COMPLICATIONS OF EXTRACORPOREAL LIFE SUPPORT SYSTEMS USING HEPARIN-BOUND SURFACES

The risk of intracardiac clot formation

Extracorporeal life support with heparin-coated extracorporeal membrane oxygenation circuits are being used with increased frequency in patients who have cardiogenic shock. We report our experience in 30 patients with cardiogenic shock, looking specifically at the complications associated with this form of life support. Thirty patients with a mean age of 46.5 ± 16.6 years received extracorporeal life support for a mean of 62.8 ± 41.1 hours (range 0.5 to 159 hours). Twenty-three patients had postcardiotomy cardiogenic shock, five had acute myocardial infarction, and one each had acute cardiac deterioration after a balloon coronary angioplasty and another after pulmonary artery balloon angioplasty. Peripheral (femoral vein to femoral artery) cannulation was used in 24 patients. Limb ischemia developed in 21 patients (70%), renal failure in 17 patients (57%), oxygenator failure requiring change in 13 patients (43%), bleeding requiring reexploration in 12 (40%), and infection in 9 patients (30%). Transesophageal echocardiography revealed intracardiac thrombus formation in 6 patients (20%) and clot was visualized grossly in the pump head in 2 patients (6%) necessitating pump-head change. Nine patients (30%) were discharged home. We conclude that the use of heparin-coated extracorporeal life support without systemic heparinization, especially after protamine has been used to reverse systemic heparinization in patients having postcardiotomy cardiogenic shock, may be dangerous. Extracorporeal life support has introduced new complications unique to itself specifically limb ischemia, oxygenator failure, and pump-head thrombus. (*J THORAC CARDIOVASC SURG* 1995;110:843-51)

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Extracorporeal life support with an extracorporeal membrane oxygenation (ECMO) circuit is being used more frequently to support adult patients who have cardiogenic shock^{1,2} and has been shown to provide excellent oxygenation and hemodynamic support.¹⁻³ Binding heparin to the extracorporeal circuit provides a more biocompatible surface, minimizing early surface-induced complement activation and platelet dysfunction, which may improve patient survival.⁴ Moreover, the heparin-coated sur-

face has been proposed, in experimental and clinical reports, to obviate the need for systemic heparinization. The absence of heparin may reduce bleeding problems,^{5,6} especially in patients who have postcardiotomy cardiogenic shock. Superb clinical results have been recorded with heparin-bound extracorporeal life support circuits without systemic heparinization.³ Nonetheless, the safety of avoiding systemic heparinization when blood is allowed to circulate outside the body despite a heparin-coated extracorporeal circuit has been questioned^{7,8} because thrombin is activated. This report demonstrates that thrombus formation within the heart and in the ECMO circuit is a potential hazard of foregoing heparin administration in patients supported by extracorporeal devices having heparin-bound surfaces. We report our experience with 30 patients treated with extracorporeal life support for cardiogenic shock, looking specifically at the complications associated with the technique.

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Table I. Causes of cardiogenic shock and procedures performed

	<i>Pts</i>
Postinfarction cardiogenic shock	5
Postcardiotomy cardiogenic shock	23
Heart transplantation	4
Redo CABG	4
CABG	4
Pulmonary artery reconstruction	2
Postinfarction VSD/CABG	2
Redo CABG/MV repair	1
Redo CABG/AVR	1
AVR/MVR	1
Septal myectomy	1
Aortic autograft (Ross)	1
Aortic homograft/MV repair	1
Descending aortic aneurysmectomy	1
Failed angioplasty	2
Pulmonary artery dilatation (angioplasty)	1
Acute myocardial infarction	1

CABG, Coronary artery bypass grafting; VSD, ventricular septal defect; MV, mitral valve; AVR, aortic valve replacement; MVR, mitral valve replacement.

