JECT. 2004;36:10–15
The Journal of The American Society of Extra-Corporeal Technology

Original Articles

Inflammatory Mediated Chronic Anemia in Patients Supported with a Mechanical Circulatory Assist Device

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Presented at the AmSECT 41st International Conference of the American Society of Extra-Corporeal Technology, Las Vegas, Nevada, March 2003

Abstract: It is widely accepted and clinically anticipated that the patient implanted with a mechanical circulatory assist device (MCAD) will develop a state of chronic anemia that will last throughout the duration of MCAD support. Large-scale hemolysis mediated by the high sheer stress transmitted to the erythrocytes (RBCs) from the mechanical action of most MCAD systems is the accustomed mechanism responsible for this anemic status. MCAD patients exhibiting chronic anemia require frequent blood transfusions placing the patients at a high infectious risk to maintain an acceptable hematocrit. It is also acknowledged that the biomaterial interaction of the MCAD with the immune system precipitates a chronic inflammatory state in this patient population. Taken together, we hypothesize that inflammatory mediation of the erythropoiesis pathway at multiple sites—limiting the replacement of lysed RBCs—dictates the extent of chronic anemia in MCAD patients more than mechanical trauma to the blood. Hematological parameters were retrospectively analyzed for 78 patients implanted with a mechanical circulatory assist device for greater than 30 days at the University of Arizona Health Sciences Center between the years 1996 to 2002. Analysis demonstrates that the rate of hemolysis slows after MCAD implantation, marked by a progressively decreasing plasma hemoglobin concentration. In addition, the absolute reticulocyte count, a marker of juvenile RBC production, increases and remains above maximum normal values after MCAD implantation. Furthermore, the mean cell hemoglobin concentration indicates sufficient substrate for RBC development and maturation. However, hematocrit, a conventional marker of anemia, drops and remains below minimum normal value throughout the measured time period. A state of anemia in the MCAD supported patient results initially from the effect of hemolysis associated with the mechanical action of the MCAD, then chronically persists as the result of another undetermined mechanism. Given the state of chronic inflammation in the patient population, immunological activation most likely limits the full production of RBCs to their mature state. **Keywords:** erythropoietin (EPO), anemia, ventricular assist device (VAD), cytokines. *JECT. 2004;36:10–15*

The anemia of patients on mechanical circulatory assist device (MCAD) support has not been extensively characterized in literature despite wide acceptance in clinical practice that such patients will exhibit profound anemia shortly after MCAD insertion and throughout MCAD support. In addition, the possible link between the inflammatory response to MCAD presence and the anemia of chronic disease (ACD) has not been connected in literature. However, the activation and release of several immunologic modulators as related to the biocompatibility of foreign objects has been documented in several human models, including circulatory support with Novacor, HeartMate, and MicroMed MCADs (1–6). Meanwhile, other areas of clinical medicine have already accepted the concept that inflammatory mediators are known to modulate the process of erythropoiesis (7). It seems to be accepted clinically that the alteration of the immune function and the loss of erythrocytes (RBCs) because of mechanical trauma are innate outcomes of MCAD support (8). Defining the immunologic modulation of erythropoiesis through the activity of proinflammatory mediators provides an unexplored mechanism for ACD associated with MCAD support in humans.

Over the past 18 years at the University of Arizona Health Sciences Center, 209 patients have received an

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MCAD in their course of treatment as a bridge to transplantation or recovery, contributing to more than 14,000 patient days experience with mechanical circulatory assistance. Despite normalization of cardiac output and blood pressure to reperfuse adequately and resuscitate the dysfunctional end organs, MCAD-implanted patients are still chronically anemic. Justification for this study is to define the hematologic conditions resulting from MCAD insertion and support; thereby, suggesting a possible mechanism of ACD by which hemolyzed RBCs are not fully replaced by the hematopoietic system.

