

# Clinical perspectives of patients with Chagas cardiomyopathy listed as high priority for heart transplantation

*Perspectivas da evolução clínica de pacientes com cardiomiopatia chagásica listados em prioridade para o transplante cardíaco*

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## Abstract

**Introduction:** Heart failure deterioration is responsible for elevated mortality rates in the heart transplantation waiting lists. In Chagas cardiomyopathy, the presence of biventricular dysfunction increases the severity of this complication.

**Method:** We studied 141 patients with cardiogenic shock, listed in priority for heart transplantation. Forty six patients presented Chagas cardiomyopathy and 95 other cardiomyopathies. Heart failure deterioration was treated with intravenous inotropic drugs and intra-aortic balloon pump insertion. Five patients with Chagas disease underwent paracorporeal left ventricular assist device implantation.

**Results:** During a mean follow-up of 2.8 months, 58 (41.1%) of the 141 patients were transplanted, while 73 (53.7%) died and 10 were removed from the waiting list. The mortality of chagasic and non chagasic patients were 45.6% and 54.7%, respectively. Otherwise, the median survival expectation of

patients with Chagas disease, without the heart transplantation performance, was only 1.5 months, and these patients presented a relative risk of mortality of 1.6 in relation to patients with other cardiomyopathies ( $p < 0.05$ ). The five patients submitted to left ventricular assist device implantation were maintained under support for a mean of 22 days. Two of them were transplanted, two died due to multiple organ failure and one still under circulatory support. None of these patients presented right ventricular dysfunction and there were no device related complications.

**Conclusion:** The evolution of heart failure deterioration seems to be rapid in patients with Chagas cardiomyopathy. Therefore, it is important the precocious indication of mechanical circulatory support as a bridge to heart transplantation in these patients.

**Descriptors:** Chagas cardiomyopathy. Shock, cardiogenic. Heart transplantation. Heart assist devices.

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### Resumo

**Introdução:** O choque cardiogênico é responsável por elevados índices de mortalidade na fila de espera para o transplante cardíaco. Na cardiomiopatia chagásica, a alta incidência de disfunção biventricular pode contribuir com a gravidade desta complicação.

**Método:** Foram estudados 141 pacientes indicados em caráter de prioridade para o transplante. Destes pacientes, 46 eram portadores de cardiomiopatia chagásica e 95 de outras cardiomiopatias. O choque cardiogênico foi tratado farmacologicamente e com o implante ocasional do balão intra-aórtico. Em cinco pacientes chagásicos, foi realizado o implante de dispositivo paracorpóreo de assistência ventricular esquerda.

**Resultados:** Num período médio de 2,8 meses, 58 (41,1%) dos 141 pacientes foram transplantados, 73 (51,7%) faleceram e 10 foram retirados da fila. A mortalidade entre os pacientes chagásicos e não chagásicos foi de 45,6% e 54,7%, respectivamente. No entanto, a expectativa média de vida,

sem a realização do transplante cardíaco, dos pacientes chagásicos foi de apenas 1,5 meses, sendo observado risco relativo de mortalidade de 1,6 para estes pacientes em relação aos não chagásicos ( $p < 0,05$ ). Os cinco pacientes chagásicos submetidos ao implante do dispositivo de assistência circulatória foram mantidos por um período médio de 22 dias, sendo que dois foram transplantados, dois faleceram por falência de múltiplos órgãos e um ainda está sob assistência. Nenhum destes pacientes apresentou disfunção do ventrículo direito, não tendo ocorrido qualquer complicação relacionada ao dispositivo.

**Conclusão:** A evolução do choque cardiogênico parece ser mais rápida na cardiomiopatia chagásica, sendo importante a indicação precoce de dispositivos de assistência mecânica como ponte para a realização do transplante cardíaco.

**Descritores:** Miocardiopatia chagásica. Choque cardiogênico. Transplante de coração. Coração auxiliar.

## INTRODUCTION

Nowadays, heart transplantation faces the serious problem of donor scarcity. It is estimated that around 10% and 40% of the selected patients die on the waiting list all over the world and a significant share of these patients die because of progressive circulatory failure [1,2]. For these patients, sometimes, the use of mechanical circulatory assist devices is the only possibility of survival while waiting for a donor.

