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Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension

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ABSTRACT (word count : 196 words)

Background: Acute right ventricular failure in the setting of pulmonary arterial hypertension (PAH) often requires hospitalization in intensive care units (ICU) to manage the subsequent low cardiac output and its consequences. There are very few data on these acute events.

Methods: We recorded demographic, clinical, biological data and therapy in consecutive patients suffering from acute right heart failure requiring catecholamine treatment in the ICU of the French referral center for pulmonary hypertension. These variables were analysed according to the survival status in ICU.

Results: 46 patients were included, mean age 50.3 years. ICU mortality was 41%. We found no difference in terms of demographics, clinical data, last hemodynamic measurements at admission. Systemic arterial pressure was significantly lower in the subgroup of patients whose clinical course was fatal. Plasma Brain Natriuretic Peptide (BNP), C-Reactive Protein (CRP), serum sodium and creatinine at admission correlated with survival.. Demonstration of an infection during the ICU stay was associated with a worse prognosis.

Conclusion: These preliminary results underline the importance of some simple clinical and biological parameters in the prognostic evaluation of acute heart failure in the setting of PAH. Whether these parameters can guide therapy has to be further investigated.

KEY WORDS

Brain Natriuretic Peptide

Heart failure

Intensive care unit

Pulmonary arterial hypertension

Survival

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a disease affecting small pulmonary arteries, with progressive vascular narrowing leading to elevated pulmonary arterial resistance and right ventricular failure [1]. PAH patients may experience acute right ventricular (RV) failure during the course of their disease [2]. These episodes often require hospitalization in an intensive care unit (ICU) because of the requirement for close monitoring and for vasoactive drugs. Many studies of acute RV failure in the absence of previous pulmonary hypertension (mainly in severe pulmonary embolism) have been performed and some guidelines are available in that setting [3]. To the best of our knowledge, no study has yet prospectively investigated cases of severe RV failure in PAH patients. Although there are undoubtedly some similarities with other causes of acute RV failure, the physiological mechanisms may differ in PAH patients where the right ventricle has adapted to the chronically elevated afterload, compared to patients with, for example, an acute pulmonary embolism where the RV is relatively 'naive' [4]. In the absence of guidelines for treatment in this specific patient population, current therapeutic endpoints are extrapolated from other etiologies of RV failure, with the use of appropriate fluid balance, inotropic and vasoconstrictive agents (including catecholamines) to maintain adequate aortic root and right coronary artery perfusion pressure to maintain cardiac output and tissue oxygenation [5,6]. Some data support the use of dobutamine because of its positive inotropic effects and beneficial right ventricular-pulmonary artery coupling [7] as well as its ability to exert minimal tachycardia compared to dopamine [8]. Norepinephrine has been reported to be used alone or in combination with dobutamine in this setting , and experimental data support its usefulness in a model of right ventricular pressure overload [9]. Neither ICU outcome following decompensated PAH leading to severe RV failure, nor the impact of one of these episodes on baseline disease course in survivors is known. In an attempt to answer these questions, and to describe the

clinical characteristics of this severe subset of patients, we performed a single center prospective study of consecutive patients admitted to our ICU.

METHODS

Design

This was a prospective single centre study involving consecutive patients.

Patients

All patients with chronic precapillary pulmonary hypertension (inoperable chronic thromboembolic disease and PAH) referred to the ICU of the French National Reference Center for pulmonary hypertension were eligible. Patients were enrolled if they exhibited an acute deterioration of their condition (within 7 days before ICU admission) and required treatment with catecholamines because of clinical features of low cardiac output and/or severe RV failure All patients had been previously diagnosed with precapillary pulmonary hypertension according to current international guidelines (mean pulmonary artery pressure ≥25 mmHg and pulmonary artery wedge pressure ≤15 mmHg at rest during right heart catheterisation). The study period began in November 2005 and ended in April 2007. Forty six consecutive patients were studied during their first ICU admission, and repeated admissions were not included. All patients gave informed consent to be entered in this analysis which was set up in agreements with the Commission Nationale de l'Informatique et des Libertés, the organization dedicated to information technology and civil rights in France.