Mechanism of Erythropoiesis

Under normoxic conditions, low-level erythropoiesis maintains a steady-state balance of the RBC mass. Old or damaged RBCs are scavenged from the bloodstream at the same rate as new cells are produced. The healthy response to hypoxic stress (Figure 1), such as in uncomplicated blood loss, includes restoration of the RBC mass and blood oxygen capacity to steady-state through a phase of hyperproliferative erythropoiesis (9). A state of hypoxia occurs whenever the O_2 delivery capacity of the blood cannot adequately serve the metabolic demand of the tissues. Typically, only chronically hypoxic states (i.e., anemia) elicit an erythropoietic response. Chronic hypoxic stress initiates adaptation through the activity of hypoxia-inducible factor-1 (HIF-1), a heterodimeric transcription factor. HIF-1 DNA-binding to the hypoxia-responsive recognition element induces gene transcription responsible for synthesis of the compensatory proteins and hormones erythropoietin (Epo), vascular endothelial growth factor (VEGF), and NO-synthase, which facilitate recovery through increased RBC production, new blood vessel growth, and vascular dilation (10).

Erythroid progenitor cells expressing the Epo receptor in the bone marrow, which arise from pluripotent stem cells, are responsible for the primary biologic actions of erythropoiesis. Specifically, burst-forming units-erythroid (BFU-E), colony-forming units-erythroid (CFU-E), and proerythroblasts are active. In chronic hypoxia, erythroid progenitor cells are stimulated to halt apoptosis, which promotes cellular viability in the erythroid-specific proliferative pathway. Proliferation allows for further development and eventual appearance in the circulation as reticulocytes and finally mature RBCs (11). Dormant BFU-E cells mobilize into the cell cycle for differentiation into CFU-E cells. Epo assists at this time in maintaining viability in the proliferative cell cycle (12–14).

Anemia from Disruptions in Erythropoiesis

Variations in the pathway of normal erythropoiesis yield a state of anemia. Hypoproliferative erythropoiesis is a variation in the normal pathway that occurs if the system is impeded, diminished, or nonexistent. The viability of the erythropoietic system influences the rate of erythroid progenitor cell function. Therefore, an inability to amplify erythroid progenitor cell activity in response to chronic hypoxic stress from diminished blood O_2 delivery would result in anemia from hypoproliferative erythropoiesis. With ACD, the impaired erythropoiesis is caused by an

