Hemodynamic Performance and Inflammatory Response During the use of VAD-InCor as a Bridge to Transplant

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Summary

Background: Cardiac transplantation faces the serious problem of lack of donors and it is estimated that 20 to 40% of the patients die while waiting for heart transplantation. For these patients, the use of mechanical circulatory assist devices is the only choice of survival while waiting for a donor. In Brazil, the experience with mechanical circulatory support is limited and there is no regular program regarding the use of these devices as a bridge to heart transplantation.

Objective: To evaluate the hemodynamic performance and the systemic inflammatory response during the clinical use of the InCor-type ventricular assist device (VAD-InCor) as a bridge to heart transplantation.

Methods: Between October 2003 and April 2006, 11 patients in the waiting list for heart transplantation presented hemodynamic deterioration due to refractory cardiogenic shock. Seven of these patients were submitted to VAD-InCor implantation for left ventricular assistance. The etiologic diagnosis was Chagas’ disease in 5 patients and idiopathic dilated cardiomyopathy in 2.

Results: The duration of left ventricular assistance ranged from 14 to 42 days (mean 26.2 days). During this period, the hemodynamic performance of the DAV-InCor was adequate to support a normal hemodynamic state. There was normalization of central venous oxygen saturation and serum lactate. Two patients were submitted to heart transplantation, while the other 5 patients died under assistance due to infection and multiple organ failure.

Conclusion: The performance of the VAD-InCor, in the hemodynamic behavior of the studied patients, was adequate for the maintenance of a satisfactory circulatory state during the studied period. There was improvement in the tissue perfusion parameters and maintenance of systemic inflammatory response signs. There was a high incidence of complications; however, complications related to the device, which could compromise the safety of its use, were not demonstrated. (Arq Bras Cardiol 2008; 91(5) : 301-308)

Key words: Heart transplantation/mortality; assisted circulation/methods; heart assist devices/utilization; heart, artificial/trends

Introduction

Despite the recent advances in the management of patients with congestive heart failure (CHF), the definitive treatment remains the cardiac transplantation. The main obstacle to this procedure is the lack of donors. According to a report regarding the waiting list for cardiac transplantation in a national institution, 41% of 256 listed patients between 1998 and 2004 died before the procedure and cardiogenic shock was the main cause of death.

Internationally, the ventricular-assist devices (VAD) have had their use and indication well established and consequently, different models have been used and the international experience in this field amounts to thousands of cases. Currently, in addition to the use of several devices as a “bridge” to transplant, other modalities that are worth mentioning are: the use of devices as a “bridge” to a future recovery, based on the concept of reverse remodeling of the cardiac muscle; and the use as definitive therapy for some patients with contraindications to transplantation. According to the International Society of Heart and Lung Transplantation (ISHLT), the period between January 2002 and December 2004, 78.3% of the patients with circulatory support had this procedure indicated as a bridge to transplantation, whereas 5.3% were used as a bridge to recovery and 11.9% as the definitive therapy.

In Brazil, the experience with the use of mechanical circulatory-assist devices in the treatment of cardiogenic shock is small and comprises only isolated case reports or experiments related to the development of new devices. In parallel, the life expectancy of the patients in this situation, particularly those of Chagasic etiology, is very limited, requiring the implementation of regular programs.
of mechanical circulatory assistance, especially as a bridge to cardiac transplantation.

The InCor Ventricular Assist Device (VAD-InCor) is paracorporeal and has a pneumatic start, which can be implanted in parallel with the left and/or right circulation, through cannulae sutured to the cardiac structures and exteriorized through a counter-opening in the abdominal region. Despite the external positioning, it provides relative mobility to the patient, being capable of maintaining the circulation for longer periods. During its assessment in an experimental calf model, it showed good hemodynamic performance and the capacity to adequately substitute left ventricular function. Experimental studies have demonstrated the possibility of maintaining this device implanted in parallel with circulation for several weeks and its first clinical use was carried out in 1993, with a favorable result.

The objective of this study was to determine the viability and safety of the implant of the VAD-InCor as a bridge to transplantation, evaluating its hemodynamic performance, the clinical evolution and the alterations of the inflammatory response of the patients.