Patients and methods

During the 22-month period between September 1992 and July 1994, 30 patients in cardiogenic shock were treated with a venoarterial extracorporeal life support system that had heparin-bound tubing (Carmeda, Medtronic, Inc., Minneapolis, Minn.). The criterion to use ECMO for cardiac support was the inability to treat shock adequately by means of conventional methods of support. The largest group of patients ($n = 23$) had postcardiotomy cardiogenic shock. These patients remained in shock despite an anatomically correct surgical procedure, after all metabolic, rhythm, and respiratory abnormalities had been corrected. The patients could not be weaned from bypass despite high doses of at least two inotropic agents (usually after intraaortic balloon pump [IABP] placement). Although the age of the patients was taken into consideration, emergency cases were not excluded. This group represented 0.38% of all patients undergoing cardiac operations during this time interval at The Cleveland Clinic. Seven patients, including five having postinfarction cardiac shock and two having shock after unsuccessful angioplasty, were treated with ECMO after all attempts at stabilization failed to produce an adequate cardiac output in the cardiac catheterization laboratory. All patients were receiving high-dose inotropic support and six of the seven had an IABP inserted. Table I describes the causes of cardiogenic shock and procedures performed. The hospital records, extracorporeal life support records, cardiopulmonary bypass records, and blood transfusion records of each patient were retrospectively reviewed. Additionally, transesophageal echocardiographic studies before and during extracorporeal life support were evaluated for the presence of intracardiac clot formation, spontaneous contrast (representing stagnant blood flow), and left ventricular dilatation (left ventricular end-diastolic diameter greater than 6 cm).

Table II. Method of cannulation for extracorporeal life support

	<i>No. of patients</i>
Femoral vein to femoral artery (percutaneous)	24
Right atrium to ascending aorta (open chest)	5
Femoral vein to ascending aorta (open chest)	1

Complications including intracardiac clot formation, stroke, oxygenator failure, pump-head failure, infection, need for reexploration for bleeding, limb ischemia (limb discoloration, coolness to touch, or loss of sensation), need for hemodialysis or ultrafiltration, and blood transfusions were recorded. Results were computed for patients as a whole. Complications were analyzed with respect to age, mode of cannulation, duration of cardiopulmonary bypass for patients having postcardiotomy cardiogenic shock, length of time receiving extracorporeal life support, height, weight, body surface area, time when support was initiated (intraoperative, postoperative, in the catheterization laboratory), use of an IABP, use of systemic heparinization, and average pump flows. Univariate logistic regression analysis of these parameters was performed to identify clinical predictors of intracardiac clot formation, ability to be weaned, and death.

The ECMO circuit was composed of a hollow-fiber, microporous membrane oxygenator (Maxima, Medtronic) and heat exchanger (Cincinnati Sub Zero, Cincinnati, Ohio), an oxygenator blender (Sechrist Industries, Inc., Anaheim, Calif.), and an arteriovenous loop made from standard 3/8-inch Tygon tubing (Norton Performance Plastics, Wayne, N.J.). A centrifugal biopump (Medtronic) was used. All components of the system with blood contact were heparin coated (Carmeda BioActive Surface), as were all cannulas. Wire-wound heparin-coated (Carmeda) arterial and venous cannulas were used for arterial return from the ECMO circuit and for venous drainage, respectively (Medtronic). Arterial cannula sizes varied from 17F to 21F and venous cannulas ranged from 18F to 20F. The decision to cannulate the femoral vessels (which were preferred) or the mediastinal great vessels was based on the size of the femoral artery and the amount of venous return. If the femoral artery was too small to accept the smallest arterial cannula or if the patient had peripheral vascular disease, then the aorta was used for blood return from the ECMO circuit. If the venous return was poor or the aorta had to be used for blood return from the ECMO circuit, then the right atrium was cannulated. Patients were treated according to the surgeon's preference, and six surgeons and four cardiologists were responsible for initial ECMO cannulation. We did not use distal leg perfusion.

Table II describes the method of cannulation for extracorporeal life support. The majority of cannulas were inserted via the femoral vein and femoral artery. In 24 patients the ECMO cannulas were placed percutaneously. These 24 include 17 patients with postcardiotomy cardiogenic shock, in all of whom the mediastinal incisions were closed to help control bleeding and prevent infection. In six other patients having postcardiotomy cardiogenic

