Management of acute severe perioperative failure of cardiac allografts: A single-centre experience with a review of the literature

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BACKGROUND: Early graft failure is associated with high mortality and is the main cause of death within the first 30 days after transplantation. The purpose of the present study was to examine the investigators' experience of severe perioperative acute graft failure and to review the literature.

METHODS: Nine of 385 cardiac transplants (2.3%) performed from 1984 through 2005 developed severe perioperative acute graft failure either in the operating room or within 24 h after cardiac transplantation. Four patients had primary graft failure, two had right heart failure secondary to pulmonary hypertension, one had hyperacute rejection, one had accelerated acute rejection and one possibly sustained a particulate coronary embolus intraoperatively.

RESULTS: All except the two patients who had right heart failure secondary to pulmonary hypertension received mechanical circulatory support. Three patients were supported with total artificial hearts, two patients received a left ventricular assist device, one patient was supported with extracorporeal life support followed by a right ventricular assist device when the left ventricle recovered, and one patient was supported for several hours with cardiopulmonary bypass. Three patients were retransplanted after mechanical circulatory support, but only one survived. Only one of the nine patients (11%) survived; this patient was supported with a total artificial heart followed by retransplantation.

CONCLUSION: The outcome of severe perioperative acute graft failure is very poor. Mechanical circulatory support and retransplantation are not as successful as in other situations. Due to the shortage of donors and poor outcomes, retransplantation for hyperacute rejection is not advisable.

Key Words: *Pulmonary hypertension; Rejection; Transplantation; Ventricular assist device*

Traitement de la défaillance peropératoire sévère aiguë des greffons cardiaques : Expérience menée dans un centre et revue de la littérature

HISTORIQUE : La défaillance précoce des greffons est associée à un fort taux de mortalité et constitue la principale cause de décès au cours des 30 premiers jours qui suivent la transplantation. Le but de la présente étude était de faire le point sur l'expérience des investigateurs au chapitre de la défaillance peropératoire aiguë sévère des greffons et de passer en revue la littérature.

MÉTHODES : Neuf transplantations cardiaques sur 385 (2,3 %), effectuées entre 1984 et 2005 se sont soldées par une défaillance peropératoire sévère aiguë du greffon, soit au bloc opératoire, soit dans les 24 heures suivant la transplantation cardiaque. Quatre patients ont connu une défaillance primaire du greffon, deux ont présenté une défaillance du cœur droit secondaire à une hypertension pulmonaire, un a présenté un rejet suraigu, un a connu un rejet aigu accéléré et le dernier a probablement subi une embolie coronarienne peropératoire particulaire.

RÉSULTATS : Tous les patients sauf deux, qui ont présenté une défaillance du cœur droit secondaire à une hypertension pulmonaire, ont bénéficié de support circulatoire mécanique. Trois patients ont reçu des cœurs artificiels totaux, deux patients ont bénéficié d'un système de support ventriculaire gauche, un patient a été placé sous circulation extracorporelle avant de recevoir un système de support ventriculaire droit lorsque le ventricule gauche a récupéré et un autre a été placé pendant plusieurs heures sous circulation extracorporelle. Trois patients ont reçu une nouvelle greffe après soutien circulatoire mécanique, mais un seul a survécu. Un seul des neuf patients (11 %) a survécu. Ce patient avait reçu un cœur artificiel total avant de subir une nouvelle transplantation.

CONCLUSION : Le pronostic est très sombre dans les cas de défaillance peropératoire sévère aiguë du greffon. La circulation extracorporelle et la retransplantation ne réussissent pas autant que dans d'autres situations. Compte tenu de la pénurie de donneurs et de son issue défavorable, la retransplantation n'est pas conseillée dans les cas de rejets suraigus.

