and underwent screening examination. A total of 32 patients (all white, 5 women), aged 19 to 71 years (mean age 55 ± 13.6 years), were enrolled and completed the study (Fig. 1). Patients were implanted with the HM3 between April 2016 and January 2018, via either sternotomy (n = 27; 84%) or left- lateral thoracotomy, combined with upper partial hemisternotomy (n = 5; 16%), both using cardiopulmonary bypass. In the HM3 group, the subjects were predominantly male (n = 27, 84 %) and had a high prevalence of smoking before implantation; ischemic etiology of heart failure was present in less than one-half of the patients (44%); the predominant indication for implantation was bridge to transplant (n = 21; 66%), and **Inte**ragency **R**egistry for **M**echanically **A**ssisted **C**irculatory **S**upport (INTERMACS)

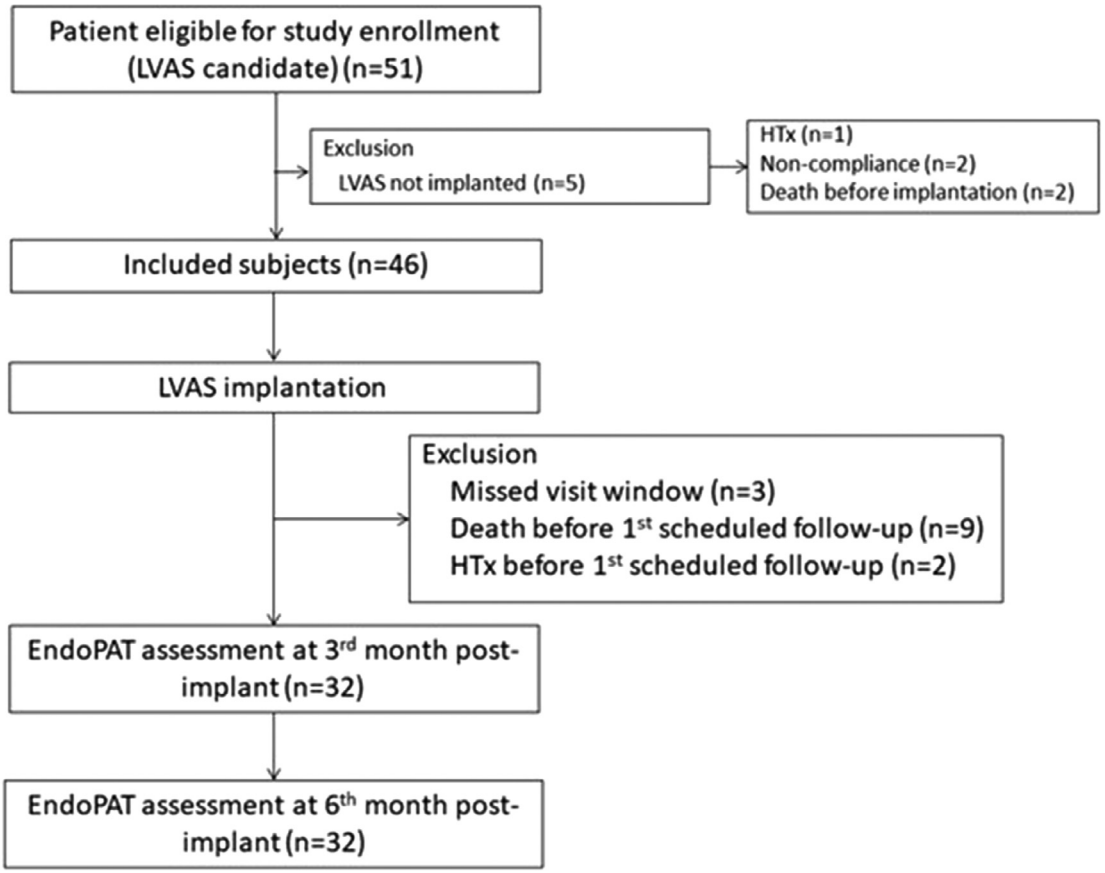

Figure 1. **Con**solidated **S**tandards **o**f **R**eporting **T**rials (CONSORT) diagram of the study. HTx, heart transplantation; LVAS, left-ventricular assist system.