Methods

This study was carried out with patients in the waiting list for cardiac transplantation, and presented a clinical picture of cardiogenic shock. The implantation of the VAD-InCor was indicated in patients who presented cardiogenic shock that was refractory to the adequate control of volemia, associated to the optimized use of medication therapy, including the use of at least two inotropic IV agents and the eventual use of the intra-aortic balloon.

The contraindications to the inclusion in the study were: age older than 65 years; weight < 40 kg; episode of pulmonary embolism or vena cava thrombosis in the last month; prolonged intubation (more than 48 hrs); episode of cardiopulmonary resuscitation in the last 24 hours; acute neurological sequela or severe chronic one; acute or chronic renal failure, with creatinine levels > 2.5 mg/dl and/or urea > 100 mg/dl; liver dysfunction with total bilirubin > 3 mg/dl; active infectious picture and hemorrhagic disorders.

The study was approved by the Ethics Scientific Committee of the institution and the National Commission for Ethics in Research (Conep). All patients signed the free and informed consent form.

The choice of circulatory assist type was carried out according to the hemodynamic criteria. Initially, the isolated implant of a left ventricular assist system was performed, with the right ventricular dysfunction being managed pharmacologically, with the use of inotropic agents and vasodilators of the pulmonary vasculature. No patient was excluded after the device implantation.

Device implantation

The device used in the present study, VAD-InCor, was the model developed by the Center of Biomedical Technology (CTB) of Instituto do Coração (The Heart Institute). It is a paracorporeal, pulsatile device that consists of a pumping unit, with two chambers separated by a flexible membrane made of several layers of polyurethane polyether (Biomer™). The blood chamber of the VAD has a volume of 65 ml; its internal lining consists of several layers of Biomer™ and has two biological valves for flow control, which are positioned at the pump connection with the entry and exit cannulae (Fig. 1). The pump start is carried out by a pneumatic propulsion mechanism that controls the use of a positive pressure pulse in the pneumatic chamber.

The implantation of the device was carried out with the use of conventional extracorporeal circulation (ECC) in normothermia. After the sternotomy, two abdominal incisions were made to exteriorize the cannulae. Initially, the lateroterminal suture was performed between the ascending aorta and the tubular graft. Subsequently, with ECC support, the insertion and suture of the cannula in the apex of the left ventricle was performed. After the connection of the cannulae with the device, maneuvers were made to remove the air and the device was started. The preferred mode of functioning was always “on demand” or “full to empty”.

During the immediate postoperative period at the Intensive Care Unit (ICU), the patients receive continuous heparin IV infusion and were administered aspirin or pyridamol. During the first three days the patients also received aprotinin.

Hemodynamic assessment

The hemodynamic monitoring was carried out during the first days through a pulmonary artery catheter, for the measurement of the pulmonary capillary pressure (PCP), pulmonary artery pressure (PAP), central venous pressure (CVP), cardiac output and cardiac index (CI). The blood flow of the device was monitored continuously by the console of the VAD-InCor device, from where the calculation of the indexed flow by the division of the device flow by the body surface was obtained. The indexed flow obtained through the device was always maintained > 2.0 l/min/m².

The diagnosis of right ventricular failure was established according to the hemodynamic criteria and followed by
echocardiographic studies. To prevent such complication, all the patients received inotropic support IV and pulmonary vasodilators, with the routine use of inhaled nitric oxide. In the presence of right ventricular dysfunction, the pharmacological support was intensified, with the associated use of inotropic agents IV and pulmonary vasodilators, such as milrinone, nitroglycerin and prostacyclin. The implantation of a right ventricular assist system must be carried out only in cases that are refractory to the optimized pharmacological treatment.

**Laboratory assessment and systemic inflammatory response evaluation**

During the immediate postoperative period, the central venous oxygen saturation (SVO₂), the levels of serum lactate, urea, creatinine, bilirubin and lactic dehydrogenase were measured daily. Serum levels of brain natriuretic peptide (BNP), interleukins (IL6 and IL8), tumor necrosis factor-α (TNFα) and C-reactive protein (CRP) were measured in the three first days of follow-up and afterward, every week.

