Impact of Intra-Aortic Balloon Support on Endothelial Function and Tissue Perfusion Markers in Severe Heart Failure

Antônio A. P. Fagundes Júnior, Liliane Kopel, Claudia Bernoche, Milena F. Macatrão-Costa, Leonardo N. Lopes, Antonio P. Mansur, and Silvia Gelás Lage*
Heart Institute, Hospital das Clínicas HCFMUSP, Brazil

Abstract

Background: The intra-aortic balloon pump (IABP) is a common therapy available for ventricular support in critical cardiac patients. The aim of this study was to characterize the effect of IABP on endothelial function, on serum B-type natriuretic peptide (BNP) levels and on central venous oxygen saturation (Svo2) and arteriovenous carbon dioxide gradient (∆PCO2) as perfusion tissue markers.

Methods and results: Twenty-three patients with severe heart failure, mean age 50±13 years, left ventricular ejection fraction of 22±8% were included. All were on IABP support and the protocol considered 3 conditions: 1) IABP ratio 1:1, 2) IABP ratio 1:3 and 3) IAPB ratio 1:1. The period of time between conditions was 20 minutes. In the three conditions the endothelial-dependent flow-mediated vasodilatation (FMD) was measured by ultrasound method. Blood was sampled to determine Svo2, ∆PCO2 and BNP. FMD was impaired, ∆PCO2 and BNP were high, compatible with severe heart failure, but did not change with IABP variation. Svo2 (%) was 68.3±10.2 and 61.3±12.5, p<0.002 (condition 1 vs. 2). The values were also significant considering the condition 2 vs. 3 when Svo2 was 61.3±12.5 and 64.8±9.7, p=0.035 respectively.

Conclusions: The FMD, ∆PCO2 and BNP were abnormal secondary to decompensated heart failure but did not change with the variation of IABP support. The Svo2 proved to be a sensitive tissue perfusion marker to evaluate the response of mechanical support even in short periods of time. The Svo2 may represent an excellent clinical monitoring tool for patients on IABP as well as assistance to their weaning.

ABBREVIATIONS

∆PCO2: Arteriovenous Carbon Dioxide Gradient; BNP: B-Type Natriuretic Peptide; CI: Cardiac Index; Dmax B: Is Brachial Artery Maximum Diameter before Reactive Hyperemia; Dmax RH: Is Brachial Artery Maximum Diameter after Reactive Hyperemia; FMD: Flow-Mediated Vasodilatation; IABP: Intra-Aortic Balloon Pump; LVEF: Left Ventricular Dysfunction; Svo2: Central Venous Oxygen Saturation

INTRODUCTION

The treatment of critical decompensated heart failure is based on the use of vasoactive agents for hemodynamic support and frequently on the necessity to implement circulatory assist devices [1,2]. Although new devices have brought considerable improvements in the clinical setting [3], the intra-aortic balloon pump (IABP) is a useful therapy available for temporary ventricular support.

Some evidence has made its benefits controversial [4-6]. However, the cardiac disease etiology and the indication of IABP should be considered. A recent clinical study showed that IABP was useful for nonischemic cardiomyopathy critical patients, especially as a bridge for cardiac transplantation [7].

Endothelial dysfunction is a pathological condition mainly characterized by an altered proportion between vasodilator, antimitogenic, and anti-thrombogenic agents (endothelium-derived relaxing factors) [8] and vasoconstrictor, prothrombotic, and proliferative agents (endothelium-derived constricting factors) [9]. In individuals with heart failure, the behavior of the endothelial function is already known from the literature [10].

A recent study demonstrated that the impairment of the endothelial glyocalyx in cardiogenic shock, particularly on circulating levels of syndecan-1 and glycosaminoglycan heparin sulfate have prognostic relevance, even in patients supported by...
IABP [11]. However, the endothelial behavior in patients with IABP support demands complementary studies.

Several biomarkers associated with heart failure are well known, especially B-type natriuretic peptide (BNP). They are associated with the diagnosis and prognosis of the disease [12], however, the impact on acute therapeutic interventions is not clear. In addition, the evaluation of markers sensitive to low peripheral perfusion, such as central venous oxygen saturation ($S_VO_2$) and arteriovenous carbon dioxide gradient ($\Delta PCO_2$) have long been studied [13-18]. There is much discrepancy in results and conclusions in view of the great heterogeneity of protocols applied in the studies, particularly in those with short-term interventions.