Table 1. Demographics and baseline characteristics of the HM3 group

Age	55 ± 13.6
Male	27 (84)
BSA, m^2	2 ± 0.2
BMI, kg/m^2	26.5 ± 4.6
Ischemic etiology	14 (44)
Indication	
Bridge to transplant	21
Destination therapy	11
INTERMACS profile	
Profile 2	5 (16)
Profile 3	16 (50)
Profile 4	8 (25)
Profile 5	3 (9)
Cardiac index, $L/min/m^2$	1.7 ± 0.6
Left ventricular ejection fraction, %	22 ± 4
Medications	
ACE inhibitor	12 (38)
Angiotensin II antagonist	3 (9)
β blocker	22 (69)
Anticoagulant/antiplatelet drug	27 (84)
Antiarrhythmic drug	12 (38)
Statins	18 (56)
Diuretics	32 (100)
Inotropes	
1	15 (47)
2	5 (16)
Hypertension	16 (50)
Diabetes	7 (22)
Previous sternotomy	3 (9)
Minimally invasive approach	5 (16)
Cardiomyopathy for more than 2 years	26 (81)
Severe COPD	2 (6)
TIA	2 (6)
Stroke	2 (6)
Renal dysfunction	7 (22)
Atrial fibrillation	15 (47)
Pacemaker/defibrillator	24 (75)
Valve disease	16 (50)
Peripheral vascular disease	1 (3)
Smoking within the past 3 months	6 (19)

Values are expressed as the number (%) or mean ± standard deviation.

ACE, angiotensin-converting enzyme; BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; INR, international normalized ratio; INTERMACS, **Inte**ragency **R**egistry for **M**echanically **A**ssisted **C**irculatory **S**upport; TIA, transient ischemic attack.

profiles were indicative of advanced heart failure, with the majority in profiles 2 to 4 (91%) (Table 1).

Routine biomarkers, such as brain natriuretic peptide, plasma creatinine, urea, total bilirubin, and ALT or AST, decreased significantly after LVAS implantation; mean pump flow and speed, pulse index and pump power were stable throughout the study (Table 2).

HM3 patients were older than HM II reference but similar in age to the HF reference group. No intergroup differences were found in the proportion of women or in smoking history, diabetes mellitus status, or renal function. In the healthy reference group, less smoking and no diabetes mellitus were reported (Table 3).

Peripheral vascular function and stiffness

At baseline, the mean RHI of HM3 group was below normal values for a healthy population (RHI = 1.36; 95% CI, 1.21-1.52; cutoff ≤ 1.67 indicative of endothelial dysfunction) and lower than that of healthy reference group (Table 3); RHI further decreased in the third month (RHI = 0.89; 95% CI, 0.80-1.00) as well as in the sixth month after implantation (RHI = 0.94; 95% CI, 0.84-1.06) compared with baseline (both $P < 0.0001$) (Fig. 2, Table 3). The difference between the third and sixth month after implantation was not significant ($P = 0.44$). Significant interaction between age and RHI ($P = 0.023$) in the HM3 group was observed. RHI was higher in subjects ≤ 60 years of age (group median) than in those > 60 years both at baseline ($P = 0.030$) and in the third month ($P = 0.034$). The difference became nonsignificant in the sixth month after implantation ($P = 0.60$) (Fig. 3). In the sixth month, higher pump flow was associated with lower RHI in a cross-sectional analysis ($P = 0.021$). Higher baseline body mass index (BMI) was predictive of a greater RHI decrease in the sixth month ($P = 0.043$). No association was found among the etiology of cardiomyopathy, history of smoking, and endothelial dysfunction ($P > 0.05$ for all interactions). In the HM II reference group, a similar pattern of changes in RHI was observed between the third and sixth month, with RHI values higher than those of the HM3 group. No associations between pump parameters and RHI/AI were observed in the HM II reference group.

