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Improved diabetic control in advanced heart failure patients treated with left ventricular assist devices

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Aims Left ventricular assist devices (LVADs) are increasingly used as therapeutic options for patients with advanced congestive heart failure (CHF), many of whom suffer from diabetes mellitus (DM). The aim of this study was to evaluate the effect of restoration of normal cardiac output using LVAD support on diabetes control in patients with advanced CHF.

Methods and results A retrospective chart review of all clinic patients supported with long-term LVADs between July 2008 and July 2009 at Columbia University Medical Center was performed. Patients with DM diagnosed prior to device implantation were included in this analysis. Clinical and laboratory data within 1 month preceding and 6 months following LVAD implantation were collected. Of 43 LVAD patients followed in our clinic during the study period, 15 had a diagnosis of DM. Thirteen of the 15 patients were male, mean age was 63 $\pm$ 11 years, and the pre-LVAD left ventricular ejection fraction (LVEF) was 16.5 $\pm$ 5.7%. Fasting glucose levels, HbA1c, and daily insulin requirement within 1 month before and an average of 4.0 $\pm$ 2.3 months after LVAD placement were 157.7 $\pm$ 50.6 vs. 104.1 $\pm$ 21.4 mg/dL, 7.7 $\pm$ 0.9 vs. 6.0 $\pm$ 0.8.%, and 53.3 $\pm$ 51.7 vs. 24.2 $\pm$ 27.2 IU, respectively ($P < 0.05$ for all comparisons). Six of the 15 patients were completely free of antidiabetic medications and had blood glucose $<$126 mg/dL as well as HbA1c $<$6% after LVAD. Body mass index (BMI) was slightly increased after LVAD (28.7 $\pm$ 5.3 vs. 30.2 $\pm$ 4.1 kg/m^2, *P* NS).

Conclusion Restoration of normal cardiac output after LVAD implantation improves diabetic control in patients with advanced CHF. Additional studies are warranted to determine the mechanisms that worsen or possibly induce DM in patients with advanced CHF.

Keywords Heart failure • LVAD • HbA1c • Insulin resistance

Introduction

The prevalence of insulin resistance (IR) manifest clinically as either metabolic syndrome or frank diabetes mellitus (DM) is increasing in the developed world.[1,2] Congestive heart failure (CHF) will eventually affect one in five Americans and is already responsible for the consumption of an extraordinary proportion of health-care resources.[3,4] A relationship between IR and CHF has long been recognized and is classically attributed to the higher prevalence of coronary artery disease and ischaemic cardiomyopathy in patients with DM. However, recent evidence suggests that, conversely, CHF itself may cause IR.[5]

Left ventricular assist devices (LVADs) are increasingly used for the treatment of advanced CHF.[6] Left ventricular assist devices are

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implanted as a bridge to transplantation or for the purpose of destination therapy.[7,8] The resulting restoration of normal cardiac output may improve end-organ function, and may favourably affect metabolic pathways in the myocardium and the periphery.[9] Accordingly, we investigated the effect of LVAD implantation on diabetes control in patients with advanced CHF and DM.

Methods

Patient population

A retrospective chart review of all patients actively followed at the Columbia University Medical Center LVAD clinic between July 2008 and July 2009 was performed. Patients with a diagnosis of DM prior to LVAD implantation were identified. Patients who required rescue LVAD support not for chronic CHF but for acute cardiogenic shock were excluded from our analysis. Diabetes mellitus was defined as follows: (i) patients treated with oral antidiabetic medication; and/or (ii) patients treated with insulin; and/or (iii) patients with a former diagnosis of diabetes on the basis of a fasting glucose level >126 mg/dL in the setting of diabetic symptoms (i.e. polyuria, polyphagia, and polydypsia). Baseline clinical characteristics, medications, and LVAD data were collected from the electronic medical record, medical charts, and operative notes. Daily insulin dosage, fasting blood glucose level, and HbA1c level were recorded within 1 month prior to LVAD implantation and between 1 and 6 months following implantation.

Statistical analysis

Data were collected using Excel Software (2007 Microsoft Corporation). All data were analysed using the Statistical Program of Social Sciences (SPSS, version 17.0, SPSS, Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation and compared using the paired *t*-test. Categorical variables are presented as proportions.

