Original Article

Advanced Heart Failure Therapy Adapted to Hemodynamic Objectives Acquired from Invasive Hemodynamic Monitoring

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Objective

To assess advanced heart failure (HF) treatment in relation to reduction of ventricular filling pressures, with the use of greater doses of vasodilators, through invasive hemodynamic monitoring.

Methods

Nineteen advanced HF patients were studied, in whom Swan-Ganz catheter was inserted to direct administration of diuretic intravenously (IV) and sodium nitroprusside, with the aim of significantly reduce ventricular filling pressures. After achieving such objective or 48 hours, oral drugs were introduced until venous medicines were removed, keeping hemodynamic benefit.

Results

From 19 patients studied, 16 (84%) were of male sex. The average age was 66 ± 11.4 years old; average ejection fraction was 26 ± 6.3%; 2 patients (10.5%) showed functional class (FC) III and 17 (89.5%), FC IV. There was a decrease of pulmonary artery occlusion pressure from 23 ± 11.50 mmHg to 16 ± 4.05 mmHg (p = 0.008), of systemic vascular resistance index from 3,023 ± 1,153.71 dynes/s/cm^{-5}/m^2 to 1,834 ± 719.34 dynes/s/cm^{-5}/m^2 (p = 0.0001) and an increase of cardiac index from 2.1 ± 0.56 l/min/m^2 to 2.8 ± 0.73 l/min/m^2 (p = 0.0003). A subgroup with hypovolemia was identified.

Conclusion

It was possible to reduce ventricular filling pressures to significantly lower values, obtaining a significant improvement of cardiac index, systemic vascular resistance index and pulmonary artery mean pressure, by using significantly higher doses of vasodilators.

Key words

invasive hemodynamic monitoring, heart failure, adjusted therapy, treatment

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Clinical assessment of heart failure (HF) patients, based only on physical exam, has been shown inappropriate, both for differential diagnosis of preserved or not systolic function[1,2], and to estimate hemodynamic condition of such patients[3]. In those with important ventricular dysfunction, such difficulty of hemodynamic adjustment may result in suboptimal treatment and perpetuation of hypervolemia condition, low output and functional worsening. Mortality among that population with advanced HF remains high, despite appearance of new therapeutic strategies. At a time prior to the use of beta-blockers, mortality among this group was estimated in 36% in 1 year, such as in CONSENSUS[4] study, and in 37% in 6 months, in FIRST[5] study. At beta-blocker use time, yearly mortality, observed in COPERNICUS[6] study, was 11.4% in carvedilol-treated patients and 18.5%, in those treated with placebo.

Heart transplantation is the best treatment available for that population, but it finds limited application due to low offer of donors. Alternative treatments have been more and more studied, aiming at the improvement of quality and quantity of life of patients. Surgery of D´Or, ventricular resynchronization therapy[7,8] and stem cell implant in the myocardium[9], among others, are examples of those treatments. The use of invasive hemodynamic monitoring (IHM), with Swan-Ganz catheter to direct advanced HF pharmacological treatment, has been used in the last years with promising results[10-12]. In most cases, ventricular filling pressures can be significantly reduced with that treatment, as well as separate subgroups of lower severity that do not respond to the treatment, improve symptoms and remove patients from implant lines[13].

This study aimed at using the strategy of treating advanced HF patients, based on data obtained through IHM, and observing whether is possible to reduce ventricular filling pressures significantly, by using high doses of vasodilators and diuretics. Consequences of that strategy in laboratorial parameters of renal and electrolytic function were also assessed.

Methods

A convenience sample consisting of 19 advanced HF patients was prospectively studied, in the period from 02/01/99 to 05/15/02. All of them were admitted in intensive care environment, where the protocol was carried out. Clinical and functional data of the studied population are displayed in table I.

Concerning etiology, 10 patients were ischemic, two idiopathic, one hypertensive, five valvar and one alcoholic.

Inclusion criteria used were: severe left ventricular dysfunction, defined as LF at the echocardiogram < 30% through Teichholz method or subjective analysis, as in the inclusion some patients could be under use of vasoactive amines, which overestimated LF value, and functional class III or IV from NYHA (New York Heart Association).

Table I - Clinical and functional data from studied population

Clinical and functional data	Studied population (n=19)
Age (years old)	66±11.4
Male sex	16 (84%)
Functional class III	2 (10.5%)
Functional class IV	17 (89.5%)
Ejection fraction (%)	26±6.3

Exclusion criteria used were: non-cardiac conditions that had death expectation in under a year, such as neoplasias, acquired immunodeficiency syndrome, etc, and acute myocardial infarction or unstable angina in the last three months.

