Severe Renal Dysfunction Complicating Cardiogenic Shock Is Not a Contraindication to Mechanical Support as a Bridge to Cardiac Transplantation

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OBJECTIVES
This study investigated outcomes in patients with cardiogenic shock and severe renal dysfunction treated with ventricular assist devices (VAD) as a bridge to cardiac transplantation.

BACKGROUND
Previous reports have documented poor survival in patients with cardiogenic shock and severe renal dysfunction treated with VAD.

METHODS
We surveyed 215 consecutive patients who received a VAD from 1992 to 2000 and selected patients who had a serum creatinine ≥3.0 mg/dl at the time of VAD placement. Demographic, laboratory, and clinical outcome data were collected.

RESULTS
Eighteen patients met the inclusion criteria. Mean serum creatinine at the time of VAD placement was 4.0 ± 0.7 mg/dl (range 3.0 to 5.2 mg/dl). Seven patients required temporary renal support with continuous venovenous hemodialysis (CVVHD). Eleven patients underwent cardiac transplantation. At six months post-transplantation, mean serum creatinine was 2.0 ± 0.6 mg/dl (range 1.3 to 3.5 mg/dl). None of the transplanted patients required subsequent renal support. Seven patients died with a VAD before transplantation. Three died early (<1 month) after VAD placement, and all three required CVVHD until death. Four patients survived for >1 month after VAD placement; all four had resolution of renal dysfunction with mean serum creatinine of 1.9 ± 1.2 mg/dl (range 0.8 to 3.6 mg/dl) without the need for renal support. Overall 30-day and six-month survival after VAD placement, survival to transplantation, and survival one year post-transplantation were similar to patients without severe renal dysfunction.

CONCLUSIONS
Contemporary use of VAD leads to resolution of severe renal dysfunction in most cardiogenic shock patients and comparable long-term outcomes to patients without renal dysfunction. (J Am Coll Cardiol 2003;41:381–5) © 2003 by the American College of Cardiology Foundation

In patients with cardiogenic shock refractory to conventional therapy, cardiac transplantation has been shown to be a highly effective treatment. However, because of donor scarcity, progressive heart failure, and difficulties in cross-matching, many patients are at a significant risk of dying before a donor organ becomes available (1). In this setting, a strategy of using mechanical circulatory support with ventricular assist devices (VAD) as a “bridge” to cardiac transplantation has become an established therapy (1). These Food and Drug Administration–approved devices are clearly able to provide partial or total support for cardiac function in critically ill patients until cardiac transplantation can occur. However, VAD are expensive, technically sophisticated, and associated with their own inherent complications such as mechanical failure, infection, and thromboembolism. Therefore, proper selection of patients who would derive the most benefit from this support is essential.

Patients in cardiogenic shock are at risk of developing other concomitant organ failure. Renal dysfunction is particularly ominous because it is associated with a dramatic increase in mortality (2). In fact, previous outcomes with the use of VAD in patients with cardiogenic shock and severe renal dysfunction have been overwhelmingly dismal (3–6). Kanter et al. (3) initially reported, in 1987, a 100% mortality in patients requiring dialysis in the peri-implantation period. In a risk factor score model for mortality after VAD placement, Oz et al. (4) showed that renal dysfunction (defined as a urine output <30 ml/h) was the most significant risk factor for mortality, increasing it by 3.9 times. In a series of 55 patients with acute renal failure and cardiogenic shock treated with VAD at the German Heart Institute, six-month survival was only 7% and survival to transplantation was only 11% (5). Finally, data from the European registry of mechanical circulatory support indicated that renal failure was one of the most powerful predictors of both short-term and long-term mortality (6). These ominous results have led some to recommend that renal failure is an absolute contraindication to VAD placement (7).

Nonetheless, a number of small studies suggest that renal failure can be reversed with mechanical support. Burnett et
al. (8) showed in a study of six patients that renal failure often resolved with VAD placement, and that these patients could then be successfully transplanted. Our institution previously reported a 40% survival in patients with renal failure (defined as the need for continuous renal replacement therapy) and subsequent recovery of renal function in the surviving patients (9). Because of this continuing controversy, we examined our recent experience with 18 patients having severe renal dysfunction and cardiogenic shock treated with VAD insertion as a bridge to cardiac transplantation.

METHODS

We surveyed 215 consecutive patients who received a VAD from 1992 to 2000 at our institution according to standard criteria (10,11). We then selected patients who had a serum creatinine ≥3.0 mg/dl at the time of VAD placement. Demographic, laboratory, and clinical outcome data were collected. A VAD registry (Unified Transplant Database) is maintained at the Cleveland Clinic Foundation to facilitate analysis of patient outcomes. The Cleveland Clinic Foundation’s institutional review board has approved research based on this Unified Transplant Database.