Heart transplantation is a well-established treatment for intractable end-stage heart failure. Survival has been improving with each successive five- to six-year era (1). The 30-day survival after heart transplantation has improved from 84% (1979 to 1985) to 91% (1996 to 2001) (2). However, there is still a significant 9% 30-day mortality rate. Early graft failure after cardiac transplantation is associated with a very high mortality rate and is the major cause of death within the first 30 days after transplantation (1,3). Causes of early graft failure include severe acute or hyperacute rejection with cardiogenic shock, pulmonary hypertension with right ventricular failure, technical errors and primary graft failure. The University of Ottawa Heart Institute (Ottawa, Ontario) total artificial heart (TAH) program began in 1986, while our ventricular assist device program was introduced later, in 1988. The purpose of the present study was to report our experience in the management of severe perioperative acute graft failure (PAGF) with a review of the literature.

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TABLE 1
Recipient pretransplant characteristics

Characteristic	1	2	3	4	5	6	7	8	9
Age, years	41	51	54	54	34	25	63	51	24
Sex	Male	Male	Female	Male	Male	Female	Male	Female	Male
Cause of end-stage heart failure	Idiopathic CM	Post-cardiotomy	Post-cardiotomy	Idiopathic CM	Viral CM	Massive myocardial infarction (septal, anterior and lateral)	Ischemic CM	Post-cardiotomy	Congenital heart disease
Mechanical support before transplant	None	TAH	Thoratec* LVAD	None	TAH	TAH	Novacor† LVAS	Symbion‡ LVAD + BioMedicus§ RVAD	IABP followed by TAH
Preoperative creatinine level, mmol/L	109	154	99	166	133	69 before first transplant, 49 before second transplant	73	181	115 before first transplant, 359 before second transplant
Preoperative pulmonary arterial pressure, mmHg	55/33 on milrinone	Not available because patient was on TAH before transplant	35/20	52/25	23/18	Not available because patient was on TAH before both transplants	63/32	70/32	66/36 before first transplant, 30/20 before second transplant

**Thoratec Laboratories Corporation, USA; †WorldHeart Inc, USA; ‡Symbion Corporation, USA; §Medtronic BioMedicus, USA. CM Cardiomyopathy; IABP Intra-aortic balloon pump; LVAD Left ventricular assist device; LVAS Left ventricular assist system; RVAD Right ventricular assist device; TAH Total artificial heart*

PATIENTS AND METHODS

From 1984 through 2005, 385 cardiac transplants were performed at the University of Ottawa Heart Institute. The present study is based on nine patients who developed severe acute graft failure in the operating room precluding separation from cardiopulmonary bypass or very shortly (within 24 h) after cardiac transplantation, leading to severe cardiogenic shock. Hospital records of these patients were reviewed. The causes of failure were primary graft failure (four patients), right heart failure (RHF) secondary to pulmonary hypertension (two patients), hyperacute rejection (one patient), accelerated acute rejection (one patient) and possibly particulate coronary embolus intraoperatively (one patient). Primary graft failure is defined as significant graft dysfunction in the early transplant period in the absence of acute or hyperacute rejection, easily identified technical errors and right ventricular failure from refractory pulmonary hypertension (4). The recipients' pretransplant characteristics are listed in Table 1. Three of the nine recipients required heart transplantation because of severe postcardiotomy failure, with inability to wean from cardiopulmonary bypass. All except two patients received mechanical circulatory support (MCS) before transplantation. Donors' demographic information is shown in Table 2. Some donor characteristics were not available in the records, but generally speaking, the donors had similar profiles to those typically encountered in cardiac transplantation donors.

