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Further Peripheral Vascular Dysfunction in Heart Failure Patients With a Continuous-Flow Left Ventricular Assist Device

The Role of Pulsatility

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ABSTRACT

OBJECTIVES Using flow-mediated vasodilation (FMD) and reactive hyperemia (RH), this study aimed to provide greater insight into left ventricular assist device (LVAD)–induced changes in peripheral vascular function.

BACKGROUND Peripheral endothelial function is recognized to be impaired in patients with heart failure with reduced ejection fraction (HFrEF), but the peripheral vascular effects of continuous-flow LVAD implantation, now used as either a bridge to transplantation or as a destination therapy, remain unclear.

METHODS Sixty-eight subjects (13 New York Heart Association [NYHA] functional class II HFrEF patients, 19 NYHA functional class III/IV HFrEF patients, 20 NYHA functional class III/IV HFrEF patients post-LVAD implantation, and 16 healthy age-matched control subjects) underwent FMD and RH testing in the brachial artery with blood flow velocity, artery diameters, and pulsatility index (PI) assessed by ultrasound Doppler.

RESULTS PI was significantly lower in the LVAD group (2.0 ± 0.4) compared with both the HFrEF II (8.6 ± 0.8) and HFrEF III/IV (8.1 ± 0.9) patients, who, in turn, had significantly lower PI than the control subjects (12.8 ± 0.9). Likewise, LVAD %FMD/shear rate (0.09 ± 0.01 $\%\Delta/s^{-1}$) was significantly reduced compared with all other groups (control subjects, 0.24 ± 0.03; HFrEF II, 0.17 ± 0.02; and HFrEF III/IV, 0.13 ± 0.02 $\%\Delta/s^{-1}$), and %FMD/shear rate significantly correlated with PI ($r = 0.45$). RH was unremarkable across groups.

CONCLUSIONS Although central hemodynamics are improved in patients with HFrEF by a continuous-flow LVAD, peripheral vascular function is further compromised, which is likely due, at least in part, to the reduction in pulsatility that is a characteristic of such a mechanical assist device. (J Am Coll Cardiol HF 2015;3:703–11)

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ABBREVIATIONS AND ACRONYMS

FMD = flow-mediated vasodilation

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HTx = heart transplantation

LVAD = left ventricular assist device

NYHA = New York Heart Association

PI = pulsatility index

RH = reactive hyperemia

V_{max} = maximal blood velocity

V_{mean} = mean blood velocity

V_{min} = minimal blood velocity

Impaired peripheral vascular function has long been associated with various cardiovascular diseases, including hypertension (1) and coronary artery disease (2), and is well-known to accompany heart failure (HF) (3–5). Of significance, peripheral vascular dysfunction may also precede the development of these conditions (6–8). Indeed, evidence of peripheral vascular dysfunction is clinically relevant, as patients that are at risk for cardiovascular events who also exhibit a low flow-mediated dilation (FMD) have increased cardiac morbidity and mortality compared with the at-risk patients with normal or mildly abnormal FMD (9). Additionally, an attenuated FMD is also an independent predictor of hospitalization, left ventricular assist device (LVAD) implantation, heart transplantation (HTx), and ultimately death (10–12). Reactive hyperemia (RH), another research tool used to quantify changes in peripheral vascular function (13,14), has also been linked to reduced microvascular function in HF (15,16).

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Over the last several decades, advances in mechanical circulatory support devices have drastically improved the clinical management of HF. Not only are LVADs a standard bridge-to-transplant therapy, but they have also become a destination therapy for individuals that may be ineligible for HTx (17,18). Although the second-generation continuous-flow LVADs have many advantages over the first-generation pulsatile devices, the current LVADs produce continuous blood flow with variable and often diminished pulsatility (19). Given that the nature and magnitude of shear stress is influenced by pulsatility and, generally, plays a positive role in the structure and function of blood vessels over time (20,21), the anticipated reduction in pulsatility in patients receiving a continuous-flow LVAD may negatively affect peripheral vascular function. However, the long-term effects of LVAD-induced continuous (i.e., nonpulsatile) blood flow on peripheral vascular function remain largely unexplored and may be potentially important in terms of end-organ health and the long-term functional capacity of these patients.

Accordingly, by using ultrasound Doppler to assess FMD, RH, and pulsatility index (PI), this study sought to determine peripheral vascular function in patients with New York Heart Association (NYHA) functional class II and III/IV heart failure with reduced ejection fraction (HFrEF), patients with NYHA functional class III/IV HFrEF following continuous-flow LVAD implantation, and healthy age-matched control subjects. We hypothesized that: 1) PI would be lowest in the NYHA functional class III/IV HFrEF patients with an LVAD and would progressively improve across the HFrEF patients to the healthy control subjects; 2) peripheral vascular function, as assessed by FMD and RH, would be lowest in the NYHA functional class III/IV HFrEF patients with an LVAD and would progressively improve across the HFrEF patients to the healthy control subjects; and, therefore, 3) there would be a significant positive relationship between peripheral vascular function and PI. A better understanding of the peripheral vascular consequences of LVAD implantation and the role of pulsatility, afforded by this study, may help guide the clinical care and rehabilitation of these patients as well as guide LVAD design.

METHODS

SUBJECTS. A total of 68 subjects (13 NYHA functional class II HFrEF patients, 19 NYHA functional class III/IV HFrEF patients, 20 NYHA functional class III/IV HFrEF patients post-LVAD implantation, and 16 healthy age-matched control subjects) were recruited from the HF clinics at the University of Utah and the Salt Lake City VA Medical Center and by word of mouth (for the control subjects). The protocol was approved by the Institutional Review Board of the University of Utah and the Salt Lake City Veterans Affairs Medical Center, and written informed consent was obtained from all subjects. The healthy control subjects were normotensive (blood pressure <140/90 mm Hg), not taking any prescription medication, and free of overt cardiovascular disease, as determined by health history. Exclusion criteria for the healthy control subjects included a diagnosis of cardiovascular disease, diabetes mellitus, hypercholesterolemia, and hypertension. Inclusion criteria for the patients with HFrEF included NYHA functional classification and an ejection fraction <35%. All patients were considered to be on optimal medical therapy by their physicians, and these medications were not withheld at the time of the study. All studies were performed in a temperature controlled environment (~23°C). Subjects reported to the laboratory in a fasted state and without caffeine, alcohol, or exercise for 12 h.

FMD AND RH MEASUREMENTS. Details of the FMD procedure have been described previously (22) and were performed in accordance with current recommendations (23). Briefly, a blood pressure cuff was placed on the right arm distal to both the elbow and the placement of the ultrasound Doppler probe on the brachial artery. The brachial artery was insonated approximately midway between the antecubital and