shock, the ascending aorta was cannulated and the sternal incisions were not closed. In total, we managed six patients by not closing the mediastinal incision. The femoral artery and vein were used in all patients in whom percutaneous ECMO was initiated in the catheterization laboratory. Patients with signs of tamponade or persistent excessive mediastinal hemorrhage despite correction of clotting factors (prothrombin time, partial thromboplastin time, activated clotting time, and platelet count) had an exploratory operation either in the intensive care unit if the chest had been left open or in the operating room if the sternotomy incision had been closed completely. Twenty-three patients had an IABP inserted before extracorporeal life support was begun. The IABP was used in an effort to decrease afterload, as described by Lazar and associates.⁹ The seven patients not treated with IABP support included four patients in whom ECMO was initiated in the postoperative period in the intensive care unit (14 to 77 hours after the operation), two pediatric patients, and one patient with postcardiotomy cardiogenic shock in whom the surgeon chose not to use it. Systemic heparinization was used in only five patients (average dose 700 units/hr) because of the surgeon's concern for not using systemic heparin with the ECMO circuit. Average pump flows during extracorporeal life support were 3.75 ± 1.05 L/min (range 1.1 to 5.8 L/min).

Transesophageal echocardiography was routinely performed in all patients at multiple times during the extracorporeal life support period. Furthermore, transesophageal echocardiography was used during attempts to wean patients from the life support circuit. Patients with intracardiac thrombus formation were managed by having the clot removed ($n = 3$) surgically or, if this was believed too dangerous, systemic heparinization was begun ($n = 3$).

In patients treated with extracorporeal life support for postcardiotomy cardiogenic shock, systemic heparinization was reversed with protamine during the operation after the ECMO circuit was in place and running. Patients in whom life support was begun in the cardiac catheterization laboratory or after the operation in the intensive care unit were given 5000 units of heparin at the time of insertion of the life support circuit and no protamine was given. All patients received 5000 units of heparin intravenously during periods of low flow or pump stasis (i.e., changing of an oxygenator or pump head). Similarly, 5000 units of heparin was given during periods of weaning from the life support circuit. Heparin was otherwise not routinely continued during support, except in five patients. In the five patients receiving intravenous heparin, activated clotting times were kept greater than 200 seconds. Otherwise activated clotting times were not measured routinely. Epsilonaminocaproic acid (Amicar) was used in six patients undergoing a second cardiac operation. Aprotinin was not used in any patient. Bleeding was treated by transfusion of packed red blood cells, fresh-frozen plasma, platelets, and cryoprecipitate when necessary. Left ventricular selective decompression was not used. During ECMO, the patients were weaned from inotropic agents if possible (except renal dose dopamine) to prevent further myocardial ischemia. No effort beyond IABP use was made to ensure that pulsatile flow was maintained.

With the aid of a transesophageal echocardiogram to

visually inspect the heart, weaning attempts were made when cardiac recovery was evident after 24 hours of assistance. Pump flow was gradually reduced as cardiac function was determined with transesophageal echocardiography. If good ventricular ejection was maintained while the patient was being weaned from the ECMO and a native cardiac index of 2.2 L/min per square meter could be maintained, extracorporeal life support was discontinued. Nine patients who were believed to have irreversible left ventricular dysfunction and who otherwise were candidates for cardiac transplantation were converted from the ECMO system to a more durable implantable left ventricular assist device (HeartMate, Thermo Cardiosystems, Inc., Woburn, Mass.). These patients were less than 65 years old, had not demonstrated adequate improvement in left ventricular function to allow weaning from the ECMO circuit, and were thought to have intact neurologic function. All patients were cleared for transplantation before receiving an implantable left ventricular assist device.

Results are recorded as mean $\pm$ standard deviation. Continuous variables were analyzed by Student's *t* test or the Wilcoxon two-sample test. Fisher's exact test for 2×2 tables was used for categorical variables. Analysis was considered statistically significant at the $p < 0.05$ level. Univariate logistic regression analyses were performed for the variables that converged and were significantly related ($p \approx 0.05$) to the outcomes. Multivariate analyses were not performed because of the small sample size.

Results

The average patient age was 46.5 ± 16.6 years (range 5 to 70 years). Twenty-one were male. Two patients were younger than 19 years and two older than 70 years of age. The average duration of extracorporeal life support was 62.8 ± 42.1 hours (range 0.5 to 159 hours). In patients having postcardiotomy cardiogenic shock, cardiopulmonary bypass lasted an average of 225.3 ± 122.4 minutes (range 87 to 626 minutes). Of the 23 patients having postcardiotomy cardiogenic shock, 15 received the ECMO in the operating room and nine during the postoperative period, an average of 70.8 ± 103.9 hours (range 12 to 122 hours) after the operation. Twelve of 23 patients having postcardiotomy cardiogenic shock required reexploration for bleeding, including six patients whose chests were left open. Nine patients received an implantable left ventricular assist device (HeartMate) as a bridge to potential heart transplantation. Five of these patients had postinfarction cardiogenic shock and the other four had postcardiotomy cardiogenic shock. Two patients who had received a left ventricular assist device later required placement of a right ventricular assist device. One of these patients remained hypoxic despite the absence of a patent foramen ovale, and

an oxygenator was added to the assist device circuit. Five patients who received a left ventricular assist device subsequently had heart transplantation, and all were discharged home after 106 ± 15 days of left ventricular assist device support (Table III).