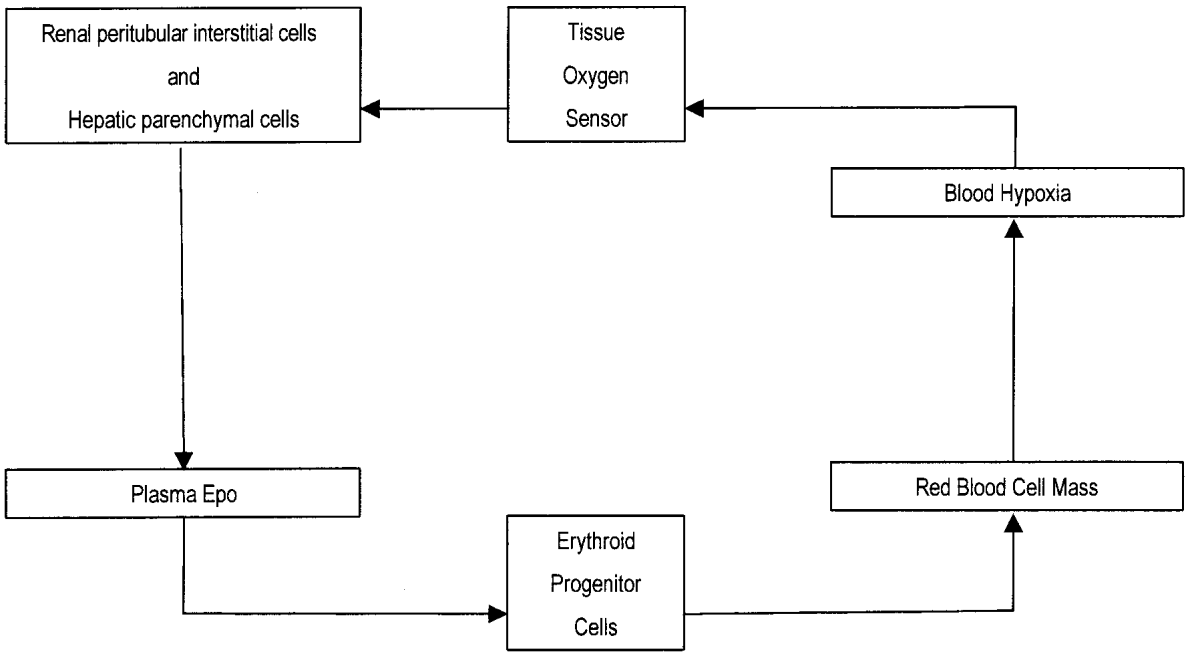

Figure 1. Mechanism of normal erythropoiesis. Tissue oxygenation sensed in the kidneys and liver effects Epo production. Changes in plasma Epo levels modulate the action of bone marrow erythroid progenitor cells in the production of RBCs to deliver adequate oxygen to the tissues (10).

immunomodulatory process that desensitizes erythroid progenitor cells through long-term inflammatory stimulation (9,15).

Potentially, the MCAD-supported patient experiences ACD primarily through the chronic immunologic inflammation of persistent cardiovascular disease preimplantation; second, through the mechanical trauma of the MCAD to old and weakened RBCs peri-implantation, and finally by further immunologic inflammation from the blood biomaterial interaction with the MCAD postimplantation. In addition to reducing the erythropoietic capacity through inflammatory immunomodulation, the highly mechanical, pressurized MCAD pumping action will impart high-sheer stress to the RBCs, leading to increased hemolysis. The contribution of inflammatory erythropoietic modulation and increased mechanical RBC hemolysis lead to a state of chronic anemia in the MCAD-implanted patient that is unmanageable and irrecoverable to the hypoxia-stimulated erythropoietic pathway.

METHODS

Retrospective analysis of hemodynamic and hematologic laboratory data was performed for 156 patients implanted with a MCAD for the purpose of bridge to transplantation or bridge to recovery from 1996 to 2002 at the University of Arizona Health Sciences Center. Three MCADs were used regularly during this period; CardioWest total artificial heart (Syncardia Systems, Tucson, AZ), Thoratec ventricular assist device (Thoratec Corp., Pleasanton, CA), and Novacor left ventricular assist system (WorldHeart Corporation, Oakland, CA). Because of the highly configurable nature of the Thoratec, biventricular support (BiVAD), patients were stratified from single left or single right ventricular support (UniVAD) patients. Table 1 characterizes the clinical capacities of the three mentioned MCADs.

The patient population was filtered to those on MCAD support for more than 30 days resulting in 78 patients being analyzed for this study. Hemodynamic and hematologic datapoints were retrieved, if available, before MCAD implantation, at MCAD implantation, and every 7 days after MCAD implantation for a period of 4 weeks. Parameters measured included patient size, MCAD output, hematocrit (HCT), mean cell hemoglobin concentration (MCHC), absolute reticulocyte count (ARC), and plasma hemoglobin concentration (PH). Regression analysis of the effects of changing cardiac index on PH, ARC, and HCT were also performed.

STATISTICS

Graphic analysis was performed on all gathered data. All data are expressed as mean ± SEM.

