Endocrine function is not impaired in patients with a continuous MicroMed–DeBakey axial flow pump

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Objectives: Pulsatile blood flow has been regarded to be of importance for the regulation of endocrine organs. A new generation of continuous flow mechanical blood pumps is now available for clinical application. Patients with implanted MicroMed-DeBakey axial pumps show nonphysiologic low-pulsatile blood flow profiles, and therefore it appeared to be of interest to evaluate their possible effect on the endocrine system.

Methods: Eight male patients and 1 female patients (mean age, 51 ± 10 years) with end-stage left-sided heart failure were implanted with a MicroMed-DeBakey axial pump. After a mean period of 67 ± 19 days, basal pituitary hormone concentrations and their responses to a bolus injection of hypothalamic releasing hormones were tested. In addition, thyroid hormones, testosterone, and plasma and urinary catecholamine levels were measured at baseline.

Results: Administration of the hypothalamic releasing hormones revealed normal responses of all pituitary hormones (adrenocorticotropic hormone, thyroid-stimulating hormone, luteinizing hormone, and prolactin), except for growth hormone, the response of which was slightly impaired (10.2 ± 6.8 vs 19.9 ± 6.5 ng/L, $P < .05$). Also, the cortisol response to the corticotropin-releasing hormone–stimulated adrenocorticotropic hormone release was normal, as were basal concentrations of thyroid hormones (triiodothyronine, thyroxine, free triiodothyronine, and free thyroxine), testosterone, and urinary catecholamines.

Conclusions: Implantation of a continuous flow axial pump with low-pulsatile blood flow profile appears to have no major effect on the hypothalamic-pituitary-endorgan system and sympathoadrenal functions. This finding is reassuring for the growing number of patients treated with this convenient new pump and could contribute considerably to their prognosis and quality of life.

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Patients with end-stage left-sided heart failure listed for cardiac transplantation might deteriorate hemodynamically, despite maximal pharmacologic support. In many cases bridge to transplantation with mechanical assist devices is the only option for these patients. Over the past 3 decades, mainly pulsatile blood pumps were used for clinical long-term support.[1,2] Since November 1998, a new generation of miniaturized, implantable axial flow pumps is available for clinical application.[3,4] These pumps offer several advantages, such as small size, no noise,

Abbreviations and Acronyms
ACTH = adrenocorticotropic hormone
CRH = corticotropin-releasing hormone
GH = growth hormone
LH = luteinizing hormone
T3 = triiodothyronine
T4 = thyroxine
TSH = thyroid-stimulating hormone

and no need for a compliance chamber. However, patients supported with implantable axial flow pumps demonstrate nonphysiologic, almost nonpulsatile blood flow patterns. Over the centuries, it was believed that pulsatility of arterial blood flow is essential for homeostasis in human subjects.

Disturbed neuroendocrine and sympathoadrenal function caused by nonphysiologic organ perfusion could be expected to have a major effect on cardiovascular and muscular function in patients with severe left-sided heart failure and thereby limit the beneficial hemodynamic effects of a miniaturized implantable system. Indeed, several studies have suggested adrenocortical dysfunction during nonpulsatile perfusion in human subjects.[5] In contrast, early experiments with nonpulsatile blood pumps in animals provided evidence that this pathophysiologic state of nonpulsatile or low-pulsatile blood flow can be tolerated for short-term support, despite alterations in the microcirculation.[6]

Because the effect of long-term low pulsatility on the endocrine system is not known, we performed pituitary gland multifunction tests in patients implanted with a continuous MicroMed–DeBakey axial flow pump and evaluated their pituitary and associated endocrine functions, as well as their sympathoadrenal states.