Complications. Complications develop frequently in patients receiving extracorporeal life support (Table IV). Limb ischemia was the most common complication and was found only in the patients cannulated percutaneously via the femoral artery. Although 21 patients (70%) had signs of ischemia (coolness, loss of sensation, or discoloration), only nine patients (30%) required thrombectomy and one an amputation. Renal dysfunction was also common. Over half of the patients (17) required either dialysis (47%) or continuous venovenous ultrafiltration (10%). Seven patients developed infectious complications. Bacteremias (all gram-positive cocci) developed in six patients and mediastinitis (*Staphylococcus epidermidis*) in one. In all but one, bacteremia was transient and cleared with antibiotics and changing of central lines. In one case the bacteremia progressed to endocarditis (*S. epidermidis*) and was the cause of death in that patient. Oxygenator failure occurred in 13 patients. The mean number of oxygenator changes was 2.25 ± 1.0 (range 1 to 4) per patient in whom an oxygenator failed. The mean time to oxygenator failure was 41.7 ± 28.9 hours (range 5 to 103 hours). Four patients required pump-head change, two because clot was detected within the pump head and two prophylactically because of excessive noise and vibration of the pump potentially signaling pending pump failure.

Table V demonstrates the significant results of transesophageal echocardiography while patients were receiving extracorporeal life support. Marked left ventricular distention developed in half the patients. In six patients, intracardiac clot was found to have developed during extracorporeal life support (see Table III). All had prior echocardiograms failing to identify thrombus. None of the patients in whom intracardiac clot developed during extracorporeal life support had received systemic heparinization. Clot developed in the left atrium in two patients (both had indwelling left atrial pressure monitoring lines) and in the left ventricle in four. In two patients intracardiac thrombus developed while protamine was being given to reverse systemic heparinization immediately after cardiopulmonary bypass. Both were being monitored with transesophageal echocardiography at the time of clot formation.

In one patient the entire ECMO circuit became clotted and he died in the operating room. Four patients who received extracorporeal life support had postoperative intracardiac thrombus, first noted at 37.5 ± 28.7 hours (range 6 to 72 hours). Table VI demonstrates the prothrombin time, partial prothrombin time, and platelet count at the time of postoperative thrombus identification in these four patients.

Blood transfusion was common during the extracorporeal life support. The amount of blood transfused during the entire hospitalization broken down by components is demonstrated in Table VII. No significant difference was noted in the amount of blood transfused to patients bridged to transplantation compared with that needed by the other patients treated only with extracorporeal life support.

Survival. Twelve patients died during extracorporeal life support (40%). Nine patients were transferred to an implantable left ventricular assist device for possible heart transplantation (30%). Of these patients, five received hearts and were discharged home. Nine patients were weaned from extracorporeal life support, and four were discharged home from the hospital. Overall, nine patients treated by extracorporeal life support (30%) were successfully discharged home.

Statistical analysis revealed that in patients in whom intracardiac thrombus developed, oxygenator changes were more frequently required (3/6 versus 9/24, $p = 0.038$), as well as red blood cell transfusion (38.29 versus 58.00, $p = 0.028$). When placed into a univariate logistic regression analysis model, the number of oxygenators changed was too small for convergence, but the greater the number of red blood cells transfused the greater the likelihood of intracardiac clot formation. Variables associated with the ability to be weaned from ECMO included male sex ($p = 0.013$). Interestingly, on univariate logistic regression analysis the presence of a dilated left ventricle was a negative predictor of ability to be weaned from ECMO ($p = 0.032$) and male sex a positive predictor of ability to be weaned ($p = 0.011$). Variables associated with hospital deaths included longer bypass time ($p = 0.045$) in patients having postcardiotomy cardiogenic shock, length of time supported by ECMO ($p = 0.008$), and number of packed red blood cells transfused ($p = 0.045$). The need for oxygenator change was also associated with death ($p = 0.049$). When placed into a univariate logistic regression analysis, none proved to be predictors of death.