Through deep venous access (subclavian or jugular vein), punctured by Seldinger technique, a direct flow catheter (Swan-Ganz) was inserted, continuous cardiac outcome model and Baxter® SVO_2 (mixed venous oxygen saturation) and, through artery access (radial, femoral or pedis artery), punctured by Seldinger technique, a catheter was inserted for mean blood pressure monitoring.

After catheter placement, each patient stayed resting for at least 1 hour, before hemodynamic measurements. Measurements were taken with patients in dorsal decubitus and bed head-rest up to 30°. Air opening faucet, connected to the transducer, was leveled to an imaginary point, formed by the middle axillary line at the height of the 4th intercostal space. The system was then reset and SVO_2 gauged. Only after such care, hemodynamic measurements were carried out. They included the following parameters: systolic (SBP), diastolic (DBP) and mean (MBP) blood pressures; systolic, diastolic and mean pulmonary artery pressure, pulmonary wedge pressure (PWP) and right atrium pressure (RAP). Cardiac index was also obtained and systemic vascular resistance (SVRI) was calculated. Oral medication was suspended after catheter insertion and then sodium nitroprusside and intravenous snare diuretic were used according to values obtained through monitoring. The following hemodynamic values were made aimed at: PWP ≤ 15 mmHg, SVRI < 2,100 dynes/s/cm^{-5}/m^2, DBP < 8 mmHg, SBP > 80 mmHg. When a PWP reached ≤ 20 mmHg, oral vasodilators were started, as shown in the flowchart, but always trying to obtain values ≤ 15 mmHg as end objective.

Carried out protocol flowchart was developed by the authors, according to the strategy forecast in the study.

Patients with initial hemodynamic values typical for protocol execution (B way in the flowchart) were fundamentally treated with sodium nitroprusside IV and snare diuretic IV, without any oral medication, until hemodynamic objectives were achieved or after 48 hours from the start of protocol. The next step was starting captopril in the dose of 6.25 mg or 12.5 mg, according to blood pressure; at every 6-hour period, its dose was doubled up to a maximum of 50 mg every six hours.

