Influence of Left Ventricular Assist on Valvular Regurgitation

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Background. The effects of mechanical left ventricular assist on the nonassisted right ventricle have not been fully elucidated. Current information indicates that the right ventricle benefits from a lower left atrial pressure; however, ventricular septal shifting and increased venous return caused by left ventricular assist impair right ventricular function. Acute intraoperative alterations in mitral and tricuspid valve regurgitation (MR and TR, respectively) may occur as a result of mechanical left ventricular assist but have not yet been documented.

Methods and Results. Eight patients undergoing implantation of a left ventricular assist device (LVAD) as a bridge to transplantation were studied during surgery by transesophageal echocardiography. MR was present in seven of eight patients, and TR was present in eight of eight patients before LVAD implant (mean MR jet area, 10.6±2.4 cm²; mean TR jet area, 4.8±1.0 cm²). Immediately after LVAD placement, MR was still present in seven of eight patients, and TR was present in eight of eight patients (mean MR jet area, 4.2±0.9 cm²; mean TR jet area, 8.4±1.9 cm²) (P<.05 preimplant versus postimplant jet area). These changes in MR and TR were associated with a decrease in left ventricular end-systolic dimension (62±4 versus 48±3 mm) and an increase in right ventricular end-systolic dimension (31±4 versus 40±5 mm) (P<.05 preimplant versus postimplant end-systolic dimension). No patients developed progressive right ventricular failure during 70 to 279 days of LVAD support.

Conclusions. Mechanical left ventricular assist causes an acute decrease in preexisting MR. However, left ventricular assist may acutely worsen TR, presumably by shifting the ventricular septum leftward and increasing venous return to the right ventricle. (Circulation. 1995;88:part 2:309-318.)

Key Words: transplantation • circulation • regurgitation

During the past three decades, a variety of ventricular assist devices have been designed to supplement or replace left ventricular function. Ventricular assist devices are currently used for temporary circulatory support pending recovery of the patient's natural heart or pending cardiac transplantation, and left ventricular assist devices (LVADs) capable of chronic support are under development. It is anticipated that chronically implantable LVADs will provide an alternative to transplantation for the treatment of end-stage cardiac failure.

One of the issues central to the development and use of LVADs is the effect of mechanical left ventricular assist on the nonassisted right ventricle. Several experimental studies have examined systolic and diastolic ventricular interactions in the setting of left ventricular assist, and the early experiences with a number of LVADs have been published. Mitral and tricuspid valve function before and 4 to 110 days after LVAD implantation have been described. However, to date, the acute effect of left ventricular assist on mitral and tricuspid valve function has not been investigated.

This report describes echocardiographic measurements of ventricular size and valvular regurgitation that were made during the implant of LVADs as a bridge to transplantation in eight patients. Comparisons were made between preimplant and postimplant ventricular dimensions and valvular regurgitation, and correlations were tested between the severity of valvular regurgitation and echocardiographic measurements of right and left ventricular size.

Methods

All eight patients had been accepted for cardiac transplantation before LVAD implantation. The patients were entered in a clinical ventricular assist device trial using LVADs from either Thoratec Laboratories Corp, Berkeley, Calif, or Thermo CardioSystems Inc, Woburn, Mass. Each patient met the specific criteria of the trial for profound heart failure (Appendix). After obtaining informed patient consent, the eight LVADs were implanted between August 27, 1990, and February 14, 1992. The only ventricular assist device available for the first three implants was the Thoratec device. Institutional and Federal Drug Administration approval for the use of the Thermo CardioSystems LVAD was received on June 1, 1991. After this date, all patients considered for LVAD support were randomized to receive one device or the other. Note that biventricular Thoratec assist devices were used in patients with intractable ventricular arrhythmias or severe right ventricular failure, as defined by a mean right atrial pressure of ≥20 mm Hg. Nine patients in our total series of
1. Thoratec and Thermo Cardiosystems ventricular assist device patients had biventricular assist devices.

All of the Thermo Cardiosystems LVADs were placed from the left ventricular apex to the aorta. In two Thoratec LVADs, the left atrium was cannulated from the right lateral aspect of the aortotomy between the right superior and inferior pulmonary veins. In the other two Thoratec LVADs, the apex of the left ventricle was cannulated (Table 1). The Thoratec LVAD outflow grafts were anastomosed to the ascending aorta. All LVADs were initially run in the fixed-rate mode but were switched to the variable-rate mode as soon as possible (ie, "automatic" pumping for the Thermo Cardiosystems drive console; "volume" pumping for the Thoratec drive console). In the variable-rate mode, the LVAD cycles asynchronously with regard to the patient’s intrinsic cardiac activity. During postimplant echocardiographic evaluation, the Thermo Cardiosystems and Thoratec devices were run in the variable-rate mode with relatively short ejection times (250 to 300 milliseconds).