Table III. Important patient characteristics

Patient No.	ECMO placement (hr)	Cannula location	IABP use	TEE findings	Heparin use	Blood transfusions, PRBC (U)	Device failures	Weaned or HeartMate LVAD	Survival	Cause of death
1	OR	RA to Ao	Yes	Dilated LV	No	49	No	Yes	Yes	
2	OR	Femoral	Yes	Dilated LV	No	44	No	HeartMate	Yes	
3	OR	Femoral	Yes	Dilated LV	No	21	No	Yes	Yes	
4	ICU (16) postop.	Femoral	Yes	Dilated LV/contrast	No	43	No	HeartMate	Yes	
5	OR	Femoral	No		No	40	No	No	No	Cardiac
6	OR	Femoral	Yes	Dilated LV/clot	No	67	No	No	No	Endocarditis
7	OR	RA to Ao	Yes		No	39	No	No	No	Cardiac
8	OR	FV to Ao	Yes	Spontaneous contrast	No	43	Oxygenator change	No	No	Multiorgan failure
9	OR	Femoral	Yes	Dilated LV/clot	No	41	No	HeartMate	No	Cardiac
10	ICU (77)	Femoral	No	Clot	No	73	Oxygenator change $\times 1$	No	No	Multiorgan failure
11	ICU (322)	Femoral	No		No	16	Oxygenator change $\times 2$	Yes	Yes	
12	ICU (48)	Femoral	Yes		No	51	Oxygenator change $\times 2$, pump-head change	No	No	Cardiac
13	ICU (14)	Femoral	No	Dilated LV/clot	No	97	Oxygenator change $\times 1$, pump clot	Yes	No	Cardiac
14	OR	Femoral	Yes	Dilated LV	No	11	Oxygenator change $\times 2$	Yes	No	Cardiac
15	Cath Lab	Femoral	Yes		No	26	Oxygenator change $\times 3$	No	No	Multiorgan failure
16	Cath Lab	Femoral	No		Yes	22	Pump-head change	No	No	ARDS
17	OR	RA to Ao	No	Dilated LV	Yes	10	No	Yes	Yes	
18	OR	Femoral	Yes	Dilated LV	No	79	No	No	No	Multiorgan failure
19	ICU	Femoral	Yes	Dilated LV	No	58	Oxygenator change $\times 2$	HeartMate	No	Multiorgan failure
20	OR	Femoral	Yes	Dilated LV	No	32	No	HeartMate	Yes	
21	ICU	Femoral	Yes	Spontaneous contrast	Yes	50	No	HeartMate	Yes	
22	OR	Femoral	Yes	Spontaneous contrast	No	65	Oxygenator change $\times 2$	No	No	Cardiac
23	Cath Lab	Femoral	Yes	Dilated LV/spontaneous contrast	No	66	No	HeartMate	No	Multiorgan failure
24	ICU (12)	Femoral	No	Clot	No	32	No	No	No	Rupture hypogastric artery aneurysm
25	ICU (29)	Femoral	Yes	Contrast	No	31	Oxygenator change $\times 2$	Yes	No	Cardiac
26	Cath Lab	Femoral	Yes	Contrast	No	40	No	HeartMate	No	Multiorgan failure
27	Cath Lab	Femoral	Yes		No	12	No	HeartMate	Yes	
28	OR	RA to Ao	Yes		No	45	No	Yes	No	Multiorgan failure
29	ICU (48)	Femoral	Yes	Dilated LV	Yes	26	Oxygenator change $\times 1$	No	No	Cardiac
30	OR	RA to Ao	Yes	Dilated LV/contrast/clot	No	44	Oxygenator change $\times 2$, pump clot	Yes	No	Multiorgan failure

ECMO, Extracorporeal membrane oxygenator; IABP, intraaortic balloon pump; TEE, transesophageal echocardiography; PRBC, packed red blood cells; LVAD, left ventricular assist device; OR, operating room; ICU, intensive care unit; Cath Lab, catheterization laboratory; RA, right atrium; Ao, aorta; FV, femoral vein; LV, left ventricle; ARDS, adult respiratory distress syndrome.