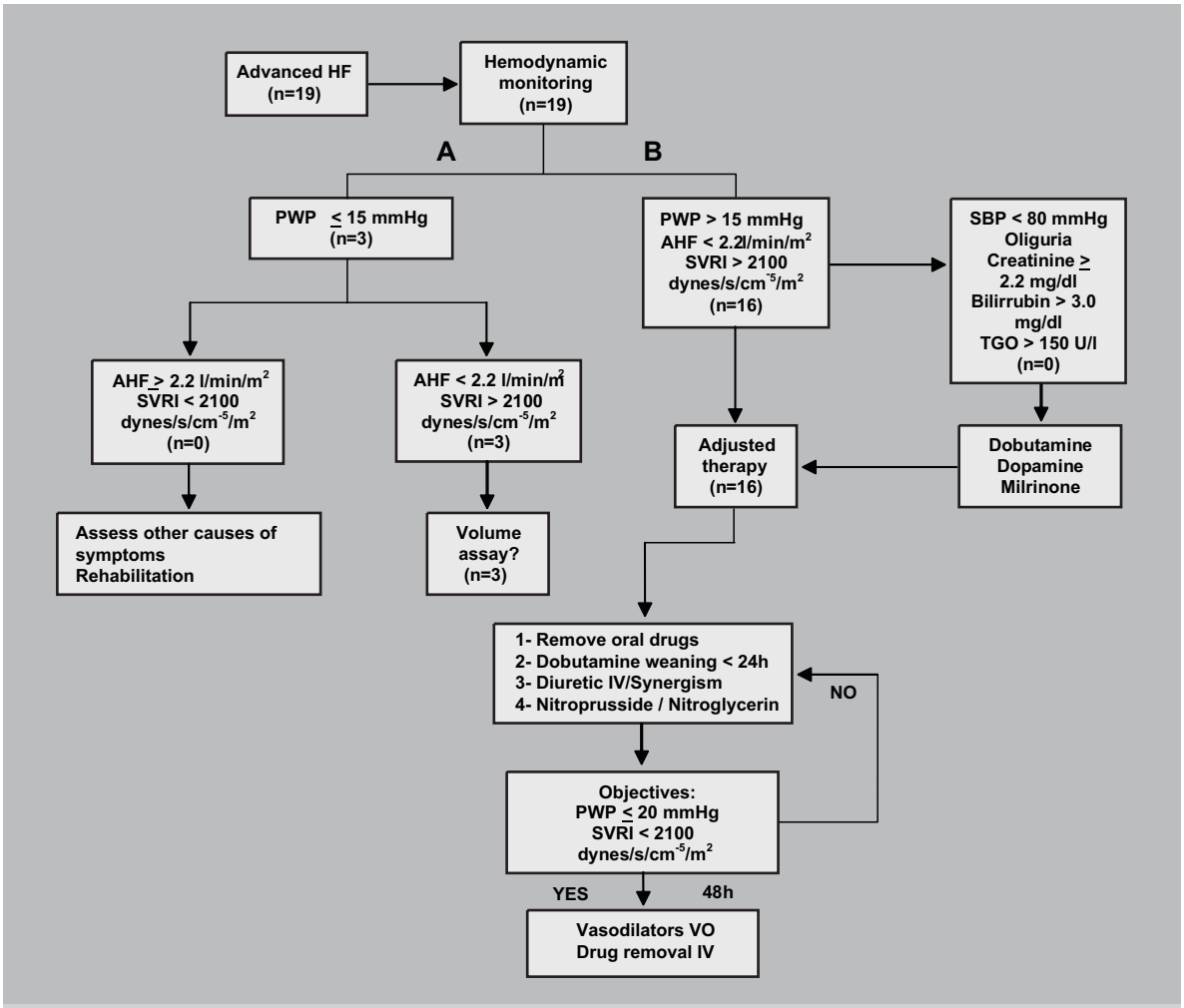

Fig. 1 *- Carried out protocol flowchart*

Sodium nitroprusside was progressively removed. In case hemodynamic measurements achieved with venous medications were not kept with maximum dose of captopril, isosorbide mononitrate was associated by starting with a 20 mg dose and doubling it every 6 hours, up to the maximum of 80 mg every six hours. In patients who did not reach optimal filling pressures and SVRI in tolerated captopril + nitrate regimen, hydralazine was introduced aiming at maximizing vasodilatation and hemodynamic response. Medication started with 12.5 mg or 25 mg and doubled at every 6 hours, up to the maximum dose of 100 mg every six hours. Diuretic dose was individualized, according to hemodynamic response, varying from 40 mg to 200 mg every 6, 8 or 12 hours. In those patients resistant to high doses of snare diuretic, thiazide and/or spironolactone was associated, with the aim of sequential nephron blocking. The use of inotropic drugs was systemically avoided, due to their injurious effects and absence of clinical benefits in scientific assays[14-16]. However, in those patients with initial dissatisfactory response to the scheme shown, fundamentally when systolic blood pressure (SBP) < 80 mmHg, very reduced urinary outcome and/or signs of reflected organic hypoperfusion due to transaminases, slag or bilirrubins were observed, dobutamine use was permitted and its use was discontinued as soon as possible (aiming at not exceeding 24 hours).

After removal of venous medications, with the maintenance of hemodynamic result at the expense of oral vasodilators and diuretics, adjuvant HF treatment was prescribed (antiarrhythmics, anticoagulants, digital, acetylsalicylic acid, spironolactone, etc). Hemodynamic data measurement was carried out many times a day and, obligatorily, before and 1 hour after oral medication administration or venous medication adjustment.

On the same day of catheter placement and protocol start, the following exams were carried out: blood count, glucose, urea, creatinine, sodium, potassium, magnesium, coagulogram, hepatogram and myocardial necrosis markers (total CK, CK-MB, Troponin I and mass CK).

Values of hemodynamic data were expressed as median ± standard deviation. Wilcoxon test was used to compare hemodynamic data. Multiple correlation analysis through Spearman's Rho was used to assess the relation

between hemodynamic factors. A main component analysis was applied to correct inter-relation effect and/or interdependence of parameters. All analyses were carried out considering a significance of 95%.

Consent from patients was obtained for their inclusion in the protocol.

