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Review

Status, Indications, and Use of Cardiac Replacement Therapy in the Era of Multimodal Mechanical Approaches to Circulatory Support: A Scoping Review

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ABSTRACT

The aim of this review is to describe the current use, indications, and outcomes of the Syncardia temporary total artificial heart (TAH) (Syncardia Systems, Tucson, AZ, USA), the only TAH currently approved as a bridge-to-transplant strategy in Canada, the United States, and Europe. With more than 1700 implantations worldwide, the Syncardia temporary TAH is the most commonly used pump. Globally, it represents 2% of the long-term mechanical circulatory support devices implanted, with a recent decrease in its use. The main candidates for TAH are heart transplant candidates suffering from acute or decompensated chronic irreversible biventricular failure at high risk of imminent death and for whom a suitable donor is not available. Most patients receiving a TAH are acutely ill, characterized by an INTERMACS profile of 1 or 2, and 20% are under extracorporeal membrane oxygenation. The TAH provides efficient circulatory support and allows the end-organ to

RÉSUMÉ

Les auteurs décrivent l'utilisation, les indications et les résultats actuels du cœur artificiel total (CAT) temporaire Syncardia (Syncardia Systems, Tucson, AZ, États-Unis), le seul CAT actuellement approuvé comme stratégie de transition vers une transplantation au Canada, aux États-Unis et en Europe. Implanté chez plus de 1 700 patients dans le monde, le CAT temporaire Syncardia est la pompe la plus utilisée. À l'échelle mondiale, il représente 2 % des dispositifs d'assistance circulatoire mécanique de longue durée implantés, bien que l'on constate depuis peu une diminution de son emploi. Les principaux candidats à un CAT sont des patients en attente d'une transplantation cardiaque souffrant d'une défaillance biventriculaire irréversible chronique aiguë ou décompensée et présentant un risque élevé de décès imminent, pour qui aucun donneur compatible n'est disponible. La plupart des patients qui reçoivent un CAT sont très malades et

Fifty years after the first heart transplantation (HT) and more than 35 years after the first implantation of a total artificial heart (TAH) in a human patient, the development of cardiac replacement therapy continues to fuel the history of cardiac surgery.[1] Over the past few years, cardiovascular disease has become the main cause of death in developed countries, and the number of patients suffering from heart failure is increasing despite significant improvements in medical therapies. For patients with advanced heart failure, HT remains the best option, offering the longest survival and the best quality of life. Unfortunately, donors are scarce, which significantly shapes our decision making and the management of these patients. Efficient and safe alternatives are therefore much needed. Cardiac replacement with a TAH provides adequate hemodynamic support for HT candidates who would not otherwise be able to wait for a donor owing to their severe clinical condition and for whom a single-ventricle assist device is not appropriate. The objective of the present scoping review was to summarize the use of, indications for, and outcomes after TAH implantation. We focused on the Syncardia temporary TAH (Syncardia Systems, Tucson, AZ, USA) as the only TAH currently approved in Canada, the United States, and Europe as bridge-to-transplant strategy. We also performed a meta-analysis of survival after TAH implantation in high-volume centers.

History of Cardiac Replacement Therapy

Over the past 50 years, 2 distinct options have been explored for cardiac replacement therapy. The first successful attempt was performed by Shumway and Lower, who developed a technique in animals known as orthotopic HT.[2] Their work culminated in the first clinical human HT performed in 1967 in South Africa by Dr Barnard. In 1968, Dr Shumway performed another HT at Stanford University in California. Meanwhile, at the University of Utah, Drs Kolff and Jarvik

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recover from the initial hypoperfusion injury. More than 60% of patients implanted with a Syncardia TAH will later undergo transplantation, with a 1-year survival rate of 70% after transplantation, compared with a 1-year survival rate of ~ 42% in nontransplant patients. Bleeding, infection, stroke, and acute kidney injury are the most common complications in this critically ill population. The new miniaturization of the console (Freedom Portable Driver) facilitates the recovery of TAH recipients by allowing ambulation, aggressive physiotherapy, and, eventually, hospital discharge. This last aspect is one of the main benefits of TAH compared with other biventricular assist devices. In conclusion, the Syncardia temporary TAH is a reasonable bridge-to-transplant option for selected patients with either biventricular failure or special anatomic conditions.