Management in the ICU

Dobutamine is first line therapy in these patients with decompensated PAH, with further addition of norepinephrine for persistent systemic hypotension as needed to maintain normotension and improve right coronary arterial perfusion pressure. In practice, the infusion of dobutamine is commenced at 5µg/kg/min, with an evaluation period of 4 to 6 hours,

following which the infusion rate is increased by 5µg/kg/min every 4 to 6 hours to a maximum of 20µg/kg/min., these changes are made according to clinical assessment of low cardiac output and/or right ventricular failure, noting that dobutamine itself may of course reduce blood pressure due to B2 effects. No further increment is made if systemic arterial pressure remains stable. If persistent low systemic pressure occurs, norepinephrine is added, and is progressively increased by 0.5 mg/h every 2 hours until systemic arterial pressure is restored. This approach is modified depending on the etiology of the acute worsening and on further associated hemodynamic challenges such as sepsis. Exact fluid balance and intravenous diuretic doses are not guided by a treatment protocol but are left at the discretion of the attending physicians, as is initiation of antibiotic therapy in cases of documented or suspected infection. Due to the potentially deleterious hemodynamic consequences of positive intrathoracic pressure on right ventricular function [10], no patient underwent mechanical ventilation in the study period. Our therapeutic approach is based on generally accepted goals in the management of acute right heart failure [5] and our group have recently discussed endpoints in acute heart failure in PH patients [11]

Data

Baseline demographic data, NYHA status and right heart hemodynamics when last stable before admission were recorded. We analysed clinical data (evidence of a triggering factor or an infection, systemic arterial pressure, heart rate, diuresis, treatments and dose regimen) and biological data (serum level of creatinine, sodium, Brain Natriuretic Peptide (BNP), C Reactive Protein (CRP), Troponin Ic) during the stay in ICU, from the day of admission to discharge or death. The primary endpoint of the study was ICU survival. We also monitored simplified acute physiology score (SAPS II), disease severity, calculated from 12 routine physiological measurements made during the first 24 hours with information about previous

health status obtained at admission [12]. Each parameter was monitored at admission and then at least once per week, and we recorded the most abnormal value for each parameter each week. Infection was diagnosed if micro-organisms were isolated, or if clinical suspicion was high, based on clinical, biological and radiological symptoms. For suspected pneumonia, microbiological confirmation of respiratory sampling using bronchoscopy was not performed because of the high associated risks in these patients.

Statistical analysis

Statistical analysis was performed using Statview 4.5 software. Results are expressed as median (min-max). Categorical variables were compared using χ^2 and Fisher's exact test as appropriate. Quantitative variables were compared using Mann-Whitney analysis. Changes of recorded variables over time were evaluated by one-way analysis of variance (ANOVA) for repeated measurements. The Kaplan Meier method was used to estimate survival status and the log-rank test was used for survival distribution comparison. A p value of less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the patients

Forty-six patients were included (table I). Median age at admission was 50.0 years (16.2-77.4), with a female/male ratio of 2.3/1 (31 females). Median body mass index was 20.9 kg/m^2 (15.9-33.6). Twenty- three patients were admitted in ICU directly from the respiratory ward of our institution, fifteen were referred from another hospital, six were referred from the emergency department of our institution and two came directly from home. Average time from PH diagnosis to ICU admission was 6.3 years (2.3-16.5). The patients suffered from idiopathic PAH (n=24), inoperable CTEPH (n=7), systemic sclerosis-associated PAH (n=5), PAH associated with connective tissue diseases other than scleroderma (n=2), HIV-related PAH (n=3), portopulmonary hypertension (n=3), PAH associated with congenital heart disease (n=2). Specific pulmonary hypertension therapy at admission included intravenous prostacyclin alone (n=9), intravenous prostacyclin in combination with bosentan (n=10) or with sildenafil (n=1), combination of intravenous prostacyclin with bosentan and sildenafil (n=3), bosentan alone (n=10) or in combination with sildenafil (n=7) or inhaled iloprost (n=2), subcutaneous treprostinil (n=1) or no specific treatment (n=3). No difference was found in baseline characteristics between patients who died in ICU versus patients discharged from ICU, although there was a non significant trend towards a older age at admission in ICU and a more severe baseline hemodynamic status among non survivors (Table II).