Results

During the study period, 43 patients who had received LVAD support for chronic CHF were followed at the LVAD clinic. Fifteen patients were diagnosed with DM prior to LVAD implantation and included in this analysis. Baseline clinical characteristics and treatment are summarized in *Tables 1* and *2*, respectively. Thirteen patients were male and mean age was 63 ± 11 years. Heart failure aetiology was ischaemic in 8 of the 15 subjects. All patients had advanced NYHA functional class IIIb or class IV prior to implant. Left ventricular ejection fraction (LVEF) averaged 16 ± 6% and left ventricular end-diastolic diameter was 6.8 ± 1.1 cm. Moderate to severe right ventricular failure was present in 12 of the 15 patients on echocardiographic evaluation. Mitral regurgitation was moderate to severe in nine patients (*Table 3*).

Prior to LVAD implantation, all but one patient (93%) received continuous intravenous inotropic support with milrinone (mean dose 0.29 μg/kg/min). All patients were treated with diuretics, 12 (80%) with β-blockers; 6 (40%) with ACE-inhibitors or ARBs, and 8 (53%) with aldosterone blockers. Nine patients (60%) received an LVAD as bridge to transplant, and 6 (40%) as destination therapy. Eleven patients were implanted with a non-pulsatile flow pump (i.e. Heart Mate II). The remaining four received a pulsatile pump (i.e. Heart Mate XVE) (*Table 1*).

Table 1 Baseline characteristics *n* = 15

Age	63.0 ± 11.06
Male sex	13 (86.7%)
Weight (kg)	87.9 ± 16.0
Height (m)	1.75 ± 0.1
BMI (kg/m^2)	28.7 ± 5.3
HF aetiology	
Ischemic cardiomyopathy	8 (53.3%)
Non-ischaemic cardiomyopathy	7 (46.7%)
LVAD	
Bridge to transplant	9 (60.0%)
Destination therapy	6 (40.0%)
LVAD type	
Pulsatile	4 (26.7%)
Non-pulsatile	9 (73.3%)

BMI, body mass index; HF, heart failure; LVAD, left ventricular assist device.

Table 2 Medication used before and after left ventricular assist device implantation

	Pre-implantation	Post-implantation
Milrinone	14 (93.3%)	0
ACE-I	4 (26.7%)	6 (40.0%)
ARB	2 (13.3%)	0 (0%)
β-Blocker	12 (80.0%)	12 (80.0%)
Diuretic	15 (100%)	12 (80.0%)
Aldosterone blocker	8 (53.3%)	5 (33.3%)
CCB	0	5 (33.3%)
Statin	7 (46.7%)	7 (46.7%)
Nitrates	2 (13.3%)	0
Anti arrhythmic	7 (46.7%)	7 (46.7%)

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

All study subjects were diagnosed with DM prior to LVAD implantation. The mean time of DM diagnosis prior to LVAD implantation was 6.0 ± 5.9 years. Four patients had neuropathy, none had retinopathy. Assessment of diabetic nephropathy was limited by the absence of kidney biopsies and by inconsistent documentation of proteinuria. However, renal function significantly improved after implant (1.7 ± 0.5 vs. 1.3 ± 0.3, $P < 0.05$), suggesting that the degree of intrinsic renal disease was only mild.

Three patients received both insulin and an oral antidiabetic agent, seven patients received insulin alone, three an oral antidiabetic agent alone, and two were on dietary control only. Mean HbA1c was 7.7 ± 0.9%, and the mean fasting glucose level was 158 ± 51 mg/dL despite a mean insulin dose of 55 IU/day (*Table 4*). Repeat measurement of these variables 4.0 ± 2.3 months after LVAD implantation revealed significantly improved diabetes control: HbA1c was 6.0 ± 0.9%, and fasting glucose was 104.1 mg/dL (*Figure 1*). These improvements were seen despite a

Table 3 Echocardiographic parameters before and after left ventricular assist device implantation

	Pre-implantation	Post-implantation	*P*-value
LVEF	16.5 ± 5.7	21.6 ± 2.2	0.062
LVEDD	6.8 ± 1.06	5.8 ± 1.1	0.001
LVESD	6.7 ± 1.5	5.0 ± 1.6	0.001
MOD-SEVERE RV dysfunction	11 (73.3%)	12 (83.3%)	0.6
MOD-SEVERE MR	9 (60.0%)	1 (6.7%)	0.001

LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; RV, right ventricular; MR, mitral regurgitation.