présentent un score INTERMACS de 1 ou 2; 20 % d'entre eux sont sous oxygénation extracorporelle par membrane. Le CAT offre une assistance circulatoire efficace et permet aux organes cibles de se rétablir après l'épisode d'hypoperfusion initial. Plus de 60 % des patients à qui on implante un CAT Syncardia subissent par la suite une transplantation et affichent un taux de survie à 1 an de 70 % après la greffe, comparativement à un taux de survie à 1 an de 42 % environ chez les patients qui ne subissent pas de transplantation. Les hémorragies, les infections, l'accident vasculaire cérébral et l'atteinte rénale aiguë sont les complications les plus courantes au sein de cette population gravement malade. La nouvelle console miniaturisée (Freedom Portable Driver) facilite le rétablissement des patients qui reçoivent un CAT, car elle leur permet de se déplacer, de suivre une physiothérapie intensive et, finalement, de recevoir leur congé de l'hôpital. Ce dernier point est l'un des principaux avantages d'un CAT par rapport aux autres dispositifs d'assistance biventriculaire. En conclusion, le CAT temporaire Syncardia constitue une option valable pour la transition vers une transplantation chez certains patients présentant une défaillance biventriculaire ou des caractéristiques anatomiques particulières.

were developing pneumatically powered versions of a TAH that they named model Jarvik-5 and Jarvik-7.[3] In 1982, Dr Devries from the University of Utah implanted a Jarvik-7 model in a 61-year-old patient who survived 112 days after implantation.[4] Dr Cooley was the first to attempt and report on the temporary use of a TAH as a bridge-to-transplant (BTT) in 1982, but his efforts at the time did not succeed.[5] Although the concept of a BTT strategy with the use of a mechanically supported heart already existed, it was not until 1985 that it became a reality, when the first successful HT was performed on a patient who had been on TAH support with a Jarvik-7 by Dr Copeland's team at the University of Arizona.[6] The patient survived after the 2 interventions of TAH implantation and HT, which opened the way to the establishment and medical recognition of the concept of the BTT strategy.

The Syncardia temporary TAH is a biventricular, pneumatic, and pulsatile blood pump that completely replaces the patient's native ventricles and the 4 cardiac valves (Fig. 1). The device's name changed several times to reflect the changes in the company's ownership. Dr Copeland's landmark study for the use of Syncardia TAH enrolled 130 HT candidates who were at high risk of imminent death due to irreversible biventricular failure from 1993 to 2002.[7] The patients were not candidates for a left ventricular assist device (LVAD) owing to clinical evidence of biventricular failure or the presence of special anatomic conditions. Survival to transplantation was significantly higher in patients who received a TAH compared with control subjects (79% vs 46%; $P < 0.001$). The overall survival rate at 1 year was also higher in patients who received the implant (70% vs 31%; $P < 0.001$). That US Food and Drug Administration (FDA)—funded study established the current role of the TAH as a valid BTT strategy. The Syncardia TAH was approved for BTT in North America in October 2004. In the Canadian publicly funded health care system, LVADs and TAHs are reimbursed through various provincial policies. TAHs are similar to LVADs in terms of initial costs and are offered exclusively to HT candidates. A destination therapy (DT) trial is currently underway, assessing the use of the Syncardia 70-cc TAH for patients presenting with life-threatening biventricular failure who are ineligible for HT.

Table 1 summarizes the important landmarks in the development of the TAH.

Current Use of the Total Artificial Heart in the Era of Left Ventricular Assist Devices

Continuous-flow LVADs remain the primary long-term mechanical circulatory support for patients with severe congestive heart failure, as either BTT or DT. However, the TAH remains a good option in specific clinical indications, especially in patients with severe biventricular heart failure. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) reports that 19,206 patients underwent continuous-flow LVAD implantation from 2006 to 2017 in 152 hospitals implanting durable FDA-approved devices in the United States.[8] Meanwhile, only 339 patients received a TAH, the device being restricted to a small subset of patients. Worldwide, fewer than 20 centers have reported their experience with the Syncardia TAH. According to the largest registry of Syncardia TAHs published so far, by Arabia et al., the patients receiving the TAH were acutely ill, 80% were characterized as INTERMACS profile 1 or 2, 82% showed symptoms of right heart failure, 23% were under ventilator support, 11% required dialysis, 50% suffered from moderate or severe tricuspid insufficiency, and 43% were on temporary mechanical circulatory support, with nearly half of them (20% of the cohort) on extracorporeal membrane oxygenation (ECMO) at the time of TAH implantation.[9] The presence of end-organ failure impaired the prognosis of these patients; moreover, the use of a TAH at the onset of acute cardiogenic shock with associated end-organ damage might contribute to the increased risk of complications after implantation. Unsurprisingly, outcomes after TAH implantation are closely related to careful patient selection and timely implantation of the device.

