Cardiopulmonary Support and Physiology

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Clinical experience with 202 adults receiving extracorporeal membrane oxygenation for cardiac failure: Survival at five years

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Objectives: We sought to determine 5-year survival after extracorporeal membrane oxygenation for cardiac failure and its predictors, to assess survival and its predictors after bridging to transplantation or weaning from extracorporeal membrane oxygenation, and to identify factors influencing the likelihood of these outcomes.

Methods: Two hundred two adults (mean age, 55 ± 14 years) were supported with extracorporeal membrane oxygenation between 1992 and July 1999 after cardiac failure. Follow-up extended to 7.5 years (mean, 3.8 ± 2 years). Multivariable hazard function analysis identified predictors of survival, and logistic regression identified the determinants of bridging or weaning.

Results: Survival at 3 days, 30 days, and 5 years was 76%, 38%, and 24%, respectively. Patients surviving 30 days had a 63% 5-year survival. Risk factors ($P < .1$) included older age, reoperation, and thoracic aorta repair. Forty-eight patients were bridged to transplantation, and 71 were weaned with intent for survival. Survival was similar after either outcome (44% vs 40% 5-year survival, respectively). Failure to bridge or wean included ($P < .03$) renal and hepatic failure on extracorporeal membrane oxygenator support, occurrence of a neurologic event, and absence of infection. The dominant modes of death were cardiac failure and multisystem organ failure.

Conclusions: Extracorporeal membrane oxygenation is versatile and salvages some patients who would otherwise die. Improvement in intermediate-term outcome will require a multidisciplinary approach to protect organ function and limit organ injury before and during this support.

Extracorporeal life support (extracorporeal membrane oxygenation [ECMO]) in newborns, infants, and children has been widely reported to have excellent results.[1,2] ECMO in adults is less widely practiced and has met with less success. The focus of most reports has been on events during and shortly after ECMO.

Evolving from the experience with postcardiotomy centrifugal pump support at The Cleveland Clinic Foundation, ECMO has been used for circulatory support in a relatively large number of adults. The purpose of this study was primarily to determine intermediate-range (5-year) survival and its pre-ECMO predictors. Secondarily, survival and its predictors were assessed separately among patients bridged from ECMO to transplantation or weaned from ECMO with the intent of survival. To achieve the secondary purpose, we also identified both pre-ECMO and ECMO factors that were related to whether a patient was bridged to transplantation, weaned from ECMO, or withdrawn from ECMO because of futility.

Patients and Methods
Patients
Between 1992 and July 1, 1999, 202 patients were supported with ECMO after cardiac failure. Patients with right ventricular failure after insertion of an implantable left ventricular assist device (LVAD) supported with ECMO as a right ventricular assist device were not included in the analysis nor were patients supported by venovenous ECMO for respiratory support. Patients supported with ECMO ranged in age from 18 to 82 years (mean, 55 ± 14 years), and 145 (72%) were men. The general clinical characteristics of these patients are presented in Appendix Tables A and B.

Of the 202 patients, 107 (53%) had undergone cardiotomy (Appendix Table C). Among the patients receiving ECMO after cardiotomy, 60 (56%) had undergone an isolated coronary artery bypass grafting procedure, 19 (18%) had undergone coronary artery bypass grafting and a valve operation, 15 (14%) had undergone a valve operation, 8 (7%) had undergone repair of congenital heart disease, 4 (4%) had undergone aortic aneurysm repair, and 1 (1%) had undergone left ventriculectomy.

Conduct of ECMO
ECMO was initiated at the discretion of the operating or transplant surgeon or interventional cardiologist, usually within 30 to 45 minutes of deciding to support the patient. For postcardiotomy patients, failure to wean from bypass on inotropic agents and intra-aortic balloon pump (IABP) support prompted ECMO insertion. Absolute hemodynamic criteria were not used. For patients in shock, ECMO was preferred over direct LVAD support because many patients had prior cardiac operations, were near death, and candidacy for transplantation had not been clarified.

Venoarterial ECMO was instituted by means of peripheral cannulation (common femoral artery and vein) in 153 (76%) patients and central cannulation (ascending aorta and right atrium or common femoral vein) in 49 (24%) patients.

The ECMO circuit and cannulation protocols have been described in detail previously.[3,4] In brief, the circuit is based on a centrifugal blood pump (Bio-Pump BP-80; Medtronic Bio-Medicus, Eden Prairie, Minn) in conjunction with an oxygenator (Maxima Plus PRF, Medtronic Cardiac Surgery; Medtronic, Inc, Anaheim, Calif). All components are heparin coated. The patient is heparinized as early as possible to attain an activated clotting time of 180 to 250 seconds.

All patients were supported with the intention to wean from ECMO. Intravenous inotropic doses were reduced but continued at a lower level to maintain ventricular ejection. IABP support was encouraged while patients received ECMO. Atrial septostomy or ventricular venting was not used. Recovery was assessed daily by means of clinical, hemodynamic, and echocardiographic findings. When recovery was unlikely or uncertain, transplant screening was initiated. Candidacy for transplantation and LVAD bridge was made on a case-by-case basis. The only absolute contraindication was profound neurologic injury, which was usually corroborated by computed tomographic scan, and severe active infection. Mild-to-moderate encephalopathy, elevated bilirubin and creatinine levels, and treated intravenous line and pulmonary infections did not exclude a patient from bridge-to-transplant consideration. In patients with absolute contraindications to transplantation, weaning was performed with the intent for survival. ECMO was withdrawn from some patients with the knowledge that survival was unlikely and continued support was futile.

Follow-up
Because the focus of this study was on time-related survival, all patients were followed up as of March 2000. At that time, the range of follow-up time among the 51 patients still alive was 1.1 to 7.5 years (mean, 3.8 ± 1.62 years). Among the 151 patients who died, median survival was 5 days, and 142 (94%) of the 151 deaths were within the first 6 months.