Table 4 Metabolic status

	Pre-implantation	Post-implantation	*P*-value
Fasting glucose (mg/dL)	158 ± 51	104 ± 21	<0.001
HbA1c (%)	7.7 ± 0.9	6.0 ± 0.8	<0.001
Number of patients with insulin	10	9	
Average insulin daily dose (IU/day)	55 ± 52	24 ± 27	0.07
Number of patients taking oral anti-glycaemics	6	4	
Weight (kg)	88 ± 16	93 ± 12	0.056
BMI (kg/m^2)	28.7 ± 5.3	30.2 ± 4.1	0.06
Serum creatinine (mg/dL)	1.7 ± 0.5	1.3 ± 0.3	0.034

BMI, body mass index.

substantially lower mean insulin requirement of 24 IU/day (*Table 4*). Six patients (all of whom had been on insulin and/or antidiabetic agents prior to implant) had normal glucose levels as well as HbA1c <6.0, although they were no longer receiving insulin or oral antidiabetic agents. Average BMI had slightly increased at the time of reassessment from 28.7 to 30.2 kg/m^2, although this change did not reach statistical significance. Improvement in diabetes control was similar in patients who received a pulsatile vs. a continuous flow LVAD.

Prior to LVAD implantation all patients were in NYHA class IIIb-IV. Three and six months after device implantation all patients were assessed as NYHA class II. Prior to device implantation only one patient, who was not receiving milrinone, completed the 6-min walk test. Six months after device implantation the mean walking distance was 331.8 ± 61.5 m.

Although there was no significant change in LVEF after device implantation, the ventricle was more decompressed and there was less mitral regurgitation (*Table 3*).

Pre-implant (14 of 15) patients were receiving intravenous milrinone, but none of the patients was on milrinone at follow-up. There was no significant difference in other heart failure medications (*Table 2*).

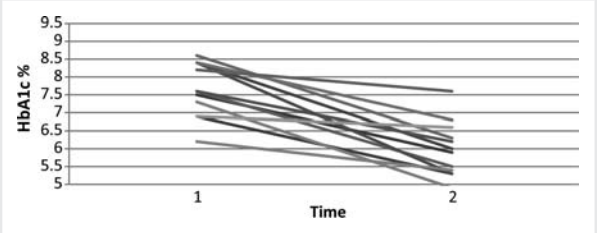

Figure 1 HbA1c before and after left ventricular assist device implantation.

Discussion

We examined the effect of LVAD implantation on diabetes control by measuring fasting glucose, HbA1c, and insulin requirements in 15 patients with DM. Left ventricular assist device implantation resulted in a significant reduction in insulin requirements and HbA1c, whereas body weight concurrently increased. The present data provide the first direct evidence that restoration of normal cardiac output with an LVAD improves diabetic control in patients with advanced CHF.

The association of CHF and DM is well established.[10] Prior studies have not only demonstrated that IR may lead to CHF,[10–12] but also that CHF itself can cause IR and that the severity of IR has an adverse prognostic impact.[13] Nikolaidis *et al.*[5] described the progressive development of IR as a function of disease severity in a dog model of systolic CHF. In their study, heart failure was induced in healthy dogs and led to the development of IR. Swan *et al.*[14] demonstrated that IR, characterized by both fasting and stimulated hyperinsulinaemia, is frequent in CHF patients whether or not concomitant DM is present. More recently,

Azadjai *et al.*[15] showed that IR is highly prevalent among non-diabetic CHF patients and is associated with decreased exercise capacity. Conceptually in line with these experiments, we demonstrate for the first time that improvement of CHF after LVAD implantation is associated with an improvement in diabetes control. It is of particular note that a subset of patients classified as diabetic prior to implant and with suboptimal diabetic control despite pharmacotherapy had normal glucose and HbA1c values only a few months after implant and *without* pharmacotherapy. This finding, if validated in a larger cohort and accounting for dietary intake, would strongly underscore the existence of a unique diabetes phenotype induced by cardiovascular decompensation and likely completely reversible. Which mechanisms are responsible for this reversal is currently unclear, although it is likely that improved cardiac output resulting in increased blood flow to peripheral and cardiac muscle[16] as well as improved physical activity plays a significant role.