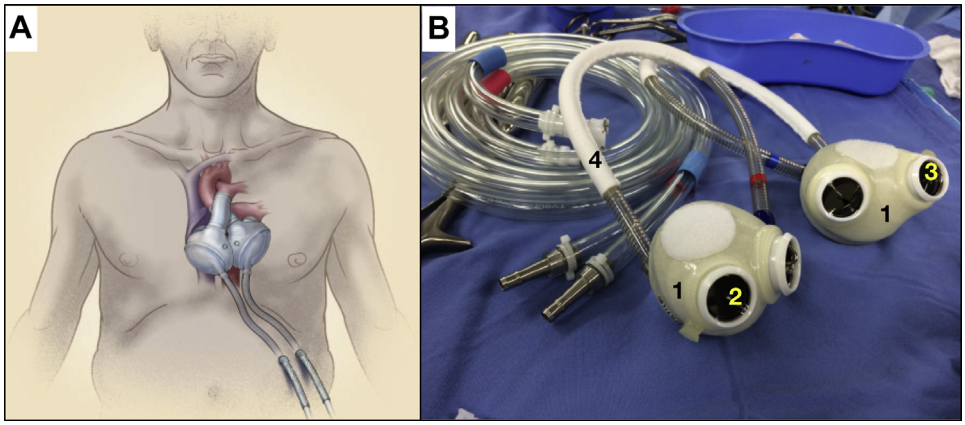

Figure 1. The Syncardia temporary artificial heart. (**A**) Anatomic position after implantation. Reproduced from Copeland et al.[6] with permission from the Massachusetts Medical Society. (**B**) Picture of the TAH before implantation. **1:** polyurethane ventricle chamber; **2:** inflow mechanical valve (tilting disk Medtronic Hall 27 mm); **3:** outflow mechanical valve (tilting disk Medtronic Hall 25 mm); **4**: pneumatic driveline, which is connected to a driver after implantation. Adapted from Tang DG, Shah KB, Hess, ML, Kasirajan, V. Implantation of the Syncardia total artificial heart. *J Vis Exp* 2014;89:e50377. Reproduced from Tang et al.[34] with permission from the *Journal of Visualized Experiments*.

Patient Selection

The implantation of a TAH can be considered in 3 different clinical situations: 1) when univentricular support will not provide adequate systemic flow to meet metabolic demand; 2) for anatomic reasons; and 3) in case of isolated cardiac neoplasms with no option for reconstruction. Potential candidates for TAH implantation must be eligible for HT (Fig. 2). Because the purpose of a TAH is to replace the native valves and ventricles, there should be no expectation of recovery from the underlying pathology. The most common indication for TAH is a patient with severe and potentially irreversible biventricular failure who faces an imminent risk of death and for whom there is no suitable donor available.

Because of the 70-cc size of the Syncardia TAH, the patient's thoracic cavity should be large enough to fit the device and to allow sternal closure. The criteria required are a body surface area (BSA) of $\geq$ 1.5-1.7 m^2 and a sternum-to-T10 distance of $>$ 10 cm or adequate room in the chest as determined by means of 3-dimensional imaging assessment or other standard clinical assessments. A 50-cc version of the pump is now available and may further expand the use of Syncardia TAH in smaller adults and children with BSAs as low as 1.0-1.2 m^2.

Table 1. Important landmarks in the journey of the total artificial heart

Year	Event
1969	Denton A. Cooley implanted the first TAH as BTT. Duration of support: 64 hours.
1982	William DeVries implanted the first Jarvik-7 artificial heart. Duration: 112 days.
1985-1989	Jack Copeland implanted the first Jarvik-7 artificial heart as BTT and the patient successfully underwent transplantation. Various medical centers in the United States implanting TAH.
1990	FDA withdraws endorsement of Jarvik.
1992	Syncardia receives FDA approval for the modified Jarvik-7 device.
1999	Syncardia approval for clinical use in Europe.
2004	FDA approval in US for CardioWest Syncardia as BTT.
2005	Syncardia CardioWest approval in Canada for use as BTT.
2014	Syncardia 50 cc approval in Europe for BTT.
2016	Syncardia 50 cc approval in Canada for BTT.
2016-2019	Destination therapy trial with Syncardia 70-cc TAH: single-arm end-stage biventricular failure patients.

BTT, bridge-to-transplantation; TAH, total artificial heart.

