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Neurohormonal Regulation and Improvement in Blood Glucose Control: Reduction of Insulin Requirement in Patients with a Nonpulsatile Ventricular Assist Device

Michael M. Koerner, MD, PhD, Aly El-Banayosy, MD, Kimber Eleuteri ACNP-BC, Christina Kline, RN, Edward Stephenson III, MD, Walter Pae, MD, Ali Ghodsizad, MD, PhD, FETCS

Department of Medicine and Surgery, Heart and Vascular Institute, Penn State Milton S. Hershey Medical Center, Penn State College of Medicine, Hershey, PA, USA

ABSTRACT

Background: Heart failure is associated with prolonged stress and inflammation characterized by elevated levels of cortisol and circulating catecholamines. Persistent sympathetic stimulation secondary to the stress of heart failure causes an induced insulin resistance, which creates a need for higher doses of insulin to adequately manage hyperglycemia in this patient population. We hypothesized that cortisol and catecholamine levels would be elevated in end-stage heart failure patients, however, would be reduced after the implantation of a left ventricular assist device (LVAD). Insulin requirements would therefore be reduced post LVAD implant and control of diabetes improved as compared with pre-implant.

Methods: Pre- and postoperative cortisol, catecholamine, glycated hemoglobin, and blood glucose levels were evaluated retrospectively in 99 LVAD patients at a single center from January 2007 through November 2011. Serum was collected before LVAD implantation and monthly after implantation for 12 months consecutively. Results were evaluated and compared to insulin requirements, if any, before and after implant. Plasma levels were measured by ELISA.

Results: There were a total of 99 patients (81 men and 18 women). Two patients were implanted twice due to pump dysfunction. Mean age was 59 years, ± 10, with a median of 63 years. Of those patients, 64 had ischemic cardiomyopathy and 35 had dilated cardiomyopathy. The total patient years of LVAD support were 92.5 years. All patients received a continuous flow left ventricular assist device. Type II diabetes mellitus was diagnosed in 28 patients. Of those patients, 24 required daily insulin with an average dose of 45 units/day. Average preoperative glycated hemoglobin (HbA1c) levels were 6.8% with fasting blood glucose measurements of 136 mg/dL. Mean cortisol levels were measured at 24.3 µg/dL before LVAD implantation, with mean plasma catecholamine levels of 1824 µg/mL. Post operatively, average HbA1c levels were 5.38% with fasting blood glucose measurements of 122 mg/dL. Mean cortisol levels were measured at 10.9 µg/dL with average plasma catecholamine levels were 815 µg/mL. There was a significant decrease in both cortisol levels post LVAD implant ($P = 0.012$) as well as catecholamine levels ($P = 0.044$). The average insulin requirements post LVAD implant were significantly reduced to 13 units/day ($P = 0.001$). Six patients no longer required any insulin after implant.

Conclusion: Implantation of nonpulsatile LVADs has become a viable option for the treatment of end-stage heart failure, helping to improve patient quality of life by decreasing clinical symptoms associated with poor end-organ perfusion. Frequently, diabetes is a comorbid condition that exists among heart failure patients and with the reduction of the systemic inflammatory and stress response produced by the support of a nonpulsatile LVAD, many patients may benefit from a reduction in their blood glucose levels, as well as insulin requirements.

INTRODUCTION

Congestive heart failure (CHF) is the global leading cause of morbidity and mortality, accounting for one in eight deaths in the US and more than 500,000 people newly diagnosed every year, despite the advancement in both pharmacologic and mechanical therapies [Jessup 2011; Jessup 2009]. Patients suffering from CHF have seen advancements in conventional therapy, ranging from pharmacologic improvements to mechanical circulatory support (MCS) in the form of left ventricular assist device (LVAD) therapy. LVADs have become the standard of care for advanced heart failure patients and are providing an improved quality of life for both patients awaiting heart transplantation as well as those considered to be destination therapy patients [Jessup 2011; Slaughter 2011; Slaughter 2009]. Patients maximized on conventional medical therapy constitute a population of patients who may benefit from long-term MCS, many times offering a much better alternative than palliative care end-of-life management. A healthier quality of life has afforded patients improved functional status, as well as improvement of other comorbidities, including diabetes mellitus (DM).