Samples were collected for the determination of the systemic inflammatory and neurohumoral responses. These samples were collected in the preoperative period, in the immediate postoperative period (6th hour), on the first three postoperative days and once a week from the 7th day on.

The samples were processed and the serum was separated by centrifuging and stored at -80 °C until the measurements were performed. The measurements of serum levels of interleukins 6 and 8 and TNFα were carried out in an automated chemiluminescence assay analyzer model IMMULITE™, with appropriate IMMULITE™ kits manufactured by DPC Medlab™. C-reactive protein measurements were carried out by a immunoturbidimetric method with ultra-sensitive detection, whereas the quantitative determination of BNP was carried out by automated radioimmunoassay in an ADVIA™ equipment manufactured by Bayer™.

Measurements were carried out in duplicate only when sample values were considered discrepant in relation to the other measurements.

**Anatomopathological analysis**

All patients that died were submitted to necropsy in order to identify and document the main complications associated to the method. The devices were evaluated at the moment of the transplantation or the necropsy, to identify the presence of thrombi inside, as well as the adequate mobility of the prostheses.

**Statistical study**

The analysis of the hemodynamic and laboratory data was carried out with the repeated measures analysis of variance, complemented by Bonferroni t test.

The analysis of the values of inflammatory response markers was carried out with Friedman’s non-parametric analysis of variance, complemented by Dunn’s test.

For the variables of normal distribution, values are presented as medians, with interquartile variations. The level of significance for the present study was set at 5%.

**Results**

**Circulatory support as a bridge to transplant**

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During the period of October 2003 to April 2006, 29 patients were referred as priority recipients for cardiac transplantation. Of these patients, 11 presented cardiogenic shock refractory to the pharmacological therapy and the implantation of the intra-aortic balloon. The implantation of the VAD-InCor was carried out in 7 of these patients; in two cases, it was not possible to perform it due to the unavailability of the equipment and in two patients, due to the lack of informed consent form.

The etiological diagnosis was Chagasic cardiopathy in 5 (71%) and idiopathic dilated cardiomyopathy in 2 (29%) of the seven patients studied. Five patients were males and age varied from 34 to 54 years (mean of 39.5 years). The general characteristics of the 7 patients are shown in Table 1.

All patients used dobutamine and intra-aortic balloon and three of them (42.8%) used milrinone. The time of use of inotropic agents varied from 5 to 81 days (mean 26.2±9.9). The mean CI in the preoperative period was 1.72 (±0.22) L/min/m² and the mean pulmonary vascular resistance was 2.43(±0.72) Wood units.

The seven patients were submitted to the VAD-InCor implantation to the left, without the need to implant circulatory assist to the right. None of the patients presented intraoperative complications, but three patients (42.8%) needed surgical re-intervention for revision of hemostasis.

The removal of the orotracheal tube in the first 24 hours of follow-up was carried out in six patients (85.7%). This fact allowed the feeding and early ambulation of these patients, a situation that was maintained until the occurrence of complications that motivated the discontinuation of these functions. Four patients (57.1%) could not be weaned from the IV inotropic agents.

The mechanical circulatory assist to the left ventricle was maintained in the seven patients for periods that varied from 14 to 42 days, with a mean of 24.2 (±9.98) days. The cardiac transplantation was carried out in two patients, on the 21st day and the 31st day after the implantation (28.6%), being considered a positive final outcome. The other five patients (71.4%) died using the VAD-InCor due to systemic infection or multiple-organ failure. Table 2 presents the variations of the hemodynamic parameters during the first three postoperative days. A significant increase in the CI was observed in association to a significant decrease in the pulmonary capillary and central venous pressures.

The right ventricle dysfunction was controlled in all patients, without the need to implant a new VAD-InCor to the right, with the use of inotropic agents such as dobutamine and milrinone and the continuous use of inhaled nitric oxide. This fact occurred in the five patients with a diagnosis of Chagasic cardiomyopathy as well as in the two patients with idiopathic dilated cardiomyopathy.