This study aimed to assess the effect of IABP support on the endothelial function and to evaluate the impact of the device on serum BNP levels and on $S_VO_2$ and $\Delta PCO_2$ as tissue perfusion markers.

**MATERIALS AND METHODS**

This experimental and prospective study was performed at the intensive care unit of the Heart Institute (InCor-HC-FMUSP). The study was designed in accordance with the Human Research Guidelines and Standards (Resolution 196/1996 of the National Health Council) and approved by the ethics committee of the Hospital das Clínicas of the University of São Paulo. We evaluated a cohort of patients hospitalized for heart failure receiving ventricular IABP support. The patients included in the study were aged >18 years and had left ventricular dysfunction (LVEF <45%), as detected on an echocardiogram through the Teichholz method. All the patients received IABP (Datascope System 98XT, NJ, USA). Meanwhile, we considered the following parameters as exclusion criteria: clinical instability of the patient that did not allow to change the IABP support; clinical signs of severe sepsis and/or septic shock according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine [19]; the necessity to modify the dose of vasoactive drugs in the course of the study; technical impossibility to obtain images of the brachial artery; cardiac arrhythmias at the time of protocol implementation; and previous brachial artery surgery.

Once included in the study, the patients received a 1:1 IABP support with maximum inflation (condition 1), which was then changed to the ratio 1:3 with maximum inflation with helium gas (condition 2) for a period of 20 min. Then, the IABP device was set to 1:1 with maximum inflation (condition 3). In the 3 periods of the study, venous blood was collected from all the patients using a central venous catheter to obtain blood gas and serum BNP. The arterial blood gas levels were determined at the 3-time points of inclusion in our study. Out of 8 patients (34%) who were using an IABP, 3 (39%) were on the waiting list for a heart transplant at the time of inclusion. Regarding the use of cardiovascular medications, dobutamine was administered to 21 patients (91%) at a mean dose of 13.0±7.6 mcg/kg/min; sodium nitroprusside to 12 patients (52%) at 1.9±1.6 mcg/kg/min; milrinone to 1 patient (4%) at 0.6 mcg/kg/min; noradrenaline to 2 patients (8%) at 0.5±0.4 mcg/kg/min; nitroglycerin to 1 patient (4%) at 0.79 mcg/kg/min; captopril to 3 patients (13%) at 70±31 mg/day; hydralazine to 2 patients (8%) at 93±79.54 mg/day; and isosorbide mononitrate to 1 patient (4%) at 120 mg/day. There was no modification to the dose of vasoactive drugs during the protocol. Nine patients (39%) were on the waiting list for a heart transplant at the time of inclusion in our study. Out of 8 patients (34%) who were using antibiotics, none had any signs of severe sepsis or septic shock, which was an exclusion criterion. Urea and creatinine serum levels were 54.1±34.2 mg/dL and 1.46±0.86 mg/dL, respectively.

Regarding the laboratory analysis 22 patients were evaluated and technical problems occurred for one patient. The results of the $S_VO_2$ (%) reveal a statistically significant difference between condition 1 and 2 (68.3±10.2 and 61.3±12.5); p=0.002 respectively. Difference was also observed between condition 2 to 3 (the last 64.8±9.7; p=0.035). There was no statistical difference (p=0.064) between conditions 1 and 3 (Figure 3). The analysis of $\Delta PCO_2$ (mmHg) in conditions 1, 2 and 3 (whose values were respectively: 7.01±4.08, 8.07±3.40 and 6.54±4.07) was not statistically significant. In addition, the results of BNP (pg/ml) conditions 1, 2 and 3 were also not statistically significant considering their respective values: 1077±791, 1228 ± 1068 and 1125±929. The mean of FMD (%) was 9.2±12.81 in condition 1, 4.32±7.15 in condition 2 and 4.14±7.11 in condition 3. Then, there was no statistical significance between the conditions (Figure 4).

The $\Delta$% of FMD was calculated using the formula:

$$\Delta\%\text{ FMD} = \frac{\text{Dmax RH} - \text{Dmax B}}{\text{Dmax B}} \times 100$$

where: Dmax RH is brachial artery maximum diameter after reactive hyperemia; Dmax B is brachial artery maximum diameter before reactive hyperemia.