Results

After obtaining initial hemodynamic measurements, it was possible to observe the presence of two distinct groups of patients: those who showed initial parameters of hypovolemia and those with typical pattern of decompensate HF, with systemic congestion and high peripheral vascular resistance. Despite inclusion criteria regard only patients with severe ventricular dysfunction and in functional class III and IV (NYHA), a 3-patient subgroup initially showed with values compatible with hypovolemia, reflected through low ventricular filling pressures, reduced cardiac index and high systemic vascular resistance. Those patients showed difficulty in progressing with doses of vasodilators due to hypotension and persistence in FC IV, besides being under use of diuretics, which kept hypovolemia condition. After identifying such condition, volemic reposition was performed until proposed filling pressures were reached. That caused an increase in the cardiac index of 52.3% (from 2.1 ± 0.28 l/min/m^2 to 3.2 ± 0.25 l/min/m^2), a 38.1% decrease in SVRI (from 3,076 ± 116.14 dynes/s/cm^{-5}/m^2 to 1,902 ± 227.60 dynes/s/cm^{-5}/m^2) and adequacy of ventricular filling pressures. So, it was possible to progress with vasodilators up to proposed doses in patients of this subgroup. Hemodynamic parameters of each patient from this group are in table II.

Hypervolemia subgroup patients (table III) also showed excellent benefits with the strategy used. After completion of protocol, there was a significant improvement of cardiac index (a 42.7% increase, with median varying from 1.85 ± 0.59 l/min/m^2 to 2.64 ± 0.75 l/min/m^2), reduction of SVRI in 40% (from 2,972 ± 1,259.3 dynes/s/cm^{-5}/m^2 to 1,784 ± 781.3 dynes/s/cm^{-5}/m^2), decrease of PWP in 37.7% (from 26.5 ± 8.5 mmHg to 16.5 ± 4 mmHg) and CVP in 38.4% (from 13 ± 4.5 mmHg to 8 ± 4.3mmHg). It is important to emphasize that three patients (9, 17, 18) showed initial PWP between 20 mmHg and 15 mmHg and were considered as hypervolemic and decompensate. The same strategy for those with PWP > 20 mmHg was used, which resulted in an expressive increase of cardiac index in the three of them and a decrease in peripheral vascular resistance in the last two.

Concerning the populational group, the analysis of hemodynamic variable adaptation, before and after pro tocol, indicates that, except central venous pressure, all other measurements showed significant improvements. Table IV displays those comparisons and respective values for p.

Doses of vasodilators achieved at the end of protocol were significantly higher than those applied before it, with ambulatory treatment. The average dose of captopril used before and after hemodynamic adjustment was, respectively, 43.3 ± 43.1 mg and 159.8 ± 61.2 mg (p = 0.0009).

Five patients were already under use of dobutamine when entering the protocol. In three of them, infusion was suspended with less than 24 hours, in one, with less than 48 hours and in the last, with less than 36 hours, all without hemodynamic impairment. In no case a start of vasoactive amines after IHM was necessary.

Despite intense diuresis obtained and important reduction of ventricular filling pressure, worsening of nitrogen slag or induction of significant electrolytic disturbance was observed, as there was an intensive laboratorial surveillance (table V).

Discussion

Pharmacological treatment of HF patients, based only on physical exam, has been the standard in handling those patients along the years. Recently, the paradigm that those patients, especially those with severe ventricular dysfunction, need high filling pressures to keep suitable cardiac output and renal function, has been questioning.

In this study it is possible to observe that advanced HF patients were shown maladjusted from hemodynamic point of view, despite being under previous use of digital

Table II - Initial and end hemodynamic parameters of patients showing initial hypovolemia

Pat	iMBP mmHg	eMBP mmHg	iPWP mmHg	ePWP mmHg	iCVP mmHg	eCVP mmHg	iSVRI dynes/s/cm-5/m2	eSVRI dynes/s/cm-5/m2	iCI L/min/m^2	eCI L/min/m^2	iMPAP mmHg	eMPAP mmHg
19	86	80	11	16	4	11	3,076	1,623	2.1	3.4	22	27
10	77	75	4	10	1	6	2,894	1,902	2.1	2.9	17	19
11	106	90	2	14	0	7	3,110	2,074	2.6	3.2	15	24
Median/	86	80	4	14	1	7	3,076	1,902	2.1	3.2	17	24
Standard	±	±	±	±	±	±	±	±	±	±	±	±
deviation	14.84	7.63	4.72	3.05	2.08	2.64	116.14	227.60	0.28	0.25	3.60	4.04

