Implications of the Hemodynamic Optimization Approach Guided by Right Heart Catheterization in Patients with Severe Heart Failure

Luís E. Rohde, Thiago Furian, Candice Campos, Andreia Biolo, Eneida Rabelo, Murilo Foppa, Nadine Clausell

Porto Alegre, RS - Brazil

Objective - *To report the hemodynamic and functional responses obtained with clinical optimization guided by hemodynamic parameters in patients with severe and refractory heart failure.*

Methods - *Invasive hemodynamic monitoring using right heart catheterization aimed to reach low filling pressures and peripheral resistance. Frequent adjustments of intravenous diuretics and vasodilators were performed according to the hemodynamic measurements.*

Results - *We assessed 19 patients (age = 48±12 years and ejection fraction = 21±5%) with severe heart failure. The intravenous use of diuretics and vasodilators reduced by 12 mm Hg (relative reduction of 43%) pulmonary artery occlusion pressure (P<0.001), with a concomitant increment of 6 mL per beat in stroke volume (relative increment of 24%, P<0.001). We observed significant associations between pulmonary artery occlusion pressure and mean pulmonary artery pressure (r=0.76; P<0.001) and central venous pressure (r=0.63; P<0.001). After clinical optimization, improvement in functional class occurred (P< 0.001), with a tendency towards improvement in ejection fraction and no impairment to renal function.*

Conclusion - *Optimization guided by hemodynamic parameters in patients with refractory heart failure provides a significant improvement in the hemodynamic profile with concomitant improvement in functional class. This study emphasizes that adjustments in blood volume result in immediate benefits for patients with severe heart failure.*

Key words: heart failure, treatment, hemodynamic optimization

Hospital de Clínicas de Porto Alegre - UFRGS
Mailing address: Nadine Clausell – Serviço de Cardiologia do Hospital de Clínicas de PA – Rua Ramiro Barcelos, 2350 - S/2060 – 90035-003 – Porto Alegre, RS, Brazil – E-mail: clausell@portoweb.com.br
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The management of patients with advanced heart failure includes the combination of different drugs that interfere with the progression of the disease, improve functional capacity, and reduce mortality. Despite the advances in managing this syndrome, the hospitalization and readmission rates due to heart failure continue to be high [1]. For some of these patients, heart transplantation is a potential alternative. However, recent data show a drop in the number of cardiac transplantations performed throughout the entire world [2], partially reflecting the stagnation in the number of donors. These findings strengthen the concept that the selection of candidates for transplantation should undergo strict stratification. An effective therapeutical approach to reduce symptoms and to better stratify the patient's risk should be undoubtedly found.

The frequent discrepancy between manifestations of clinical congestion and the actual status of blood volume in advanced heart failure [3] sometimes hampers the management of these patients, leaving them inadequately hypervolemic and functionally limited [4]. In the last few years, a differentiated approach to the management of so-called refractory patients has gained attention. Based on the observation of patients referred for evaluation prior to heart transplantation, Stevenson et al [5,6] showed that this hemodynamic inadequacy deserves specific management. This management includes the intravenous use of high dosages of vasodilators and diuretics guided by invasive hemodynamic monitoring, aimed at reducing ventricular filling pressures and vascular resistance. Therefore, inclusion on the waiting list for transplantation could be postponed for those patients who reach an adequate hemodynamic response with hemodynamic optimization, allowing space for more critically ill and refractory patients [4,7,8].

We report our experience with invasive hemodynamic monitoring in patients from the heart failure and heart transplantation outpatient clinic, when worsening of the clinical findings or difficulty in ambulatory management occurs, with a persistence of New York Heart Association (NYHA)

functional class III or IV. We also analyzed the behavior of the filling pressures of the left and right ventricles, and their possible correlations prior to and after changes caused by intravenous diuretics and sodium nitroprusside. Finally, we also reported the clinical and laboratory implications of this strategy.