**Statistical analysis**

For categorical variables, the absolute and relative frequencies were calculated. Continuous variables were summarized as the mean and standard deviation values. The paired Student’s t test was used for comparisons between the conditions (1 vs. 2; 2 vs. 3; 1 vs. 3). The level of significance was set at p<0.05 [23]. Statistical analyses were performed by an independent statistician using SAS Software 9.0 version (SAS Institute., Cary, NC).

**RESULTS**

The etiology of heart failure, 8 patients (34%) presented with idiopathic dilated cardiomyopathy; 9 (39%), ischemic cardiomyopathy; 4 (17%) cardiomyopathy induced by Chagas disease; and 2 (8%) valve heart disease. The LVEF, estimated through an echocardiogram performed during patient hospitalization, ranged from 14% to 40%, with a mean of 22±8%. Regarding the use of cardiovascular medications, dobutamine was administered to 21 patients (91%) at a mean dose of 13.0±7.6 mcg/kg/min; sodium nitroprusside to 12 patients (52%) at 1.9±1.6 mcg/kg/min; milrinone to 1 patient (4%) at 0.6 mcg/kg/min; noradrenaline to 2 patients (8%) at 0.5±0.4 mcg/kg/min; nitroglycerin to 1 patient (4%) at 0.79 mcg/kg/min; captopril to 3 patients (13%) at 70±31 mg/day; hydralazine to 2 patients (8%) at 93±79.54 mg/day; and isosorbide mononitrate to 1 patient (4%) at 120 mg/day. There was no modification to the dose of vasoactive drugs during the protocol. Nine patients (39%) were on the waiting list for a heart transplant at the time of inclusion in our study. Out of 8 patients (34%) who were using antibiotics, none had any signs of severe sepsis or septic shock, which was an exclusion criterion. Urea and creatinine serum levels were 54.1±34.2 mg/dL and 1.46±0.86 mg/dL, respectively.

Considering the laboratory analysis 22 patients were evaluated and technical problems occurred for one patient. The results of the $S_VO_2$ (%) reveal a statistically significant difference between condition 1 and 2 (68.3±10.2 and 61.3±12.5); p=0.002 respectively. Difference was also observed between condition 2 to 3 (the last 64.8±9.7; p=0.035). There was no statistical difference (p=0.064) between conditions 1 and 3 (Figure 3). The analysis of $\Delta PCO_2$ (mmHg) in conditions 1, 2 and 3 (whose values were respectively: 7.01±4.08, 8.07±3.40 and 6.54±4.07) was not statistically significant. In addition, the results of BNP (pg/ml) conditions 1, 2 and 3 were also not statistically significant considering their respective values: 1077±791, 1228 ± 1068 and 1125±929. The mean of FMD (%) was 9.2±12.81 in condition 1, 4.32±7.15 in condition 2 and 4.14±7.11 in condition 3. Then, there was no statistical significance between the conditions (Figure 4).
Figure 1: Study design, IABP: intra-aortic balloon; condition 1 and 3: ratio 1:1; condition 2: ratio 1:3; BNP: B-type natriuretic peptide; US: ultrasound.

Figure 2: Flow velocity curves of brachial artery - A: Double pulse using the IABP support at baseline; B: double pulse using the IABP support after reactive hyperemia (HR).

Figure 3: Variation of central venous oxygen saturation (SV_O₂%) between condition 1, condition 2 and condition 3, paired t-Student test, mean ± standard error, significance p<0.05.
DISCUSSION

The patients included in this study were hospitalized for decompensated heart failure. They had a severe myocardial damage and despite the optimized pharmacological support, mechanical devices to control the low cardiac output were necessary.

It is important to note that the sample of this study did not include patients with circulatory collapse secondary to acute coronary insufficiency. It included patients with chronic cardiomyopathy whose mechanical support was necessary to overcome acute decompensation or as a bridge for cardiac transplantation. Thus, as we have seen in previous studies [7], the perspectives for IABP benefit are quite different from studies evaluating acute myocardial infarction [4] and surgical patients [6].

Considering this perspective of benefit, our purpose was to evaluate possible markers of improvement of the peripheral flow provided by the mechanical support.

In this cohort we evaluated the effect of the IABP support on endothelial function, its influence on BNP serum levels and on tissue perfusion markers (ScVO\textsubscript{2} and ∆PCO\textsubscript{2}).