Pat- patient; iMBP- initial mean blood pressure; eMBP- end mean blood pressure; iPWP- initial pulmonary wedge pressure; ePWP- end pulmonary wedge pressure; iCVP- initial central venous pressure; eCVP- end central venous pressure; iSVRI- initial systemic vascular resistance index; eSVRI- end systemic vascular resistance index; iCI- initial cardiac index; eCI- end cardiac index; iMPAP- initial mean pulmonary artery pressure; eMPAP- end mean pulmonary artery pressure

Table III - Initial and end hemodynamic parameters of patients showing initial hypervolemia

Pat	iMBP mmHg	eMBP mmHg	iPWP mmHg	ePWP mmHg	iCVP mmHg	eCVP mmHg	iSVRI dynes/s/cm^{-5}/m^2	eSVRI dynes/s/cm^{-5}/m^2	iCI L/min/m^2	eCI L/min/m^2	iMPAP mmHg	eMPAP mmHg
1	80	83	38	15	15	6	4,286	2,729	1.7	2.5	58	31
2	98	61	36	11	12	2	3,851	2,477	1.8	1.9	47	21
3	75	65	35	15	11	4	2,807	1,734	1.8	2.8	39	16
4	86	57	30	9	13	5	4,233	1,608	1.3	2.5	34	22
5	84	68	24	22	6	10	3,489	1,834	1.7	2.5	36	37
6	97	57	23	17	13	14	5,504	2,567	1.2	1.3	43	29
7	67	65	23	21	21	15	1,932	1,355	1.9	2.9	32	30
8	71	52	22	12	13	8	2,108	1,599	2.2	2.2	28	26
9	103	114	18	16	12	8	2,719	2,723	2.2	2.9	43	28
12	96	73	34	19	19	14	5,726	3,692	1.0	1.2	45	33
13	86	59	29	24	17	12	2,072	960	2.6	3.9	46	33
14	82	66	35	18	9	4	3,736	2,833	1.5	1.7	38	26
15	100	90	45	18	17	8	3,023	2,358	2.2	2.7	46	29
16	65	57	20	20	14	15	1,133	1,018	3.5	3.3	40	45
17	90	50	16	15	6	7	2,921	1,074	2.3	3.2	38	37
18	84	79	19	14	6	5	2,667	1,627	2.3	3.6	26	19
Median/	85	65	26,5	16,5	13	8	2,972	1,784	1.85	2.64	39.5	29
Standard	±	±	±	±	±	±	±	±	±	±	±	±
deviation	11.7	16.4	8.5	4.0	4.5	4.3	1,259.3	781.3	0.59	0.75	7.97	7.40

Pat- patient; iMBP- initial mean blood pressure; eMBP- end mean blood pressure; iPWP- initial pulmonary wedge pressure; ePWP- end pulmonary wedge pressure; iCVP- initial central venous pressure; eCVP- end central venous pressure; iSVRI- initial systemic vascular resistance index; eSVRI- end systemic vascular resistance index; iCI- initial cardiac index; eCI- end cardiac index; iMPAP- initial mean pulmonary artery pressure; eMPAP- end mean pulmonary artery pressure

drugs, diuretics and vasodilators. It is important to mention the presence of three patients showing hypovolemia as decompensation perpetuation. Those findings corroborate the fact that patients with chronic ventricular dilation develop adaptative mechanism that do not allow for the physical exam to notice hypervolemia or hypovolemia.

There was an expressive decrease of DBP (± 4 mmHg) after protocol in populational group. However, such decrease did not achieve statistic significance. It is probably due to the fact that there were hypovolemic patients before the beginning of the protocol and that, in fact, increased CVP with volemic reposition instituted, contaminating global result. When the difference only in hypervolemia group is analyzed, an even more expressive reduction, approximately 5 mmHg, is observed.

Results from this study confirm that advanced HF patients not only bear with reduced filling pressures, but also achieved a significant improvement of cardiac index, systolic volume index, and peripheral vascular resistance index, when submitted to IHM. Besides, despite some studies suggest that it may there be renal function worsening in advanced HF patients submitted to intensive therapy[16], in the studied population, despite intensive diuresis obtained and reduction of ventricular filling pressure, slag worsening was not observed. Those results are also similar to those from Rohde et al[18] (2002), in which, after intensive reduction of filling pressures and peripheral resistance using IHM, hemodynamic adjustment without renal function deterioration was observed.

Despite the hemodynamic benefit observed, as the follow up period only included hospital admission stage, it was not possible to study whether such hemodynamic, and even symptomatic, improvement keeps a favorable effect for a longer observation period.