Methods

In our study, we analyzed adult patients who consecutively sought the heart failure and heart transplantation outpatient clinic of the Hospital de Clínicas de Porto Alegre. These patients had clinical findings of NYHA functional class III or IV heart failure and a progressive difficulty in ambulatory management with or without clinical evidence of congestion. The data analyzed refer only to the admission period, and no further ambulatory follow-up was analyzed.

The patients were admitted to the intensive care unit of the Hospital de Clínicas de Porto Alegre to undergo hemodynamic monitoring and therapeutical optimization. Initially, the internal jugular or subclavian vein was punctured with the patient under local anesthesia. A catheter was inserted into the pulmonary artery and introduced with control of the intracavity pressure curve until the occlusion pressure pattern was obtained by the floating balloon. The hemodynamic assessment included the following parameters: central venous pressure; systolic, diastolic, and mean pulmonary artery pressures; and pulmonary artery occlusion pressure. A mean of 3 injections of saline solution was used to estimate cardiac output with the thermodilution technique. Systemic and pulmonary vascular resistance and the work of the right and left ventricles were also calculated. All measurements were adjusted for body surface, and the respective indices were calculated.

Generally, the medications being used were maintained until the initial measurements were obtained. The hemodynamic objectives to be achieved were as follows: pulmonary artery occlusion pressure <15mmHg, right atrial pressure <8mmHg; and peripheral systemic resistance index <2,000 dynes.seg.cm^{-5}, maintaining systemic systolic blood pressure $\geq$80mmHg. If the baseline measurements did not reach the objectives reported, the medications being used were with drawn, and the protocol with intravenous furosemide associated with sodium nitroprusside, according to Stevenson et al[6], was started. The search for hemodynamic optimization was performed with repeated measurements of the hemodynamic profile and frequent adjustments in the dosages of the diuretic and vasodilator. For the statistical analyses performed in this study, we selected the first hemodynamic measurement and the best subsequent hemodynamic profile, according to the objectives cited, which, most of the time, corresponded to the last measurement prior to withdrawal of the Swan-Ganz catheter. All patients were restricted to 1,000mL/day of fluid during the testing period and also to a sodium amount of 2g of salt per day. The time necessary to reach the objectives or to decide on the refractoriness of each case was not pre-established. Routine biochemical laboratory tests, such as urea, creatinine, sodium, and potassium, were performed prior to the protocol, during the protocol, according to clinical requirements, and at the end of the protocol. A subgroup of patients underwent 2-dimensional echocardiography with color Doppler prior to and after the protocol of hemodynamic optimization. The calculation of left ventricular ejection fraction in these patients was performed by M-mode analysis and the Teichholz formula.

Continuous variables were reported as mean ± standard deviation. Comparisons between continuous variables that had a normal distribution prior to and after the intervention were performed using the Student *t* test and correlations between variables using the Pearson's coefficient. Values of $P<0.05$ were considered statistically significant.

Results

In this study, we performed 25 invasive hemodynamic monitorings in 19 patients with severe heart failure, who sought treatment at the heart failure and heart transplantation outpatient clinic of the Hospital de Clínicas de Porto Alegre from January 1996 to July 2000. All patients studied were considered refractory to ambulatory treatment according to the criteria proposed by the Guidelines on Heart Failure of the Brazilian Society of Cardiology. Their ages ranged from 25 to 72 years, 76% of them were in NYHA functional class IV, and only 16% had heart failure of ischemic nature. The mean left ventricular ejection fraction was 21% (range: 11% to 28%). Clinical characteristics of the sample are shown in table I.

The initial hemodynamic parameters were compatible with the profile of patients with severe and advanced heart failure, which comprised low cardiac output, high systemic and pulmonary resistances, and high filling pressures. In this sample, the mean pulmonary artery occlusion pressure was 28mmHg, and systemic vascular resistance was greater than 2,800 dynes.seg.cm^{-5}. The intravenous use of sodium nitroprusside and furosemide significantly reduced ventricular filling pressures, with a concomitant improvement in cardiac performance. A drop of 12mmHg (relative reduction of 43%) occurred in pulmonary artery occlusion pressure

Table I – Clinical characteristics of patients undergoing right cardiac catheterization

	N (%)
Number of procedures	25
Age (years) *	48±12
Sex (% male)	70
Etiology of HF (%)	
Ischemic	4 (16)
Nonischemic	21 (84)
NYHA functional class (%)	
II	1 (4)
III	5 (20)
IV	19 (76)
Ejection fraction (%) *	21±5

* mean ± SD; HF- heart failure.