RESULTS

Demographic analysis (Table 2) of the 78 patients remaining on MCAD support for more than 30 days yielded 38 patients (49%) on CardioWest, 22 patients (28%) on Thoratec, and 18 patients (23%) on Novacor support, with 77% of the total population male and 23% female. Biventricular MCAD support encompassed 56 patients (72%), while univentricular MCAD support included 22 patients (28%). Mean age ranged from 41 years with the Thoratec BiVAD to 60 years with the Novacor. Of those patients requiring biventricular support, larger sized patients typically received CardioWest support (BSA = 2.02 m^2 ± 0.16), while smaller patients received Thoratec BiVAD support (BSA = 1.75 m^2 ± 0.29). Size difference for patients requiring univentricular support was negligible between Novacor (BSA = 1.96 m^2 ± 0.21) and Thoratec UniVAD (BSA = 2.02 m^2 ± 0.02). Primary disease etiology warranting MCAD insertion included ischemic cardiomyopathy (n = 35), idiopathic cardiomyopathy (n = 22), viral cardiomyopathy (n = 9), and cardiogenic shock (n = 4). Other indications of heart failure (n = 7) included post-partum cardiomyopathy, valvular cardiomyopathy, failure to wean from cardiopulmonary bypass, and acute transplant rejection.

PH measurements count the amount of hemoglobin protein liberated into the blood plasma as the result of RBC destruction and, thus, are a simple marker of hemolysis. PH concentrations (Figure 2) for CardioWest, Thoratec BiVAD, and Thoratec UniVAD remained elevated beyond the maximum normal value (5 mg/dL) throughout the 4 weeks post implantation, despite exhibiting a downward trend toward normalization, characterizing a reduction in the hemolytic rate. Only Novacor patients exhibited a clinically acceptable PH in the first week post implantation, when the CardioWest and Thoratec patients exhibited the highest PH values measured in the time

Table 1. Characteristics and clinical capacities of the three studied MCADs.

VAD	Type of Support	Driving Mechanism	Stroke Volume	Clinical Cardiac Output Maximum
CardioWest TAH	Bilateral only	Pneumatic	70 mL	8–9 L/min
Thoratec VAD	Bilateral, Left or Right	Pneumatic	65 mL	5–6 L/min
Novacor LVAS	Left only	Electromechanical	70 mL	8–9 L/min

Table 2. Demographic breakdown of the MCAD patient population studied.

VAD	Male	Female	Age (yrs)	Size (m^2)	Ischemic CM	Idiopathic CM	Viral CM	Post-Partum CM	Cardiogenic Shock	Other Indication
CardioWest TAH	32	6	50.79 ± 10.47	2.02 ± 0.16	16	14	3	1	0	3
Thoratec BiVAD	11	7	40.72 ± 18.63	1.75 ± 0.29	7	2	5	1	2	1
Thoratec UniVAD	3	1	58.50 ± 10.34	2.02 ± 0.02	2	0	0	0	2	0
Novacor LVAS	14	4	60.11 ± 6.02	1.96 ± 0.21	10	6	1	0	0	1

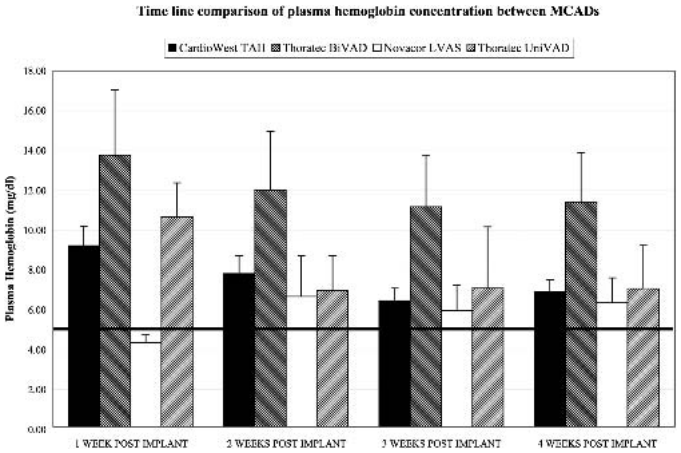

Figure 2. PH values for all MCADs measured throughout the first 4 weeks post implantation. Bold horizontal lines mark the range of clinically normal values (Max = 5 mg/dL, Min = 0 mg/dL).