Figure 2 shows the normalization of lactate plasma levels and the central venous oxygen saturation on the first
Table 1 – Preoperative characteristics of the patients submitted to the implant of circulatory assist paracorporeal device.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Etiology</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Type of pharmacological support</th>
<th>Time of use</th>
<th>Cardiac index (l/min/m²)</th>
<th>Pulm. vasc. resist. (Wood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pat.1</td>
<td>Male</td>
<td>Chagasic</td>
<td>36</td>
<td>60</td>
<td>Dobutamine IAB</td>
<td>28 days</td>
<td>1.40</td>
</tr>
<tr>
<td>Pat.2</td>
<td>Male</td>
<td>Chagasic</td>
<td>46</td>
<td>75</td>
<td>Dobutamine IAB</td>
<td>12 days</td>
<td>1.87</td>
</tr>
<tr>
<td>Pat.3</td>
<td>Male</td>
<td>Chagasic</td>
<td>35</td>
<td>60</td>
<td>Dobutamine IAB</td>
<td>5 days</td>
<td>1.69</td>
</tr>
<tr>
<td>Pat.4</td>
<td>Male</td>
<td>Dilated</td>
<td>57</td>
<td>84</td>
<td>Dobutamine Milrinone IAB</td>
<td>81 days</td>
<td>1.90</td>
</tr>
<tr>
<td>Pat.5</td>
<td>Fem.</td>
<td>Dilated</td>
<td>43</td>
<td>48</td>
<td>Dobutamine Milrinone IAB</td>
<td>23 days</td>
<td>1.47</td>
</tr>
<tr>
<td>Pat.6</td>
<td>Male</td>
<td>Chagasic</td>
<td>34</td>
<td>50</td>
<td>Dobutamine Milrinone IAB</td>
<td>25 days</td>
<td>1.72</td>
</tr>
<tr>
<td>Pat.7</td>
<td>Fem.</td>
<td>Chagasic</td>
<td>45</td>
<td>46</td>
<td>Dobutamine IAB</td>
<td>10 days</td>
<td>1.96</td>
</tr>
</tbody>
</table>

IAB - Intra-aortic balloon.

Table 2 – Hemodynamic behavior up to the third postoperative day

<table>
<thead>
<tr>
<th>Preoperative</th>
<th>POI</th>
<th>1st PO</th>
<th>2nd PO</th>
<th>3rd PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>1.72±0.22 *</td>
<td>3.43±0.75 *</td>
<td>3.68±0.44 *</td>
<td>3.74±0.35 *</td>
</tr>
<tr>
<td>VADi</td>
<td>2.66±0.48</td>
<td>2.88±0.36</td>
<td>2.98±0.26</td>
<td>2.95±0.33</td>
</tr>
<tr>
<td>MAP</td>
<td>66.29±10.93</td>
<td>72.43±5.77</td>
<td>77.57±6.95</td>
<td>76.57±7.63</td>
</tr>
<tr>
<td>PAP</td>
<td>37.29±11.74</td>
<td>31.71±7.91</td>
<td>29.29±10.18**</td>
<td>32.29±8.42</td>
</tr>
<tr>
<td>PCP</td>
<td>26.43±6.60</td>
<td>19.86 ± 7.38**</td>
<td>16.86±7.10*</td>
<td>19.57±4.43**</td>
</tr>
<tr>
<td>CVP</td>
<td>26.71±4.68</td>
<td>19.14 ± 5.79**</td>
<td>17.71±3.09**</td>
<td>21.43±2.99**</td>
</tr>
</tbody>
</table>

CI - cardiac index; VADi - VAD-indexed flow; MAP - mean arterial pressure; PAP - mean pulmonary artery pressure; PCP - Pulmonary capillary pressure; CVP - central venous pressure. (*) = p < 0.01 in relation to the preoperative period. (**) = p < 0.05 in relation to the preoperative period.

Postoperative days. Concurrently, there were no significant alterations in urea and bilirubin levels, which remained elevated, especially in patients that presented organ failure; however, it was not possible to establish a statistical correlation between these markers and the device performance.