Methods of Data Analysis
Descriptive. Descriptive statistics are summarized as means and SDs for continuous variables when they were approximately normally distributed but as medians, 25th and 75th percentiles, and ranges when they were not. Categorical variables are expressed as percentages.

Analytic strategy. The primary end point for this study was death at any time after the start of ECMO. Secondarily, we examined time-related survival after weaning from ECMO with the intent for survival (n = 71) or bridge to transplantation (n = 48). This secondary aim required that we also identify the predictors of bridging, weaning, or withdrawal of ECMO life support.

Nonparametric estimates of survival were obtained by following the method of Kaplan and Meier.[5] A parametric method was used to resolve the number of phases of instantaneous risk of death (hazard function) and to estimate their shaping parameters.[6]* For the primary end point of survival, time zero was taken as the start of ECMO. For the secondary analysis of survival after bridging or weaning, time zero was taken as the time the patient was removed from ECMO.

Multivariable analyses. For the primary multivariable analysis of time-related survival, the question being answered was as follows: What are the factors associated with time-related survival that are known at the time of decision making for ECMO? Thus, the variables entered into the analysis included demography, cardiopulmonary comorbidity, noncardiac comorbidity, the type of cardiac procedure that may have preceded ECMO, and indications for ECMO (Appendix 1).

*Available by anonymous ftp from ftp:\\uabcvsr.cvsr.uab.edu.

TABLE 1. Complications during ECMO

Complication	No.	%
Infections	99	49
Dialysis	81	40
Neurologic events	66	33
Pump thrombus	12	6
Limb complications	51	25
Ischemia*	37	18
Fasciotomy	4	2
Vascular repair	6	3
Amputation	4	2

*Medically treated.

TABLE 2. Highest values during ECMO support

| Variable | n | Percentile | | | | |
		Minimum	25	50	75	Maximum
BUN (mg/dL)	170	9	25	40	59	167
Creatinine (mg/dL)	173	0.6	1.5	2.2	3.3	6.5
AST (U/L)	170	1	92	204	475	21,000
Total bilirubin (mg/dL)	179	0.3	1.7	3.1	8.9	103

BUN, Blood urea nitrogen; *AST*, aspartate aminotransferase.

For the secondary analyses of survival after bridging or weaning, the question being answered was as follows: What are the pre-ECMO factors associated with survival, and what additional contribution did events during ECMO make? Thus, a sequential analysis was performed, first with pre-ECMO variables as delineated above and then with variables related to events occurring during ECMO and maximal recorded values for measurements made during ECMO (Tables 1 to 3).

Initial screening of variables possibly related to survival used the log-rank test and the Cox proportional hazards model. Continuous and ordinal variables were assessed univariably by means of decile analysis to suggest transformations of scale to incorporate into the multivariable analysis to ensure that the relation of these variables to outcome was well calibrated with respect to model assumptions. For each of the hazard models, the analysis was performed simultaneously for each hazard phase. Variables were identified by a guided technique of entry of variables into the multivariable models.[7]

The *P* value criterion for retention of variables in the final model was .1. This liberal criterion was chosen because of the possibility that important variables related to survival would be overlooked by too stringent a variable retention criterion as a result of the relatively small number of deaths (type II error). However, this strategy exposed us to the risk of model overdetermination, whereby risk factors cease to be general common denominators and become identifiers of specific individuals in the data set who have died (type I error). Therefore, the low frequency of occurrence variables was not used to balance these

TABLE 3. Neurologic complications during ECMO support

| Event | Weaned (n = 71) | | Bridged (n = 48) | | Withdrawn (n = 83) | |
	n	%	n	%	n	%
Encephalopathy	14	20	10	21	23	28
Intracranial bleeding	4	6	1	2	8	10
Stroke	2	3	1	2	3	4
Total	20	28	12	25	34	41

errors, and all analyses were supplemented with bootstrap resampling variable selection.[8,9] For this, observations were sampled at random (with replacement) from the data set to generate a new data set 75% the size of the original. This process was repeated 1000 times. An automated stepwise variable selection was performed (retention criterion, *P* = .1) for each bootstrap data set. For clusters of highly correlated variables, such as transformations of the same or similar variables (age and body size), only one member of each cluster was entered. By means of this tactic, the frequency of occurrence of variables within each category yielded an accurate assessment of the likelihood that one member of that cluster should belong in the final model, and it identified which transformation was the most likely one. Thus, the risk factors identified were not only statistically significant but also must have occurred with the highest frequency, as determined with bootstrap analysis.[10]

The final strategy for the analysis was to identify those factors that resulted in patients either being considered unsalvageable (withdrawn, n = 83), bridged (n = 48), or weaned with intent for survival (n = 71). These were considered competing risks. Therefore, multivariable logistic regression analysis was used with the variables and strategies as stated above but with pairwise conditional groupings of patients, such that in the final analysis the probability of an individual patient belonging to each of the 3 groups added to 100%.[11] For these analyses, we sequentially used factors known before ECMO and again after the addition of the factors concerning the complications of and the process of ECMO.

Presentation. Because only 12 (6%) patients have been followed up beyond 5 years, presentation of time-related survival has been truncated at 5 years.

Nonparametric Kaplan-Meier time-related estimates are accompanied by asymmetric confidence limits equivalent to 1 SE.[12] Parametric estimates are accompanied by confidence limits equivalent to 1 SE.[12]

Tables of risk factors identified in the hazard domain are presented with their regression coefficients rather than hazard ratio because the model is one of nonproportional hazards. Instead, because the hazard function multivariable analyses are completely parametric (generating an equation), nomograms from the analyses are presented in which specific variables, such as age and creatinine level, are entered into the equations, the equations are solved, and the results are presented graphically with confidence limits. This same strategy was used in the logistic regression domain.