Survival

The mean ICU length of stay was 14 (range 1-87) days. Overall mortality in ICU was 41.3%. (**Figure 1**). There was no difference in terms of time to discharge or death according to outcome in ICU. Six out of the 27 patients discharged from ICU were dead at 3 months, giving a 3-month mortality of 22.2% for patients discharged from ICU. Among patients

discharged from ICU, 7 were subsequently referred at least a second time to ICU for similar symptoms.

Clinical and biochemical data at admission in ICU

There was no clinical difference between survivors and non-survivors on admission to ICU. No difference was found in terms of diuresis, but it is of note that the furosemide level to achieve a diuresis on the first day was higher in patients with an unfavourable outcome. Triggering factors for PH decompensation were identified in 19 patients: unplanned modification or withdrawal of pulmonary vasodilator therapy (n=3), unplanned withdrawal of diuretics (n=1), septicemia (n=5), pneumonia (n=3), purulent pleural effusion (n=1), septic state without bacterial documentation (n=2), cardiac arrhythmia (n=3), unplanned pregnancy (n=1). There was no difference in outcome according to the identification of a triggering factor. At admission, median serum level of BNP was 1415 (449-3550) pg/mL in non-survivors versus 628 (87-1460) pg/mL in survivors (p=0.0007). Serum creatinine was also increased in non-survivors as compared to survivors 112 (42-144) vs. 95 (82-151) µmol/L, respectively, p=0.04, and median CRP level was 40 (0-270) mg/L in non-survivors versus 12 (0-200) mg/L in survivors (p=0.01) (Table III). We performed a logistic regression with three variables considering the small sample of our cohort (CRP, creatinine and BNP) and found that BNP was the only independent predictor of mortality (p=0.005, 95% confidence interval 1.001 to 1.004). No difference in troponin Ic or serum sodium was found between survivors and non-survivors. CRP serum levels at admission were associated with evidence of an infectious episode irrespective of patients clinical course (16 (0-197) mg/dL if no infection was found versus 92 (0-277) mg/dL with confirmed infection, p=0.01). We also found a significant association between simplified acute physiology score II (SAPS II) and the clinical course in ICU (32 (11-49) in non survivors versus 22 (6-43) in survivors, p=0.001).

Clinical and biochemical data during hospitalization according to survival in ICU

During the first three weeks of hospitalization, the only clinical parameter associated with survival was systemic arterial pressure (systolic and mean systemic arterial pressure, ANOVA for repeated measurements, $p=0.003$ and $p<0.0001$ respectively). Biochemical parameters associated with outcome included serum levels of BNP, CRP, creatinine and sodium. ANOVA for repeated measurements, $p<0.0001$ for all variables. (Figure 2)

The occurrence of an infection during ICU hospitalisation was associated with a worse outcome, with 14 out of 19 of the non-survivors exhibiting an in hospital acquired infection compared with 6 out of the 27 survivors ($p=0.0005$)

Treatments during ICU stay according to survival

Changes in dobutamine doses over time were associated with ICU survival; progressive increase in dobutamine administration rate was associated with poorer outcome (Figure 3). Changes in norepinephrine dose over time were no different between survivors and non-survivors. Continuous intravenous prostacyclin was administered 15 times, in a non-randomized fashion, twice in combination with bosentan, and continuous nitric oxide inhalation was used 13 times. These treatments were given to patients whose severity was considered very high, and who were not already receiving these treatments as background PH therapy. Neither of these treatments significantly influenced survival, although this study was not designed nor powered to evaluate this association with outcome.

DISCUSSION

This is the first prospective study analysing consecutive patients requiring ICU admission for severe acute right ventricular failure due to decompensated PAH. We found a very high overall ICU mortality (41.3%), which was predicted by high admission BNP levels. Patients who had higher baseline serum creatinine and CRP levels, and those receiving higher baseline doses of oral furosemide also did worse. The presence of a better pre-ICU functional class did not influence ICU outcome. Non-survivors required much higher doses of dobutamine.

