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Research Paper

The Role of Noninvasive Hemodynamic Monitoring in the Early Evaluation of Patients Affected by Sepsis and Septic Shock in the Emergency Department.

Emergency Department

KEYWORDS : sepsis; monitoring; stroke volume; cardiac output.

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ABSTRACT

Septic patients admitted to the Emergency Department of a teaching hospital, underwent noninvasive continuous monitoring through Nexfin®, which allows to derive patients hemodynamic profile.Of 80 patients included in the study,48 died (60%). Survivors showed higher mean values of stroke volume (P= 0,001), cardiac output (P=0,005), cardiac index (P= 0,004) and left ventricle contractility index (P=0,002) than nonsurvivors.In the same subjects also the BMI was higher than in nonsurvivors (P=0,014), as well as the lactate levels (P= 0,029). Analysis of each of these variables showed a positive correlation with survival. Considering the relation between all the above mentioned variables taken together and the risk of death it is evident that a dP/dTmax and a BMI lower than the median value increase the death risk.The noninvasive hemodynamic monitoring has shown to be useful in the early stratification of patients with sepsis and septic shock in Emergency Department.

INTRODUCTION

Cardiovascular derangements during sepsis lead to hypoperfusion and to development of multiple organ failure[1]; therefore the initial management of sepsis in the emergency department (ED) is crucial to prevent this evolution. In the early phases the hemodynamic profile is characterized by increased capillary leak and low systemic vascular resistance[2], with consequent tachycardia and elevated cardiac output, both sympathomediated that attempt to restore the arterial blood pressure toward normal values [3]. In some cases this hemodynamic response is inadequate and hypotension persists, also despite therapeutic volume restoration, depending on the degree of decreased systemic vascular resistance and on myocardial depression[2,4].

Different methods of hemodynamic monitoring are available, most of them involving invasive procedures and admission in intensive care units[5]. Currently, the recommended procedures in severe sepsis and septic shock are arterial cannulation for continuous blood pressure measures and central venous catheterization to assess intravascular volume and central venous oxygen saturation; all these parameters are mandatory in order to achieve the early goal-directed therapy (EGDT)[6]. EGDT has been shown to reduce mortality in patients with severe sepsis/septic shock; however, implementation of this protocol in the ED is sometimes difficult. Arterial line and central venous catheterization represent a difficult challenge for a community-based ED[7]. These methods require expertise, carry the risks related to blood vessel catheterization and are performed in intensive care unit. However, the hospital gateway for patients affected by severe sepsis and septic shock is usually the ED, where it would be desirable to start the clinical and therapeutic managing[6]. Transthoracic and transesophageal echocardiography have been tested as alternative bedsides methods to estimate the hemodynamic pattern in ED. Indeed, these techniques are burdened with some limitations; in particular they are discontinuous and closely operator dependent.

We used a noninvasive device to assess the hemodynamic profile in patients admitted to our ED in sepsis or septic shock. No risks of infections or vascular complications are related to this non invasive method.

Aim of the present study has been to assess a possible predictive value of noninvasive hemodynamic parameters in the attempt to early stratify the risk of these patients.

METHODS

Study design Patients in sepsis and septic shock, admitted to the ED of our teaching hospital, were included in the study, from September 2011 to December 2013. The inclusions criteria were those used for the diagnosis of sepsis and septic shock according to the 2001 International Sepsis Definition Conference[8].

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We included patients that fulfill two out of four criteria for the systemic inflammatory response syndrome plus documented or suspected infection for sepsis, and a systolic blood pressure less than 90 mmHg unresponsive to fluid restoration for septic shock. The criteria for exclusion from the study were an age <18 years, pregnancy, or the presence of an acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, cardiac dysrhythmias, gastrointestinal hemorrhage, seizure, drug overdose, burn injury, trauma, a requirement for immediate surgery, do-not-resuscitate status. This study was approved by the institutional review board for human research. All patients or their legally authorized representatives provided written informed consent.

Measurements Cardiovascular parameters were detected by Nexfin® (Nexfin®, Edwards Lifesciences Corporation, USA). This device allowed noninvasive, continuous cardiovascular monitoring by ECG tracing and capillary pulse derived blood pressure measurement. An inflatable cuff was wrapped around the middle phalanx of the finger and clamped the digital artery producing an arterial pressure waveform. Digital arterial pressure was then reconstructed into brachial arterial pressure waveform using a transfer function and a level correction based on a large clinical database[9]. The resulting brachial pressure waveform served as the basis for determining continuous Cardiac Output. Real-time continuous CO and other hemodynamic parameters were derived by a novel pulse contour method (Nexfin CO-Trek®), which is based on the systolic pressure area and a physiological three-element Windkessel model individualized for each patient[10,11]. In this way it was possible to obtain the following parameters: blood pressure, heart rate, cardiac output (CO), cardiac index (CI), stroke volume (SV), left ventricle contractility index (dP/dTmax) and systemic vascular resistance (SVR)[9], which have shown in several studies a good correlation with the invasive hemodynamic measures[5,10,12,15]. The blood pressure measurements obtained by Nexfin were validated with the sphygmomanometer, according to the Riva-Rocci/Korotkoff technique. The pressure waveform detected by Nexfin was visually inspected during the whole monitoring period and only patients with normal waveforms were included in the study.