Hemodynamic benefit achieved with intravenous vasodilator and diuretic drug doses was kept with the transition to oral administrated drugs in demonstrated doses. Most patients needed full doses of vasodilators, sometimes over those dosages traditionally recommended by the literature. However, it is important to emphasize that, in some, cases, non-maximal doses were sufficient for hemodynamic adjustment. As the impact on survival has not been tested with that strategy yet, it is fundamental to highlight that, despite hemodynamic adjustment, with doses lower than the full vasodilator doses, has occurred in some cases, those preconized in great clinical assays must be always used due to their positive impact on survival.

The practice of using agents that increase cardiac contractility (inotropics) in HF patients, although it shows benefic hemodynamic effects, is associated tro mortality increase when used in long term[16]. Despite that, inotropics have been commonly used in acute chronic HF handling. Dobutamine was replaced for sodium nitroprusside, without hemodynamic worsening. In fact, there was additional hemodynamic benefit to that of inotropic with the use of vasodilator. The study by Capomolla et al[19], comparing the effect of dobutamine with sodium nitroprusside on severe HF patients, showed that both improved cardiac output similarly. However, dobutamine has an unpredictable effect on PWP and mitral regurgitation, whereas nitroprusside significantly improves filling pressures and mitral regurgitation. Therefore, as there was success in all patients with dobutamine removal

and benefits with the strategy of adjusted doses of vasodilators and diuretics directed by IHM, inotropic use must be reserved for those who do not respond to that strategy. A similar approach was suggested by Rohde et al[20], in which a staggered and progressive approach must be carried out, keeping inotropics for those without benefit with the use of IHM.

In order to respond to the impact of that strategy concerning mortality, results from a clinical, randomized, multicenter study (ESCAPE)[21] have been recently shown, comprising 433 patients with HF in FC IV, comparing the group with an IHM-directed strategy with the other group only directed by clinical data. It was observed that mortality after 30 days was not different, being 4.7% for the group using Swan-Ganz and 5.0%, for the group only clinically treated. Results, at the end of six months, did not show significant difference either and are displayed in table VI.

Concerning adverse events and intra-hospital complications there was no difference between groups either. Therefore, the study demonstrated that it is safe to use such strategy for patients with persistent HF symptoms and that it seems reasonable to consider the use of IHM to direct the treatment in a single patient.

Concluding, the present study showed that an important reduction of ventricular filling pressures is possible, safe and desirable, as that strategy implies a significant improvement of cardiac output and peripheral resistance among that population. Only with hemodynamic data it was possible to identify patients with persisting hypovolemia and others with clinically unidentified hypovolemia, and thus adapt the treatment with volemic reposition in the first group and with use of significantly higher doses of vasodilators and diuretics in the other. New non-invasive hemodynamic assessment methods must be researched, with the aim of treating a higher number of patients with objective data and not only with findings from physical exam.

Table IV - Hemodynamic variables before and after the protocol from the whole group

Variable	Initial	End	p value
MBP (mmHg)	86 ± 11.91	66 ± 16.01	0.000838
PWP (mmHg)	23 ± 11.50	16 ± 4.05	0.008975
CVP (mmHg)	12 ± 5.88	8 ± 4.01	0.070158
SVRI (dynes/s/cm^{-5}/m^2)	3,023 ± 1,153.71	1,834 ± 719.34	0.000155
CI (L/min/m^2)	2.1 ± 0.56	2.8 ± 0.73	0.000386
MPAP (mmHg)	38 ± 11.04	28 ± 7.19	0.006601

MBP- mean blood pressure; PWP- pulmonary wedge pressure; CVP- central venous pressure; SVRI- systemic vascular resistance index; CI- cardiac index; MPAP- mean pulmonary artery pressure

Table V - Nitrogen slag and electrolytes before and after protocol

Exam	Initial	End	p value
Urea (mg/dL)	75,0±39,2	83,7±47,6	0,29
Creatinine (mg/dL)	1,4± 0,5	1,3±0,5	0,70
Sodium (mEq/L)	135,8±4,8	135,8±4,6	0,83
Potassium (mEq/L)	4,3±0,9	4,1±0,4	0,61

Table VI - Clinical objectives after 6 months

Objectives	Swan-Ganz, n=215 (%)	Clinical, n=218 (%)
Mortality	20.9	17.4
Re-hospitalizations/patient (mean)	2.1	2.1
Days in hospital (mean)	11	11

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