There has been only one other recent retrospective study of PAH patients, where 27% of episodes of decompensated RVF were precipitated by infection, 48% had no obvious precipitant (so were presumed due to disease progression) and overall mortality was high, especially in those with infection-related episodes (50%) and in 'cold-dry' hemodynamic profiles (at 100%). Similarly, the presence of a triggering factor made no impact on outcome [13]. It has been recently emphasised that we lack an evidence-based consensus to manage acute RV failure in these patients [5], which are difficult to manage, despite the fact that, as in acute left ventricular failure [14], these episodes account for significant patient mortality.

BNP and NT-proBNP have been shown to be associated with long-term outcome in stable PAH [15,16], and are useful biomarkers of RV dysfunction in patients with acute pulmonary embolism, in the setting of acute right ventricular pressure overload [17,18]. This is the first study to test the prognostic significance of absolute value of BNP in the setting of acute right heart failure in decompensated PAH. BNP is secreted by cardiac ventricles trough a constitutive pathway and is increased according to the degree of myocardial stretch, damage and ischemia. Previous work has shown an increase in BNP mRNA expression as early as the first day following pulmonary artery coarctation in rats [19]. Despite the absence of right

heart catheterisation at admission in our cohort resulting in uncertainties concerning the fluctuations of hemodynamic during worsening, our results suggest that BNP can be used as a prognostic marker in these patients. NT-proBNP has also been shown to be a valuable prognostic marker in stable PAH [20], but since it is only excreted renally without prior degradation, its accuracy in patients with possible renal failure might be diminished [21].

Troponin has been shown to be associated with prognosis in PAH when evaluated on a long-term basis [22]. Right ventricular dysfunction in acute pulmonary embolism is also associated with increased levels of troponin [23,24]. Nevertheless, despite the difference in BNP results between survivors and non-survivors, our results for troponin did not show a statistical link with survival in the setting of acutely worsened PAH. This was a similar finding in the study by Kurzyna et al [13]. Whether our sample of patients, our dosage technique sensitivity, or the physiology of ventricular injury may explain this absence of link remains to be further investigated. In future studies the most sensitive assays for troponin measurements should be used.

The concept of rapidly introducing a specific PAH therapy in ICU in these patients remains questionable, and some concern exists about possible unfavourable systemic hemodynamic effects with these treatments which presumably act at least in part through an antiproliferative and a vasodilatory effect on a long-term basis [25]. Experimental animal data in a model of acute load-induced right ventricular failure has indicated that intravenous prostacyclin improves right ventricle to pulmonary artery coupling and cardiac output [26]. The use of specific PH treatment was not associated with improved survival in our study. In the absence of a comparator and a systematic randomisation of patients to receive specific PAH therapy or not, one cannot make conclusions regarding the benefit of initiating such therapies in the ICU. Given the absence of precise guidelines in this setting, we introduced novel PAH therapy in the most severe patients, using intravenous epoprostenol as the best evidenced vasodilatory

drug in NYHA class IV patients [27,28]. This might have biased our analysis in favour of the less severe patients. Furthermore, as we did not perform right-heart catheterization, we cannot discuss the hemodynamic effects of such rescue "specific" PAH treatment in our patients. Thus no conclusions can be drawn based on the present study on that point and we suggest that more studies are urgently needed. Further to the lack of benefit from these available medical therapies, our data demonstrate the poor prognosis of acute heart failure in patients with PAH, emphasizing the need to consider novel therapeutic approaches in these subjects such as listing for urgent lung transplantation and the possible use of right ventricular assistance devices [29,30].

Renal impairment and water regulation imbalance have been extensively studied in left ventricular failure [31], however no study has addressed this in acute right-heart failure complicating PAH. Recent data suggest that cardiac output but also right atrial pressure in pulmonary hypertension may contribute to the complex pathophysiological network including renin-angiotensin-aldosterone, natriuretic peptides, vasopressin and sympathetic nervous systems, resulting in the observed metabolic abnormalities [32]. In left heart disease, data suggest that these abnormalities are linked to survival [33], and it has been recently found that hyponatremia is predictive of poor survival for PAH patients in stable condition. The pathophysiological mechanisms have been proposed to mirror those in left heart failure [34]. Some studies have tested the efficacy of specific therapeutic interventions antagonizing the vasopressin pathway in left heart failure (outside the ICU setting), showing an improvement in serum level of sodium and dyspnoea, but no change in survival [35,36]. We also found a link between survival and changes of serum level of sodium during follow-up, reinforcing the importance of its measurement in this setting. A recent study also provides evidence that serum level of creatinine is associated with survival in patients with stable PAH, although the pathophysiological mechanism has not yet been elucidated [37].