One patient (14.2%) presented significant hemolysis characterized by jaundice, with serum free hemoglobin levels of 125 mg/dl, presence of hemoglobinuria and LDH levels of 1,744 U/l during a picture of systemic inflammatory response syndrome (SIRS); later the free hemoglobin decreased to 32 mg/dl and DHL to 684 U/l. Three patients presented slight signs of hemolysis, with free hemoglobin levels of up to 40 mg/dl, all of them associated to hemodialysis.

There was no significant decrease in BNP levels, even in patients in whom it was possible to perform the weaning of inotropic agents.

The results of the measurements of inflammatory response markers (TNF-α, interleukins IL6 and IL8) and CRP performed during the postoperative follow-up period in the seven patients, are shown in Figures 3 and 4. Although no significant alterations were observed in the first three inflammatory response markers, a punctual increase can be observed in these variables in some of the patients, soon after the implantation of the VAD and after the first week of follow-up. A significant elevation in CRP levels could be observed throughout the postoperative follow-up period. This fact occurred mainly in the four patients that developed infectious complications in the postoperative period.

Four patients (57.1%) presented infectious complications with two (28.7%) being of respiratory origin and two in the bloodstream, leading to a septic picture. These patients developed worsening of the renal and liver function, a fact that contributed to the final picture of multiple-organ failure.

Two patients (28.5%) presented digestive bleeding, with the need to temporarily interrupt the anticoagulant therapy. One of these patients presented an embolic vascular accident.

The assessment of the VAD-InCor, carried out at the time of its removal, showed evidence of partial thrombosis at the entry
Figure 2 - Mean serum lactate values (a) and central venous oxygen saturation – SvO₂ (b) during the patients' postoperative evolution; Values are shown as means ± 95% confidence interval (* = p<0.05 in relation to the preoperative period through analysis of variance of repeated measures and Bonferroni t-test).

Figure 3 - Interleukin (IL6, IL8) values during the patients' postoperative evolution. Values are shown as medians and quartiles; There was no significant variation of Interleukin (IL6, IL8) values through the non-parametric Friedman analysis of variance.

Figure 4 - Tumor Necrosis Factor-alpha (TNF-α) and C-reactive protein (CRP) values during the patients' postoperative evolution; Values are shown as medians and quartiles. (*) = p<0.05 in relation to the preoperative period regarding the CRP values, through the non-parametric Friedman analysis of variance, complemented by Dunn's test.
pathway of the device in one of the patients that presented digestive bleeding five days before death. There was presence of blood in the stomach and intestinal loops of this patient. The necropsy of the five patients who died during the use of the VAD-InCor showed signs of pulmonary and hepatic congestion and dilation of the cardiac chambers in all patients.

Discussion

The use of circulatory assist devices is a well-established worldwide practice. In Brazil, however, there is lack of experience in this area, despite the high number of patients that could benefit from programs organized to promote the use of such devices.

In the present study, we presented a choice of a ventricular assist device, pulsatile and paracorporeal, to be used as a bridge to heart transplantation. The hemodynamic performance of the device was satisfactory, especially regarding the maintenance of adequate cardiac output and drainage in the cardiac chambers, demonstrated by the normalization of lactate levels and central venous oxygen saturation, as well as of the other hemodynamic measurements.

In spite of the strict inclusion criteria of the study, the selected patients were in a very advanced clinical state, considering the high incidence of use of the intra-aortic balloon (100%) in comparison to the data of the ISHLT\(^\text{(1)}\), in which only 4.5% of the patients are referred to transplantation while using an intra-aortic balloon. Other data that corroborate the clinical severity of the patients are the elevated levels of systemic inflammatory response and BNP levels at the moment of the device implantation.

The neurohumoral response was evaluated in the present study through the determination of the BNP levels. The release of BNP in the circulation is proportional to the ventricular distension caused by the volumetric overload, and therefore, it reflects a state of hemodynamic decompensation.

Several authors have described the BNP as good marker for the hemodynamic state of the patient with HF\(^\text{(2)}\). The implantation of the VAD determines a decrease in the myocardium load and hemodynamic recovery, reversing the situation of volemic imbalance within the ventricles, which can normalize the neurohumoral state.