Table IV. *Complications of extracorporeal life support*

	Patients	
	No.	%
Limb ischemia (discoloration, coolness, or loss of sensation)	21	70
Dialysis	14	47
Oxygenator failure	13	43
Bleeding necessitating reexploration	12	40
Infection	9	30
Bacteremia	6	
Pneumonia	2	
Mediastinitis	1	
Pump head change	4	13
Cerebral vascular accident	3	10
Continuous venovenous ultrafiltration	3	10

Table V. *Transesophageal echocardiographic findings during extracorporeal life support*

	Patients	
	No.	%
Dilated left ventricle	15	50
Sluggish intracardiac blood flow	8	27
Intracardiac thrombus	6	20
Microbubbles coming from arterial cannula	2	7

Discussion

The first successful use of a ventricular assist device for postcardiotomy cardiogenic shock was reported by Spencer and associates¹⁰ in 1965. In 1979 we began a program using centrifugal pumps for patients with postcardiotomy cardiogenic shock. During the 12-year period from August 1979 to August 1991 a total of 91 patients were supported with such devices.¹¹ Although we were able to wean 62% of our patients from ventricular assist device support, only 25.3% were discharged from the hospital. Moreover, the major morbidity was due to bleeding (87.3%), as well as renal failure (46.8%), which eventually led us to look at alternative modes of ventricular support associated with less bleeding and multiorgan failure. During this time there was a resurgence in the use of ECMO for adults having cardiogenic shock. In 1984 Pennington and colleagues¹² reported on a group of 14 patients with postcardiotomy cardiogenic shock who were supported with venoarterial extracorporeal life support for almost 60 hours. Only three patients were weaned, but all were young and were not bleeding when the life support system was inserted. The other patients in this series had significant problems with

Table VI. *Clotting parameters at the time of clot detection*

Prothrombin time (sec)	15.9 ± 2.8 (range 12.7-19.6)
Partial thromboplastin time (sec)	39.7 ± 14.8 (range 30.3-61.5)
Platelet count	85.3 ± 43.3 100,000 (range 60-150,000)

Table VII. *Average blood products transfused per patient*

Packed red blood cells (U)	42.4 ± 21.0 (range 10-97)
Fresh frozen plasma (U)	7.9 ± 11.0 (range 0-5)
Platelets (U)	55.3 ± 39.2 (range 12-192)
Cryoprecipitate (U)	46.3 ± 37.2 (range 0-144)

bleeding hemolysis and progressive multisystem organ failure. In 1991, the Carmeda Corporation in Stockholm, Sweden, released a heparin-coating process that was used to produce an antithrombogenic surface.¹³ This process was applied to extracorporeal tubing in addition to the hollow-fiber microporous oxygenator surface.⁴ Subsequent clinical reports demonstrated reduced fibrin deposition, granulocyte activation,¹⁴ and complement activation.¹⁵ The heparin-bonded surface appeared to protect against the inflammatory response of prolonged extracorporeal support and reduced the amount of bleeding when little or no systemic heparinization was used.^{6, 16} Bindler,¹⁶ Mottaghy,⁶ and their coworkers reported excellent hemodynamic support with minimal postoperative blood loss using a heparin-coated (Carmeda) extracorporeal circuit without systemic heparinization in experimental animals for up to 5 days. Clinically, Magovern and colleagues³ reported excellent results in patients with postcardiotomy cardiogenic shock using a heparin-coated ECMO circuit and no systemic heparinization. They were unable to demonstrate any evidence for disseminated intravascular coagulation, and thrombin was not measured. Data were unavailable as to whether patients had evidence of stagnant intracardiac blood, left ventricular distention, or intracardiac clot formation. The 20% incidence of intracardiac thrombus formation in our series detected by transesophageal echocardiography, in patients treated with heparin-coated ECMO circuits without routine systemic heparinization, represents a major limitation to this technique. Moreover, we have probably underestimated the risk of intracardiac thrombus formation because some thrombi could have been below the resolution

of transesophageal echocardiography. As an example, in one of our patients an old intracardiac thrombus was noted at the time of left ventricular assist device placement as a bridge to heart transplantation. This thrombus had not been detected on transesophageal echocardiography and, if counted, would actually increase the incidence of intracardiac thrombus in our report to 23.3%. Moreover, it is unlikely that clot detected on transesophageal echocardiography was misdiagnosed as intracardiac thrombus. In all six patients having intracardiac thrombus, the clotting was documented on pathologic specimens. In three patients the thrombus was confirmed at a second operation; in another one patient the entire ECMO circuit became clotted, and the patient died; in another patient clot was removed at the time of left ventricular assist device implantation as a bridge to cardiac transplantation; and in the sixth patient thrombus was confirmed at autopsy.