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Correspondence: Michael M. Koerner, MD, PhD, Department of Medicine, Division Cardiology, Heart and Vascular Institute, Penn State Milton S. Hershey Medical Center, Penn State College of Medicine, 500 University Drive Mail Code H047, Hershey, PA 17033; +1-717-531-7954; fax: +1-717-531-0499 (e-mail: mkoerner@hmc.psu.edu).

Table

Values	Pre-LVAD Implant	Post-LVAD Implant	*P* Value
Glucose	136 mg/dL	122 mg/dL	
Cortisol	24.3 µg/dL	10.9 µg/dL	0.012
Noradrenalin	1824 µg/mL	815 µg/mL	0.044
HbA1c	6.8%	5.38%	
Insulin Dosage	45 units/day	13 units/day	0.001

Much like CHF, DM is prevalent worldwide, impacting significant numbers, and is predicted to escalate to 50% by the year 2025 [Solomon 2007; Fonarow 2007]. It is estimated that one-third of patients suffering from heart failure also have diabetes, with the incidence predicted to reach epidemic proportions over the next decade [Chaoyang 2007; Eser 2011; Reiss 2008]. Moreover, diabetes is a major independent risk factor for mortality of hospitalized heart failure patients, especially in women [Topkara 2005]. The deteriorating progression of CHF in patients with diabetes is likely to be multifactorial, not always occurring from structural insults, such as myocardial infarction, coronary artery disease, valvular disease, or hypertension. Other physiologic states may lead to the development of heart failure, specifically, insulin resistance, either secondarily from diabetes mellitus or pre-diabetes, particularly, metabolic syndrome [Chaoyang 2007; Gülmisal 2007]. Insulin resistance and diabetes mellitus are key contributors in the development and progression of CHF, even in the absence of any other etiologies or risk factors [Eser 2011; Fantoni 2008; Wisniacki 2005; Paolisso 1991]. Both the prevalence and severity of insulin resistance are directly related to the severity of CHF, and greatly impact the mortality in this sizeable population of patients [Doehner 2008]. Consequently, we evaluated the effect of nonpulsatile LVAD support for diabetic patients on their insulin requirements, as well as, neurohormones.

METHODS

A retrospective chart review was performed looking at pre- and postoperative cortisol, catecholamine, glycated hemoglobin, and blood glucose levels in all patients of a single center who received a nonpulsatile LVAD between January 2007 and November 2011. Serum was collected before LVAD implantation and monthly after implantation for 12 months consecutively. Results were evaluated and compared to insulin requirements, if any, before and after LVAD implant. Twenty-four out of 28 patients with diabetes mellitus were identified as requiring insulin on a daily basis. All patients were diagnosed with diabetes mellitus prior to LVAD implant. Data was obtained from the patient's medical records and included pre-, peri-, and post-operative notes, clinic records, history and physicals, hospitalizations, medication records, and laboratory results.

RESULTS

From January 2007 through November 2011, 99 patients were implanted with a nonpulsatile LVAD at a single center (two patients were implanted twice due to pump failure). Of those, 81 were men and 18 women, with a mean age of 59 years, ± 10, and a median of 63. The etiology of CHF was ischemic cardiomyopathy in 64 patients. Twenty-eight patients were identified as also having diabetes mellitus, and of that population, 24 required insulin with an average dose of 45 units/day. Average preoperative glycated hemoglobin (HbA1c) levels were 6.8% with fasting blood glucose measurements of 136 mg/dL. Post operatively, average HbA1c levels were measured at 5.38% with fasting blood glucose measurements of 122 mg/dL. Average insulin requirements post LVAD implant were significantly reduced from a documented 45 units/day to 13 units/day ($P = 0.001$). Six out of 24 insulin dependent patients no longer required any insulin after LVAD implant. Mean cortisol levels were measured at 24.3 µg/dL before LVAD implantation, with mean plasma catecholamine levels (norepinephrine) of 1824 µg/mL. Post nonpulsatile LVAD implantation mean cortisol levels were measured at 10.9 µg/dL with average plasma catecholamine levels 815 µg/mL. There was a significant decrease in both cortisol levels post LVAD implant ($P = 0.012$) as well as catecholamine levels ($P = 0.044$) compared to the results pre-LVAD implantation.