Patients With Biventricular Failure

Right ventricular failure (RVF) requiring the support of a right ventricular assist device (RVAD) is the most significant risk factor for morbidity and mortality in LVAD recipients, and many studies have demonstrated poor outcomes in patients requiring secondary RVAD.[10-18] Recently, Amsallem et al. reported their experience at Stanford University with 194 patients undergoing continuous-flow LVAD implantation.[16] Survival1 year after LVAD implantation was significantly lower in patients with clinical evidence of RVF after LVAD surgery, and even worse in those needing a RVAD (92% vs 70% vs 39%, respectively; Fig. 3). The incidence of RVF after LVAD implantation ranges from 9% to 30% despite the new generation of pumps.[19] Thus, careful assessment of the right ventricle and prediction of postoperative RVF is a critical step in the decision-making process. Assessment of right ventricular function must be multimodal (clinical, biological, hemodynamic, ultrasound, magnetic resonance imaging, calculated functional parameters) and is still under study.[13,14,17,20,21] Evidence regarding the possible reversibility of severe RVF over the long term makes the decision even more difficult.

In patients with left ventricular dysfunction associated with moderate to severe right ventricular dysfunction, therapeutic strategies include transplantation, TAH, LVAD with temporary RVAD (Centrimag, right-right ECMO), or other long-term biventricular assist devices (BiVADs) with the off-label use of chronic continuous-flow devices.[14,15,18,22] Several studies have demonstrated the negative impact of the need of unplanned or delayed RVAD after LVAD implantation.[11,12,15,18] In the absence of randomized trials comparing TAHs with other biventricular support strategies

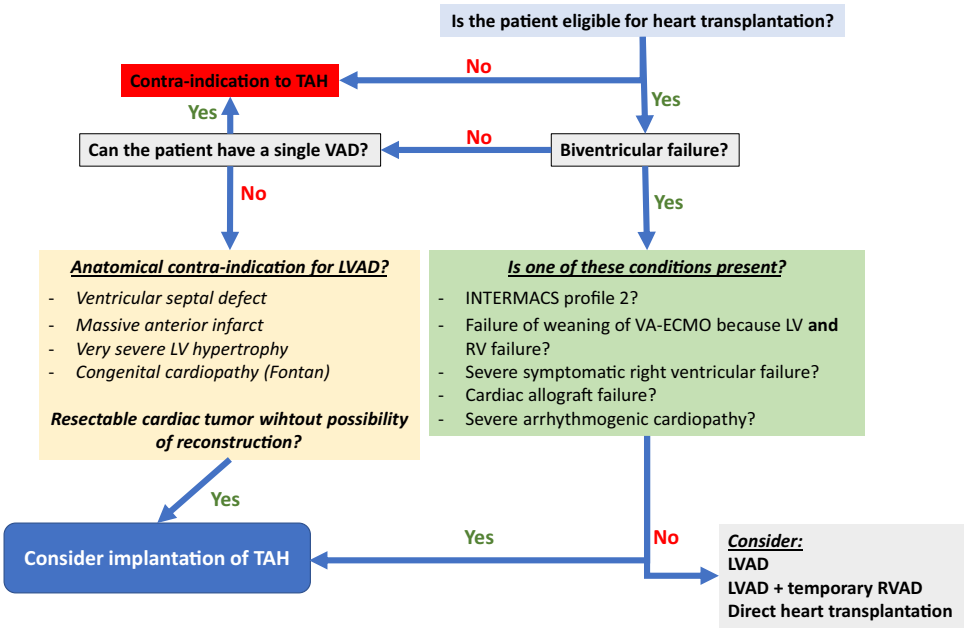

Figure 2. Algorithm for decision making and indications for total artificial heart (TAH) at the Montréal Heart Institute. Noneligibility for heart transplantation and eligibility for LVAD implantation are contraindications to TAH. LV, left ventricular; LVAD, left ventricular assist device; RV, right ventricular; RVAD, right ventricular assist device; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VAD, ventricular assist device.

(LVAD with temporary RVAD, BiVAD with off-label use of devices designed to assist the left ventricle), the decision is usually taken based on institutional and surgeon preference. The main advantages of TAHs remain their relative ease of management compared with other BiVADs and their low rate of technical failure. One other advantage is that a TAH allows the patient to be ambulatory and to potentially be discharged from hospital.