RESULTS

Management and outcomes after PAGF are shown in Table 3. All patients, except for two with RHF secondary to pulmonary hypertension, received MCS when the cardiac graft failed. An intra-aortic balloon pump was used in four patients. Extended time on cardiopulmonary bypass was used as MCS in one of the seven patients supported. Three patients were supported with a TAH, two patients received left ventricular assist devices (LVADs) and one patient was sustained on extracorporeal life support (ECLS) followed by a right ventricular assist device (RVAD) after recovery of the left ventricle. Devices used for MCS to manage PAGF included: the CardioWest Total Artificial Heart (CardioWest Technologies Inc, USA), formerly known as Jarvik-7 and Symbion TAH; the Novacor left ventricular assist system (WorldHeart Inc, USA); the Thoratec pneumatic ventricular assist device (Thoratec Laboratories Corporation, USA); and the centrifugal Medtronic BioPump (Medtronic BioMedicus, USA), which was used as a ventricular assist device or as a part of ECLS. The Symbion LVAD (Symbion Corporation, USA) was used once to support one patient before heart transplantation. None of the three patients who were supported by a TAH developed multiorgan failure. These three patients were adequately supported by a TAH until they were retransplanted. These were the only patients who were retransplanted after MCS – one for primary graft failure, one for hyperacute rejection and one for accelerated acute rejection – but only one survived. This patient who survived was the only survivor among the four patients who developed primary graft failure and the only survivor among the nine patients with PAGF. Two patients died at two months – one patient with RHF secondary to pulmonary hypertension when she pulled out her tracheostomy tube and the other from fulminant cytomegalovirus pneumonia after retransplantation for accelerated acute rejection. The remaining six patients died within 30 days, three of whom died intraoperatively. Among the three patients who died in the operating room, two developed primary graft failure. The third patient, who developed hyperacute rejection after his first transplant, died in the operating room from hyperacute rejection of his second transplant. Pathology results of the explanted hearts are detailed in Table 4.

TABLE 2
Donor information (by transplant recipient)

Characteristic	1	2	3	4	5	6	7	8	9
Age, years	First: 19 Second: 27	49	50	33	40	First: 55 Second: 23	32	46	First: 14 Second: 28
Sex	First: male Second: female	Male	Male	Female	Female	Female (both transplants)	Female	Male	Male (both transplants)
Cause of brain death	First: gun shot Second: intracerebral hemorrhage following thrombolysis for frontal sinus thrombosis	Spontaneous intracerebral hemorrhage	Primary brain tumour	External sagittal sinus thrombosis due to meningitis	Motor vehicle accident	First: spontaneous intracerebral hemorrhage Second: drug overdose	Motor vehicle accident (brain injury)	Subarachnoid hemorrhage	Motor vehicle accident (both transplants)
Donor's pressors	First: dopamine 5 μg/kg/min, neosynephrine 1 μg/kg/min Second: dopamine 5 μg/kg/min	Dopamine	Dopamine 12 μg/kg/min	Phenylephrine 25 μg/min	Dopamine 5 μg/kg/min	First: no inotropes	Dopamine 1 μg/kg/min	Dopamine 5 μg/kg/min	First: not available Second: not available, but normal donor heart on echocardiogram
Ischemia time, min	First: 69 Second: 350	220	112	260	228	First: 120 Second: 240	270	321	First: 190 Second: not available

DISCUSSION

In our series, the incidence of severe PAGF was 2.3% (nine of 385 patients). All except two patients received MCS. The incidence of early allograft failure reported in the literature varied from 1.4% to 9.7% (4-8).

Medical therapy alone is associated with a uniformly dismal outlook (7). The two patients in our series who did not receive MCS died; both had severe RHF secondary to pulmonary hypertension. MCS until the transplanted heart recovers or the patient undergoes retransplantation offers the only chance of survival. However, compared with the use of MCS in postcardiotomy and bridge-to-transplantation patients, the results of mechanical support following heart transplantation are markedly worse. In our series, only one out of seven patients (14%) who received MCS survived. The only survivor was retransplanted after support with a TAH. The same patient was the only survivor among the four patients with primary graft failure. Minev et al (5) reported an 80% mortality in all subgroups, including those with primary graft failure, RHF and acute rejection. These authors suggest that at the time of initiation of support, these patients are generally in a disastrous condition, and that there is no time to adapt to the hemodynamic deterioration compared with bridging patients. In the Kavarana et al (7) series, seven of the nine patients with primary graft failure died, while four of the nine patients with RHF survived. On the other hand, Petrofski et al (6) reported 71% survival to discharge in their group of seven patients (three patients with primary graft failure and four with severe acute rejection) after MCS using the Abiomed BVS5000 assist device (Abiomed, Inc, USA). These results stand in marked contrast to those reported from other centres. The authors indicated that the difference between their results and those seen in other series may be related to the early systematic application of MCS and the type of ventricular assist device support.