Methods

From September 2000 through February 2002, 9 patients (8 men and 1 woman; mean age, 51 ± 10 years; age range, 36-64 years) with end-stage left-sided heart failure were implanted with a continuous MicroMed–DeBakey axial flow pump as a bridge to transplantation. Despite maximal pharmacologic support with inotropic therapy, vasodilator therapy, or both, patients showed signs of acute hemodynamic deterioration and end-organ dysfunction at the time of implantation. In 4 patients the underlying disease was ischemic cardiomyopathy, and 5 patients had dilated cardiomyopathy. Patients recovered completely after implantation of the ventricular assist device (VAD) and were started on a regular physical training program to overcome long-term immobilization preoperatively. The early postoperative period was characterized by complete nonpulsatile arterial flow patterns. Partial recovery of the natural left ventricle added a certain degree of pulsatility not exceeding pulse pressures greater than 10 mm Hg. Because our strategy in those patients supported with left VADs was to maintain high pump support for maximal exercise capacity, all patients presented high pump flows in the average range between 4.5 and

6 L/min with the aortic valve closed over the whole pumping period. End-organ function normalized, and postoperative pharmacologic therapy consisted of angiotensin-converting enzyme inhibitor treatment with 40 mg/d lisinopril, anticoagulation with phenprocoumon (international normalize ratio target levels of 2.5-3.5), and antiaggregation with 100 mg of salicylic acid and 225 mg of dipyridamol. Endocrine testing was performed after full rehabilitation of the patients after a mean pumping period of 67 ± 19 days. The control group consisted of 10 healthy men matched for age and weight. The protocol was approved by the institutional ethics committee.

All tests were performed at 10 AM, and all subjects were starved for at least 8 hours. Patients were tested for basal serum hormone concentrations and anterior pituitary hormone response to bolus injection of hypothalamic releasing hormones (corticotropin-releasing hormone [CRH], 100 μg: Ferring, Kiel, Germany; thyreotropin-releasing hormone, 200 μg: Aventis Pharma, Frankfurt, Germany; growth hormone [GH]–releasing hormone, 100 μg: Ferring; luteinizing hormone–releasing hormone, 100 μg, Aventis Pharma). Blood samples were assayed for adrenocorticotropic hormone (ACTH), cortisol, thyroid-stimulating hormone (TSH), luteinizing hormone (LH), GH, and prolactin at multiple time points (-15, 0, 15, 30, 60, 90, and 120 minutes). In addition, we measured basal serum concentrations of thyroid hormones, testosterone, the binding proteins thyroxin-binding globulin and sex hormone–binding globulin, and plasma and urinary catecholamines (epinephrine, norepinephrine, and dopamine). Blood for determination of plasma ACTH concentrations was drawn in prechilled ethylenediamine tetraacetic acid tubes that were immediately centrifuged and stored at $-20°C$ until assayed with a commercially available radioimmunoassay. GH, cortisol, and sexual hormone–binding globulin levels were measured with commercially available radioimmunoassays. Serum concentrations of triiodothyronine (T3), thyroxine (T4), free T3, free T4, testosterone, TSH, LH, and prolactin were measured by using electrochemiluminescence (ELECSYS, Roche Diagnostics GmbH, Mannheim, Germany). Epinephrine, norepinephrine, and dopamine excretion in 24-hour urinary samples was analyzed by using high-performance liquid chromatography.

Data are expressed as medians and standard errors of the mean. To analyze individual serial measurements of ACTH, cortisol, TSH, LH, GH, and prolactin, we calculated the area under the curve according to the trapezoid rule[7] divided by the elapsed time interval. Further maximum increase of ACTH, cortisol, TSH, LH, GH, and prolactin was calculated for each patient. The Mann–Whitney U test was used to compare groups of continuous data. All data were computed with Microsoft Excel for Windows, version 6.0 (Microsoft, Redmond, Wash) and SPSS for windows (SPSS, Chicago, Illinois).