It is of note that CRP serum levels in patients without identified infection at admission were also slightly elevated, even though statistically lower than in patients with a documented infection. A very recent study underlined the value in predicting outcome and response to therapy of this marker in stable PAH [38]. This raises the question about the involvement of inflammatory mechanisms whose origin and nature remain elusive, but are being studied in the pathophysiology of chronic PAH [39,40]. Such inflammatory pathways stress the need for more studies on inflammation in both stable and decompensated PAH, in order to identify novel therapeutic targets. Infection caries a very bad prognosis in PAH patients referred for acute heart failure. In sepsis, both experimental models and clinical examples support the notion that both left and right ventricular injury is relatively common, leading to primary myocardial dysfunction [41]. The poor prognosis associated with the occurrence of an infection in ICU therefore underlines the need for efficient preventive, diagnostic and prompt treatment strategies in PAH patients admitted in ICU with suspected infection.

Our study has limitations that have to be acknowledged. Firstly, this is a single centre study, however our National Reference Centre for Pulmonary Hypertension is one of the largest Pulmonary Vascular Centre worldwide which recruits more than 50% of French patients treated for PAH [42]. In addition it is one of the very few centres with an ICU devoted to the care of pulmonary hypertensive patients. Therefore, this single centre characteristic may also have the advantage of allowing recruitment of consecutive PAH patients with a similar management approach performed by the same team. Second, our cohort is rather small (n=46) and was limited to patients with severe RV failure requiring catecholamine. Considering that the main objective of the study was to describe the clinical course of PAH patients in the setting of primary acute circulatory failure, this characteristic may prevent the extrapolation of

our findings to the other subgroups. Nevertheless, PAH is a rare condition with prevalence ranging from 5 to 25 cases per million in France [42], highlighting the major difficulty in obtaining large numbers of patients for clinical studies. Also, some of the parameters could not be recorded every week of the study thus limiting the analysis of the true variability of each factor during the entire study period. Despite this, our data are sufficiently powered to determine the clinical and laboratorial parameters associated with poor prognosis during ICU admission. Finally, the lack of invasive hemodynamic monitoring is a weakness that may have meant we missed important pathophysiological parameters and potential prognostic factors. Nevertheless, invasive hemodynamic monitoring may be hazardous in severe unstable PAH patients. Further studies should include at least echocardiographic parameters already validated as prognostic factors in stable PAH patients such as heart chamber size, systolic pulmonary artery pressure, pericardial effusion and/or TAPSE index [43,44]. Although echocardiography may provide important data on systolic PAP and cardiac index, appropriate "right ventricular preload" and the way to monitor it safely on a regular basis needs to be determined in further studies.

In conclusion, we have described the first prospective cohort of PAH admitted in ICU due to acute right heart failure. ICU and 3 month mortality rates found in our study confirmed the dismal prognosis of such episodes. Some simple clinical and biological variables appear to be strongly linked with the clinical course in ICU and these findings stress the need for further studies in order to propose future recommendations in this devastating complication of PAH.

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LEGENDS FOR FIGURES

Figure 1: Survival in overall population

Figure 2: Clinical and biochemical data during ICU stay according to survival in ICU.

White circles represent patients discharged from the ICU (survivors), black circles represent patients dead in ICU (non-survivors).

Figure 2 A: Changes in mean systemic arterial pressure (MAP) during ICU stay.

Figure 2B: Changes in systolic systemic arterial pressure (SAP) during ICU stay

Figure 2 C: Changes in C reactive Protein (CRP) serum levels during ICU stay.

Figure 2 D: Changes in sodium serum levels during ICU stay.

Figure 2 E Changes in creatinine serum levels during ICU stay.

Figure 2 F: Changes in Brain Natriuretic Peptide (BNP) serum levels during ICU stay.

Figure 3: Changes in dobutamine doses according to survival in ICU

White circles represent patients discharged from the ICU (survivors), black circles represent patients dead in ICU (non-survivors).