All confidence limits presented in this article are equivalent to 1 SE (68%) for consistency with the presentation of mean values to 1 SD.
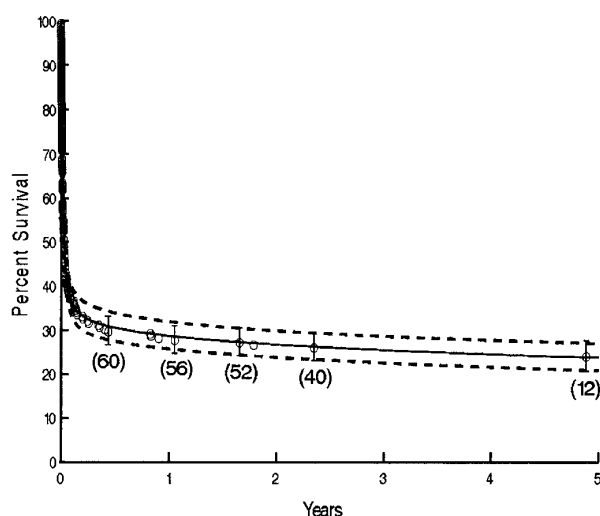
Figure 1. Survival after commencing ECMO (time zero). Each *symbol* represents a death positioned at the time of death on the horizontal axis and by the Kaplan-Meier estimator on the vertical axis. Periodically, *vertical bars* represent asymmetric confidence limits equivalent to 1 SE. The *numbers in parentheses* are the number of patients remaining at risk at the time interval shown. The *solid lines* are parametric estimates enclosed in confidence limits equivalent to 1 SE.
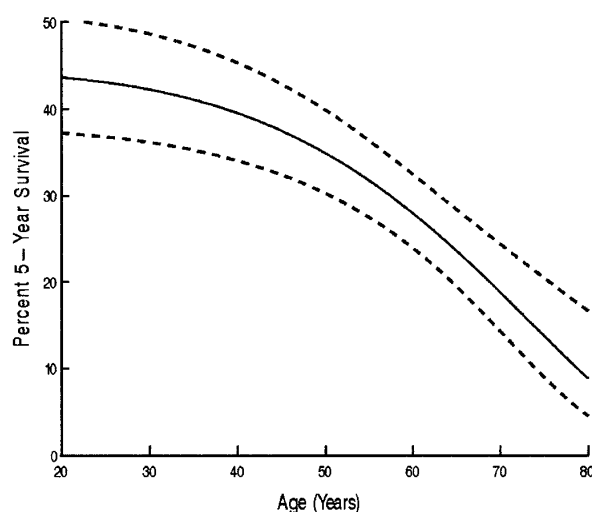

Figure 2. Risk-adjusted relation of age and 5-year survival. This is a so-called nomogram of Table 4, in which height was set to 170 cm, creatinine level was set to 1.5 mg/dL after a primary nonthoracic aortic operation, no preoperative decompensation was used, and IABP was used.

Results
Survival

Survival at 24, 48, and 72 hours after initiation of ECMO was 90%, 83%, and 76%, respectively. By 1 week, 2 weeks, and 30 days, survival had fallen to 58%, 45%, and 38%. By 90 days, 1 year, 3 years, and 5 years, survival was 33%, 29%, 26%, and 24%. Patients surviving at 30 days had a 63% 5-year survival. The instantaneous risk of death had 2 distinct phases: an early high initial rate of death fell to merge at about 1 year with a slowly declining hazard rate (Figure 1).

Pre-ECMO risk factors for death are shown in Table 4. They included older age, with an evident difference in survival above approximately age 55 years (Figure 2). Shorter height was a risk factor that was stronger than female sex. Four patients had prior operations on the thoracic aorta, and all died within 4 days of the start of ECMO. Patients who had a history of an open-chest operation before the present hospitalization leading to ECMO support were at higher risk, as were patients in whom an IABP was not used and patients who were experiencing decompensated heart failure or cardiogenic shock.

ECMO Complications and Values

Complications occurring while patients were receiving ECMO included infection in 49%, requirement for dialysis in 40%, neurologic events in 33%, and limb complications in 25% (Table 1). The median transfused units of packed

TABLE 4. Pre-ECMO risk factors for death after initiating ECMO

Incremental risk factors for death	Coefficient ± SD	*P* value
Early hazard phase		
Demographic		
Older age*	0.29 ± 0.101	.004
Shorter height	−0.031 ± 0.0113	.006
Cardiac comorbidity		
Primary operation†	−0.56 ± 0.26	.03
Procedure		
Thoracic aortic operations	2.1 ± 0.63	.0007
Late hazard phase		
Cardiac comorbidity		
Reoperation†	1.68 ± 0.51	.001
Nonuse of IABP	−0.93 ± 0.41	.02
Indication for ECMO		
Decompensated heart failure-shock	1.18 ± 0.46	.01

*$[age/50]^3$; cubic transformation.
†The negative coefficient indicates that patients undergoing reoperation were more likely to survive the early phase of risk, but the positive coefficient in the late hazard phase indicates they were more likely to have poor survival. Thus, in total their death was somewhat protracted in time.

cells was 14 (25th percentile, 8; 75th percentile, 21; minimum, 0; maximum, 99).

ECMO Outcomes

Forty-eight patients were bridged to transplantation, 71 were weaned from ECMO with intent for survival, and 83

TABLE 5. Factors increasing the likelihood of bridging from ECMO

Variable	Logistic coefficient ± SD	*P* value
Pre-ECMO model		
Demographic		
Younger age*	−0.24 ± 0.079	.002
Noncardiac comorbidity		
Nondiabetic	−1.28 ± 0.64	.05
Cardiac comorbidity		
Use of IABP	1.01 ± 0.43	.02
Indication for ECMO		
Decompensated heart failure-shock	1.54 ± 0.51	.003
Intercept	13.8	
C statistic	0.79	
Pre-ECMO and on-ECMO model		
Demographic		
Younger age*	−0.27 ± 0.087	.002
Taller†	0.61 ± 0.26	.02
Indication for ECMO		
Decompensated heart failure-shock	1.68 ± 0.57	.003
During ECMO		
Lower total bilirubin‡	−0.67 ± 0.26	.01
Absence of neurologic events§	−1.36 ± 0.41	.0009
Additional lower limb cannulation	1.40 ± 0.57	.01
Intercept	16.0	
C statistic	0.86	