Informed consent was obtained from all patients before transesophageal echocardiography. Transesophageal echocardiographic examinations were performed using a 5.0-MHz phased-array transducer (Hewlett-Packard Sonos-1000, Andover, Mass; Aloka 870 Color Doppler System, Wallingford, Conn). Standard transesophageal imaging planes were obtained in all patients. These planes included four chamber and transtegast line views. Pulsed Doppler interrogation of the left and/or right superior pulmonary veins near their entrance into the left atrium was also performed in six patients. In two patients, adequate preimplant transesophageal echocardiographic examinations were not obtained during surgery; therefore, closed chest transthoracic studies obtained before LVAD implantation were used for the comparisons. Transthoracic echocardiographic studies were performed with a 2.5-MHz phased-array transducer (Hewlett-Packard Color Doppler Imaging System). The transthoracic imaging included recordings of parasternal long-axis, short-axis, and apical four-chamber views.

During the transthoracic and transesophageal color Doppler studies, the color gain setting was optimized by gradually increasing the gain until static background noise first appeared. If mitral or tricuspid regurgitation was noted, the maximum regurgitant jet area was measured by planimetry. According to the measurement system of Yoshida et al, a regurgitant jet of <4 cm² represents mild regurgitation, 4.0 to 7.0 cm² represents moderate regurgitation, and >7.0 cm² represents severe regurgitation. At the University of Alabama at Birmingham (UAB) a slightly different scale is used. A jet of <6 cm² is associated with mild valve regurgitation, a jet of 6.0 to 10.0 cm² is associated with moderate regurgitation, and a jet of >10 cm² is associated with severe regurgitation (unpublished data, N.C. Nanda). In this study, the UAB scale was used to describe valvular regurgitation as mild, moderate, or severe.

Left and right ventricular end-diastolic and end-systolic dimensions were obtained before and after LVAD implantation from the four-chamber view. The end-diastolic dimension represents the maximum distance between the endocardial surface of the ventricular septum and the ventricular free wall; the end-systolic dimension represents the minimum distance between the endocardial surface of the ventricular septum and the ventricular free wall. These distances were measured at a point 3 cm below the mitral or tricuspid annulus. Pulmonary vein flow velocities were obtained by pulsed Doppler interrogation. The maximum amplitudes of the pulmonary vein systolic and diastolic waveforms were measured for subsequent comparisons.

All patients were off cardiopulmonary bypass with the chest open at the time of the postimplant echocardiogram. Each patient’s blood volume was adjusted according to the operating surgeon’s judgment of attaining optimal LVAD function without raising the mean right atrial pressure above clinically acceptable limits. At the time of postimplant echocardiography, negative pump pressure had not been activated in the Thoratec device.

Statistical analysis of the data was performed using SAS-PC software (SAS, Inc; Cary, NC). Within-group comparisons were made with a paired Student’s t test (contained in the “Means” procedure of SAS-PC). Pearson’s coefficients and P values for correlations were computed using the “Corr” procedure of SAS-PC. Subgroup comparisons (Tables 5 and 6) were made using an analysis of variance procedure (least-squares means test in the “General Linear Models” procedure of SAS-PC).
Results

The eight LVAD patients included one patient with acute myocarditis, four patients with idiopathic dilated cardiomyopathy, and three patients with ischemic heart disease. All patients had profound heart failure (Appendix) despite maximal conventional medical therapy. The patient with myocarditis was taken to the operating room on an emergency basis because of severe hypotension. One patient with ischemic heart disease was transferred to this institution on a centrifugal pump (Medtronic Bio-Medics Inc, Eden Prairie, Minn) LVAD after surgery for acute myocardial infarction. After evaluation and acceptance for cardiac transplantation, the centrifugal pump was replaced with a Thoratec LVAD. Other demographic and baseline hemodynamic data are contained in Table 1.