Table I: baseline characteristics of the patients

age (years)		50.0 (16.2-77.4)
gender (f/m)		2.3/1
Body Mass Index (Kg/m2)		20.9 (15.9-33.6)
Type of PAH	Idiopathic PAH	24
	inoperable CTEPH	7
	Systemic sclerosis-associated PAH	5
	PAH associated with connective tissue diseases other than scleroderma	2
	HIV-related PAH	3
	Portopulmonary hypertension	3
	PAH associated with congenital heart disease	2
NYHA functional class when last stable	II	5
	III	26
	IV	15
pulmonary hemodynamic when last stable	mPAP (mmHg)	52 (32-103)
	PVR (Dyn.s.cm-5)	1016 (525-2400)
	RAP (mmHg)	12 (0-32)
	CI (L/min/m2)	2.23 (1.47-5.0)
SAPS II		24 (6-49)

mPAP=mean pulmonary arterial pressure, PVR= pulmonary vascular resistance, RAP= right atrial pressure, CI= cardiac index, SAPS II: simplified acute physiology score II

Table II: Baseline characteristics of patients according to survival in ICU

		non survivors (n=19)	survivors (n=27)	p
age (years)		52.9 (20.4-77.4)	42.5 (16.2-76.3)	0.07
gender (f/m)		2,3/1	2,2/1	0.7
Body Mass Index (Kg/m2)		21.7 (16.7-30.8)	20.3 (15.9-33.6)	0.7
Type of PAH	Idiopathic PAH	8	16	ND
	inoperable CTEPH	3	4	
	Systemic sclerosis-associated PAH	4	1	
	PAH associated with connective tissue diseases other than scleroderma	1	1	
	HIV-related PAH	1	2	
	Portopulmonary hypertension	1	2	
	PAH associated with congenital heart disease	1	1	
NYHA functional class when last stable	II	2	3	0.5
	III	9	17	
	IV	8	7	
Pulmonary hemodynamic when last stable	mPAP (mmHg)	52 (32-87)	52 (40-103)	0.6
	PVR (Dyn.s.cm-5)	1054 (623-2400)	990 (525-2315)	0.5
	RAP (mmHg)	12 (3-32)	10 (0-21)	0.7
	CI (L/min/m2)	2.14 (1.48-3.10)	2.26 (1.47-5.0)	0.4

ND: not done, mPAP=mean pulmonary arterial pressure, RAP= right atrial pressure, CI= cardiac index, PVR= pulmonary vascular resistance

Table III: Clinical and biochemical data at admission according to survival in ICU

	Non-survivors (n=19)	survivors (n=27)	p
Triggering factor (yes/no)	9/19	14/27	0.8
Mean systemic arterial pressure (mmHg)	64 (32-95)	67 (43-91)	0.9
Heart rate (bpm)	112 (42-144)	110 (82-151)	0.9
Diuresis (mL/day)	1500 (100-8500)	1550 (500-3900)	0.7
furosemide dose (mg/day)	250 (60-1500)	170 (40-1000)	0.04
Serum level of creatinine (µmol/L)	112 (76-446)	95 (53-204)	0.04
BNP (pg/mL)	1415 (449-3550)	628 (87-1460)	0.0007
C reactive protein (mg/L)	40 (0-277)	12 (0-200)	0.01
Troponin Ic (ng/ml)	0 (0-7.35)	0 (0-1.14)	0.4
SAPS II	32 (11-49)	22 (6-43)	0.001