*Uniform age relation to age 60 years and then continuous age thereafter.
†[ln[−ln[height−100]/100]]^2; normalized squared transformation.
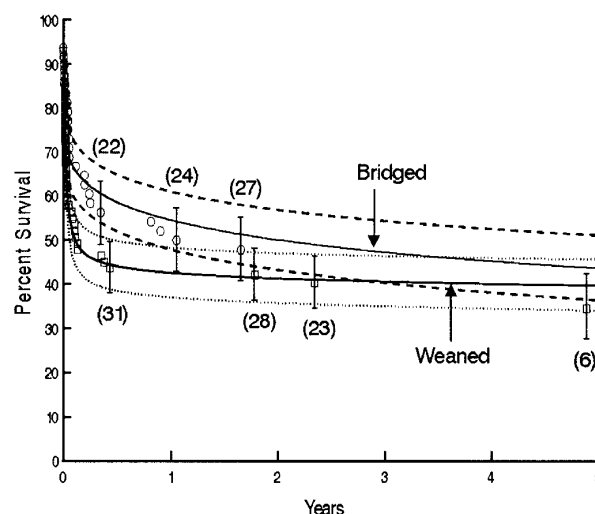‡ln[total bilirubin]; natural logarithmic transformation.
§0 = None, 1 = encephalopathy, 2 = stroke; negative coefficient indicates less likelihood of bridging when neurologic events occurred.

Figure 3. Survival after discontinuing ECMO (time zero) stratified according to the outcome of ECMO: bridged or weaned. Format of the depiction is as for Figure 1.

TABLE 6. Pre-ECMO and on-ECMO factors increasing the likelihood of weaning from ECMO

Variable	Logistic coefficient ± SD	*P* value
Pre-ECMO factors		
Use of IABP	0.57 ± 0.33	.08
Intercept	−0.48	
C statistic	0.57	
On-ECMO factors		
Infection	1.76 ± 0.42	<.0001
Lower total bilirubin*	−0.57 ± 0.21	.008
Lower creatinine†	1.94 ± 0.84	.02
Surgically managed limb	1.70 ± 0.81	.03
Intercept	−1.37	
C statistic	0.77	

*ln[total bilirubin]; natural logarithmic transformation.
†[1/creatinine]; inverse transformation.

were withdrawn from ECMO because of futility. Forty-one percent of those withdrawn from ECMO experienced a neurologic event (Table 3).

Bridged patients. Patients were more likely to be considered for bridging to transplantation if they were younger than 60 years of age and if their heart failure had severely decompensated, leading to ECMO support (Table 5). In addition, nondiabetic patients were more likely to be bridged, as were patients in whom an IABP was used. When events occurring during ECMO and measurements made during ECMO (Tables 1-3) were added to the analysis, lower total bilirubin levels during ECMO, the need for additional lower limb cannulation, and the absence of neurologic events were added (Table 5).

Survival after being bridged from ECMO to an LVAD (n = 42) or directly to transplantation (n = 6) was 85%, 67%, 54%, and 44% at 7 days, 30 days, 1 year, and 5 years, respectively, after cessation of ECMO (Figure 3). Survival to transplantation was 67%, with 92% of these patients alive 6 months after transplant. Of the 42 patients bridged to an

LVAD, 25 (60%) survived to transplantation. The only risk factor for death was older age (*P* = .02). Patients who had encephalopathy during ECMO experienced reduced survival after being bridged, with 1- and 5-year survivals of 14% among these 10 patients compared with 61% and 55% among the 38 without this complication (*P* = .04).

Weaned patients. Patients were more likely to be weaned if IABPs were being used (Table 6). Thus, of the 71 patients weaned, 45 (63%) were receiving pre-ECMO IABP support compared with 41 (49%) of the 83 withdrawn from ECMO (*P* = .08). When events during ECMO and measurements were added to the analysis, use of IABP was displaced by
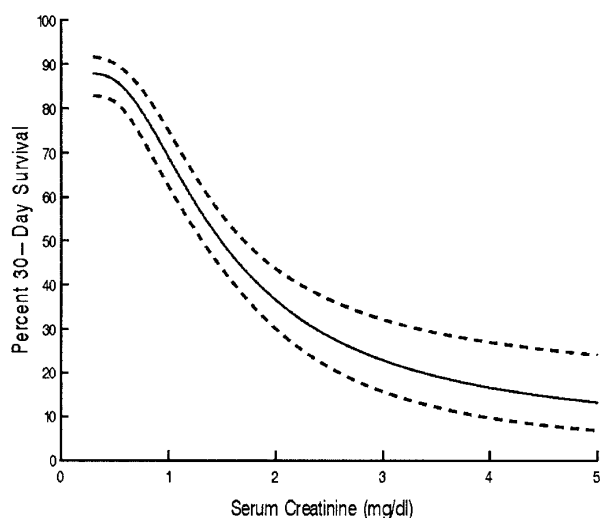
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Figure 4. Risk-adjusted relation of 30-day survival after being weaned from ECMO to pre-ECMO serum creatinine levels. The depiction is a nomogram of Table 7, in which height was set to 170 cm and international normalized ratio to 1.2.