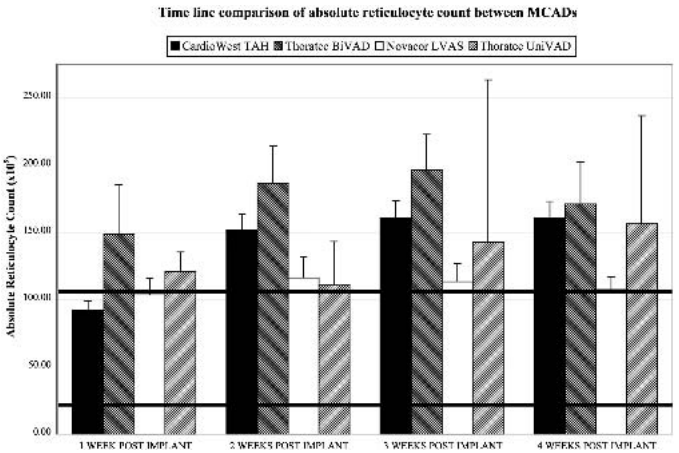

Figure 3. ARC values for all MCADs measured throughout the first 4 weeks post implantation. Bold horizontal lines mark the range of clinically normal values (Max = 105 × 10^9 cells, Min = 22 × 10^9 cells).

frame. PH values for Novacor patients rose to a plateau above the maximum normal value in the second through fourth weeks post implantation, but remained the lowest of the MCADs measured.

The ARC is the most effective tool for accurate analysis of the erythropoietic response to anemia because of its ability to sense the number of immature RBCs produced by the bone marrow over that of normal maintenance RBC replacement. ARC values above the maximum normal value (105 × 10^9 cells) indicate an elevated erythropoietic response to reduced RBC numbers with increased bone marrow production, while values below the normal range indicate a pathologic process in reduced production capabilities (16). An elevation and normalization in the ARC was seen within 4 weeks of implantation for all MCADs studied (Figure 3). Within 2 weeks of implantation, the ARCs for CardioWest, Novacor, and Thoratec elevated above the maximum normal value. Peak values for Thoratec BiVAD and Novacor were reached at 3 weeks and for CardioWest and Thoratec UniVAD were reached at 4 weeks post implantation.

MCHC is a very useful marker in determining if nutritional anemia, secondary to iron deficiency, is present. Iron deficient anemias are characterized by a reduction in MCHC below the minimum normal value (33 mg/dL) (16). All four MCADs exhibited MCHC values within normal clinical values (Figure 4) for all time points from before through 4 weeks after MCAD implantation.

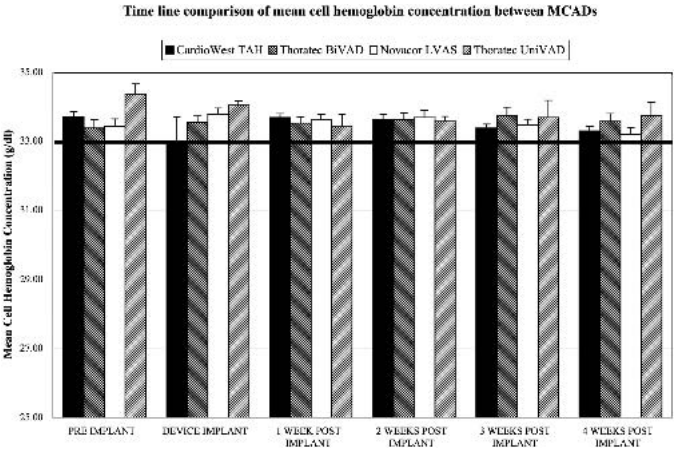

Figure 4. MCHC values for all MCADs measured from pre-implantation up to 4 weeks post implantation. Bold horizontal lines mark the range of clinically normal values (Max = 35 mg/dL, Min = 33 mg/dL).