Several types of devices have been employed as bridges for future heart transplantation and the international experience in this field sums up to thousands of cases [3-6]. Based on this experience, the indication criteria of circulation assistance are well established, as is the impact of application of this therapy on the patients' life expectancy.

Being an illness that gives high mortality in the more advanced phases of myocardial involvement, chagasic cardiomyopathy is one of the most indicated diseases for heart transplantation in Brazil [7,8]. On the other hand, in spite of the satisfactory results of heart transplantation employed in the treatment of chagasic cardiomyopathy [9, 10], a high number of patients with this illness evolve to cardiogenic shock, usually resulting from a biventricular complication, which leads to death while waiting for a donor. Due to the lack of experience with the use of mechanical circulatory assist devices in Brazil, there are no studies evaluating the impact of an adequate therapeutic control of these patients during the transplantation waiting period.

The objective of this study is to analyze the development of patients with chagasic cardiomyopathy, who present with periods of cardiogenic shock on the waiting list for heart transplantation. Additionally, the initial experience of the employment of a paracorporeal left ventricular assist device in the treatment of these patients will be reported.

## METHOD

### Patients

In the Heart Institute, in the period from January 1998 and March 2005, heart transplantations were indicated for 256 patients with ages varying from 10 to 69 years old. The indications for transplantations were idiopathic dilated cardiomyopathy in 100 (39.0%) patients, chagasic cardiomyopathy in 68 (26.5%), ischemic cardiomyopathy in 62 (24.2%) and other etiologies in 26 (10.3%) patients. One hundred and forty-one patients (54.8%) were on the waiting list for an urgent transplantation because they were using endovenous inotropic drugs for cardiogenic shock. Out of these patients, 46 suffered from chagasic cardiomyopathy composing the group of interest in this study.

### Handling of circulatory failure whilst waiting for transplantation

All the patients that evolved to a diagnosis of cardiogenic shock on the waiting list for transplantation were submitted to pharmacological endovenous support. This support consisted, initially, on the use of dobutamine

(dose of up to 20  $\mu\text{g}/\text{kg}/\text{min}$ ) associated, when necessary, with other drugs such as milrinone, dopamine or noradrenaline. The indication of the use of intra-aortic balloons was normal for patients that were resistant to the pharmacological therapy.

From October 2003, a bridging program for heart transplantation was initiated with the implantation of a paracorporeal ventricular assist device. This program was approved by the Scientific and Ethics Commission of the Heart Institute and by the National Research Council (CNPq). Written informed consent was obtained from the patients or legal guardians. The implantation of this device was indicated for patients who presented cardiogenic shock refractory to the optimal medical therapy and to adequate volemic control. In this situation, the following factors are related to a bad postoperative prognosis and were considered counter-indications for the surgery: age greater than 65 years old, weight less than 40 kg (88.2 pounds), an episode of pulmonary embolia in the month preceding surgery, prolonged intubation, (longer than 48 hours), episode of cardiopulmonary resuscitation within the previous 24 hours, acute neurological lesions, acute or chronic renal failure with creatinine greater than 2.5 mg/dL or urea above to 100 mg/dL, hepatic dysfunction with total bilirubin above 3 mg/dL, active infectious state or hemorrhagic disorders.

The choice of the type of circulatory assistance (left ventricular or biventricular) was made according to hemodynamic criteria of the definition of left or right ventricular failure. Initially, an isolated implantation of a left ventricular assist system was attempted with pharmacological treatment for the right ventricular dysfunction.

#### **Implantation and follow-up of the ventricular assist device**

The paracorporeal InCor model ventricular assist device developed by the Centro de Tecnologia Biomédica of the Heart Institute was employed in this study (Figure 1). The implantation of cannulae and the InCor ventricular assist device was made using conventional cardiopulmonary bypass at normothermia. After a median sternotomy, the abdominal skin incisions were made through which cannulae are exteriorized. The end-to-side anastomosis of the tubular graft of the arterial cannulae to the ascending aorta or the pulmonary artery trunk was performed after systemic anticoagulation under cardiopulmonary bypass. The insertion and suturing of the ventricular cannulae in the end of the left ventricle or in the right ventricle free wall were always performed under circulatory assistance, followed by the connection of the cannulae to the device and removal of air from the system.