TABLE 7. Risk factor for death after weaning from ECMO with intent for survival

Risk factors for death	Coefficient ± SD	P value
Early hazard phase		
Demographic		
Shorter height*	11.8 ± 4.0	.003
Noncardiac comorbidity		
Higher creatinine†	−1.02 ± 0.28	.0003
Late hazard phase		
Higher INR‡	−2.7 ± 1.25	.03

INR, International normalized ratio.
*[170/height (cm)]; inverse transformation.
†[2.5/creatinine]; inverse transformation.
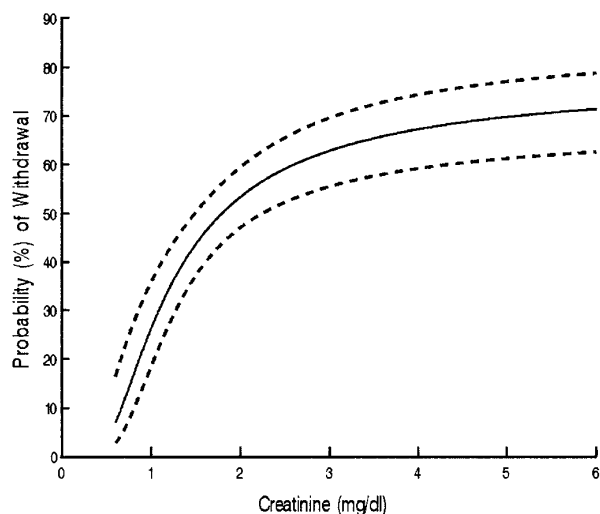‡[1/INR]^2; inverse squared transformation.

Figure 5. Risk-adjusted relation of ECMO serum creatinine levels to the probability of withdrawal of ECMO. The depiction is as in Figure 4, except bilirubin was set at 3.5 mg/dL, neurologic events were set to "no," pump head clots were set to "no," and infection was set to "no."

TABLE 8. Pre-ECMO factors increasing the likelihood of withdrawal of ECMO

Variable	Logistic coefficient ± SD	P value
Pre-ECMO model		
Demographic		
Shorter height*	−0.28 ± 0.156	.07
Cardiac comorbidity		
Nonuse of IABP	−0.60 ± 0.30	.04
Intercept	0.33	
C statistic	0.60	
On-ECMO model		
Demographic		
Shorter height*	−0.36 ± 0.177	.04
On-ECMO factors		
Higher creatinine†	−2.3 ± 0.83	.005
Higher bilirubin‡	0.55 ± 0.193	.005
Neurologic events§	0.53 ± 0.25	.04
No infection‖	−1.70 ± 0.38	<.0001
Pump head clots	1.38 ± 0.71	.05
Intercept	1.00	
C statistic	0.77	

*[In [−In[height−100]/100]]^2.
†[2.5/creatinine]; inverse transformation.
‡In [total bilirubin]; natural logarithmic transformation.
§0 = None, 1 = encephalopathy, 2 = stroke.
‖Negative coefficient indicates less likelihood of withdrawal.

them (Table 6). These factors related to less subsystem failure and intensity of treatment of infections.

Survival after being weaned from ECMO was 72%, 52%, 43%, and 40% at 7 days, 30 days, 1 year, and 5 years, respectively, which is similar to that of bridged patients (Figure 3). Survival after weaning was influenced by the pre-ECMO factors of shorter height, higher creatinine lev-

els, and higher international normalized ratio (Table 7). The most powerful was the pre-ECMO serum creatinine level (Figure 4).

Withdrawal from ECMO. Patients withdrawn from ECMO for futility represent the complementary group to bridged and weaned patients. Thus, their pre-ECMO risk factors included shorter height and nonuse of IABP (Table 8). With the addition of factors during ECMO (Table 8), worse renal and hepatic function and complications of

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TABLE 9. Modes of death

| Mode	Weaned (n = 71) n*	Weaned (n = 71) % of 34	Bridged (n = 48) n*	Bridged (n = 48) % of 16	Withdrawn (n = 83) n*	Withdrawn (n = 83) % of 82
Cardiac failure	16	47	1	6	40	49
Multiorgan system failure	14	41	14	88	28	34
Neurologic	4	12	1	6	14	17
Total deaths	34	100	16	100	82	100

*Number of deaths within failure subgroups.

Figure 6. Risk-adjusted relation of ECMO total bilirubin levels to the probability of withdrawal of ECMO. The depiction is as in Figure 5, except serum creatinine level was set to 2 mg/dL.

ECMO dominated (Tables 3 and 8). Figure 5 shows the profound influence of higher creatinine levels during ECMO, and Figure 6 shows the influence of higher levels of bilirubin, leading to withdrawal of ECMO. Of the 12 patients in whom pump head clots were found, two thirds were withdrawn from ECMO compared with 39% of other patients ($P = .06$).

Modes of Death
The modes of death differed according to the outcome of ECMO (Table 9). Both those withdrawn from ECMO and those weaned from ECMO died most commonly of cardiac failure, whereas this occurred in only 1 bridged patient; the cause of death was nearly exclusively multiorgan system failure.

Discussion
ECMO technology is simple to use, is rapidly initiated and applicable to patients of all sizes, and can rapidly reverse ischemia and anoxia. Questions remain as to the utility of this type of support in adult patients and whether the numerous complications previously reported are derived from the insult leading to the need for ECMO or caused, perpetuated, or both by the course of ECMO.

Principal Findings
Early mortality and morbidity remain very high for patients requiring ECMO support. Older age, evidence of organ system dysfunction either before or during the course of ECMO support, a history of previous cardiac operations, extensive aortic operations, neurologic events, and nonuse of IABP support were variables predictive of death during ECMO or after ECMO was withdrawn. If the patient survived the hospitalization, intermediate-term survival was quite good and was sustained for over 5 years.

The predictors of bridging in part reflect our clinical practice and an aggressive ECMO bridge approach to patients already on the transplant list (severe heart failure
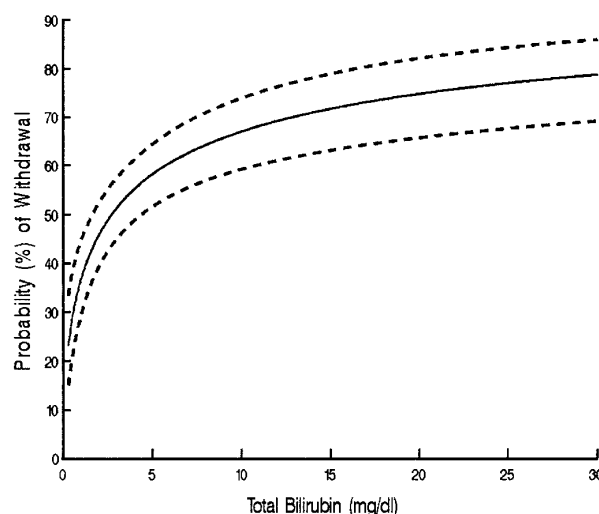
group). Bridging to transplantation successfully salvaged a sizeable group of young patients who otherwise would have died. Although the survival is less than that of those bridged to transplantation without preceding ECMO support,[13] it is useful as a temporizing strategy, allowing time for organ recovery and transplant assessment.