In HM3 group, AI significantly increased relative to the baseline value (−32.28; 95% CI, −42.49 to −22.07) at the third (−3.56; 95% CI, −15.34 to 8.23) and the sixth month (−0.62; 95% CI, −11.94 to 10.70) (both $P < 0.001$) (Fig. 4). Differences between the third and sixth month were not significant ($P = 0.72$). At baseline, AI was significantly higher in patients with histories of smoking and ischemic etiology of heart failure ($P = 0.012$ and $P = 0.046$, respectively). AI had no interactions with age or pump parameters.

No significant association between aortic valve opening and RHI (in the third and sixth month) or AI (in the third month) was observed. In the sixth month, aortic-valve opening was associated with a lower (improved) AI in patients with aortic-valve opening within each cardiac cycle than in patients without aortic-valve opening ($P = 0.03$).

In the third month, patients in HM3 group had significantly lower RHI values than in HM II, HF, or the healthy reference groups. The AI in HM3 group was significantly lower than that of HM II or healthy reference groups but higher than that of the HF reference group (Fig. 3). In the HM II reference group, similar longitudinal changes in AI were found, but AI was significantly higher than in the HM3 group. The HF reference group had a higher AI than HM3 group at baseline but a lower AI after 3 and 6 months. The AI of the healthy reference group was higher than that of the HF reference group or the HM3 group but lower than that of the HM II reference group.

Clinical events

In the 6 months after implantation, the HM3 group experienced no fatal clinical events (Fig. 1). Nonfatal events (hemocompatibility adverse events including hemorrhage, thrombosis, ischemic stroke, and hemorrhagic stroke) were observed as follows: 2 ischemic strokes and 1 gastrointestinal bleeding. The low incidence of clinical adverse events precluded analysis relating to RHI and AI.

Table 2. Changes in laboratory and pump characteristics in HM3 group during the course of the study

	Baseline	Third month	Sixth month	*P*1	*P*2	*P*3
Reactive hyperemia index	1.36 (1.21-1.52)	0.89 (0.80-1.00)	0.94 (0.84-1.06)	< 0.0001	0.44	< 0.0001
Augmentation index	−32.28 (−42.49 to −22.07)	−3.56 (−15.34 to 8.23)	−0.62 (−11.94 to 10.70)	< 0.001	0.72	< 0.001
Brain natriuretic peptide (ng/L)	1655 (1232-2223)	428 (318-574)	378 (286-500)	< 0.0001	0.38	< 0.0001
Lactate dehydrogenase (μkat/L)	4.24 (3.68-4.90)	3.69 (3.22-4.23)	3.66 (3.19-4.19)	0.04	0.86	0.04
Hemoglobin (g/L)	117.7 (110.9-124.5)	116.3 (109.5-123.0)	123.7 (116.9-130.5)	0.74	0.28	
Creatinine (μmol/l)	107.9 (96.4-120.8)	84.3 (75.3-94.4)	94.5 (84.4-105.8)	< 0.0001	0.03	0.03
Urea (mmol/L)	10.0 (8.4-12.0)	7.1 (6.0-8.4)	7.5 (6.3-8.9)	0.001	0.54	0.005
Total bilirubin (μmol/L)	31.1 (24.4-37.8)	13.8 (10.3-17.3)	15.7 (12-19.5)	< 0001	0.16	< 0001
Alanine aminotransferase (μkat/L)	1.63 (1.09-2.45)	0.50 (0.34-0.75)	0.56 (0.37-0.83)	0.003	0.71	0.004
Aspartate aminotransferase (μkat/L)	1.03 (0.75-1.40)	0.50 (0.37-0.68)	0.52 (0.38-0.71)	0.003	0.84	0.003
Total cholesterol (mmol/L)	3.4 (3.0-3.8)	4.6 (3.8-5.3)	4.4 (3.8-5.1)	0.03	0.77	0.03
C-reactive protein (mg/L)	32.7 (14.7-50.7)	20.2 (6.9-33.4)	15.88.1-23.6)	0.96	0.51	0.12
White blood cell counts (× 10^9/L)	8.2 (7.3-9.4)	8.3 (7.3-9.4)	7.9 (6.9-8.9)	1.00	1.00	1.00
Pump parameters						
Pump speed (RPM)	NA	5284 (5220-5349)	5291 (5224-5357)	NA	0.79	NA
Pump flow (LPM)	NA	4.1 (3.9-4.3)	4.1 (3.9-4.3)	NA	0.43	NA
Pulse index	NA	4.2 (3.7-4.6)	4.4 (3.9-4.9)	NA	0.27	NA
Pump power (W)	NA	3.8 (3.7-4.0)	3.8 (3.7-4.0)	NA	0.75	NA