Loforte et al. compared the outcomes after the implantation of a LVAD with temporary RVAD with Centrimag (n = 46) vs a BiVAD or TAH (n = 31) in patients with left ventricular failure associated with moderate to severe right ventricular dysfunction.[15] They reported similar in-hospital and 1-year survival rates in both groups (54% vs 45%), despite a higher mortality rate when still on support in the BiVAD/TAH group (26% vs 45%; $P = 0.02$). As stated earlier, outcomes were worse for patients

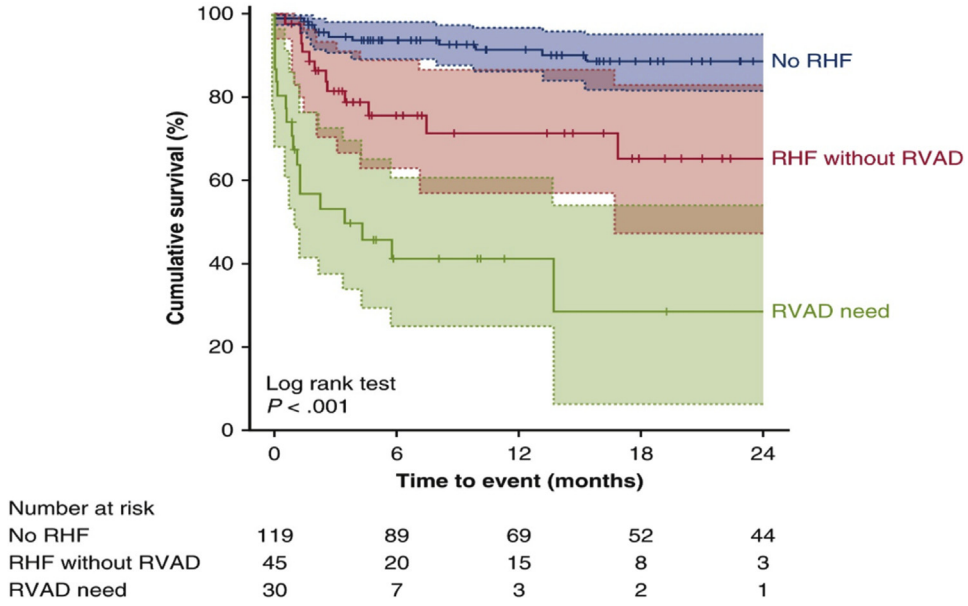

Figure 3. Impact of right ventricular failure after left ventricular assist device (LVAD) implantation. Kaplan-Meier curves show a lower actuarial survival rate in LVAD recipients who had right heart failure (RHF) with or without need for a right ventricular assist device (RVAD). Patients who underwent heart transplantation were censored at the time of transplantation. Unadjusted comparisons between the 3 groups were performed with the use of a log-rank test. Reproduced from Amsallem et al.[16] with permission from Elsevier.

Table 2. Survival in the current era of multimodal mechanical approaches to circulatory support

Study	n	Device(s)	Survival to HT	1-y survival	5-y survival
Total Artificial Heart					
Copeland, 2012[26]	101	Syncardia temporary TAH	68%	55%	43%
Arabia, 2018[9]	450	Syncardia temporary TAH	60%	66%	–
Copeland, 2004[7]	81	Syncardia temporary TAH	79%	70%	55%
Kirsch, 2013[33]	90	Syncardia temporary TAH	61%	50%	43%
Biventricular assist device					
Aissaoui, 2014[10]	84	Thoratec paracorporeal BiVAD, HeartWare BiVAD	–	48%	–
Loforte, 2013[15]	31	Thoratec paracorporeal BiVAD, Heartware BiVAD, Berlin Heart Excor, Syncardia temporary TAH	19%	45%	–
CF-LVAD					
Kormos, 2019[8]	14,427	Axial pumps	–	84%	46%
	3853	Centrifugal pumps	–	85%	49%
LVAD with temporary RVAD (overall)					
Aissaoui, 2014[10]	57	Thoratec PVAD, Centrimag RVAD	12%	46% (6-months)	–
Loforte, 2013[15]	46	Centrimag RVAD	15%	54% (6-months)	–
Kormos, 2019[8]	667	Continuous flow with RVAD	–	58%	31%
LVAD with temporary RVAD (planned)					
Aissaoui, 2014[10]	20	Thoratec PVAD, Centrimag RVAD	–	55%	–
Loforte, 2013[15]	35	Centrimag RVAD	–	54%	–
LVAD with temporary RVAD (delayed)					
Aissaoui, 2014[10]	37	Thoratec PVAD, Centrimag RVAD	–	41%	–
Loforte, 2013[15]	11	Centrimag RVAD	–	18%	–
Heart transplantation					
Lund, 2017[43]	30,503	–	–	86%	75%
Bridge-to-transplant with total artificial heart					
Copeland, 2012[26]	101	Syncardia temporary TAH	–	77%	60.5%
Copeland, 2004[7]	81	Syncardia temporary TAH	–	86%	64%
Kirsch, 2013[33]	90	Syncardia temporary TAH	–	78%	62%
Bridge-to-transplant with CF-LVAD					
Lund, 2017[43]	12,010	Axial and centrifugal pumps	–	86%	75%