ECMO Morbidity and Mortality: The Event or the Device?
The need for ECMO support occurs after profound cardiopulmonary collapse, failure to wean successfully from cardiopulmonary bypass, and decompensation of chronic congestive heart failure. All these processes are associated with either ischemic or reperfusion organ injury or alterations in the inflammatory response leading to complement, neutrophil, platelet, and cytokine activation.[14] ECMO produces similar responses, and this undoubtedly compounds the initial insult.[15] The unanswered question is why this occurs in some patients, but not in others.

Initiating ECMO before complete hemodynamic collapse is ideal, but in most cases the insult has already occurred. Therapies must be developed that alter the reperfusion injury, preserving renal and hepatic function. Agents that affect the inflammatory response in general, such as steroids, aprotinin, and plasmapheresis, or more specific blockades, such as leukocyte depletion or direct cytokine inhibition, will need evaluation in the adult patients undergoing ECMO.

Heparin coating or bonding of the ECMO circuit was used with the hope that it would reduce cellular and mediator activation in addition to the reduction in the anticoagulation requirements. We found that the failure to use heparin resulted in a high occurrence of thrombotic complications

during ECMO.[16] Although pump thrombus was uncommon, when it did occur, it was nearly always associated with the patient dying. It has been suggested that microthromboemboli are occurring continuously during ECMO support and contribute to organ injury and dysfunction.[17] Strategies to reduce these events must be developed. The prolonged use of a centrifugal pump and a microporous membrane oxygenator may have perpetuated cell damage and an inflammatory response. The use of a less traumatic roller pump and silicone membrane oxygenator, as used by the University of Michigan group, may have reduced these complications. However, using this system to bridge patients to an implantable LVAD, Pagani and colleagues[14] found a 44% 1-year survival, which is similar to that observed by us.

Current anticoagulation protocols are suboptimal. Although they reduce pump thrombosis, bleeding remains excessive. Undoubtedly, this is multifactorial and includes surgical trauma, anticoagulation, and thrombocytopenia. The use of aminocaproic acid (Amicar) and aprotinin has been advocated with mixed results in neonatal patients.[18] These agents will need to be used cautiously, weighing the risks of bleeding with those of thrombosis.

Another explanation for the poor early outcome is the absence of pulsatile perfusion. Patients with an IABP were more likely to be weaned or bridged than those without an IABP. This may reflect the beneficial effects of afterload reduction on myocardial recovery or improved organ function with pulsatile flow. Our findings support the recommendation that all patients requiring ECMO support for cardiac failure have concomitant IABP support.[19] Whether better left ventricular decompression with apical drainage and pulsatility with the BVS 5000 LVAD (Abiomed, Danvers, Mass) would improve myocardial recovery or survival is unclear. The overall postcardiotomy survival reported by Guyton and colleagues[20] with the BVS 5000 LVAD was only 29%. In addition, the early experience with continuous flow pumping for the bridge to transplantation has been similar to that of the implantable devices, which supports the concept that organ function can be maintained without pulsatility.

Implications for Patient Care

The majority of patients supported with ECMO were young and justified an aggressive approach. In the older patient survival was markedly reduced, especially in association with pre-ECMO renal or hepatic dysfunction or post-ECMO neurologic injury. In this group ECMO cannot be advocated, and if ECMO is initiated and rapid clinical improvement is not seen, early termination of ECMO support is warranted.

ECMO provides hemodynamic stabilization and, in the patient with insufficient myocardial recovery, time to assess the patient for transplantation. We aggressively bridged patients from ECMO to an implantable LVAD, with 60% of the patients surviving to transplantation. The only contraindications for this bridge-to-bridge therapy were severe neurologic injury and active untreated infection. The absence of predictors of survival in this subgroup suggests that some patients with significant alteration in organ function can survive through the double bridge, albeit with a lower survival than in a group of patients with LVADs who are not supported with ECMO.

A substantial number of patients dying during ECMO or after weaning from ECMO died from irreversible myocardial injury. Golding and colleagues[21] found that 69% of patients autopsied after postcardiotomy ventricular support had extensive myocardial injury. In the group of patients who are not transplant candidates and who do not have end-organ injury but do have insufficient myocardial recovery, a permanent implantable cardiac assist device would salvage these patients. The ongoing Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial will help answer whether the current generation of devices are a durable and cost-effective alternative in this situation.[22]

Limitations

The analysis of a single clinical experience and the management protocols were evolving over the time period studied. However, results did not change substantially over time and concur with the published results of adult patients receiving ECMO.

Conclusions

ECMO is versatile and can salvage patients who would otherwise die. Improvement in outcome will require a multidisciplinary approach to protect organ function and limit organ injury that results before and during ECMO support.