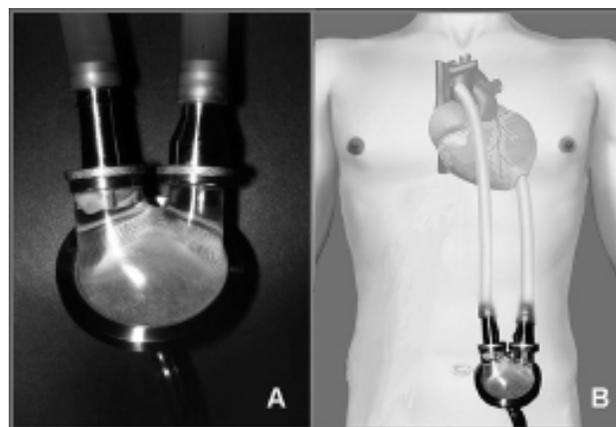


Fig. 1 – Photograph (A) and Diagram (B) of InCor paracorporeal ventricular assist device implanted as a circulatory assist device in parallel to right and left ventricles.

After device implantation, patients were maintained in the Intensive Care Unit during the first two postoperative weeks, and were later transferred to the Semi-Intensive Unit. Hemodynamic monitoring by the insertion of a Swan-Ganz catheter was performed, for the first few days in the postoperative period for patients maintained on isolated left ventricular assistance. During all the post-implantation follow-up, the ventricular assist device provides continuous monitoring of sanguineous output of the apparatus.

During left ventricular assistance, the flow through the device must always be greater than 2.5 L/min/m<sup>2</sup>. Additionally, the left atrium and pulmonary capillary pressures should be maintained at between 5 and 15 mmHg. In biventricular assistance, the same aforementioned measures should be maintained in relation to the left ventricular assist device, stressing the importance of always maintaining the flow of the right ventricular assist device 10% lower than to the left device.

Diagnosis of right ventricular failure was established according to hemodynamic and echocardiography criteria. All the patients were submitted to prevention of this complication in the first days in the follow-up period, by maintaining endovenous inotropic support and pulmonary vasodilators, specifically with the routine use of nitric oxide by inhalation. In the case of right ventricle dysfunction, the pharmacological assistance was intensified with the use of endovenous inotropic drugs and of pulmonary vasodilators, such as milrinone, nitroglycerine and prostacyclin. The implantation of a right ventricular assist device system should only be performed in cases that present resistance to the optimal pharmacological treatment.

**Statistical analysis**

The survival rates of patients who do not undergo heart transplantation were calculated using the Kaplan-Meier method and shown with a 95% confidence interval (CI). The obtained survival curves were compared using the log-rank method. The chi-squared test was used for the comparison of the proportions. The hemodynamic measurements obtained from patients submitted to circulatory assistance were compared using the Friedman non-parametrical test. The established level of significance was 5%.

**RESULTS**

Of the 256 patients that were on the waiting list for heart transplantation in InCor, 112 (43.7%) were submitted to transplantation, 105 (41%) died, 27 (10.5%) were removed from the waiting list because of a clinical improvement or because of other complications and 12 (4.7%) continue on the list for a donor. The mortality rate on the waiting list was greater for the 141 (51.7%) patients that were given priority on the waiting list, while heart transplantation was performed for only 41.1% of these cases. Additionally, the life expectancy of the patients who did not undergo heart transplantation was only  $66.6 \pm 8.3\%$  over one month of follow up,  $51.6 \pm 9.5\%$  over two months and  $35.7 \pm 11\%$  in 6 months, as is shown in Figure 2.

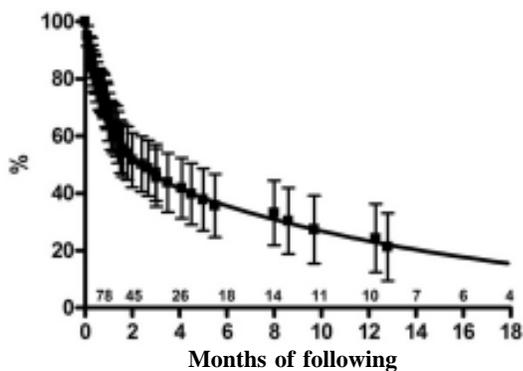


Fig. 2 – Life expectancy curve of patients on the waiting list for urgent heart transplantation. Numbers indicate patients at risk in specific periods (mean  $\pm$  CI 95%)

In relation to chagasic cardiomyopathy, 37 (54.4%) of the 68 patients suffering from this disease were submitted to transplantation, while 27 (39.7%) died waiting and only 3 (4.4%) were removed from the list because of clinical improvement. The indication of urgent heart transplantation was significantly higher for the patients with chagasic cardiomyopathy (67.6%) than for patients with

cardiomyopathies due to other etiologies (50.5%) ( $p = 0.026$ ), giving a relative risk of 1.31 (1.05 to 1.634, 95% CI).