Therefore, the determination of BNP levels could be an adequate marker, not only of the ideal moment for the device implantation, but also of the treatment efficacy and eventually, of the possible recovery\(^\text{(2)}\). In the present study, there was no normalization in BNP levels, despite a tendency to decrease, which could be explained by the maintenance of the ventricular distension to the right.

In our study, the right ventricular dysfunction, a much feared disorder as it determines a worse evolution of these patients\(^\text{(22,23)}\), was managed with inotropic agents and pulmonary vasodilators. There was no need for right VDA implantation in any of the cases and four patients were weaned from the inotropic agents with the maintenance of adequate flow through the device. However, despite the significant decrease in the filling pressures (PCP and CVP), these values did not reach normal levels and there was no normalization in bilirubin and urea levels, which can represent the maintenance of a state of venous hypertension in the hepatic and renal sites, favoring the increase in the incidence of dysfunction in these organs.

The other complications presented in our study are the same reported by the international literature, in their experience with other models. The incidence of surgical bleeding was 42.8% and of thromboembolic events, 14.2%, similarly to what is reported in the literature. The incidence of reoperation due to bleeding varies, in the literature, from 20% to 60%, regardless of the type of device and the etiology of the indication for transplantation\(^\text{(24,25)}\). The data suggest that the causes of postoperative bleeding are multifactorial and can include previous hepatic dysfunction, platelet dysfunction, previous anticoagulant therapy, anemia and a shift in the coagulation/fibrinolysis balance towards fibrinolysis.

The onset of late symptomatic thromboembolic phenomena varies from 20% to 40% in the literature\(^\text{(26)}\). Clearly, there is an initial tendency to bleeding whereas later, this tendency reverts to thrombosis and not even the newer models with higher technological development are free from this problem and all of them need some type of anticoagulation and/or platelet aggregation from a certain moment on, depending on the adopted protocol\(^\text{(27)}\).

The adequate control of anticoagulation is a very subtle process, as the importance of this control is not restricted to the protection against thromboembolic phenomena.

It is also important to minimize the triggering of the systemic inflammatory response, in an attempt to decrease the release of pro-inflammatory factors and the injury to figured blood elements, decreasing the degree of hemolysis and platelet degradation.

The contact of blood with biomaterials used in the devices can trigger an increase in the systemic inflammatory response, already activated by the hemodynamic state of the patients, through the activation of cell response and plasma protein systems.

The main systems involved in this response are: coagulation cascade/fibrinolysis; complement system and cytokines related to cell activation.

In patients with VAD, the serum levels of pro-inflammatory cytokines TNFα, IL-6 and IL-8 do not have a well-established role. The literature data suggest that pro-inflammatory cytokines and complement factors are elevated in the preoperative period in patients that underwent VAD implantation. The circulatory support seems to be associated to a better prognosis when there are favorable changes in the levels of these mediators\(^\text{(28-30)}\).

In our study, there were no significant alterations in the levels of interleukins IL-6 and IL-8 and TNFα, demonstrating the maintenance of an elevated systemic inflammatory response. The CRP levels, however, showed a significant elevation in the postoperative follow-up period, which can correspond to the onset of infectious complications or be associated to an increase in the inflammatory response due to the contact of the blood with the contact surface of the device.

We also observed a high incidence of infectious complications, higher than that reported by the literature\(^\text{(21,32)}\), which can be
related to the clinical severity of the studied patients or even to immunological alterations caused by the circulatory support.

Based on the data presented herein, we can conclude that the performance of the VAD-InCor was adequate in maintaining a satisfactory circulatory state during the circulatory assist period. There was a high incidence of complications during the clinical and laboratory evolution of the studied patients, which is compatible with the international experience.

Study limitations

The small sample size is the main limitation of the present study, limiting the statistical power of the results and preventing the determination of causal factors for the main complications. The high incidence of infectious complications also influences the final assessment of the systemic inflammatory response findings.

Future perspectives

The absence of regular programs of circulatory assist and the high number of patients that would benefit from the use of such devices make it necessary to stimulate other centers to use circulatory support devices, aiming at increasing the experience with this type of patient.

In parallel, the elevated cost of the existing devices in the international market encourages us to continue researching national devices, either by studies with larger sample sizes, studies with other devices, or by comparative studies.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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