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Appendix 1
Variables Considered in Multivariable Analyses

- Demographic: age (in years), height (in centimeters), weight (in kilograms), body mass index, body surface area, sex
- Cardiopulmonary comorbidity: reoperation, preoperative use of IABP, duration of ventilation support
- Noncardiopulmonary comorbidity: diabetes mellitus, history of peripheral vascular disease, history of chronic obstructive pulmonary disease, dialysis, blood urea nitrogen (in milligrams per deciliter), serum creatinine (in milligrams per deciliter), aspartate aminotransferase (in units per liter), total bilirubin (in milligrams per deciliter), international normalized ratio (in units), infection
- Preceding operations: coronary artery bypass graft, valve, coronary artery bypass graft and valve, thoracic aortic aneurysm, congenital, lung transplant, heart transplant, left ventriculectomy
- Indications for ECMO: cardiac failure, postcardiotomy, postcardiac catheterization, acute myocardial infarction, acute respiratory disorder, cardiac arrest, myocarditis, postcardiac transplant, after lung transplant, decompensated heart failure, postpartum cardiomyopathy, after left ventriculectomy
- Cardiomyopathy variables: dilated cardiomyopathy, ischemic cardiomyopathy
- ECMO details: peripheral cannula used, central cannula used, duration of ECMO, oxygenator count, number of blood transfusions during ECMO, years from January 1, 1992, to ECMO
- ECMO complications: head clot in pump count, additional lower limb cannulation, medically managed limb complication, surgically managed limb complication, dialysis, intracranial bleeding, embolic stroke, encephalopathy, infection
- Highest values during ECMO: blood urea nitrogen (in milligrams per deciliter), serum creatinine (in milligrams per deciliter), aspartate aminotransferase (in units per liter), total bilirubin (in milligrams per deciliter), infection, international normalized ratio (in units)

Discussion

Dr Robert H. Bartlett *(Ann Arbor, Mich).* There is a huge amount of data in this article, and it takes hours or days to analyze it, even with the article in hand. I am going to comment on a few of the factors that were raised in this fascinating review.

First, the statistical analysis is superbly done. It is very well described in the article. A tremendous diversity of cardiac and respiratory patients are mixed together in this analysis. What the authors learned, of course, is that older patients (and the oldest was 84 years) and sicker patients with more organ failure tend to die. Well, I guess we all knew that, but it is nice to see it confirmed. You mentioned that older was worse, but you did not tell us what age is "older." Maybe you might comment on that. The subgroup analysis is the really interesting part. A total of 198 patients had partial ventricular assist bypass, almost all of which was femoral-femoral bypass, for cardiac failure, half of which occurred postoperatively and half during cardiogenic shock for some reason; 34% of those patients survived. One aspect of this article is that death or survival is defined in time increments, and we do not really know when hospital discharge occurred. Therefore, I am assuming they probably were discharged from the hospital if they survived somewhere between 30 and 90 days. Two thirds of the surviving patients (either bridged to spontaneous cardiac recovery or to transplantation) lived for 5 years. This is a very good outcome for those patients, and it begins to define the outcome of the algorithm. About half of the 198 patients receiving ventricular assist bypass were withdrawn from support because they were not candidates for an LVAD or they were not candidates for transplant. However, that is not bad; that is the algorithm. You do the best you can, you get them on bypass, and then you sort things out.

Therefore, with that algorithm, those patients receiving ECMO who have good brain function and reasonable organ function and are transplant candidates go on to LVAD. Their survival was remarkably good: 85% in this particular group. Our experience is the same.

Thirty-one patients had respiratory failure, and 10 survived. I would advise the authors to write up the respiratory patients separately.

The authors raised the following question: To what extent do the technology and the devices contribute to the mortality? It is a very good question and something we all have to worry about.

APPENDIX TABLE A. Patient characteristics before ECMO placement

Patient characteristic	No.	%
Demographic		
Men	145	72
Cardiac comorbidity		
Pre-ECMO use of IABP	115	57
Reoperation	79	39
Noncardiac comorbidity		
Diabetes	42	21
Peripheral vascular disease	30	15
COPD	36	18
Chronic dialysis	7	3.5
Infection	33	16

COPD, Chronic obstructive pulmonary disease.

APPENDIX TABLE B. Patient characteristics before ECMO placement

Patient characteristic and general indication	n	Mean ± SD	Percentile Minimum	25	50	75	Maximum
Demographic							
Age (y)	202	55 ± 14	18	47	57	65	82
Height (cm)	200	171 ± 9.4	142	165	171	178	196
Weight (kg)	200	81 ± 18	42	69	78	90	159
Noncardiac comorbidity							
BUN (mg/dL)	196	28 ± 20	5	15	22	33	129
Serum creatinine (mg/dL)	196	—	0.3	1.0	1.4	1.8	11.6
Serum AST (U/L)	168	—	1.4	23	56	181	20,300
Total bilirubin (mg/dL)	156	—	0.05	0.8	1.1	1.8	26.7
INR (units)	140	1.4 ± 0.65	0.9	1.0	1.2	1.5	5

BUN, Blood urea nitrogen; *AST*, aspartate aminotransferase; *INR*, international normalized ratio.

APPENDIX TABLE C. Indications for ECMO

Indication	No.	%
Postcardiotomy	107	53
Acute MI	33	16
ARDS	1	0.5
Decompensated heart failure	28	14
Cardiac arrest	12	6
After cardiac transplantation	7	3.5
After lung transplantation	2	1
After cardiac catheterization	7	3.5
Myocarditis	3	1.5
Postpartum cardiomyopathy	1	0.5
After left ventriculectomy	1	0.5

MI, Myocardial infarction; *ARDS*, acute respiratory distress syndrome.

Their technique included the use of a centrifugal pump, which is great for 2 hours of bypass but (in our experience) causes unacceptable amounts of hemolysis and pump thrombus when used for a long time. They used a microporous membrane oxygenator, which undoubtedly leaked plasma and probably had to be changed from time to time. The average activated clotting time was about 200 seconds, and we would usually use much lower than that. Thus, there are issues in the technology that could be changed to improve results even more.

These cases are always emergencies. Maybe you cannot stop bypass in the operating room, or worse yet, it is the middle of the night and your postoperative patient's condition is suddenly deteriorating, or a new patient with a myocardial infarction is admitted with profound cardiogenic shock. My question is, how do you do it? How long does it take you to mobilize the team and get the patient on bypass?

My second question is this: What would you consider to be the contraindications? What patients would you not put on ECMO if you cannot come off bypass in the operating room or have a patient in cardiogenic shock?

Dr Moazami. Dr Bartlett, thank you very much for your comments. We are certainly all aware of your excellent contributions over the years to this technology. I will address your questions.