(P<0.001) with a concomitant increment of 6mL per cardiac beat in stroke volume (relative increment of 24%, P<0.001). Significant reductions in the systemic and pulmonary resistances also occurred ($P \leq 0.01$). These hemodynamic objectives were reached based on relatively small reductions in the mean blood pressure and heart rate, indicating maintenance of adequate systemic perfusion (tab. II).

When assessing the correlations between left and right cavity filling pressures, we observed positive and statistically significant associations between pulmonary artery occlusion pressure and mean pulmonary artery pressure (r = 0.76; P<0.001), and between pulmonary artery occlusion pressure and central venous pressure (r = 0.63; P<0.001) (figs. 1 and 2). Interestingly, the correlation between the variation in pulmonary artery occlusion pressure prior to and after pharmacological intervention and the variation in mean pulmonary artery pressure was also significant (r=0.77; P<0.0001); this correlation, however, was not observed with the variation in central venous pressure (r=0.38; P=0.08) (figs. 1 and 2).

After invasive hemodynamic optimization, a significant improvement in functional class was observed, as well as a tendency towards improvement in left ventricular ejection fraction. These positive results occurred without any harmful effect on renal function (tab. III). The relation between the serum levels of urea and creatinine, even though relatively elevated prior to hemodynamic optimization, was maintained unaltered after the interventions. Except for digoxin, the doses of the remaining drugs were increased after hemodynamic optimization, with a significant increase particularly in the use of vasodilating medications (tab. IV).

Discussion

For a long time, the paradigm for treating heart failure was based on the assumption that the natural history of heart failure could be altered if myocardial contractility, a fundamental problem, could be controlled [9,10]. In addition,