All patients with renal failure had formal nephrology consultation. Urinalysis was performed and microscopic examination was conducted in all patients by the nephrologist. Renal ultrasound to rule out obstruction and document kidney size was performed in all patients. If patients had significant proteinuria on urinalysis, 24-h urine was collected to measure the level of protein excretion. If there were disparities in kidney size, either renal duplex ultrasound or renal magnetic resonance angiography was performed. Patients with significant proteinuria or small kidneys were excluded from consideration for VAD placement.

Peritransplant management consisted of avoidance of calcineurin antagonists, administration of cytolytic therapy early after transplantation, and initiation of cyclosporine both at reduced dose and at a later time after transplantation. Renal dose dopamine was administered as long as it did not cause tachyarrhythmias.

The treatment groups were compared using a Pearson chi-square test (gender, overall 6-month survival, and survival to transplantation), or if expected cell counts were small, a Fisher exact test (diabetes mellitus; extracorporeal membrane oxygenation pre-VAD; continuous venovenous hemodialysis [CVVHD] pre-VAD; overall 30-day survival; and 30-day, 6-month, and 1-year survival post-

RESULTS

Of 215 consecutive patients, 197 patients had a serum creatinine of <3.0 mg/dl; their demographic characteristics are outlined in Table 1.

Eighteen patients met the search criteria of serum creatinine ≥3.0 mg/dl (Table 1). This group consisted of 14 men and 4 women. The mean age was 53 ± 12 years (range 33 to 68 years). The etiology of cardiogenic shock was ischemic in 12 patients and nonischemic in six patients. Chronic renal insufficiency (serum creatinine ≥1.5 mg/dl) was noted in eight patients. One patient was on hemodialysis before VAD insertion for approximately one year. Further demographics are listed in Table 1.

The Thoratec HeartMate (Thoratec Corp., Pleasanton, California) device was implanted in 11 patients, and seven patients received the Novacor left ventricular assist system (World Heart Corp., Ottawa, Canada) device. The median time between the onset of renal failure and placement of a VAD was three days (range 0 to 370 days). The mean serum creatinine at the time of VAD placement was 3.0 ± 0.7 mg/dl (range 3.0 to 5.2 mg/dl). Seven patients required temporary renal support with CVVHD during the periimplantation period; four patients had it before VAD placement, and three patients had it after VAD placement. The mean time for dialysis support was 23 ± 6 days (range 1 to 70 days).

Seven VAD patients died before transplantation. In this group, three patients died early (<1 month) after VAD placement. All required renal support until the time of death (Fig. 1). Four patients survived for more than one month after VAD placement but ultimately died before transplantation; all four had resolution of severe renal dysfunction with mean serum creatinine of 1.9 ± 1.2 mg/dl at the time of death (range 0.8 to 3.6 mg/dl) without the need for transplantation. Analysis of variance f test results were used for continuous variables. Values are listed as mean ± SD.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-Renal Failure (n = 197)</th>
<th>Renal Failure (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>55 ± 11</td>
<td>53 ± 12*</td>
</tr>
<tr>
<td>Male</td>
<td>170/197 (86%)</td>
<td>14/18 (78%)*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>26/197 (13%)</td>
<td>1/18 (6%)*</td>
</tr>
<tr>
<td>ECMO pre-VAD</td>
<td>37/197 (19%)</td>
<td>7/18 (39%)*</td>
</tr>
<tr>
<td>CVVHD pre-VAD</td>
<td>2/197 (1%)</td>
<td>4/18 (22%)*</td>
</tr>
<tr>
<td>Time from hospital admit to VAD (days)</td>
<td>11.6 ± 19.4</td>
<td>11.8 ± 10.3*</td>
</tr>
<tr>
<td>Serum creatinine at VAD placement (mg/dl)</td>
<td>1.6 ± 0.6</td>
<td>4.0 ± 0.7‡</td>
</tr>
</tbody>
</table>

*p = NS; †p < 0.05; ‡p < 0.001.
CVVHD = continuous venovenous hemodialysis; ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.
further renal support (Fig. 1). In these patients, the cause of death was sepsis or stroke.

Eleven patients subsequently underwent cardiac transplantation. Serum creatinine had fallen from 4.1 ± 0.6 mg/dl at VAD placement to 1.6 ± 0.5 mg/dl at transplantation (Fig. 1). This improvement persisted at both three-month and six-month follow-up (Fig. 1). No patient required renal support therapy after transplantation. Of note, the patient on hemodialysis for one year before VAD placement had a serum creatinine of 2.1 mg/dl at six months post-transplantation.