In terms of "older" patients not doing well, our analysis shows that the inflection point is around 60 years, with patients older than 60 years really not doing well with this technology. I think one of the factors that we tried to highlight in the article, and that I am also trying to emphasize here, is that it is true that the ECMO complications and ECMO factors affect survival, but pre-ECMO factors—in other words, the overall condition of a patient before ECMO is instituted—are also contributing factors. Thus, a patient who has baseline renal insufficiency at the time of insult or hepatic insufficiency actually does not do well with ECMO. If we add these together, I would say a patient who is 65 years old and has a creatinine level of 2 mg/dL and a low bilirubin level of 2 to 3 mg/dL probably has about an 80% mortality on ECMO.

Your second question referred to how long it takes for us to actually implement the ECMO system. Obviously, we all recognize that the sooner we can resuscitate the patients and put them on ECMO

for circulatory support, the better the patients will do. We, as is the case in many other centers, have a mobile system that can be implemented rapidly. The nurses are also very familiar with the management of the system. Although I do not have exact numbers to give you, once it is recognized that ECMO or some other form of support is necessary, the majority of these patients are taken down to the intensive care unit, where support is initiated within 1 hour.

As you mentioned, our approach in 80% of these patients was peripheral cannulation, which is relatively easy. When we put patients on venovenous bypass for respiratory support, we usually use a percutaneous method based on the Seldinger technique. In patients in whom we use venoarterial support, we primarily do a cutdown in the groin and place the cannulas under direct vision. That also includes placement of a distal perfusion cannula into the superficial femoral artery, which is now a routine practice and has actually cut down significantly on the limb ischemia complications

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that we used to see, particularly those that require a surgical intervention in terms of fasciotomy, revascularization, or even amputation.

In terms of contraindications to ECMO support in the postcardiotomy patients, it is a difficult question, as many of the surgeons who have been faced with this problem would know. If you are in the operating room and you cannot get the patient off bypass, it is difficult to give up. We generally have a graded response to this sequence, which includes maximizing pharmacologic support by addition of inotropic agents (epinephrine and milrinone). Our next step usually is an IABP. Finally, if we cannot get the patient off bypass, then we go to ECMO support.

Dr James Magovern *(Pittsburgh, Pa).* I just have a couple of brief questions. We also have experience using ECMO for cardiac support. In our experience patients who have a lot of bleeding and require extensive blood transfusion often have multisystem organ failure. Have you seen a relationship between the need for transfusion and subsequent outcome of the patient?

The second issue that we have seen is that patients who recover generally do so within 2 days. The decision, and it becomes an important one, is how long to keep the patient on ECMO. The mean duration of support for survivors in our 10-year experience has been about 44 hours. Therefore, it makes little sense to continue the support past 3 or 4 days if the patient has not recovered function by then. My second question is this: What is the time period under which you see recovery, and when would you give up and stop the ECMO?

Dr Moazami. Dr Magovern, we also see a significant amount of bleeding complications from ECMO support, to which you have alluded. In our patient group there was a large range of blood transfusions, anywhere from 1 to 99 units, but overall, our median transfusion was 13 units per patient. We did not identify transfusion as a risk factor for development of multisystem organ failure. I am aware that this is certainly a key factor, specifically in patients who are receiving assistance from support devices.

In terms of how long we keep the patients on ECMO, our protocol generally is to evaluate the patients within 24 hours to see whether they can be weaned from support. At the same time, we also initiate evaluation for whether the patient is a transplant candidate. During this 24 hours, as I mentioned, we optimize pharmacologic support and subsequently assess whether the patient can be weaned from support by using a combination of clinical parameters; looking at the pulmonary artery pressures, the cardiac output, and the mixed venous saturations; and using transesophageal echocardiography.

Our median duration of support for the cardiac failure group was 2½ days, which is very close to what you are suggesting, and usually, at that point, we have a clear idea whether we can bridge the patient to an LVAD as a more long-term form of support, whether the patient can be weaned from support, or whether we should withdraw support.

Dr Shyam K. Kolvekar *(London, England).* We have extensive experience in ECMO, and I just wanted to know who manages your ECMO in the intensive care unit. The second question mainly concerns your bleeding problem in transfusion and whether you have bleeding from your operative wounds or the cannulations.

Dr Moazami. The initial management of the ECMO system is by the physicians and perfusionists; however, the day-to-day and hour-to-hour management is done by our intensive care unit nurses, who have been trained in the management of ECMO and can recognize problems that may arise and notify the appropriate personnel. We usually have a perfusionist in house who can respond quickly, and obviously, the physicians are available.

In terms of your second question, we notice bleeding from the cannulation site, and in some cases in which we have placed the cannulas in the operating room, bleeding can obviously come from the mediastinum. There have been occasions in which we had to pack the chest open and re-explore later.

Dr Marko I. Turina *(Zurich, Switzerland).* You are surely aware that ECMO is rapidly being developed as a very efficient method for postoperative support in newborns and patients with congenital heart disease after complex reconstructions with results that are definitely better than those seen in adults. Do you have any idea whether it is the disease or the system and why it works better in newborns and in children for postoperative support?

Also, do you routinely decompress the left ventricle in these cases?

Dr Moazami. In response to your first question, I think the indications for placement of neonatal patients on ECMO are quite different from what we see in the adult population; generally, most of them are receiving respiratory support, and the most excellent results have been reported in that subgroup of patients.

In terms of your second question, whether we use any kind of left ventricular decompression, we do not employ such decompression. It is a recognized fact that ECMO support can increase the afterload. I believe that the Michigan group, in some instances when they think there is increased afterload, performs an atrial septostomy. In some cases apical ventriculectomies have been reported, but we do not use those techniques. However, we do, as I mentioned earlier, keep the patients on inotropic support and maintain ventricular ejection during this period. Part of the reason is because of the issue with ventricular distention, but part of it is also because we are always worried about stasis in the left ventricle and formation of intraventricular thrombosis.