HCT is a classic clinical indicator of the overall condition of the patient's blood tissue with its oxygen and nutrient carrying capacities. Anemic values are less than the minimum normal value (40%) and are indicative of diminished physiologic function and capacity with respect to blood oxygen transport. Typically, at values less than half the minimum normal HCT, blood transfusions are given to the patient. From pre-MCAD through 4 weeks after implantation, all patients presented an anemic status (Figure 5). HCT dropped sharply in the peri-implant period before slowing its decline to a plateau by the fourth week post implant.

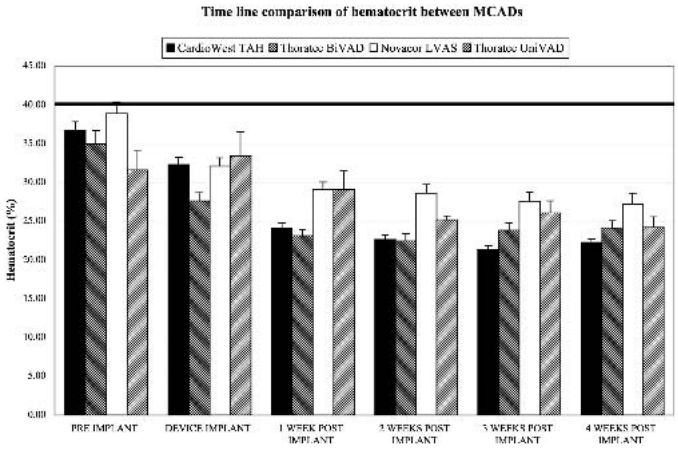

Figure 5. HCT values for all MCADs measured from pre-implantation up to first 4 weeks post implantation. A single bold horizontal line marks the minimum value of clinically normal (Min = 40%).

Regression analysis of cardiac index against PH, ARC, and HCT was performed to reveal any connections between increased MCAD flow rate and the hematologic changes found. Cardiac index measurements include body size as a factor for increased MCAD output in larger patients requiring greater circulation. Table 3 shows minimal correlation for any of the parameters in the CardioWest and Novacor patient population. The patient data for both the Thoratec BiVAD and Thoratec UniVAD groups were combined to minimize error associated with the small data size. Analysis shows increased correlation of PH, ARC, and HCT to increased cardiac index in the Thoratec populations.

DISCUSSION AND CONCLUSIONS

The findings of this research show that the hemolytic anemia of MCAD support is extensive at first exposure of the blood to the biomaterial during implantation. Evidence that the anemia is hemolytic and not nutritional in nature is supported by the elevated PH values and normal MCHC values throughout the duration of MCAD support. The rate of hemolysis, most likely from mechanical destruction, slows to a steady, predictable state shortly after MCAD implantation. The patient responds appropriately to the hypoxia, by increasing Epo production, with a concomitant ARC increase, in an effort to increase the red cell mass and O_2 delivery capacity. Unfortunately, the reticulocyte development from juvenile to mature RBC never is completed because the HCT remains anemic. Differences in patient size and MCAD output on the extent of the hemolytic anemia are unlikely with regression analysis demonstrating a poor correlation between function and hematologic changes in CardioWest and Novacor patients. Also, a small sample size discounts the validity in the regression analysis results for the Thoratec population. Throughout the findings, no extensive differences are noted between MCADs and measured values, implying that the factor affecting the suppression of HCT is a common one that is not altered by type of support or mechanism of pumping action.

Conventional treatment for anemia includes transfusion of packed red cells from donor blood. Aside from the remarkable cost and drain on the nation's banked blood supply, allogenic blood transfusions carry an increased risk for viral infections, bacterial contamination, and immune activation by leukocyte exposure (17–19). It is hoped that further understanding of the erythropoietic pathway will yield a proactive approach toward anemic patients and a reduced need for allogenic blood transfusion, which will be helpful at transplantation.