Figure 3 demonstrates that the life expectancy for chagasic patients listed for urgent heart transplantation was lower than that observed for patients in this condition, indicated because of other illnesses. For the patients with chagasic cardiomyopathy, the life expectancy without heart transplantation was  $57.9 \pm 16.3\%$  over one month of follow up,  $41.8 \pm 19.6\%$  over two months and  $5.2 \pm 21\%$  in 6 months. Moreover, the life expectancy of patients with other etiologies was  $70.3 \pm 9.6\%$ ,  $55.2 \pm 10.9\%$  and  $38.6 \pm 12.4\%$  for the same periods, respectively. These data can also be expressed by a mortality risk ratio of 1.606 (1.041 to 3.304, CI 95%) for chagasic patients in relation to non-chagasic patients, with an average survival of only 1.5 month for these patients.

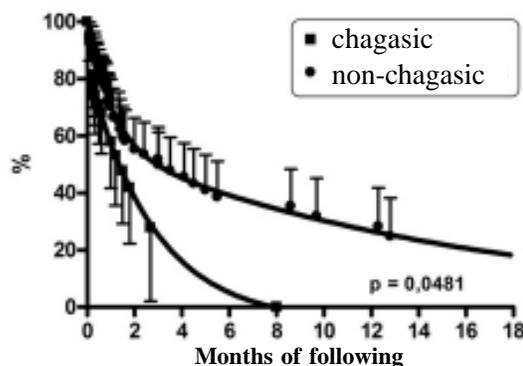


Fig. 3 – Life expectancy curve of chagasic and non-chagasic patients on the waiting list for urgent heart transplantation (mean  $\pm$  CI 95%)

When analyzing the causes that led to the death of 73 priority heart transplantation patients, we see that 23 (31.5%) patients died because of complications that excluded them from the waiting list and the use for circulatory assistance before the final event. Another 10 (13.5%) patients died later, when the circulatory failure responsible for the priority indication was reverted. Thirty-six (49.3%) patients evolved with resistance to the optimal endovenous inotropic drug support and in some cases to the insertion of an intra-aortic balloon. These patients constitute a group of patients potentially eligible for mechanic circulatory assist device implantation, together with the six patients that were actually submitted to this kind of intervention since October 2003.

Out of the six patients that received the InCor paracorporeal ventricular assist device implantation, five presented cardiogenic shock secondary to chagasic

cardiomyopathy. All the patients were on the priority waiting list and presented signs of resistance to the pharmacological treatment or to the use of the intra-aortic balloon at the moment of indication for the circulatory assist device. None of them was under ventilatory mechanic assistance or presented any contraindications for the procedure. The other pre-operative data of these patients are described in Table 1.

Five patients were submitted to isolated left ventricular assist device implantations under cardiopulmonary bypass. The use of pharmacological endovenous assistance with dobutamine and milrinone was associated to the use of nitric oxide inhalation in all patients with the objective of controlling the right ventricle dysfunction in the immediate post-operative period. From the hemodynamic viewpoint, there was maintenance of an adequate flow through the left ventricular assist device during all the post-operative period, always maintaining heart indexes above 2.5 L/min/m<sup>2</sup>. This condition occurred associated to a progressive decrease in the pressures of the right chambers of patients, as demonstrated in Figure

4. A decrease in venous pressures was observed in these patients under progressively smaller doses of endovenous inotropic drugs.

It was possible to remove the ventilatory assistance in all five patients between the first and fourth day of the follow-up period. This fact made early feeding and walking possible, a situation that was maintained until the occurrence of complications that required the discontinuation of these functions in two patients who died under circulatory assistance.

The results of implantation of the ventricular assist device as a bridge for heart transplantation in the five patients are presented in Table 2. In spite of the complications related to coagulation alterations, the evolution of renal and hepatic functions was always normal in the two patients with the longer follow-up periods. In the other two patients who evolved with pulmonary and infectious complications, there was a late deterioration of the renal and hepatic functions, collaborating with the final situation of multiple organ failure.