Endothelial dysfunction

Heart failure alters the endothelial function of large conductance and small resistance arteries [24]. The specific mechanisms that modulate endothelial function include decreased peripheral blood flow, cytokine activation, increased activity of the angiotensin-converting enzyme, increased oxidative stress, and enhanced endothelin production [10, 25]. These factors contribute to the decreased synthesis and release of nitric oxide and its increased inactivation because of the generation of oxygen free radicals. Moreover, the vascular tone increases with the endothelin production, which competes with nitric oxide vasodilation [26].

Endothelial dysfunction may induce heart failure progression, which may cause peripheral and central effects. Increased arterial stiffness and reduced compliance increase the ventricular afterload and left ventricular end-diastolic stress, which leads to heart dilatation and failure [27-29].

This is the first study that analyzed the endothelial function in critical cardiac patients, receiving ventricular IABP support, being excluded AMI patients.

In our study, although patients had full IABP support, we observed that FMD was diminished since the condition 1, in accordance with with previous findings in the literature considering patients with heart failure [30]. Considering condition 2, there was a reduction in FMD, which remained unrecovered after the IABP was in condition 3 (Figure 3). This trend was not statistically significant but showed severe endothelial dysfunction, with mean FMD values of less than 10%, which did not recover following the return of full IABP support. It is possible that the 20-minute interval between condition 2 and condition 3 was not enough to restore endothelial function to basal levels, which was already quite impaired.

Biomarkers

BNP can be considered a marker of the severity of ventricular dysfunction. The literature shows that plasma levels of BNP have a possible correlation with LVEF and glomerular filtration [31].

In our study, we observed high levels of plasma BNP, confirming the severity of ventricular dysfunction in the sample of patients included. Under the conditions of the protocol, there were fluctuations of BNP levels without significant modification at constant high values.

The literature demonstrates that BNP and other serum biomarkers in cardiogenic shock can be reduced with mechanical circulatory support; however, with a longer period (7 days) of patients’ observation [32].
Tissue perfusion markers

The $\Delta$PCO$_2$ measurements reflect the adequacy of cardiac index (CI) to oxygen demand. It has an inverse relationship with CI, which means an elevated $\Delta$PCO$_2$ may be a marker of low cardiac index [33, 34].

In fact, the $\Delta$PCO$_2$ values observed in our study were high, consistent with low cardiac output. They oscillated consistently with the IABP intervention, however the value trend was not statistically significant to demonstrate a sufficiently sensitive tissue marker in the short time of the intervention.

Finally, we consider $SVO_2$ as a tissue perfusion marker. In an outstanding study, $SVO_2$ served as a parameter to guide the early treatment of septic shock setting the value of 65% as the ideal endpoint [35]. For patients with severe heart failure or cardiogenic shock, the values are certainly lower and there is no value established. The time of installation of cardiac decompensation and the baseline condition of myocardial function may make it different for each patient, with compensatory adaptation to high oxygen extraction at low cardiac output.

In our study, we were able to eliminate this factor of variation, since each patient was evaluated comparatively with his own baseline between the interventions. We found a significant reduction of $SVO_2$ in condition 2 and an increase with the support in condition 3 (Figure 2). The intervals between the interventions were 20 minutes, that is considered short periods, and $SVO_2$ was sensitive to changes notwithstanding. This marker had already drawn our attention in a previous study with IABP [7], however, with longer time interval (48 h). This study confirms the variation of $SVO_2$ in a short period of time, which makes the parameter an important and sensitive tissue perfusion marker, which can be extremely useful in the overtime evaluation of the critical patient and establish partial criteria to proceed to weaning mechanical support.

Study limitations

The patients included had partial hemodynamic stability in order to be able to disconnect the IABP for 20 minutes without impairment to their clinical evolution. Therefore, the results, obtained from short time lapses between conditions, may have been less meaningful.

CONCLUSION

The endothelial-dependent flow-mediated vasodilatation was impaired according to severe decompensated heart failure and did not change with IABP support.

The BNP and $\Delta$PCO$_2$ values were high and compatible with cardiovascular condition, yet may not be considered as good tissue markers for therapeutic variations in short periods of time. $SVO_2$ proved to be a sensitive and suitable tissue perfusion marker to evaluate the response of the mechanical support even in short periods of time. $SVO_2$ monitoring may represent an excellent clinical tool for patients in IABP as well as assistance to their weaning.

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

19. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit...