DISCUSSION

CHF is defined as either a systolic or diastolic dysfunction or a combination of both, and exhibits a myriad of clinical symptoms, including fluid retention, pulmonary congestion, peripheral edema, end-organ dysfunction, and failure secondary to poor cardiac output. More than 23 million people worldwide are diagnosed with CHF, which accounts for over one in eight deaths in the US alone [Pocock 2006]. Readmission rates for exacerbation of CHF symptoms are more than 50% within six months of discharge from initial admission, and the mortality rates at one year are surpassing 45% [Solomon 2007; Fonarow 2007]. CHF is a complex syndrome often with no solitary causative factor implicated. The ineffective pumping process of the heart cannot keep up with

the metabolic demands of the periphery to sustain an aerobic metabolism. Studies have identified persistent activation of the neuroendocrine system, insulin resistance, and oxidative stress as a result of the failing heart [Chaoyang 2007; Gülmisal 2007]. Oxidative stress is defined as an excess production of reactive oxygen species (ROS) in comparison to the amounts and levels of antioxidants and has been shown to cause cardiac cell damage. Subsequently, this process triggers deleterious effects on cardiac structure and function ultimately causing remodeling and failure [Hiroyuki 2011]. DNA strand fracturing secondary to ROS also causes the initiation of the activation of inflammatory mediators. Inflammatory markers such as C-reactive protein (CRP), Interleukin 6 (IL-6), and tumor necrosis factor (TNF) have been shown to be independently predictive of mortality in patients with end-stage heart failure, despite ejection fraction [Wisniacki 2005; Funder 2005]. This deteriorating cascade, further worsened by the secretion of neurohormones, attempts to compensate in order to maintain adequate perfusion to end organs and maintain arterial blood pressure. Long-term consequences of these mechanisms cause worsening heart failure due to ventricular remodeling, impairment in cardiac contraction, poor end-organ perfusion, and ultimately end-stage heart failure and cachexia [Doehner 2008; Hall 2011]. It is apparent that oxidative stress creates an abundance of harmful and damaging consequences. Hyperglycemia occurs as a consequence of oxidative stress, capable of causing a state of hyperinsulinemia leading to chronic sympathetic activation and insulin resistance (IR) [Chaoyang 2007; Wisniacki 2005; Tsutsui 2011]. IR and hyperinsulinemia often occur long before the diagnosis of diabetes mellitus is confirmed and has been found to be present in those exhibiting a metabolic syndrome [Chaoyang 2007; Parsonage 2002; Butler 2005]. Matthews et al described a reliable calculation of IR using the homeostasis model assessment (HOMA) equation [Aguilar 2008], as seen below:

$$HOMA = \frac{glucose(mmol/l) \times insulin\ (\mu U/ml)}{22.5}$$

DM directly impacts the pliability of the left ventricle, rendering it stiff and hypertrophied. This process leads to diastolic dysfunction, which ultimately contributes to the development of cardiomyopathy and CHF [Funder 2005]. Insulin, as well as other oral antihyperglycemics, is often used to control Type 2 Diabetes and is a necessity in the treatment of Type 1 Diabetes. Although helping to decrease blood glucose levels, insulin exerts a strong anabolic effect, and impaired insulin sensitivity or IR may be a fundamental reason for the anabolic/catabolic imbalance in CHF, leading to tissue wasting, and inevitably, cardiac cachexia [Doehner 2008; Zain 2012; Matthews 1985]. Hyperglycemia triggers various maladaptive responses, which in turn, potentiate the development of CHF. Attempts have been made to correlate IR with CHF, postulating that insulin acts as a growth factor in the myocardium, causing enlargement of the myocardium, thus creating an ineffective pump providing poor cardiac output and perfusion [Tsutsui 2011]. Poor glycemic control is indicated by elevated glycated hemoglobin levels or HbA1c concentrations. It has been demonstrated that there is a direct correlation between HbA1c and elevated left ventricular end diastolic pressure, which is associated with diastolic dysfunction [Butler 2005]. In fact, Stahrenberg et al found that a 1% rise in HbA1c is linked to an increased risk of CHF between 8% and 32% [Chaoyang 2007; Butler 2005; Stahrenberg 2010].