Unfortunately, the majority of the literature concerning mechanical circulatory assistance for cardiac allograft failure consists of sporadic case reports, often describing the use of a variety of devices in a small patient population with a complete spectrum of indications (9). Intra-aortic balloon pump counterpulsation is usually the first line of mechanical support, which is what was used in four of our nine patients. ECLS has been used by some groups (4,10). In our series, only one patient with primary graft failure was sustained by ECLS with recovery of left ventricular function, but his right ventricular function remained poor and he required an RVAD, off which he could not be weaned. Eventually, he succumbed to septicemia and multiple organ failure. In general, the use of ECLS is limited by hemorrhage, human resource considerations, lifetime of the oxgenator and cost. The use of the Carmeda BioActive (Medtronic Blood Systems, USA) surface circuit, which limits heparin requirements, can limit bleeding (11). Another limitation of ECLS is that it can provide only partial cardiopulmonary support, which may not be sufficient in patients with very poor cardiac function. Therefore, Ko et al (10) recommend the exclusion of patients with uncontrollable bleeding, very poor cardiac function and refractory ventricular arrhythmias from receiving ECLS. They also recommend earlier institution of ECLS, when it is indicated, before end-organ damage ensues.

Other methods of MCS include a univentricular or biventricular assist device (BVAD). In our experience, all patients who were supported by either LVADs or RVADs died. We did not use BVADs in our series. Others (12-16) used different BVADs, with successful outcomes, in single case reports of primary graft failure. These reports substantiate the use of biventricular support for biventricular failure. Because primary graft failure is usually biventricular, it is intuitive to treat such a condition with either a BVAD or a TAH. In our series, the only survivor of the four patients with primary graft failure was the one who received a TAH. The others received intra-aortic balloon pump counterpulsation and an LVAD (one patient), ECLS followed by RVAD when the left ventricle recovered (one patient) or an extended period of reperfusion on cardiopulmonary bypass (one patient), but all of them died. Kavarana et al (7) noted that 70% of their patients with

TABLE 3
Management of perioperative acute graft failure, complications and outcome

	1	2	3	4	5	6	7	8	9
Etiology of graft failure	Primary graft failure	Primary graft failure	Primary graft failure	Primary graft failure	Particulate coronary embolus	Hyperacute rejection	Right heart failure due to pulmonary hypertension	Right heart failure due to hypertension	Accelerated acute rejection
Type of support after heart transplant	IABP + inotropes; arrest in operating room (TAH inserted)	IABP + inotropes + LVAD	Several hours on cardio-pulmonary bypass	Several hours on cardiopulmonary bypass, ECLS for 24 h, then RVAD (BioMedicus* RVAD for 3 days, then Thoratec† RVAD for 19 days	IABP + inotropes + Thoratec LVAD	Intropes, then TAH after first heart transplant; inotropes and extended reperfusion on cardiopulmonary bypass heart heart transplant	Inotrope (graft failed within a few hours post-operatively)	Inotropes	First heart failed 18 h postoperatively, requiring inotropes + IABP + TAH
Outcome	Retransplant; alive	Died intra-operatively	Died intra-operatively	Died of MOF 23 days post-transplant	Died intra-operatively	Died intra-operatively after second transplant	Died 2 days post-transplant	Died 2 months later, after patient pulled out her tracheostomy tube	Retransplant but died two months later of fulminant pneumonia and MOF
Renal	Acute tubular necrosis; recovered			Acute tubular necrosis (dialysis)			Acute renal failure	Dialysis, but kidneys recovered	Acute renal failure
Pulmonary	Pneumonia			Pneumonia				Tracheostomy	Fulminant cytomegalo-virus pneumonia
Stroke						While on a TAH		Recent large cerebral infarct on autopsy	
Bleeding	Reopened			Chest left open for 3 days					
Sepsis				Septicemia				Yes	Yes