BiVAD, biventricular assist device; CF, continuous-flow; HT, heart transplantation; LVAD, left ventricular assist device; PVAD, paracorporeal ventricular assist device; RVAD, right ventricular assist device; TAH, total artificial heart.

requiring a secondary RVAD. Unfortunately, the population in the study was heterogeneous in terms of type of device and only 6 patients were implanted with a TAH, making it difficult to draw any definitive conclusions.

Using the United Network for Organ Sharing Registry from 2005 to 2014, Cheng et al. compared the outcomes of 212 patients under TAH support with those of 366 patients under BiVAD support at the time of HT.[23] Overall, TAH patients spent 170 days and BiVAD patients 142 days on the waiting list for HT. Although no information was given on the clinical status of patients before TAH or BiVAD implantation, patient survival rates on the waiting list and after transplantation were similar in both groups. Of interest, the pre- and post-HT survival rate of patients supported with continuous-flow BiVADs was lower. The authors concluded that both approaches were reasonable, with the TAH becoming a necessity for patients with sustained ventricular arrhythmia and restrictive disease. However, BiVADs can be better suited for patients of smaller stature. Table 2 reports survival rates after various strategies of cardiac replacement and support.

In patients with end-stage biventricular failure without potential of recovery and INTERMACS profile 2 we favour TAH over ECMO (Fig. 2). The biventricular Centrimag or a double CF-LVAD also can be used as bridge-to-bridge strategy, but there are no clear data yet to favour one strategy over another. For patients with INTERMACS profile 1 supported with veno-arterial (VA) ECMO, we use transesophageal echocardiography in addition to hemodynamic parameters during weaning trials of VA-ECMO. However, a thorough evaluation of the RV function by means of right catheterization or magnetic resonance imaging is difficult in these patients. When VA-ECMO cannot be weaned owing to right and left ventricular failure, TAH has been a valuable option in patients with severe RVF that would otherwise be candidates for a durable BiVAD.

Special Clinical Indications for Total Artificial Heart

The use of TAHs in the setting of primary cardiac tumour remains debated and is based mostly on case reports.[24] Outcomes are variable in this indication. Acquired ventricular septal defect secondary to myocardial infarction could be very challenging to repair. The use of mechanical circulatory support is increasing, but the best strategy has yet to be determined. In a case series, a small number of patients were

Table 3. Overall complication rates after total artificial heart implantation in the current era

Studies	N	Timing	Infections	Bleeding	Liver failure	Respiratory failure	Renal failure	Neurologic event	Reoperation	Device malfunction
Copeland, 2004[7]	81	30 d after HT	77%	62%	37%	36%	29%	27%	24%	17%
Haddad, 2004[30]	31	Under TAH support	35%	9%	—	—	3%	19%	35%	0
El-Banayosy, 2005[38]	42	Under TAH support	—	21%	26%	12%	15%	10%	19%	—
Roussel, 2009[34]	42	Under TAH support	83%	52%	—	7%	64%	9%	54%	9%
Copeland, 2012[26]	101	Under TAH support	63%	42%	—	—	—	16%	24%	—
Kirsch, 2013[33]	90	Under TAH support	14%	—	—	—	—	10%	39%	1%
Arabia, 2018[9]	450	Under TAH support	39%	41%	5%	22%	16%	15%	6%	6%

HT, heart transplantation; TAH, total artificial heart.

treated with TAHs with encouraging outcomes despite disease severity in this population.[25] Copeland et al. stated that some situations appeared to be best suited for TAH support, including acute or chronic failed cardiac transplantation, massive myocardial infarction,[26] acquired ventricular septal defect,[25] diffuse and massive mural intracardiac thrombosis, failed Fontan circulation,[27] and severe hypertrophic cardiomyopathy. As always, all patients must first be eligible for cardiac transplantation. Other unusual indications also have been described, including resection of right ventricular sarcoma.[28] Figure 2 represents the algorithm behind the decision-making process in our center.