All patients survived LVAD implantation. One patient required mediastinal reexploration for delayed tamponade followed by a second reexploration for removal of an infected expanded polytetrafluoroethylene membrane that had been used to reconstruct the pericardium. Another patient experienced a cerebral air embolism from the LVAD; however, he ultimately made a full neurological recovery. All patients required catecholamine support during the immediate postimplant period; however, the right atrial pressures of the eight patients were maintained at ≤20 mm Hg (range, 11 to 20 mm Hg). Catecholamines were discontinued within the first 5 postimplant days in all patients. Temporary mechanical right ventricular assist or prostaglandin infusions were not used.

There was an improvement in circulatory function noted immediately after LVAD placement (Table 2). The mean systolic blood pressure rose from 84±4 to 111±7 mm Hg. The mean cardiac index rose from 1.8±0.1 to 2.8±0.2 L·min⁻¹·m⁻². This circulatory improvement was accompanied by a fall in the mean left atrial pressure from 26±2 to 5±1 mm Hg and a rise in the mean right atrial pressure from 10±2 to 16±1 mm Hg.

Transesophageal echocardiography demonstrated a decrease in left ventricular size and an increase in right ventricular size after initiating left ventricular assist (Table 3). The preimplant to postimplant changes were significantly (ie, P<.05) different for the left ventricular end-diastolic dimension, the left ventricular end-systolic dimension, and the right ventricular end-systolic dimension. The postimplant increase in right ventricular end-diastolic dimension bordered on significance (P=.051).

The determination of valvular regurgitant jet area by echocardiography (Table 3, Figs 3 and 2) showed a decrease in mitral jet area from 10.6±2.4 to 4.2±0.9 cm² and an increase in the tricuspid jet area from 4.8±1.0 to 8.4±1.9 cm². The raw data describing valvular regurgitant jet area before and after initiating LVAD pumping are displayed in Figs 3 and 4. Analysis of pulmonary vein flow velocity showed an increase in postimplant systolic flow that bordered on significance (0.1±0.2 to 0.6±0.1 m/s) (P=.056).

The four-chamber view of the heart suggested that there was a leftward displacement of the septum after initiating LVAD pumping (Fig 5A and 5B); however, this could not be accurately quantitated. Specifying septal position at various times in the cardiac cycle was difficult because the septum moved between the right and left ventricular cavities in a passively moving partition rather than an actively contracting muscular structure.

Correlations were sought between ventricular dimensions and regurgitant jet areas (Table 4). Significant correlations were discovered between the preimplant and postimplant dimensions of the right ventricle and the size of the tricuspid regurgitant jet as well as between the change in the right ventricular dimensions and the change in the tricuspid regurgitant jet. Interestingly, similar consistently significant correlations were not found for the left ventricular dimensions and the mitral regurgitant jet.

Subgroups of patients were compared according to the patient's pathology (ischemic cardiomyopathy, idiopathic dilated cardiomyopathy, or myocarditis), pump inflow cannulation site (left atrium or left ventricular apex), and type of LVAD (Thermo CardioSystems Inc and Thoratec) (Tables 5 and 6). Analysis according to cardiac pathology did not demonstrate any significant differences in ventricular dimensions or valvular regurgitation.
Fig 1. Transesophageal four-chamber view. Top, Examination before implantation of left ventricular assist device (LVAD) shows mosaic signals filling a large portion of the left atrium (LA) indicative of severe mitral regurgitation (MR). Bottom, Post-LVAD examination in the same patient demonstrates marked decrease in MR. LV indicates left ventricle; RA, right atrium; RV, right ventricle; and TR, tricuspid valve regurgitation.

Giant jet areas between the ischemic cardiomyopathy and the idiopathic dilated cardiomyopathy groups of patients. The patient with acute myocarditis had smaller ventricular dimensions and smaller valvular regurgitant jet areas than the patients with ischemic or idiopathic cardiomyopathy.
Fig 2. Transesophageal four-chamber view. Top, Examination before implantation of the left ventricular assist device (LVAD) shows a small area of mosaic color signals in the right atrium (RA) originating from the tricuspid valve during systole indicative of mild tricuspid regurgitation (arrowheads). Bottom, Post-LVAD examination in the same patient demonstrates the mosaic signals filling a large portion of the RA indicative of severe tricuspid regurgitation (TR). LA indicates left atrium; LV, left ventricle; and RV, right ventricle.

The left atrium was cannulated in patients considered to have potential for cardiac recovery. In this series, one patient with acute myocarditis and one patient with an acute infarction had ventricular assist device cannulations of the left atrium. These two patients tended to have smaller ventricular dimensions.
and valvular regurgitant jet areas than the other six patients, who were judged to have irreversible end-stage cardiac dysfunction.