Sustained hyperglycemia exerts detrimental effects on the myocardium, causing a number of unfavorable consequences, including impaired calcium homeostasis, mitochondrial dysfunction, altered substrate metabolism, increased oxidative stress, and activation of the renin-angiotensin aldosterone (RAAS) system [Hall 2011; Butler 2005; Andraws 2007]. Stimulation of RAAS can lead to myocyte damage, fibrosis, and apoptosis. Initially, intensified sympathetic activity in heart failure is beneficial. It increases cardiac output and redistributes blood flow from the splanchnic area to the heart and skeletal muscles. Renal vasoconstriction leads to salt and water retention, which initially helps to improve perfusion of the vital organs. However, long-term vasoconstriction becomes detrimental and commences the downward spiral of heart failure symptoms. Aldosterone levels, when elevated, prove to be detrimental in the progression of CHF and cardiovascular inflammatory response causing endothelial dysfunction, elevated blood pressure, and arrhythmias. Systemic inflammation secondary to sympathetic stimulation also creates elevated levels of glucocorticoids, primarily cortisol. Long term, chronic exposure to elevated levels of cortisol has been noted in patients with Cushing's syndrome, causing left ventricular hypertrophy and dilated cardiomyopathy [Packer 1992; Yamaji 2009]. Much like the Cushing's syndrome patient, end-stage CHF patients also exhibit elevated levels of cortisol with chronic elevations ultimately leading to cardiac deterioration and demise [Slaughter 2009].

Persistent sympathetic stimulation is implicated in the worsening of myocardial injury and CHF. It is characterized by elevated levels of noradrenaline, vasopressin, endothelin, epinephrine, angiotensin II, atrial natriuretic peptide (ANP) levels, and plasma renin activity (PRA). PRA typically has been used as a measure of RAAS activity because angiotensin II is difficult to measure. CHF consensus therapy targeted at reducing neurohormonal activation such as beta-blockers, angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, nitrates, and aldosterone antagonists has greatly improved the prognosis of patients with CHF in both the diabetic and non-diabetic population [Eser 2011; Uriel 2011]. Neurohormonal suppression helps to reduce the risk of DM in CHF patients by up to 25% [Ingelsson 2005]. Other strategies, such as cardiac resynchronization therapy (CRT) have been shown to impede the harmful influences that are caused by chronic sympathetic stimulation [Fantoni 2008]. Fantoni et al found that the application of CRT on patients with CHF Class III or IV NYHA was successful at reversing some of the detrimental effects of CHF, particularly LV remodeling, sympathetic stimulation, and worsening of overall

functional capacity [Fantoni 2008]. Although it is apparent that neurohormonal suppression with the use of pharmacologic agents has been successful in the treatment of CHF patients both with and without DM, there have been few studies examining the physiologic impact of nonpulsatile LVADs on the neuroendocrine system [James 1995].