Results

Administration of a bolus injection of maximally effective doses of hypothalamic releasing hormones resulted in a prompt increase of ACTH, TSH, LH, GH, and prolactin serum concentrations in all subjects. Peak levels of pituitary hormones were reached in both groups 30 minutes after stimulation, except for prolactin, for which peak levels were attained 15 minutes after thyreotropin-releasing hormone
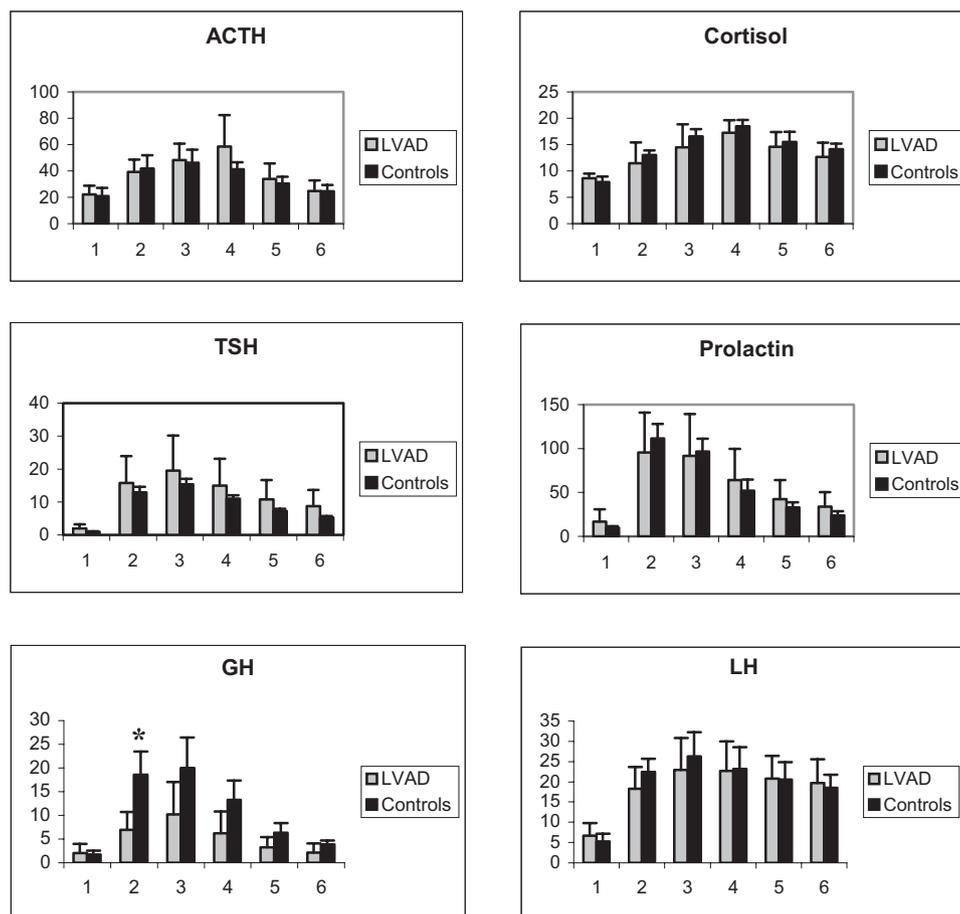
Figure 1. Adrenocorticotropic hormone (*ACTH*; in picograms per milliliter) and cortisol (in micrograms per deciliter) responses after 100 μg corticotropin-releasing hormone are shown. Thyroid-stimulating hormone (*TSH*; in milliunits per liter [TSH = μU/mL]) and prolactin responses to 200 μg of thyreotropin-releasing hormone are shown. Growth hormone (*GH*; in nanograms per milliliter) response to 100 μg of growth hormone–releasing hormone and luteinizing hormone (*LH*; in units per liter) response to 100 μg of luteinizing hormone–releasing hormone are shown. Patients receiving a left ventricular assist device *(LVAD)* are indicated by *shaded gray bars*, and control subjects are indicated by *filled bars*. *1*, Zero minutes; *2*, 15 minutes; *3*, 30 minutes; *4*, 60 minutes; *5*, 90 minutes; and *6*, 120 minutes.