Overall 30-day survival after VAD placement, six-month survival after VAD placement, survival to transplantation (Fig. 2), and survival 30 days, 6 months, and 1 year post-transplantation were similar in patients without renal failure and those with renal failure (Fig. 3).

**DISCUSSION**

In patients with severe renal dysfunction complicating cardiogenic shock, placement of a VAD as a bridge to cardiac transplantation is generally associated with overall excellent recovery of renal function in our series. No patient who ultimately received cardiac transplantation required long-term renal support, and transplantation was associated with excellent long-term outcomes. Even in patients who
did not receive transplantation, long-term (>1 month) survival with a VAD led to resolution of severe renal dysfunction in all cases despite eventual mortality from other causes. Only in those patients not transplanted who had early (<1 month) mortality did severe renal dysfunction and the need for renal replacement therapy persist.

Multiple factors may explain the differences in outcomes between our results and those of other investigators. One potential factor is that the definition of renal failure differs greatly between studies. Specifically, the need for renal replacement therapy defined renal failure in some studies, whereas other studies used urine output or elevations in serum creatinine. A series of patients needing renal replacement therapy may select a much sicker population that has developed irreversible end-organ damage. However, more than half of our patients who required renal replacement therapy were able to survive to transplantation. Thus, the requirement for dialysis support does not explain the difference in outcomes.

The type of renal replacement therapy used may have an impact on outcomes. Most of the studies documenting poor outcomes used either hemodialysis or hemofiltration as their primary means of renal replacement therapy. These methods of renal replacement therapy are known to be hemodynamically stressful and often difficult to use in these critically ill patients. In Kanter's study, for example, despite early institution of hemodialysis, adequate renal support was unable to be maintained (3). The use of continuous renal replacement therapy may be an attractive alternative because it has been shown to be an effective and well-tolerated therapy in hemodynamically unstable patients (12–14). Our institution has previously documented excellent management of fluid status, uremia, and electrolytes when continuous renal replacement therapy is used to treat acute renal failure in patients with VAD (9). Therefore, our exclusive use of continuous renal replacement therapy rather than hemodialysis may have contributed to our improved outcomes.

Yet, the majority of our patients did not require any renal replacement therapy. What explains their excellent outcome? The hemodynamic improvements after VAD insertion have been well described with dramatic improvements...
in cardiac output and significant decreases in elevated filling pressures (15). By rapidly improving cardiac function in these critically ill patients, VAD likely lead to reversal of renal hypoperfusion and a subsequent stabilization or improvement of renal function. Bank et al. (16) have shown that VAD placement, when compared with standard inotropic therapy, is associated with a reduction in the risk of developing acute renal failure, implying a renal protective effect of mechanical support. In addition, VAD placement in patients with renal failure has been shown to improve renal function, and in one nonrandomized study was shown to be associated with a dramatic improvement in mortality when compared with standard non-mechanical therapy (17). The improvements in renal function are likely explained by not only improved cardiac function but also subsequent correction of the abnormal neurohormonal milieu found in cardiogenic shock. James et al. (18) have shown that elevated levels of atrial natriuretic peptide, plasma aldosterone, plasma renin, and arginine vasopressin all significantly decrease after VAD insertion. In the end, these findings reflect the principle that the most effective therapy for renal failure in these patients may be correction of the cardiogenic shock with mechanical support.

Temporal trends in the use of VAD may also explain our results. Although our series included patients from as early as 1992, nearly all of our patients with severe renal dysfunction underwent VAD placement after 1994. Nearly all of the investigations indicating poor outcomes with renal failure included patients from the 1980s and early 1990s (3–6). Our report, therefore, reflects a more contemporary use of VAD than earlier reports. Increasingly, these devices have become first-line therapies for cardiogenic shock rather than a salvage therapy for patients who have failed conventional therapy. This change in the role of VAD has made it available to critically ill patients earlier in their illness before the development of permanent end-organ dysfunction. Therefore, one would expect that abnormal renal function would have a less negative impact on outcomes in more recent cohorts of patients. This view is supported by recently presented data from investigators at Columbia University. In their longitudinal study of risk factors for poor outcome after VAD placement, renal dysfunction, which in the past had a profound negative impact on survival, no longer adversely affects outcomes in patients treated after 1995 (19).

CONCLUSIONS

In patients with severe renal dysfunction complicating cardiogenic shock, early mechanical support with VAD led to subsequent long-term recovery of renal function. Furthermore, clinical outcomes including 30-day and six-month survival, survival to transplantation, and one-year survival after transplantation were comparable to those in patients without severe renal dysfunction. The development of acute renal failure should therefore not be viewed as an absolute contraindication to the placement of a VAD as a bridge to cardiac transplantation. In fact, its development may identify patients with an acutely deteriorating condition that would most benefit from stabilization with early institution of mechanical support.

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REFERENCES