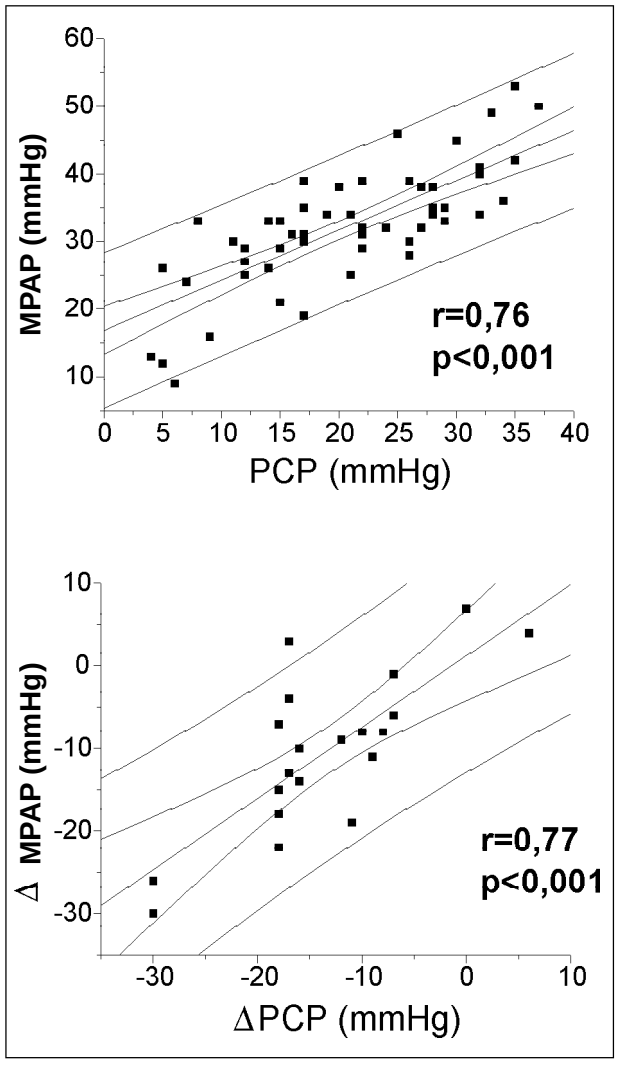

Fig. 1 - Correlation between mean pulmonary artery pressure and pulmonary artery occlusion pressure (above) and the variations of the 2 measurements after pharmacological intervention (below). MPAP - mean pulmonary artery pressure; PAOP - pulmonary artery occlusion pressure.

Table II - Hemodynamic parameters prior to and after optimization guided by right cardiac catheterization

	Before	After	P
Heart rate (bpm)	97±10	92±9	< 0.001
Mean blood pressure (mmHg)	77±11	70±10	< 0.001
Central venous pressure (mmHg)	12±7	6±4	< 0.001
Systolic pulmonary artery pressure (mmHg)	48±8	38±10	< 0.001
Mean pulmonary pressure (mmHg)	38±7	29±7	< 0.001
Pulmonary artery occlusion pressure (mmHg)	28±6	16±7	< 0.001
Cardiac index (L/min)	1.9±0.5	2.3±0.5	< 0.001
Stroke volume (mL/beat)	19±5	25±6	< 0.001
Pulmonary vascular resistance index (dynes-seg.cm^{-5})	468±241	415±203	< 0.001
Peripheral vascular resistance index (dynes-seg.cm^{-5})	2,866±907	2,284±652	= 0.01

"Before" refers to evaluation immediately prior to starting the protocol, and "after" refers to the final moment prior to withdrawal of the pulmonary catheter.

the concept that the improvement in cardiac output in these patients guided by the rule of Frank-Starling justified the maintenance of high filling pressures. This strategy favored the maintenance of the patients in permanent states of relative hypervolemia, but with no clear clinical manifestations of congestion, due to adaptive systems of chronic heart failure [1]. Invasive hemodynamic monitoring provided a new understanding of these patients, in whom the intravenous use of vasodilators and diuretics, instead of positive inotropic agents, significantly improved the hemodynamic profile and symptoms [5,7].

In our study, the initial hemodynamic profile of the patients was compatible with the severity of heart failure: reduced cardiac indices, high pulmonary artery occlusion pressure, and high systemic and pulmonary resistances. With the progressive reduction in filling pressures due to the use of intravenous diuretics and vasodilators, we observed significant improvement in most parameters assessed. This behavior is usually contrary to that observed