Applying the knowledge gained from studies of the inflammatory suppression of erythropoiesis is as essential clinically as scientifically. The simultaneous presence of elevated inflammatory mediators in MCAD patients and the proved state of chronic anemia cannot be denied. Just as it is appropriate in other patient populations with similar symptoms, ACD is a justified characterization for MCAD-supported patients. The elevation of the ARC demonstrates that erythropoietic stimulation is occurring and is, therefore, not a limiting factor in the attempt to correct MCAD support anemia. Normal MCHC values throughout this time period also prove that iron and substrate availability are not responsible for the anemic state. Steady PH values within 4 weeks of support demonstrate that a steady rate of hemolysis is occurring rather than massive hemorrhagic RBC damage. All of the necessary components are in place for a well-perfused, healthy erythropoietic system to return the HCT to a homeostatic normal. The pathway must be sufficiently impeded or immunomodulated if its reaction to the stimulation of constant hypoxic stress yields no positive response. Because this clinical course repeated with nearly all 78 patients for

Table 3. Regression analysis results for cardiac index vs. PH, ARC, and HCT. Equation for line of best fit and corresponding R^2 values shown.

	Cardiac Index vs. PH		Cardiac Index vs. ARC		Cardiac Index vs. HCT	
VAD	Equation	R^2	Equation	R^2	Equation	R^2
CardioWest TAH	y = 0.9477x + 3.5227	0.0102	y = −30.968x + 262.83	0.0317	y = −2.5282x + 30.804	0.1067
Thoratec VAD	y = 29.032x − 64.883	0.9779	y = 48.891x + 75.29	0.1032	y = −4.8435x + 39.211	0.5688
Novacor LVAS	y = −1.8058x + 12.927	0.0244	y = −14.393x + 149.54	0.0878	y = −5.3996x + 42.04	0.2616

the first 30 days of implantation, and continued throughout the time of MCAD support (data not shown), it is reasonable to assume that a sufficient process of ACD occurs in almost all MCAD-supported patients. Such a common trait between patients helps to explain the inflammatory mediated deficiency of viable RBC turnover in response to hypoxia. Although much work remains to be done to elucidate the implications of this connection, recognizing that MCAD-stimulated inflammation influences anemia is essential in progressing to a reduced morbidity for all MCAD patients. Furthermore, the hematologic characteristics associated with support by other MCADs, including axial flow pumps and other widely used MCADs, should be compared with the presented data to corroborate these findings.

There is an estimated prevalence of 61.8 million U.S. citizens with cardiovascular disease, of which 4.9 million have congestive heart failure (CHF). Total mortality in the year 2000 from CHF was 262,300; many of which could have benefited from a heart transplant. Unfortunately, only 2,197 heart transplants were performed in 2000 (20). With the incidence of CHF increasing each year, medicine is beginning to look at MCADs for more than just the niche bridge to transplant. With MCADs set to be used in the burgeoning new treatment of alternative to transplant, problems such as chronic anemia related to MCAD support now become clinically relevant, rather than just a short-term condition to allay in the duration of a bridge to heart transplantation. With the potential for indefinite long-term MCAD support, blood transfusions to briefly increase the HCT to clinically acceptable levels now become a very costly chronic treatment. Within MCADs lies great promise for helping the remaining portion of the 4.9 million CHF patients each year who do not receive a donor heart. However, the treatment must not function to further another malady, such as ACD. With further research, the pathway of inflammatory mediators responsible for modulation of erythropoiesis can be characterized and an appropriate treatment developed.

ACKNOWLEDGMENTS

This research was supported by the University Medical Center Perfusion Training Grant and the Steinbron Foundation for Heart Failure Research.

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