Estimated marginal means and 95% confidence intervals are presented. *P*1 difference between baseline and third month; *P*2 difference between third and sixth month; *P*3 difference between baseline and sixth month.

NA, not applicable.

Table 3. Clinical characteristics of the HM3 group and reference groups

	HM3 (n = 32)(Third month)	HM II reference group(n = 30) (Third month)	HF reference group(n = 15)	Healthy reference group (n = 13)
Age, years	55.1 ± 13.8	48.4 ± 15.38	51.2 ± 9.17	50.1 ± 13.52
Sex (male), n (%)	27 (84)	25 (83)	12 (80)	8 (61.5)
(Past) smokers, n (%)	24 (75)	22 (73)	9 (60)	3 (23)*
Diabetes mellitus n (%)	7 (22)	8 (27)	5 (33)	0‡
Ischemic cardiomyopathy n (%)	14 (44)	12 (40)	8 (53)	0
Creatinine, μmol/L	84.3 (75.3-94.4)	97.4 (71.9-123.0)‡	103.6 (89.2-118.1)‡	NA
Urea, mmol/L	7.1 (6.0-8.4)	7.7 (5.4-10.0)	8.7 (7.0-10.4)	NA
Hemoglobin, g/L	116.3 (109.5-123.0)	125 (118.1-131.9)‡	139.8 (129.0-150.6)‡	143.1 (138.6−147.6)‡
Reactive hyperemia index	0.89 ± 0.34	1.50 ± 0.68‡	1.6 ± 0.30‡	1.77 ± 0.54‡
Augmentation index	−3.56 ± 27.12	23.5 ± 22.48†	−16.53 ± 26.77	6.9 ± 11.45

HF, heart failure; HM3, HeartMate 3 (Abbott, Chicago, IL); HM II, HeartMate II (Abbott); NA, not available.
*$P < 0.05$.
†$P < 0.005$.
‡$P < 0.0001$ vs HM3.

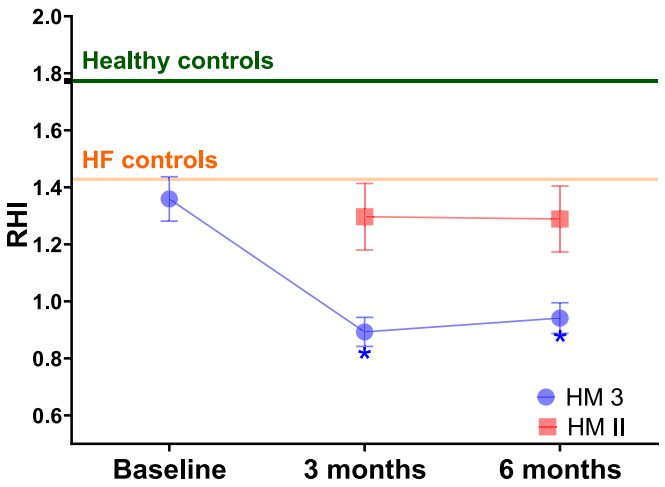

Figure 2. Longitudinal changes in the reactive hyperemia index (RHI) during the study period in HeartMate 3 (HM3) (Abbott, Chicago, IL) group (**blue line**). Longitudinal changes in RHI in HeartMate II (HM II) (Abbott) reference group between the third and sixth months (**red**). Data are presented as estimated marginal means and standard error. *$P < 0.05$ vs baseline. **Solid orange line**, estimated marginal mean for heart failure (HF) reference group; **solid green line**, estimated marginal mean for healthy reference group. **Dashed lines** represent 95% confidence intervals.