Thrombus formation in patients supported with heparin-coated ECMO circuits without systemic heparinization is not a new finding. Magovern and coworkers³ reported that thrombus developed in three of 21 patients (14.2%) in whom this support strategy was used. Two patients had clot in a cannula and one had a cerebrovascular accident and was retrospectively noted to have an intracardiac thrombus after the ECMO system had been removed. Transesophageal echocardiography has also been shown to be sensitive in detecting thrombus formation in patients in whom a heparin-coated ECMO circuit and reduced systemic heparinization were used. Cheung and coworkers⁸ reported on a patient in whom intracardiac thrombus developed after mitral valve replacement for which the systemic heparin dose was 1 mg/kg during the bypass run. A low concentration of systemic heparin was used because the patient had had a hemorrhagic brain infarction and required an urgent operation. Post-bypass intraoperative transesophageal echocardiography before protamine administration demonstrated that a thrombus had formed on the bioprosthesis. Emergency reoperation was performed and the clot was removed.

Several factors may be responsible for the formation of intracardiac thrombi. The abnormal albeit heparin-coated surface of the extracorporeal circuit may have contributed significantly. Blood contact with abnormal surfaces, even in the presence of heparin, causes activation of factor XII (Hageman factor),¹⁷ which initiates a body defense reaction resulting in thrombin formation in an effort to

prevent bleeding. Hageman factor activates factor X, which is the gateway to the common coagulation pathway producing thrombin. Heparin works by neutralizing thrombin formation largely after the clot is formed, not before. In addition to blood being exposed to abnormal surfaces, stagnant intracardiac blood flow may also have contributed to thrombus formation. With decompression of the heart during full extracorporeal life support, stagnant blood flow was frequently documented on transesophageal echocardiographic scans. Although decompressing the failing heart in an effort to diminish myocardial oxygen demand by decreasing left ventricular end-diastolic pressure is theoretically beneficial, this practice may actually promote clot formation. The increased afterload inherent to ECMO circuits compounds this problem by inhibiting blood from exiting the heart. Use of IABP has been advocated as a method of decreasing afterload in these patients and thereby hastening myocardial recovery.⁹ Unfortunately, the IABP represents another abnormal intravascular foreign body, which may further stimulate the coagulation system. It is unclear whether selective left ventricular decompression would have prevented intracardiac clot or improved myocardial recovery. Even when the left ventricle was able to eject blood, as demonstrated by pulsatile blood flow on an arterial pressure monitoring trace, intracardiac thrombus was still able to form in several of our patients. Therefore, intracardiac blood flow is not the only answer to preventing intracardiac clot formation. Furthermore, heparin boluses given at times of decreased blood flow, such as during weaning or oxygenator changes, were inadequate to prevent intracardiac clot formation; therefore, systemic heparinization is probably required for the duration of support, preferably after massive bleeding has subsided.

Giving protamine at the conclusion of cardiopulmonary bypass to reverse heparin after the life support system had been implemented may also have promoted thrombin generation. von Segesser and associates⁵ recently demonstrated that reversing systemic heparinization with protamine in animals supported by a heparin-coated ECMO circuit markedly increased fibrin formation within the circuit and promoted platelet and red blood cell deposition. Protamine administration effectively neutralized the heparin surface coating. This finding has also been shown in *in vitro* experiments with toluidine blue. Artificial surfaces with heparin surface coating are stained readily with toluidine blue. (This test is