An analysis was performed according to the type of LVAD used (Thermo Cardiosystems or Thoratec device). No consistent trends or significant differences were noted between groups.

Discussion

Controversy persists regarding the ability of an LVAD to provide adequate circulatory support in patients with an intermediate degree of right ventricular failure. Right ventricular function is difficult to quantitate precisely in the setting of severe left ventricular failure because of the increased afterload imposed on the right ventricle by elevated left ventricular diastolic pressure as well as the diminished volume stress on the right ventricle that results from poor left-sided systolic function. The inability to accurately quantify right ventricular function in the setting of severe left ventricular failure, in turn, makes it difficult to predict the response of the right ventricle to the acute decrease in afterload and increase in preload that result from mechanical left ventricular assist.

Predicting the function of the right ventricle after LVAD implantation in patients with an intermediate degree of right ventricular failure has been the subject of several experimental studies that examined systolic and diastolic ventricular interactions\(^1\) as well as reports that described clinical results of LVADs used as a bridge to transplantation.\(^4\)\(^-\)\(^15\) Currently available experimental evidence indicates that anatomic ventricular interactions play a relatively minor role in the normal heart subjected to mechanical left ventricular assist.\(^7\)\(^-\)\(^8\)

However, in experimental models of congestive heart failure, leftward septal shifting due to left ventricular unloading and volume loading of the right ventricle due to increased venous return appears to be detrimental to right ventricular function.\(^1\)\(^-\)\(^2\) Clinical studies of LVADs\(^1\)\(^-\)\(^1\)\(^5\) document a low incidence of right ventricular failure following LVAD implantation. However, temporary right ventricular assist devices have been necessary to sustain some patients immediately after LVAD implantation, and the mortality in this group of patients is higher than in the group that did not require temporary right-sided assist.\(^5\)\(^-\)\(^1\)\(^6\)

The present study documents the effect of left ventricular assist on mitral and tricuspid valve regurgitation. Some degree of mitral and tricuspid insufficiency was present in seven of the eight patients before surgery. One patient, who had acute myocarditis, had no detectable mitral valve regurgitation before or after LVAD placement. The other seven patients had predominantly mitral valve regurgitation (ie, mitral jet area tricuspid jet area) before LVAD implant. The severity of preimplant mitral valve regurgitation was correlated with preimplant left ventricular size, and the severity of preimplant tricuspid valve regurgitation was correlated with preimplant right ventricular size. These findings suggest that annular dilatation and chordal tension were responsible for the observed valvular insufficiency and that shifts in pressure and volume loads resulting from left ventricular assist could alter the severity of this insufficiency.

The mitral regurgitant jet area and the left ventricular dimensions decreased in allseven of the patients with preimplant mitral valve regurgitation after initiating LVAD pumping. The increase in the pulmonary vein systolic flow measurement, although of borderline significance, corroborates the decrease in mitral valve regurgitation observed after LVAD implant. Neither the changes in left ventricular dimensions nor the absolute postimplant left ventricular dimensions were significantly correlated with the postimplant mitral regurgitant jet area. This lack of correlation may be related to the small number of patients in the study.

Right ventricular dimensions increased, and the severity of tricuspid valve regurgitation increased after initiating left ventricular assist in six of the eight patients. In contrast to the left ventricle, the postimplant right ventricular end-systolic and end-diastolic dimensions were significantly correlated with the postimplant tricuspid regurgitant jet area. Moreover, the preimplant to postimplant change in right ventricular dimensions was significantly correlated with the preimplant to postimplant change in tricuspid regurgitant jet area. It is possible that, in the six patients with a postimplant increase in tricuspid regurgitation, the volume load imposed on the right ventricle by increased venous return and leftward shifting of the ventricular septum acutely diluted the tricuspid annulus and increased
Fig 5. Transesophageal four-chamber view. Examination after implantation of the left ventricular assist device (LVAD) demonstrates marked leftward displacement of the interventricular septum (arrowheads, bottom) that is not present in the pre-LVAD study (top). LA indicates left atrium; RA, right atrium; LV, left ventricle; and RV, right ventricle.

Tricuspid chordal tension. Thus, an increase in venous return to the right ventricle and leftward shifting of the ventricular septum may have caused the observed increase in tricuspid valve regurgitation.