Table 1. Pre-operative characteristics of patients submitted to circulatory assist paracorporeal device implantation.

Patient	Gender	Age	Weight (kg)	Type of Pharmacological support	Time of use	Heart rate (l/min/m <sup>2</sup> )	Vasc. Pulm. Resist. (Wood)
1	F	48	66	Dobutamine Nor-adrenaline	2 days	1.47	1.72
2	M	46	60	Dobutamine IAB	28 days	1.53	2.68
3	M	47	75	Dobutamine IAB	12 days	1.87	2.34
4	M	52	85	Dobutamine Milrinone IAB	81 days	1.69	3.11
5	M	33	57	Dobutamine Milrinone IAB	25 days	1.72	1.9

IAB = intra-aortic balloon

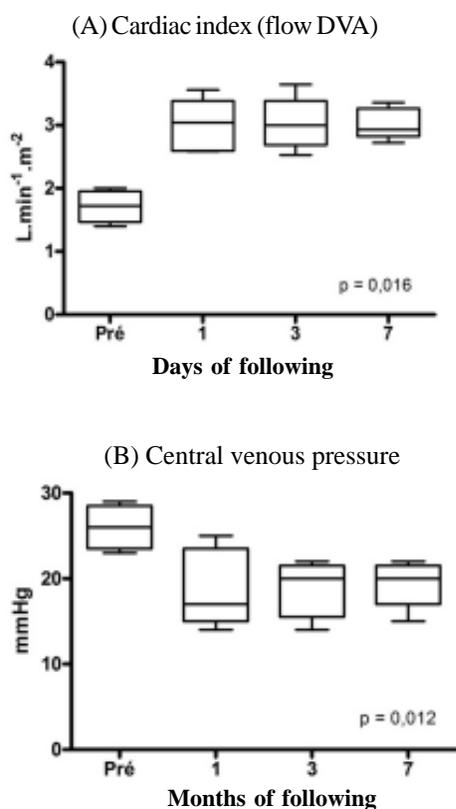


Fig. 4 – Flow maintained by the left ventricular assist device (A) and central venous pressure (B) during circulatory assistance in the five patients.

Thromboembolic complications related to the circulatory assist device did not occur in any of the patients studied. Moreover, significant alterations of the internal surfaces or of the artificial ventricle valves were not observed on their removal. The two patients who died under assistance were submitted to an anatomopathological study that also did not discover any signs of thromboembolic phenomena of the investigated organs.

COMMENTS

This study demonstrated that chagasic cardiomyopathy is an illness with a high risk of mortality among heart transplantation patients as there is a high incidence of cardiogenic shock with its fast evolution to death in the absence of adequate mechanisms of circulatory assistance. Thus, the use of mechanic circulatory assist devices as a bridge for heart transplantation offers new perspectives for patients suffering from this illness, providing a significant increase in the possibility to perform the transplantation and a reduction of mortality rates on the waiting list.

Table 2. Results of circulatory assist paracorporeal device implantation as bridge for heart transplantation.

Patient	Time of Assistancia	Complications	Number of Reoperations	Final Result
1	11 days	Coagulopathy; Pulmonary Emboli; multiple organ failure	1	Death
2	21 days	Coagulopathy; Surgical Bleeding.	3	Transplantation
3	31 days	Coagulopathy; Surgical bleeding.	2	Transplantation
4	18 days	Pulmonary infection; multiple organ failure	-	Death
5	38 days	Renal Insufficiency; Digestive Bleeding; Pulmonary Infection	-	Assistance

Previous studies already demonstrated that the life expectancy of patients suffering from chagasic cardiomyopathy showing important symptoms of cardiac insufficiency is lower than that observed for patients with cardiomyopathies of other etiologies [7,8]. This fact seems to be related to the frequent occurrence of biventricular dysfunctions and complex ventricular arrhythmias in chagasic patients [7,11]. However, although the myocardium complications are more severe in the presence of this illness, the patients indicated for heart transplantations are younger, giving results that are comparable to those observed with other indications [9].