**Medtronic BioMedicus, USA; †Thoratec Laboratories Corporation, USA. ECLS Extracorporeal life support; IABP Intra-aortic balloon pump; LVAD Left ventricular assist device; MOF Multiple organ failure; RVAD Right ventricular assist device; TAH Total artificial heart*

primary graft failure required right ventricular support and speculated that this may imply that primary graft failure is commonly associated with biventricular dysfunction, and that these patients may benefit from biventricular support at the earliest sign of refractory graft failure. However, Hooper et al (17) reported a case of primary graft failure with a successful outcome using only an LVAD in addition to inotropic support to augment right ventricular function. For right ventricular failure secondary to pulmonary hypertension, Esmore et al (18) recommended an RVAD in addition to prostacyclin infusion. For our two patients with RHF secondary to pulmonary hypertension, we used only inotropic support, and both patients died.

The only survivor in our series was a patient who was supported with a TAH. The other two patients in our series who were supported with TAHs died after retransplantation; one died of hyperacute rejection and the second died of fulminant cytomegalovirus pneumonia two months after retransplantation. All three patients were very adequately supported with TAHs before retransplantation. The main limitation of TAHs is that a patient is required to have a retransplantation; otherwise, as Kavarana et al (7) suggested, it may be used as destination therapy.

We retransplanted three of the patients in this series; one for primary graft failure, one for hyperacute rejection and one for accelerated acute rejection. The first is still alive and doing well, the second died intraoperatively from hyperacute rejection and the third died two months after the second transplant because of fulminant cytomegalovirus pneumonia. All three patients were supported with TAHs before retransplantation. The results of retransplantation after acute allograft rejection and primary graft failure are very poor (7,19-21). John et al (22) reported that survival after retransplantation significantly improved when they excluded patients with primary graft failure and those with intractable acute rejection within six months after transplantation. Srivastava et al (23) and Ensley et al (24) have shown that the shorter the intertransplant period, the worse the outcome.

CONCLUSION

The survival of patients with PAGF is poor. MCS and retransplantation are not as successful as in other situations. Due to the shortage of donors and poor outcomes, retransplantation for hyperacute rejection is not advisable.

TABLE 4
Pathology results of explanted hearts

1	2	3	4	5	6	7	8	9
RV: focal endocardial hemorrhage LV: patchy contraction band necrosis and coagulative necrosis, with moderate interstitial edema but no significant interstitial hemorrhage	RV: edema, with very minute foci of contraction band necrosis (midwall) LV: contraction band necrosis in both the inferior wall and inferior septum extending from midwall to subendocardium, with interstitial edema	RV: minute areas of early necrosis in subendocardium, with some contraction band necrosis LV: similar scattered areas of recent ischemic necrosis most pronounced in interventricular septum	Extensive coagulative necrosis and dystrophic calcification of subendocardial myocytes extending to the endocardial surface of both ventricles, consistent with peritransplant reperfusion ischemic injury/infarction	LV: very large LV infarct with reperfusion changes Note: Thromboemboli in pulmonary artery, with large right upper lobe infarct	Hyperacute rejection with interstitial hemorrhage	RV: recent (24 h to 48 h) extensive subendocardial RV infarct; no pre-existing donor heart disease, with widely patent coronary arteries and no evidence of rejection LV: relatively spared, with very recent subendocardial infarct (mild and patchy) Note: Changes of pre-existing pulmonary hypertension were noted	Mild to moderate rejection	Accelerated acute rejection in the first heart transplant

LV Left ventricle; RV Right ventricle

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