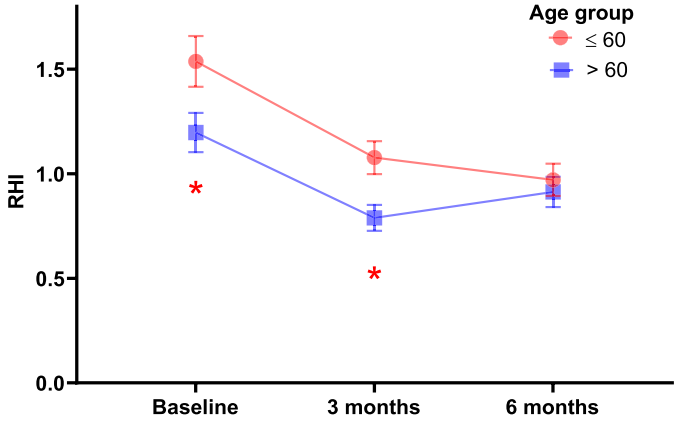

Figure 3. Longitudinal changes in the reactive hyperemia index (RHI) by age group: ≤ 60 vs > 60 years of age. Data are presented as estimated marginal means and standard errors. Statistically significant differences in RHI at baseline and 3 months at the $P < 0.05$ level are marked by **asterisks**.

Discussion

We describe worsened vascular function in patients after HM3 implantation during the 6- month follow-up. The observations do not support our primary hypothesis about the potentially favourable effect of the artificial pulsatility of the HM3 on vascular function measured as the RHI. RHI significantly decreased after HM3 implantation and remained low in the sixth month. RHI was below physiological values at baseline, reflecting the endothelial dysfunction associated with advanced heart failure.[7] Increased arterial stiffness (decreased AI) in the HM3 group after implantation further supports presence of unfavourable vascular changes. Previous reports indicated that continuous-flow LVAS implantation could impair vascular function.[3,20-23] An association between impaired vascular function and occurrence of cardiovascular adverse events was also observed.[3,22] Mechanistic explanations come from experimental studies demonstrating that endothelial function is dependent on mechanical stimulation.[24-26] In this context, our results do not support the hypothesis that the artificial pulsatility produced by the HM3 attenuates unfavourable vascular processes. Instead, these findings confirm that the favourable clinical outcomes of HM3 are mediated by original purpose of artificial pulsatility: to avert blood stasis and enable pump washout.

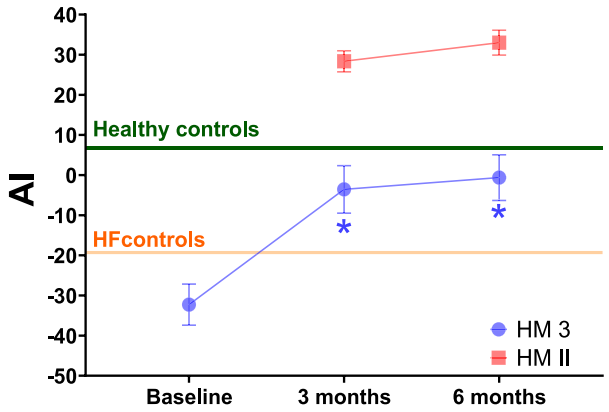

Figure 4. Longitudinal changes in the augmentation index (AI) in HeartMate 3 (HM3) (Abbott, Chicago, IL) group (**blue**). Longitudinal changes in AI in HeartMate II (HM II) (Abbott) reference group between the third and sixth months (**red**). Data are presented as estimated marginal means and standard error. *$P < 0.05$ vs baseline. **Solid orange line**, estimated marginal mean for heart failure (HF) reference group; **solid green line**, estimated marginal mean for healthy reference group. **Dashed lines** represent 95% confidence intervals.