On the other hand, the high number of chagasic patients who urgently need heart transplantation and the high mortality rate observed on the waiting list demonstrate the importance of mechanic circulatory assist devices as bridges to heart transplantation in the case of this illness. In spite of the wide international experience with this type of procedure, there is only one published report of a patient with Chagas disease submitted to the implantation of a paracorporeal ventricular assist device before transplantation [12]. This report refers to the pioneering employment of the initial model of the device used in this experience, which provided left circulatory assistance for four days.

The indication criteria for circulatory assistance devices as bridges for transplantation, according to international experience, usually include patients in earlier phases of ventricular failure. [3,5,6]. This situation is motivated by the negative influence of complications of other organs on the circulatory assistance results. In respect to this, the observation that death among patients on the waiting list for urgent transplantation occurs earlier with chagasic patients, as seen in this study, also reinforces the need for an early indication of assist devices in these cases.

The employment of mechanic circulatory assist devices as a bridge for transplantation nowadays involves thousands of cases, which demonstrates its irrefutable impact on the survival of patients who evolve with cardiogenic shock on waiting list [3-6]. This impact can be better evaluated analyzing the REMATCH study results [13]. This study randomly compared the results of Heartmate left ventricular assist device implantation with the evolution of patients maintained clinically, with the objective of offering an alternative for cases that present contraindications for heart transplantation.

The period of assistance provided by the different types of devices can vary from a few weeks to some months, a fact that depends on their specific characteristics. Thus, currently there are several types of devices in clinical use. The most common ones are the paracorporeal pneumatic ventricles and implanted electromechanical propulsion ventricles [4,5]. The paracorporeal devices can be employed to assist the

systemic and pulmonary circulation and are less expensive. Their utilization though, requires that patients remain in hospital. Implanted ventricles can only be employed to assist the left heart and are more expensive. However, they are able to maintain patients for periods of more than a year.

The best results with the employment of circulatory assist devices are being obtained mainly with patients submitted to isolated left ventricular assistance [4,5,14], while patients who need biventricular assistance present with limited results because of higher rates of infections and pulmonary complications [15,16]. In chagasic cardiomyopathy, the biventricular dysfunction and ventricular arrhythmias could be factors responsible for the necessity of biventricular assist employment. In the cases in the current study however, it was only possible to reverse right ventricular dysfunction using pharmacological support in the post-operative period. This situation is common in relation to the use of mechanical assist devices in the treatment of other illnesses [17] and demonstrates that the right ventricular dysfunction may be secondary to the involvement of the left heart in chagasic cardiomyopathy.

Another important aspect observed in publications is that the duration of assistance can significantly affect the result of transplantation. Patients who were maintained on assistance for more than 30 days presented a lower mortality rate than those maintained less than a month [3]. This might be attributed to the reversal of effects of cardiac insufficiency on the function of other organs after the installation of assistance, providing better conditions for transplantation. On the other hand, the contact of blood with the biomaterials used in circulatory assist devices may trigger an increase in the inflammatory response that involves the activation of cellular and plasmatic protein response systems [18]. Thus, the control of the biocompatibility of artificial systems becomes of great importance in the success of the use of these devices. Apart from modifications used on the contact surfaces of biomaterials, this control can be obtained by the inhibition of biological cascades that lead to sanguineous activation and by the control of the final products of these cascades.

The ventricular assist device employed in this study is a nationally-developed paracorporeal device that has its clinical application linked to a trial protocol approved after several 'in vitro' studies and its use in animal experimentation [19,20]. In this study, the maintenance of patients for periods that varied from 11 to 31 days without complications related to the circulatory assist system itself is promising for its routine use. It is important to observe that the average time for heart transplantation of patients waiting for a donor varies. In Brazil it can take one or two

months, a period that can be bridged using paracorporeal circulatory assist devices.

In relation to complications reported in this study, the follow up of patients submitted to the implantation of InCor paracorporeal ventricular assist devices, it is important to stress the necessity of a protocol to individually adjust the anti-coagulation in the first cases of the experiment. This situation is reflected in the high incidence of bleeding and reoperations, which did not however endanger the final results of the procedure, similar to other published reports [21]. Other complications observed have also often been reported in the literature [4,22], constituting aspects that demonstrate the complexity of the postoperative management of these patients.

In conclusion, chagasic cardiomyopathy is an illness in which mortality will only be diminished with heart transplantation programs associated with mechanical circulatory assist devices. It should always be remembered that in chagasic patients, these devices should be utilized as bridges for heart transplantations at an early stage, similar to their use in the treatment of other illnesses.

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