SAPS II: simplified acute physiology score II

BNP: brain natriuretic peptide

Figure 1

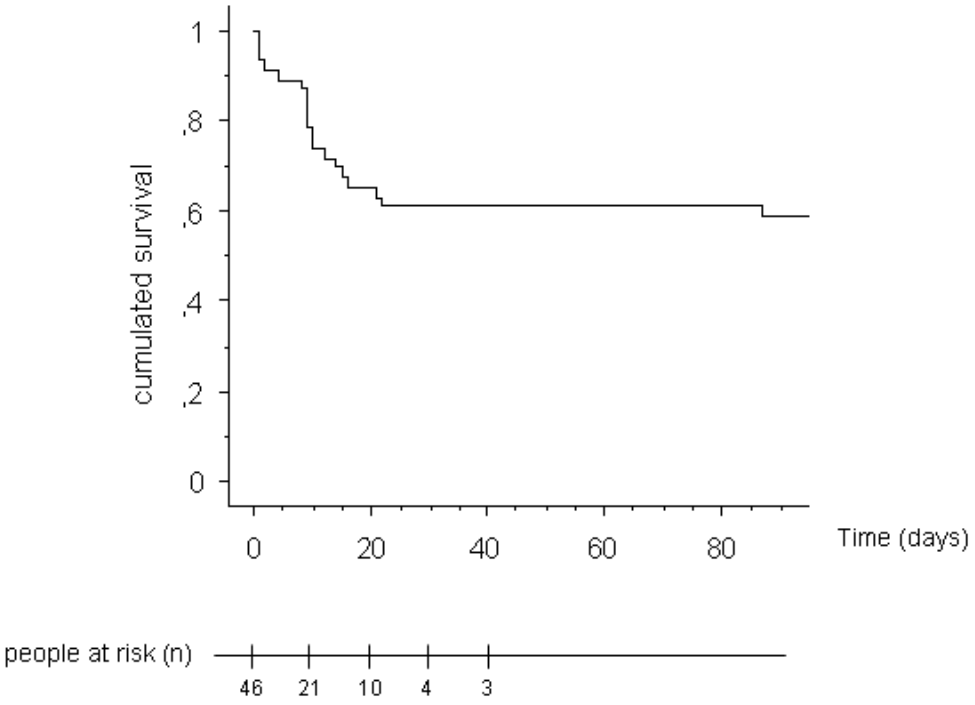

cumulated survival
1
,8
,6
,4
,2
0
0
20
40
60
80
Time (days)
people at risk (n)
46
21
10
4
3