In the HM II reference group, identical trends for RHI and AI were observed, but with higher values of RHI, indicating less severe vascular dysfunction. This finding could be explained by the younger age of HM II recipients (Table 3). As expected, the RHI in HF reference group (measured once) was similar to the baseline values of HM3 group. In the healthy reference group, the RHI was in the physiological range and thus substantially higher than that of any of the other groups. On the other hand, we detected increased arterial stiffness in the HM II reference group compared with the HM3 group. AI was even higher in the healthy reference group than in the HM3 group or the HF reference group, indicating higher arterial stiffness. We suppose that these results were modified by technical limits reflecting the combined effect of abnormal pulsatility and abnormal cardiac output, the latter supported by AI increase in the HM3 group early after implantation. Indirect evidence for potential modification of measurements of arterial stiffness comes from a study of cardiac patients and healthy subjects, in which the AI was determined by chronotropic rather than inotropic effects, thus by factors other than wave reflection.[27]

Therefore, interpretation of the AI data needs to be made with caution. Nevertheless, in our study, the baseline values of the HM3 group were similar to that of the HF reference group. Increase of arterial stiffness in the HM3 group during study period reached higher values than that observed in HF reference group. This finding supports the concept, that HM3 pulsatility does not modify the vascular properties favourably.

Further subanalysis showed that the alterations in RHI were negatively affected by age, BMI, and pump flow in the sixth month. These findings may indicate role of these parameters in the progression of peripheral vascular dysfunction after LVAS implantation. Through the course of the study, the RHI values at baseline and in the third month were influenced by the median age of the patients. The differences were not present in the sixth month after implantation, probably caused by the prolonged influence of the low pulsatility, possibly linked to accelerated processes associated with vascular

aging, even in younger patients.[28] A subanalysis of factors related to pulsatility showed that aortic-valve opening with each heartbeat favourably influenced arterial stiffness in the sixth month. This observation may indicate a favourable effect of pulsatility, in general; this is further supported by a study by Patel et al., describing the difference in aortic strain, distensibility, and stiffness between pulsatile and continuous flow LVASs, favouring the LVASs with pulse.[29]

Limitations

Limitations of this single-centre prospective observational study include moderate number of patients and use of EndoPAT 2000 to measure arterial stiffness. The measurement of arterial stiffness using the EndoPAT2000 is currently used mostly for research purposes. Nevertheless, although AI could be altered also by nonvascular factors, making this parameter less reliable for arterial stiffness assessment, especially in LVAS recipients, RHI was a reliable method to measure vascular function in a broad range of subjects in the study. Also, the data from early postoperative period were not collected and analyzed to avoid the effect of complex hemodynamic changes present immediately after implantation.[20] In addition, only the devices from 1 manufacturer were analyzed, as the devices form other manufacturers (eg, Medtronic HeartWare HVAD) are rarely implanted at our site.

We are well aware of some limitations of our study discussed here. Nevertheless, to the best of our knowledge, only sparse data are available from the longitudinal assessment of endothelial function in LVAS patients. This is the first study in a relatively large population of LVAS recipients that analyzed effects of artificial pulsatility of HM3 on vascular properties. Therefore, this study provides additional evidence that suppressed pulsatility exerts unfavourable effects on peripheral vascular function. Further research focused on a pulse amplitude augmentation and synchronization with native cardiac cycle, and its potential implementation in future devices could provide positive effect on vascular function and thus positively influence the clinical outcomes.

Conclusions

Despite the restoration of central hemodynamics, peripheral vascular function was further compromised 6 months after HM3 implantation. The feature of artificial pulsatility, which enhances blood flow washout, may contribute to a significant improvement in clinical outcomes in HM3 recipients than in other clinically available LVASs.[14] Nonetheless, our observations suggest that the intensity of the artificial pulse wave may not represent a physiologically relevant stimulus that averts endothelial dysregulation in continuous-flow LVAD circulation.

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Disclosures

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