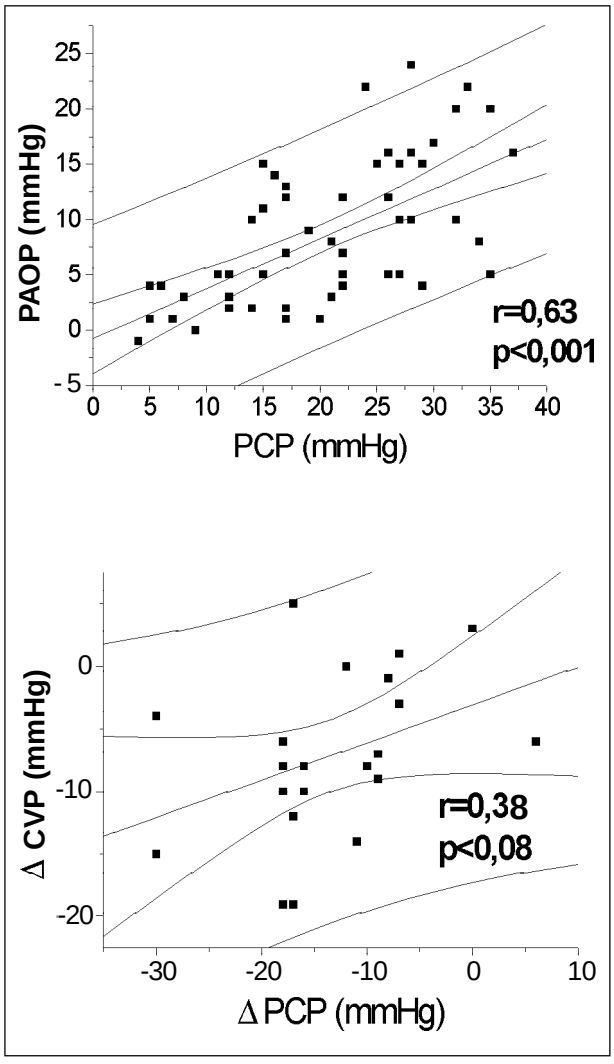

Fig. 2 - Correlation between central venous pressure and pulmonary artery occlusion pressure (above) and the variations in the 2 measurements after pharmacological intervention (below). CVP – central venous pressure; PAOP - pulmonary artery occlusion pressure.

Table III - Functional class, ejection fraction, and renal function before and after optimization guided by right cardiac catheterization

	Before	After	P
NYHA functional class	3.7±0.5	2.6±0.9	<0.05
Ejection fraction (%)	21±5.5	24±5.2	0.08
Renal function			
Serum creatinine (mg/dL)	1.1±0.2	1±0.2	NS
Serum urea (mg/dL)	62±28	60±31	NS
Urea/Creatinine ratio	56±18	57±21	NS

"Before" refers to evaluation prior to placement of the catheter in the pulmonary artery, and "after" refers to evaluation in the ward.

in acute ventricular failure, such as in the postinfarction period, in which ventricular volumes are normal. In chronic heart failure with large ventricular dilation, several specific mechanisms may contribute to this response. One of them involves a reduction in mitral regurgitation, invariably present in this condition, secondary to ventricular dilation.

Table IV – Use of drugs before and after optimization by right cardiac catheterization

	Before	After	P
Captopril (mg/day)	75±50	143±84	<0.01
Hydralazine (mg/day)	17±51	76±83	<0.01
Isosorbide dinitrate (mg/day)	25±43	57±66	<0.01
Oral furosemide (mg/day)	51±62	76±87	<0.01
Spironolactone (mg/day)	15±62	30±42	<0.05
Digoxin (mg/day)	0.2±0.06	0.2±0.07	NS

"Before" refers to evaluation prior to placement of the catheter in the pulmonary artery, and "after" refers to evaluation in the ward.

The vasodilating therapy promotes a reduction in afterload and favors optimization of cardiac output secondary to a redistribution of the transmitral flow [11-13]. The reduction in blood volume may also induce decreases in ventricular volumes, which optimize the preload, because they reduce parietal tension and stress secondary to excessive distension of the sarcomeres. This set of events favors better systolic performance. Improvement in right ventricular function may also result from an increase in left ventricular compliance, because of the interdependence between the ventricles [14].

The strategy guided by invasive hemodynamic parameters has proved useful in managing patients with severe heart failure, but it requires intensive care units. Perhaps the great advance of the approach guided by hemodynamic parameters is the recognition of the importance of the search for low or almost normal filling pressures, without fearing a drop in cardiac output and in peripheral perfusion. Usually, this may be obtained in a sustained way simply by careful use of high doses of diuretics and vasodilators [15]. Once these concepts are known and incorporated into clinical practice, their use in decompensated but functionally and hemodynamically less critically ill patients would be interesting on an ambulatory basis. Therefore, understanding the relation between the filling pressures that translate the status of blood volume in the right and left cavities becomes a crucial point. In our study, significant correlations were shown between pulmonary artery occlusion pressure and mean pulmonary artery pressures, and between pulmonary artery occlusion pressure and central venous pressure. The results were similar to those obtained in a recent study by Drazner et al [16] assessing approximately 1,000 invasive hemodynamic monitorings. In that study, the authors suggested that pulmonary artery occlusion pressure could be obtained with a small margin of error, dividing the systolic pressure of the pulmonary artery by 2. On the other hand, our data also show that the variations occurring in pulmonary artery occlusion pressure after a pharmacological intervention (which usually guides the increase in drug doses or the inclusion of other drugs) were followed by similar variations in direction and magnitude of the pressures in the right cavities, mainly in mean pulmonary artery pressure. All these findings create a potential scenario where hemodynamic measurements estimated in a noninvasive

manner could be used to assess the blood volume status of patients with heart failure. In accordance with this, several studies have shown a high degree of correlation between data obtained invasively and those obtained using echocardiography in patients with severe and refractory heart failure [17].