routinely used for qualitative screening of heparin-coated surfaces in the development of manufacturing techniques for heparin-coated devices). If a heparin-coated polyvinylchloride tubing segment is dipped on one side in protamine solution and thereafter stained with toluidine blue, the part exposed to protamine does not fix the staining agent. The protamine deactivates surface-bound heparin. It is interesting that thrombus only developed in our patients having postcardiotomy cardiogenic shock after protamine was given and in no patients receiving systemic heparin. The patients in Magovern's series³ in whom clot developed also had been given protamine to reverse systemic heparinization after heart operations. Therefore, no protamine should be given during perfusion with heparin-coated equipment. Although protamine is useful after standard cardiopulmonary bypass, it can be avoided. Heparin spontaneously degrades with time, and fresh-frozen plasma and coagulation factors can be given to avoid protamine administration. More recently, an extracorporeal heparin reversal device in which the hollow fibers are immobilized with poly-L-lysine has been developed,¹⁸ which obviates the need for protamine. Had we not reversed systemic heparin with protamine in patients having postcardiotomy cardiogenic shock, the incidence of thrombus formation may have been lower. However, if protamine does neutralize the heparin coating on extracorporeal tubing, it remains to be seen whether systemic heparinization is needed if protamine is not used.

Our study points out the high rate of complications associated with extracorporeal life support systems for which peripheral cannulation without systemic heparinization is used. The most frequent complication we observed was limb ischemia, and clearly better ways of peripheral cannulation are needed. The reported advantages of percutaneous peripheral cannulation include the ease of initiating extracorporeal life support in emergency situations. Peripheral cannulation also allows for chest closure, and no re sternotomy is required to remove the cannula. Methods of dealing with limb ischemia in patients cannulated peripherally have included separate proximal and distal femoral artery catheters to perfuse the patient as well as the limb distally, using right-angled high-flow arterial cannulas to permit bidirectional arterial cannula flow.¹⁹ More recently, we have begun to use distal leg perfusion and have found this to significantly reduce the incidence of leg ischemia.

Moreover, the incidence of complications associated with the use of ECMO is similar to the rate of complications with centrifugal pumps at our institution. It is difficult, however, to determine if most complications are a result of the treatment rather than a complication of the disease state. Nonetheless, renal failure necessitating dialysis or continuous venovenous ultrafiltration was similar to the 43.2% incidence of patients requiring hemodialysis and the 13.5% incidence of patients requiring continuous ultrafiltration in our cohort of 91 patients supported with a centrifugal mechanical ventricular support system reported in 1992. Moreover, the transfusion requirements for patients managed with extracorporeal life support with heparin-bound extracorporeal circuits not maintained on systemic heparinization was not different from the 87.3% of patients requiring massive transfusion supported with the centrifugal mechanical ventricular support devices with systemic heparinization reported in our earlier study in 1992.¹¹ Similarly, the incidence of cerebral vascular accidents and infections was comparable. New complications unique to extracorporeal life support, however, were recognized, as described earlier.

The need to change the oxygenator occurred in 43%. Thirteen percent of our patients required pump-head changes, half of the time because of clot formation in the pump head. Had heparinization been used during the extracorporeal run, this may have reduced the number of pump-head changes required; however, whether it would have influenced the rate of oxygenator failure is unclear. Clearly, hollow-fiber oxygenators fail more frequently if clots form in the oxygenator. Intracardiac thrombus was more frequently seen in patients requiring oxygenator changes. One limitation of our study was that the patients who underwent oxygenator change did not have their oxygenators examined microscopically for thrombus formation. Adding systemic heparinization potentially could have reduced the need for oxygenator changes and pump-head changes. Another limitation of our study is that the two types of circulatory support were not compared during the same trial period in comparable patients or in a prospective fashion. Nonetheless, the incidence of complications and survival rates appear to be similar.

In conclusion, the strategy of using heparin-coated extracorporeal life support systems without systemic heparinization is not without risk. Intracardiac thrombus formation and perhaps an increased

incidence of oxygenator failure appears to limit this strategy. Until clinical studies document the safe use of these circuits without systemic heparinization, especially when protamine has been avoided, systemic heparinization should be used. Use of heparin throughout the period of support appears justified and protamine should not be given. Furthermore, the use of peripheral cannulation in an effort to reduce mediastinal blood loss after postcardiotomy cardiogenic shock must also be questioned, and distal leg perfusion with a separate catheter may help prevent leg ischemia. Transfusion requirements were similar to those in historical reports of patients cannulated via the mediastinum with centrifugal pumps. Although we were not able to find an advantage of extracorporeal life support using a heparin-coated ECMO circuit compared with our historical results using centrifugal pumps and systemic heparinization, many of the problems unique to ECMO support may be surmountable.

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