Outcomes After Total Artificial Heart Implantation

Using the INTERMACS Registry, Arabia et al. reviewed data from 450 patients who underwent TAH implantation from 2006 to 2017.[9] Patients averaged 50 years of age, had an INTERMACS profile of 1 or 2, and were on inotropes or ECMO. Patients were characterized by dilated cardiomyopathy with clinical evidence of severe biventricular failure. According to the authors, the patients receiving TAHs were sicker than the patients receiving LVADs. Despite their critical clinical state, 266 patients (59%) underwent HT, with an overall survival rate averaging 53% at 1 year. The encouraging survival rate in this patient population subset provides support for considering TAH as a suitable alternative to the use of VADs in patients with severe biventricular failure. Multisystem organ failure and neurologic dysfunction were the main causes of death, and bleeding and infection were the most common adverse events. In a multivariate model predicting death after implantation, older age, preimplantation dialysis, and lack of center experience with TAHs were significant risk factors. Of interest, 109 patients (24%) were discharged home or to a rehabilitation unit 1.6 months after TAH implantation, with a notable increase seen in the most recent years of experience. Table 3 summarizes the complication rates reported in high-volume centers.

Recently, our experience at the Montréal Heart Institute was reported in part by Nguyen et al.[29] Since 1987, a total of 24 patients have undergone TAH implantation at our center. All patients were candidates for HT and were characterized by an INTERMACS profile of 1 or 2. Most patients were men, averaging 44 years of age, and 86% survived to later undergo HT. The waiting time to HT under TAH support averaged 51 ± 42 days. Although dilated cardiomyopathy with evidence of severe biventricular heart failure was the most common indication for implanting a TAH, a variety of unusual conditions warranted its preferential use, including sustained ventricular arrhythmia, extensive thrombus formation in the ascending aorta and aortic mechanical valve, post-HT failure, and ventricular sarcoma. Three patients died from multiple organ failure,

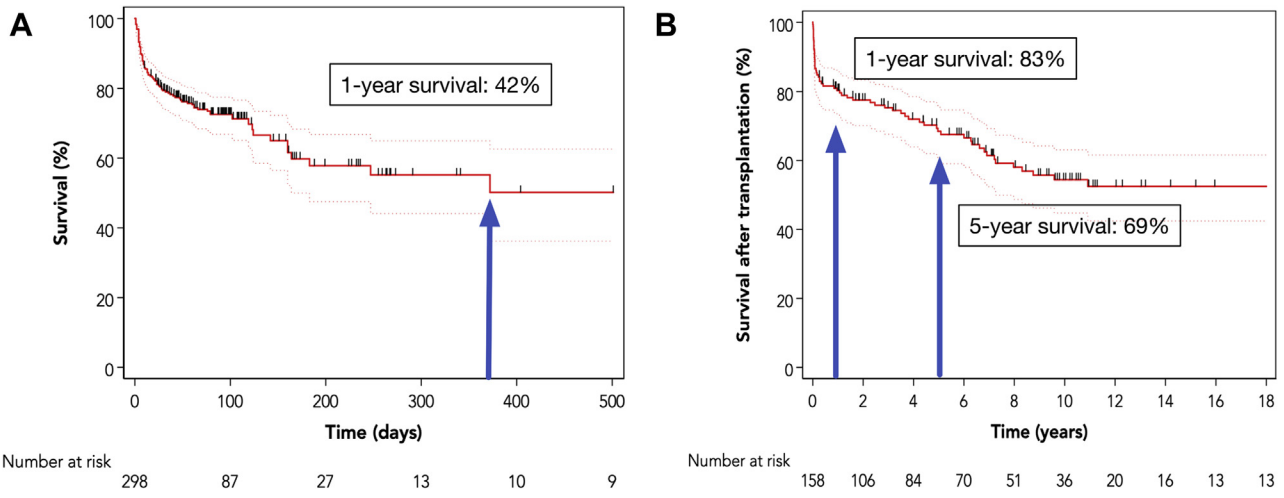

Figure 4. Pooled survival from 5 studies with > 30 TAH recipients. (**A**) Survival under TAH support (patients undergoing transplantation were censored); (**B**) Survival after transplantation.

acute necrotizing pneumonia, and stroke, respectively, while on support. Total actuarial survival rates averaged 77% and 53% at 30 days and 1 year, respectively. In 2004 the Ottawa Heart Institute reported the outcomes for 31 patients who had received TAHs. They observed an improvement of hospital survival in the later segment of their experience (61% vs 84%).[30]