Ambulatory management of patients with severe heart failure is extremely complex. The cardiologist faces a syndrome of apparently inexorable progression with clinical manifestations usually of difficult interpretation and a hemodynamic profile that is frequently characterized by low cardiac output, arterial hypotension, and high ventricular filling pressures. Parallel to this scenario are the challenge and the need for multiple drugs at increasing dosages, aiming to reach the benefits stressed by clinical evidence.

We studied a population referred to a specialized heart failure clinic, where all reported components are part of a daily routine. Despite the specialized care and the multidisciplinary management, several patients returned in functional class III or IV. Frequently, the absence of pulmonary crepitations may wrongly indicate that hypervolemia was not implicated in functional limitation. However, due to the chronic adaptations to dilations of the ventricles and to lymphatic drainage, great increases in the pulmonary artery occlusion pressure are known to be present even in the absence of alveolar interstitial fluid [1]. In the group of patients studied, the pulmonary artery occlusion pressures were extremely elevated, and their reduction was associated with a significant and acute improvement in functional class. It is possible that only the reduction in the levels of pulmonary pressure, due to a reduction in blood volume, may have contributed to an improvement in the sensation of dyspnea. It is interesting that this occurred with no clinically relevant reduction in the levels of systolic blood pressure. Finally, this acute improvement in functional class does not necessarily indicate that a chronic and continuous improvement will occur. However, it is known that if these patients are intensively followed up in a specialized multidisciplinary outpatient care unit for heart failure, this profile will very probably be maintained [15].

A common concern in the clinical management of these patients is the risk of inducing renal failure with the aggressive use of intravenous diuretics and high doses of angiotensin-converting enzyme inhibitors. In this study, however, the renal function of the patients was preserved, even when the serum levels of urea and creatinine were analyzed. The improvement observed in the systolic stroke volume may have contributed to an improvement in renal perfusion. Finally, when the pattern of oral use of drugs prior to and after hemodynamic optimization is analyzed, a significant increase can be identified in the doses of most drugs, with no clinically significant impact on blood pressure and peripheral perfusion. Once again, improvement in cardiac output may have enabled the use of more elevated doses, which got closer to those recommended in clinical trials. In addition, other vasodilators (hydralazine and nitrates) were introduced to more efficiently reduce systemic and pulmonary vascular resistance.

The results of this study do not support definitive conclusions about the benefit of this strategy because it did not involve a comparison with another approach. The outcome is awaited with the result of the ESCAPE clinical trial, in which conventional clinical management is being compared with that using a catheter in the pulmonary artery in patients with advanced heart failure. In addition, in this study, we report only data of in-hospital acute response, which hinder making conclusions about the midterm benefits. Finally, the risks of using this approach should be considered, because in the intensive care unit scenario, an increase in mortality was observed with the use of a catheter in the pulmonary artery to guide therapy [18]. In our study, however, no major complications were observed .

In summary, our study showed a pattern of hemodynamic response to the intravenous use of diuretics and vasodilators in patients with heart failure and a severe functional limitation. A significant improvement in the hemodynamic profile of these patients, with concomitant improvement in their functional classes, no impairment in renal function, increases in the doses of drugs, and addition of new drugs were observed. These findings emphasize the concept that adjustments in blood volume based on the use of diuretics and vasodilators have immediate clear benefits for patients with severe heart failure. Data about an ongoing randomized clinical trial may perhaps clarify whether this strategy is accompanied by mid- and long-term sustained improvement.

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