The right atrial pressure increased significantly, and the left atrial pressure decreased significantly after LVAD implantation; however, clinical evidence of right ventricular failure did not develop in these eight pa-
Table 4. Correlation Testing

|                         | Pre TR | Post TR | ΔTR |
|-------------------------|--------|---------|-----|
| Pre RVED                | 0.72   |         |     |
| (P = .04)               |        |         |     |
| Pre RVES                | 0.76   |         |     |
| (P = .03)               |        |         |     |
| Post RVED               |         | 0.95    |     |
| (P = .003)              |        |         |     |
| Post RVES               |         | 0.99    |     |
| (P = .003)              |        |         |     |
| ΔRVED                   |         | 0.92    |     |
| (P = .001)              |        |         |     |
| ΔRVES                   |         | 0.76    |     |
| (P = .03)               |        |         |     |
| Pre MR                  | 0.75   |         |     |
| (P = .00)               |        |         |     |
| Pre LVES                | 0.68   |         |     |
| (P = .06)               |        |         |     |
| Post LVED               |         | 0.66    |     |
| (P = .06)               |        |         |     |
| Post LVES               |         | 0.51    |     |
| (P = .20)               |        |         |     |
| ΔLVED                   |         | 0.20    |     |
| (P = .03)               |        |         |     |
| ΔLVES                   |         | 0.10    |     |
| (P = .02)               |        |         |     |

Pre indicates before implant; TR, tricuspid regurgitant jet area; Post, after implant; RVED and RVES, right ventricular end-diastolic and end-systolic dimension, respectively; MR, mitral regurgitant jet area; and LVED and LVES, left ventricular end-diastolic and end-systolic dimension, respectively.

Table 5. Subgroup Analyses of Regurgitant Jet Areas

| Subgroup       | n | Pre TR, cm² | Post TR, cm² | Pre MR, cm² | Post MR, cm² |
|----------------|---|-------------|--------------|-------------|--------------|
| Pathology      |   |             |              |             |              |
| Idiopathic CM  | 4 | 6.2±1.8     | 11.9±2.5     | 11.5±1.8    | 4.2±0.7      |
| Ischemic CM    | 3 | 3.8±0.9     | 9.7±5.1      | 13.0±3.8    | 5.6±1.7      |
| Myocarditis    |   | 2.4         | 2.3          | 0           | 0            |
| Cannulation site|  |             |              |             |              |
| LA             | 2 | 2.4±0.1     | 2.2±0.1      | 1.6±1.6     | 1.4±1.4      |
| LV apex        | 6 | 5.7±1.2     | 10.5±1.9     | 13.6±1.9    | 5.1±0.9      |
| Type of LVAD   |   |             |              |             |              |
| Thermo         | 4 | 4.7±1.4     | 10.5±2.3     | 12.3±2.7    | 4.2±0.7      |
| Thor           | 4 | 5.0±1.7     | 6.4±3.1      | 8.9±4.3     | 4.2±1.9      |

Pre and Post TR indicate tricuspid regurgitant jet area before and after, respectively, initiating left ventricular assist device (LVAD) pumping; Pre and Post MR, mitral valve regurgitant jet area before and after, respectively, initiating LVAD pumping; CM, cardiomyopathy; LA, left atrium; LV, left ventricular; Thermo, LVAD from Thermo Cardiosystems Inc, Woburn, Mass, and Thor, LVAD from Thoratec Laboratories Corp, Berkeley, Calif. Values are mean±SEM.

Appendix

Inclusion Criteria for Thoratec and Thermo Cardiosystems Clinical Trials

I. Thoratec ventricular assist device
   A. Inclusion criteria
      1. Male or female aged 15 to 54 years
      2. Acceptable heart transplant candidate
      3. Inevitable risk of dying before donor heart procurement
      4. Dependence on, or incomplete response to, continued vasopressor support
      5. Hemodynamic guidelines for cardiac failure
         a. Cardiac index < 1.8 L·min⁻¹·m⁻²
         b. Systolic arterial pressure < 90 mm Hg
         c. Left atrial pressure > 20 mm Hg
         (In spite of appropriate use of conventional therapies, such as inotropic agents, vasodilators, and an intra-aortic balloon pump)
      6. Informed consent of the patient or family
      7. Adequate psychological criteria and external psychological support
   B. Exclusion criteria
      1. Fixed pulmonary hypertension (ie, pulmonary vascular resistance > 6 Wood units)
      2. Irreversible hepatic or renal failure