Physical activity typically improves after LVAD implantation.[6,7] The resultant reduction in body weight may, in turn, favourably impact IR. In our cohort, although there was a clear improvement in physical activity, there was no reduction in patient's weights between baseline and follow-up. Rather, there was a consistent trend towards weight gain. Thus, the improved IR in our patients cannot be ascribed to weight loss due to increased physical activity. Prospective studies that measure physical activity and, more importantly, body composition to assess changes in fat vs. muscle mass after LVAD implantation are needed to mechanistically address the individual contributions of these factors to the observed changes in IR.

While our retrospective data clearly provide proof of concept for decreased IR and possibly its reversal in CHF, it does not provide insights into other candidate mechanisms likely contributing to our observation, such as changes in neurohormonal activation and inflammation.

Neurohormonal activation

Peripheral vasoconstriction resulting in decreased tissue perfusion is a hallmark of the syndrome CHF and is mediated by increased levels of circulating neurohormones, such as noradrenaline, endothelin, and angiotensin II. Several studies have demonstrated that neurohormonal suppression with ACE-Is or ARBs reduces the risk of developing DM by more than 25% in CHF patients.[17] Although ACE-I, ARB, and β-blocker use was similar before and after LVAD implantation and plasma neurohormones were not measured, it is conceivable that restoration of normal cardiac output after LVAD implantation had a favourable impact on neurohormonal activity in our patient cohort and thereby improved IR. The same may hold true for other mechanical interventions that increase cardiac output and reduce neurohormonal activation, such as cardiac resynchronization therapy.[18]

Inflammation

Symptomatic CHF is associated with an elevation of pro-oxidant and pro-inflammatory circulating cytokines, such as tumour necrosis factor-α (TNF-α), interleukin-1β, and interleukin-6 (IL-6).[19,20] Circulating levels of IL-6 have been correlated with adiposity and type 2 DM[21–23] as well as with the induction of IR in hepatic cells.[24] Tumour necrosis factor-α, a major marker of inflammation in CHF can also cause IR.[25,26] Unfortunately, plasma cytokines were not measured before or after LVAD implantation in our study.

Lastly, although we consider mechanically induced reversal of the CHF syndrome with an LVAD the principal intervention causing the observed improvement of diabetic control, it is of note that 14 of our 15 patients were receiving intravenous milrinone at baseline, but not at follow-up. Milrinone has been shown to increase IR in various animal models.[27,28] Although there is no data in human CHF, it remains conceivable that milrinone may either induce IR through a direct pharmacological effect or alternatively may improve IR through indirect effects, such as an improvement in tissue perfusion and congestion. Either way, the discontinuation of milrinone in all but one patient receiving LVADs in this study must be taken into consideration when interpreting our data.

In conclusion, restoring cardiac output and decreasing CHF severity with LVAD treatment is associated with a marked improvement of glucose control in diabetic patients with advanced CHF. Little attention has been paid to date to the metabolic effects of LVAD implantation, although they likely play an important role in at least two major issues of LVAD therapy: (i) Infections, as they are more frequent in patients with poorly controlled DM[29] and (ii) LV recovery, as it may be hampered by abnormal fuel metabolism in the setting of IR. Our study is clearly limited by its retrospective nature, the absence of serial measures of neurohormonal or inflammatory activation, as well as by the lack of a control group. Nevertheless, the described improvements in diabetes control occurred in each and every one of the 15 patients, clearly suggesting that reversal of CHF by restoring cardiac output with an LVAD may be sufficient to antagonize CHF-induced IR. Prospective mechanistic studies that investigate the cardiac and systemic effects of LVAD support on glucose metabolism and on the development or progression of diabetic macro- and microvascular complications in CHF patients are needed. Such studies may significantly improve our understanding not only of LVAD therapy, but also of CHF and DM in general.

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Conflict of interest: none declared.

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