For the present scoping review, we performed a meta-analysis regarding survival after TAH implantation. The PubMed and EMBASE databases as well as the Cochrane Central Register of Controlled Trials were searched for monocentric studies reporting on survival after TAH implantation that included $\geq$ 30 patients, with no time or language limits. To improve the sensitivity of the literature search, we performed citation chasing in Google Scholar, Scopus, and Web of Science. For the cited reference searches, we used a narrative review published in 2017 by Yaung et al. Related journals and lists of references of selected articles were also crosschecked for other relevant studies. Study selection was performed by 2 independent reviewers (W.B.A. and M.C.) through 2 levels of screening: first the titles and abstracts of the searched studies were screened, and then full texts were reviewed. In case of multiple publications with sample overlap, the most recent report was retained. Controversies were discussed and resolved via e-mail discussions. Quality assessment of the included studies was performed with the use of the ROBINS-I tools.[31] Five studies published from 2005 to 2014 were retained.[26,32-35] All of the studies showed at least a moderate risk of bias according to the ROBINS-I tools. Only 4 studies reported Kaplan-Meier (KM) curves for survival.[33-36] Each KM curve was digitized with the use of digitalization software (Digitizelt, Braunschweig, Germany). The individual patient data were derived from the KM curve via the digitalization software. In the same manner, extraction of censored information was performed where censoring marks were present on the KM graph. Derived KM curves were graphically checked with the original curves with the use of a ratio of restricted mean survival time (RMST) for each curve. The RMST is defined as the area under the KM curve calculated according to the trapeze rule. A ratio $>$ 0.98 was mandatory. Once validated, the KM data from different studies were stored together in the study database. Statistical methods for time-to-event data were used to analyze outcomes at follow-up, including the KM estimator with the log-rank test for comparisons. Four studies including 299 patients reported survival under TAH. Overall survival under TAH is shown in Figure 4A. Survival at 1, 3, 6, and 12 months was 85.8% (95% confidence interval [CI] 81.8%-89.8%), 76.3% (71.1%-81.5%), 63% (54.2%-71.8%), and 42.2% (29.0%-55.4%), respectively. Three studies including 149 patients reported post-HT survival. Survival after transplantation at 1, 5, and 10 years was 83% (95% CI 77%-89%), 69% (61%-77%), and 55% (46%-64%), respectively (Fig. 4B).

The Challenge of Hospital Discharge Under TAH Support

According to the INTERMACS Registry, 24% of patients implanted with a TAH were discharged home with their device after 1.6 months,[9] with this number increasing over time. In the FDA trial, 75% of recipients were walking by 1 week after implantation and $>$ 60% could walk $>$ 30.5 m within 2 weeks.[7] Even if TAHs improve quality of life for most of the implanted patients, rehabilitation and hospital discharge remain very challenging for patients and their care providers.[37,38] A 6-kg driver that permits hospital discharge is now available to patients waiting for HT and supported with the Syncardia TAH.[39] For years, one of the major disadvantages of the use of a TAH was the necessity of keeping the patient in-hospital while waiting for transplantation. Clinical experience with the new small TAH driver has allowed a few centers to discharge patients home.[38,39]

Future Directions for the TAH

Although many newer devices are currently under study, the Syncardia TAH is still the only TAH authorized for clinical use in patient care by the FDA and Health Canada. The current indication remains for patients who are acceptable candidates for HT.

Total artificial hearts offer several advantages over the use of BiVADs in patients with biventricular heart failure. A cardiac output of 6-7 liters per minute allows end organs to recover from peripheral shock and the associated stress with INTERMACS profiles 1 and 2. Sustained ventricular arrhythmia and restrictive cardiomyopathy can both be addressed with the use of TAH. Moreover, several clinical and peculiar anatomic conditions that would otherwise be fatal can now be addressed with the use of TAH and HT.

Cardiologists, emergency care physicians, and intensivists are now using short-term mechanical support offered by a variety of devices, such as ECMO and Impella (Abiomed, Danvers, MA) blood pumps, to support patients who would otherwise succumb to their acute clinical conditions, which most often arise from cardiogenic shock.[40-42] Even though many of these patients recover from the acute event after a few days of support, a significant number need much more support and will likely require a BTT approach. Consequently, TAH use will remain a serious option to bridge these difficult patients to HT.

Conclusion

The clinical use of the TAH has a long history characterized by the perseverance of a handful of investigators to help the sickest patients in modern cardiac care. Of interest, the emergence of wider clinical use of short-term mechanical devices by a greater number of interested physicians is again changing the landscape of acute cardiology. The TAH will likely continue to play a significant role in the care of these critically ill patients.

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