administration. There was no significant difference between the 2 study groups as to plasma/serum concentrations of ACTH (48.2 ± 12.4 vs 46.3 ± 9.9 pg/mL), TSH (19.5 ± 10.7 vs 15.38 ± 1.65 mU/L [TSH = μU/mL]), LH (22.9 ± 7.8 vs 26.3 ± 5.9 U/L), and prolactin (91.6 ± 47.7 vs 96.6 ± 14.4 μg/L [ng/mL]) at 30 minutes after stimulation and prolactin (95.5 ± 45.3 vs 111.5 ± 16.5 μg/L [ng/mL]) 15 minutes after stimulation (Figure 1). Also, the adrenocortical (ie, cortisol) response to a normal ACTH increase after CRH stimulation was comparable between study patients and healthy control subjects (Figure 1). In every patient the maximum increase of cortisol (peak concentration minus basal concentration) was 7 μg/dL or more, which is considered the cutoff point for normal adrenocortical function.

In contrast, mean GH response to a supramaximal dose of the hypothalamic releasing peptide GH-releasing hormone was slightly diminished (10.2 ± 6.8 vs 19.9 ± 6.5 μg/L, *P* < .05). However, all patients had a GH response of greater than 3 μg/L, which is considered the cutoff point for diagnosis of severe GH deficiency.

Peripheral thyroid hormones and sex steroids (T4, T3, free T4, free T3, and testosterone) and their binding proteins (thyroxin-binding globulin and sexual hormone–binding globulin) were found to be within the normal range. Furthermore, urinary excretion of epinephrine (5.3 ± 2.0 μg/24 hours), norepinephrine (60.8 ± 15.8 μg/24 hours), and dopamine (419.8 ± 121.3 μg/24 hours) did not deviate from normal in this cohort (Table 1).

TABLE 1. Baseline concentrations of hormones and sexual hormone binding globulin

	Patients with LVADs	Normal range
Urinary epinephrine excretion (24 h)	5.3 ± 2.0	<20 μg/24 hours
Urinary norepinephrine excretion (24 h)	60.8 ± 15.8	23-105 μg/24 h
Urinary dopamine excretion (24 h)	419 ± 123	190-450 μg/24 h
TSH	2.0 ± 1.3	<4 U/L
Thyroxine	90 ± 15	50-120
Triiodothyronine	1.4 ± 0.2	0.6-2.0
Sexual hormone–binding globulin	72.8 ± 11.7	16-76 nmol/L
Testosterone	5.7 ± 1.3	2.7-10.7 ng/mL
IGF-I	205.7 ± 91	105-330 ng/mL

LVADs, Left ventricular assist devices; *TSH,* thyroid-stimulating hormone; *IGF-I,* insulin-like growth factor I.

Discussion

It was believed for decades that pulsatility of arterial blood flow is essential for homeostasis in human subjects and that substantial changes in pulse pressure would cause critical disorders in many sensitive regulation systems of the human body. Therefore pulsatile pump mode for prolonged mechanical circulatory support was assumed to be superior to the nonphysiologic pulseless perfusion of continuous flow rotary blood pumps.

It has been shown recently, however, that maintenance of systemic circulation with implanted continuous axial flow blood pumps for bridge to transplantation is feasible and well tolerated in patients for several months.[3,4] Problems experienced in early animal experiments, such as increased total peripheral resistance, increased circulating blood volume, reduced oncotic pressures, and low hematocrit values,[6] were not seen in these first patients with implanted axial flow pumps. It is known that essential organs of the body are able to autoregulate their perfusion pressures in a certain range to maintain an adequate blood flow to guarantee regular metabolism and protect themselves from damage. The brain, for instance, keeps cerebral blood flow constant over a range of approximately 60 to 150 mm Hg mean aortic pressure. It has been observed, however, that cerebral blood flow and cerebral metabolic rate for oxygen are reduced by approximately 30% during cardiopulmonary bypass surgery when a nonpulsatile pump flow mode is maintained.[8] Furthermore, it is known that patients with advanced chronic heart failure present with endocrine dysregulations. In chronic heart failure norepinephrine, epinephrine, cortisol, prolactin, and human GH levels are increased, and thyroid function is impaired. Insulin-like growth factor I, testosterone, and estrogen levels appear to be normal.[9-11] This study