Table 4 of the report from Circulation Vol 88, No 5, Part 2, November 1993.
TABLE 6. Subgroup Analyses of End-Systolic and End-Diastolic Dimensions

| Subgroup                  | Pre RVES, mm | Post RVES, mm | Pre RVED, mm | Post RVED, mm | Pre LVES, mm | Post LVES, mm | Pre LVED, mm | Post LVED, mm |
|---------------------------|--------------|---------------|--------------|---------------|--------------|---------------|--------------|--------------|
| Pathology                 | n            | Pre RVES, mm  | Post RVES, mm| Pre RVED, mm  | Post RVED, mm| Pre LVES, mm  | Post LVES, mm| Pre LVED, mm  | Post LVED, mm|
| Idiopathic CM             | 4            | 36±4          | 38±4         | 56±2          | 67±3         | 52±4          | 69±3         | 55±4         |
| Ischemic CM               | 3            | 30±6          | 35±6         | 41±5          | 63±2         | 48±4          | 66±3         | 53±7         |
| Myocarditis               | 1            | 16            | 17           | 21            | 22           | 33            | 34           | 42           | 41           |
| Cannulation site          |              |               |              |               |              |               |              |              |
| LA                        | 2            | 21±5          | 22±5         | 26±7          | 27±5         | 47±13         | 37±3         | 52±9         | 42±1         |
| LV apex                   | 6            | 35±4          | 46±5         | 37±4          | 53±5         | 66±2          | 52±3         | 69±2         | 56±3         |
| Type of LVAD              |              |               |              |               |              |               |              |              |
| Thermo                    | 4            | 29±3          | 44±6         | 32±3          | 52±7         | 65±2          | 49±4         | 67±3         | 52±3         |
| Thor                       | 4            | 33±8          | 36±9         | 38±7          | 41±9         | 57±8          | 47±6         | 62±7         | 53±6         |

Pre and Post RVES indicate right ventricular end-systolic dimension before and after, respectively, initiating left ventricular assist device (LVAD) pumping; Pre and Post RVED, right ventricular end-diastolic dimension before and after, respectively, initiating LVAD pumping; Pre and Post LVES, left ventricular end-systolic dimension before and after, respectively, initiating LVAD pumping; Pre and Post LVED, left ventricular end-diastolic dimension before and after, respectively, initiating LVAD pumping; CM, cardiomyopathy; LA, left atrium; LV, left ventricular; Thermo, LVAD from Thermo Cardiovascular Inc. Woburn, Mass.; and Thor, LVAD from Thoratec Laboratories Corp, Berkeley, Calif. Values are mean±SEM.

3. Severe peripheral or cerebrovascular disease (recent stroke, flat electroencephalogram, fixed dilated pupils)
4. Diabetes requiring insulin
5. Active systemic infection
6. A recent pulmonary embolus
7. The absence of adequate psychological criteria and external psychosocial support

II. Thermo Cardiovascular ventricular assist device
A. Approved patient categories
1. Category I
   a. Approved transplant candidate
   b. On inotropes
   c. On a balloon pump (if possible)
   d. Left atrial pressure or pulmonary capillary wedge pressure of ≥20 mm Hg with
   1. Systolic blood pressure of ≤80 mm Hg
   2. Cardiac index of ≤2.0 L·min⁻¹·m⁻²
2. Category II
   a. Approved transplant candidate
   b. On inotropes; on intra-aortic balloon pump, if possible
   c. Cardiac arrest
   d. Systolic blood pressure of ≤60 mm Hg
B. Exclusion criteria
1. Body surface area of <1.5 m²
2. Age of >70 years
3. Chronic renal failure
4. Refractory anuria
5. Creatinine level of >5.0 mg/dL
6. Blood urea nitrogen level of >100 mg/dL
7. Severe cardiomyopathy
8. Severe chronic obstructive pulmonary disease
9. Unresolved pulmonary infarction
10. Severe pulmonary hypertension, with pulmonary vascular resistance of ≥8 Wood units
11. Depressed right heart function, with right ventricular ejection fraction of ≤10%
12. Intractable ventricular tachycardia
13. Severe hepatic disease
14. Cerebral vascular disease with cerebral impairment
15. Severe gastrointestinal malabsorption
16. Active systemic infection
17. Severe blood dyscrasia
18. Cancer, unresolved malignancy

19. Diffuse severe peripheral vascular disease
20. Long-term high-dose steroid therapy
21. Positive HIV test
22. Prolonged (>60 minutes) unsuccessful attempts to resuscitate the fibrillating or arrested heart

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