Figure 2

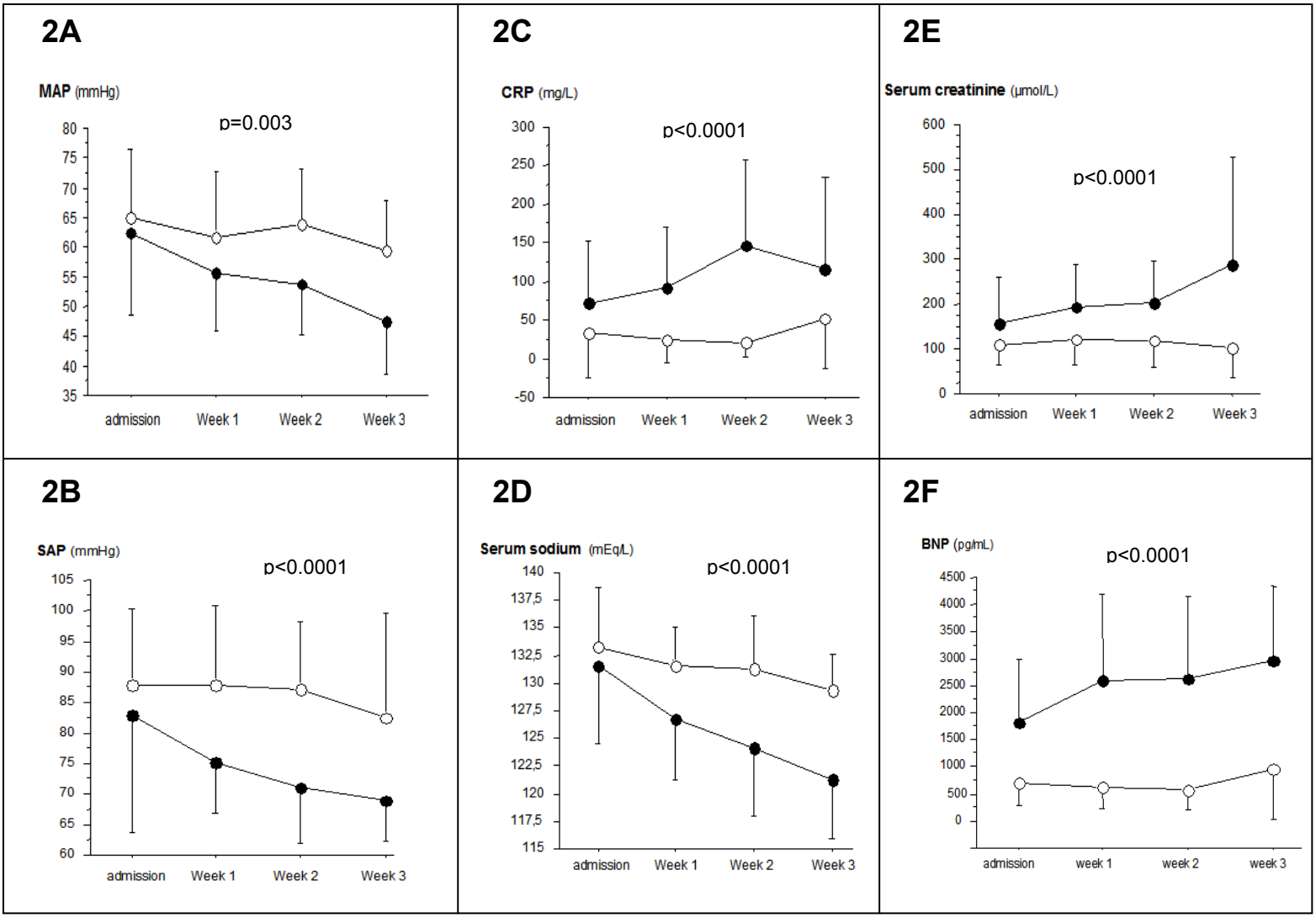
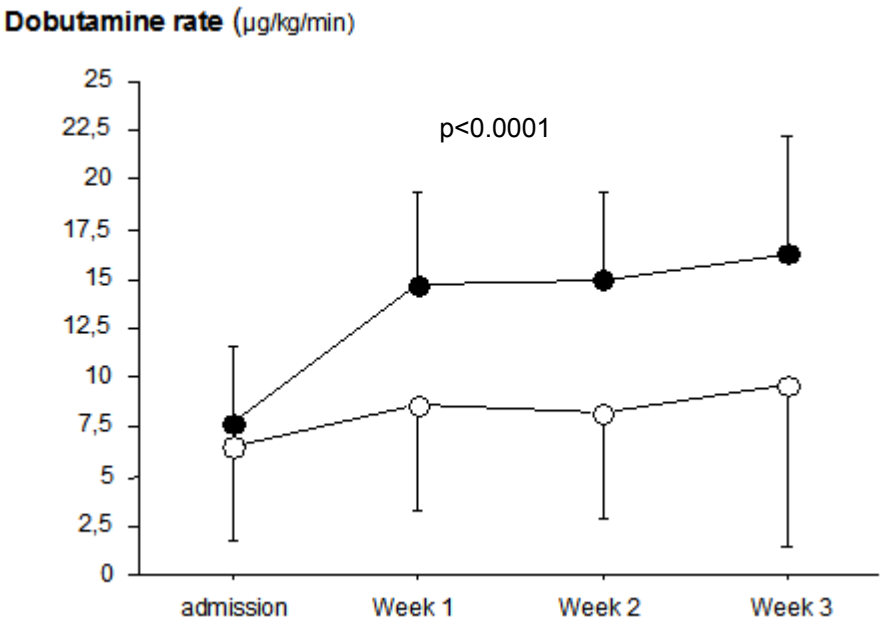

2A
MAP (mmHg)
p=0.003
admission
Week 1
Week 2
Week 3
2C
CRP (mg/L)
p<0.0001
admission
Week 1
Week 2
Week 3
2E
Serum creatinine (µmol/L)
p<0.0001
admission
Week 1
Week 2
Week 3
2B
SAP (mmHg)
p<0.0001
admission
Week 1
Week 2
Week 3
2D
Serum sodium (mEq/L)
p<0.0001
admission
Week 1
Week 2
Week 3
2F
BNP (pg/mL)
p<0.0001
admission
week 1
week 2
week 3

Figure 3


Dobutamine rate (µg/kg/min)
25
22,5
20
17,5
15
12,5
10
7,5
5
2,5
0
p<0.0001
admission
Week 1
Week 2
Week 3