demonstrates that adenohypophyseal function in response to stimulation by hypothalamic releasing hormones is maintained in patients, except for GH, the response of which was diminished. It should be stressed, however, that no single patient exhibited severe GH deficiency, defined as a maximal GH concentration of 3 μg/L or less at the Port Stephens Consensus Conference.[12] Because of the positive inotropic effects of GH, the finding of only mild impairment of somatotropic function appears to be relevant in patients with heart failure.[13,14] Normal or only slightly impaired GH concentrations also facilitate physical training[15] and rehabilitation of these patients, which must be considered of great importance for further prognosis and outcome after heart transplantation.

Furthermore, hypothalamic-pituitary-adrenocortical function was not impaired in our patients with implanted devices, as evidenced by a normal cortisol response to a normal ACTH increase after administration of a maximally effective dose of CRH. The criteria for intact adrenal function include the attainment of a maximal plasma cortisol concentration of at least 18 μg/dL, a cortisol increment of at least 7 μg/dL greater than the basal value, or both. This finding is not only remarkable in view of the nonpulsatile blood flow but also points toward a well-adapted general health condition of patients with MicroMed–DeBakey axial flow pumps implanted for a mean time of 67 ± 19 days. Chronic stress as a consequence of a severely impaired general health status would have lead to increased cortisol concentrations and deranged hypothalamic-pituitary feedback, with deleterious effects on cardiovascular, metabolic, and immune functions.[16-18] Furthermore, this observation is in agreement with previous studies during and after cardiopulmonary bypass surgery using pulsatile and nonpulsatile perfusion.[19,20] In contrast, several earlier studies had suggested that nonpulsatile blood flow during cardiopulmonary surgery decreases plasma cortisol levels,[5] which also might be expected to compromise cardiovascular function caused by impairment of fluid and mineral homeostasis and the loss of the permissive effects of glucocorticoids for catecholamines in peripheral blood vessels. Because our investigations were performed about 70 days after implantation of the MicroMed–DeBakey VAD, we cannot rule out that the patients might have adapted themselves to the nearly nonpulsatile flow pattern. Tsutsui and Nose[21] report in early animal experiments with complete nonpulsatile flow that idioperipheral pulsations could be observed. They suggested that the animals were able to add pulsatile components of their own, allowing them to maintain sufficient circulation. From our patients with implanted continuous blood pumps, we learned that pulsatility of blood flow occurs as soon as contractility of the natural heart recovers.[3,4]

Whereas high catecholamine levels have been described in patients with cardiomyopathy and immediately after implantation of mechanical assist devices,[22,23] we found normal plasma catecholamine concentrations and urinary catecholamine excretion. This further suggests good physical adaptation of our patients maintained several weeks after implantation of the DeBakey VAD.

No changes versus those seen in healthy subjects were seen as to thyroid hormone concentrations. This is in contrast to a study by Buket and colleagues,[24] in which nonpulsatile flow has been shown to affect thyroid hormone levels. In this study both pulsatile and even more nonpulsatile flow decreased free T3 levels but not TSH, T4, and free T4 levels. Such low T3 syndrome was observed within 24 hours after cardiopulmonary bypass surgery and is related to the severe medical condition of these patients rather than to the choice of cardiac assist device.[25] The normal thyroid function test results again document the good physical condition of our patients and their adaptation to the nonpulsatile blood flow pump 70 days after implantation of the assist device.

In conclusion, this study demonstrates an almost normal endocrine regulation in patients receiving a continuous MicroMed–DeBakey axial flow pump. This proves that prolonged support with a nonpulsatile mechanical assist device is well tolerated by endocrine organs, which play a major role in the maintenance of homeostasis in human subjects. In addition, this finding documents the good long-term adaptation of these patients, which could have a major effect on their prognosis and quality of life.

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