Therapy with nonpulsatile LVADs has become the standard of care for patients with end-stage CHF, NYHA Class IIIb and IV. Many of these patients are above the age of 70, thus necessitating the need for long-term support, since most septuagenarians still are considered not to be candidates for orthotopic heart transplantation [Slaughter 2010]. As the technology has improved tremendously since the initial introduction of the LVAD in the 1960s, favorable results have been shown in long-term survival for patients with end-stage CHF. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) was developed as a response to the mandate set forward by the Centers for Medicare & Medicaid Services. This national database is a collaboration between the U.S. Food and Drug Administration, Centers for Medicare & Medicaid Services, and National Heart, Lung, and Blood Institute. Data that is collected on all patients with FDA-approved mechanical circulatory support (MCS) systems is entered into the registry and can then be collated and reviewed to help improve both the technology, as well as overall patient management. As knowledge expands and technology progresses, patients have been shown to live longer on nonpulsatile LVAD support. In 2009, the INTERMACS data showed that the actual survival rates were 74% at one year and 55% at two years [Slaughter 2009]. With the introduction of third generation, nonpulsatile LVAD devices, one can expect to see even better survival rates in the upcoming years. LVAD therapy is proving to be a viable option for patients awaiting a cardiac transplant, those who are living out their time with LVAD support, and those having the potential to recover. The benefits of MCS also will be recognized in the diabetic patient population. CHF patients with concurrent hyperglycemia and IR now can hope to have their DM more controllable, demonstrated by a reduction in their insulin requirements.

Although the overall improvement in hemodynamic status in patients supported with an LVAD is reflected by improved LV unloading, cardiac output and end-organ perfusion [Slaughter 2010], the connection between CHF, inflammatory markers, and IR has not yet been fully explored in this growing patient population. It is common for end-stage CHF patients to have varying degrees of organ dysfunction, and LVAD therapy is directed at those whom it may show improvement, specifically, the mild- to moderate-organ dysfunction subgroup [Fang 2004]. Studies have shown that there is significant improvement in end-organ function in patients supported with LVAD therapy, whether it is in the form of bridge to transplantation (BTT) or destination therapy (DT) [Uriel 2011; Slaughter 2010; Burnett 1993]. We hypothesize that the improvement in hemodynamic status and reverse remodeling in the LV after LVAD implantation causes a reduction in the amount of overall stress, thus decreasing sympathetic stimulation and inflammatory response. In turn, this may contribute to the normalization of neurohormones, cytokines, and blood glucose levels to near-normal values. As a result of this process, IR also improves, allowing patients to use a lower amount of insulin to control their DM.

Study Limitations

Several limitations should be noted when reviewing the results of this study. First, this was a retrospective chart analysis performed at a single center without a control group. A larger, prospective study is warranted to confirm the results of overall improvement in IR and neuroendocrine activity in patients supported with an LVAD. Second, most CHF patients are on some type of pharmacological agent to block neurohormonal activation, and this should be taken into account when looking at results, specifically blood glucose levels and noradrenaline levels. Cortisol levels in general are quite variable and in order to have a more accurate compilation of these levels, they should be drawn at the same time during the day, specifically, in the morning after wakening, since levels tend to fluctuate due to circadian rhythm. Third, we did not study other neurohormone levels, such as epinephrine, angiotensin II, endothelin, vasopressin, insulin-like growth hormone, free testosterone, PRA, and ANP. This may be beneficial when forming a global hypothesis that neuroendocrine activity in CHF patients improves with nonpulsatile LVAD support. Follow-up studies would be more robust with the inclusion of measurements of inflammatory markers, TNFά, IL-6, and CRP. Fourth, interpretation of IR in our study was based on a reduction of blood glucose levels and insulin requirements. In future studies, it would be beneficial to examine the degree of insulin resistance by using the homeostasis model assessment (HOMA) to measure and calculate IR. Lastly, we evaluated in our analysis insulin doses pre- and post-LVAD implantation in diabetic patients, however, neglected to look at patients taking oral antihyperglycemic medications. We could only assume that the requirement of oral medications would also be decreased, but should confirm this in future studies.

CONCLUSION

CHF has been described as an insulin-resistant state associated with significant risk for the future development of diabetes. It is common for these two pathophysiological conditions to coexist, therefore it is crucial for the clinician to recognize the association between the two when treating independently or concurrently. This retrospective analysis demonstrates that patients supported with a nonpulsatile LVAD for end-stage CHF show significant improvement in diabetic control and insulin requirements. This improvement of IR is also accompanied by the overall improvement in cortisol and noradrenaline levels, demonstrating that LVAD therapy improves heart function, lessens the degree of CHF, and ultimately diminishes the negative impact of systemic inflammatory response and neuroendocrine activity.

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