Study Protocol Each patient enrolled in the study underwent a continuous, noninvasive, beat-by-beat hemodynamic monitoring for a 30 min-duration, as soon as the diagnosis of sepsis was done. Clinical data were collected for each patient including age, sex, body mass index (BMI), site and the type of infection, serum procalcitonin levels, SOFA score, use of vasopressor and/or inotropic agents, and complete list of the other drugs. Drugs regimen was decided by the division physician, according to the international guidelines[13]. The drug regimen was not a target of our study, and the data obtained from the noninvasive monitoring did not influence the therapy which has been chosen independently by the treating physician. The follow up was conducted for 60 days after the study enrollment, using a telephone interview.

Data Analysis All analyses were carried out using the SPSS v. 21 software package (SPSS Inc. Chicago, IL). Descriptive results are presented as means and standard deviation (SD), medians with interquartile ranges and proportions. Cardiovascular parameters, age, sex, BMI and SOFA score were all considered as possible mortality predictors. Student's *t*-test and Levene test, cross tabulation, Spearman and Pearson correlations were used for univariate data analysis. Data were also analyzed with univariate binary logistic regression. Multivariate models were employed to analyze hazard ratios (age, systolic, diastolic and mean arterial pressure, heart rate, SV, CO, dP/dT max and SVR) using the forward conditional method. This allows a stepwise entry in the model only for covariates with significant adjusted correlation with the outcome. It was possible to analyze the dP/dT max only for 77 of 80 patients. In all cases the endpoint was the death and the follow-up duration was 60 days after the acute event. Significance was defined as P ≤0,005.

RESULTS

Eighty-five patients were enrolled in the study (54 males, 31 females), five of them were excluded from the analysis because it was not possible to detect a well defined peripheral waveform. The definitive number of patient considered was eighty (52 males, 28 females), overall mortality rate was 60% (48 patients). Clinical informations and baseline parameters of patients enrolled are resumed, respectively, in Table 1 and Table 2.

Gender did not show any statistical difference between survivors (56,2% males vs 43,7% females) and nonsurvivors (71% males vs 29% females), as well as the analysis of mean age between survivors (69,1 years; SD±13) and nonsurvivors (72,2 years;SD±17), *P*= 0,39. BMI was lowest in nonsurvivors (25,04 SD±4 vs 27,6 SD±5; *P*=0,014) and the mortality rate increase of 14% for each unit of reduction in BMI (HR 1,14; 95%CI 1-1,2, *P*=0,021). In our sample the SOFA score at the recording time was 6,89 SD±3,8 among nonsurvivors and 4,12 SD±2,6 in survivors (*P*= 0,001), the lactates values was 2,52 mmol/L for nonsurvivors and 1,78 for survivors (P= 0,029). Clinical differences between survivors and nonsurvivors are resumed in table 3.

Comorbidities, such as hypertension, diabetes and ischemic cardiomyopathy, analyzed by logistic regression, did not influence the mortality (Hypertension HR 1,88; 95%CI 0,7-4,6, *P*= 0,17. Diabetes HR 1,05; 95%CI 0,3-2,8, *P*=0,9. Ischemic cardiomyopathy HR 1,26; 95%CI 0,4-3,6, *P*= 0,66).

As shown in Table 4, significant differences in cardiovascular parameters, expressed as mean ±SD, were detected between survivors and nonsurvivors. In particular survivors showed the highest SV, CO, CI and dP/dTmax, while in the same group SVR were lowest.

Stroke volume. The logistic regression, by forward stepwise inclusion of different variables, shows that higher SV values are associated with a higher chance of survival. The hazard ratio (HR) for survival is 1,25 (95% CI 1 – 1,4), *P*= 0,001. In other word, for each 5 ml of reduction in SV the mortality risk increases of 25% and if we consider the SV median value of our sample (60 ml) the mortality rate in subjects with values higher than this threshold is decreased of 75%.

Cardiac output. CO has a positive correlation with survival. The mortality rate increases of 43% for each 1 L/min of reduction in CO (HR 1,44; 95%CI 1,1-1,8; *P*=0,005).

Cardiac index. Mortality rate is doubled in patients with reduction of a unit in CI (HR 2; 95% CI 1,2-3,2; *P*=0,004).

Left ventricle contractility. Also dP/dTmax shows a positive association with survival: the mortality rate increases of 10% for every 50 mmHg/s of decrease in this variable (HR 1,1; 95%CI 1-1,1; *P*=0,005).

Systemic vascular resistances. SVR are not significantly correlated with death risk (HR 1; 95%CI 0,9-1; *P*= 0,3).

Analyzing all the hemodynamic variables together with sex, age, BMI, procalcitonin and lactate values in a multivariate data analysis, dP/dTmax and BMI have shown to be the most important elements to influence the survival. The risk of death for patients with dP/dTmax lower than median value (625 mmHg/s) is 5,8 times greater than those with values higher than median (HR 5,9; 95%CI 2-16; *P*=0,001).The risk of death for subjects with BMI lower than median value (25,4) is 1,1 time higher than those

with value inferior to the median (HR 1,1; 95%CI 1-1,2; *P*=0,05). If we consider patients with both dP/dTmax and BMI inferior to medians the risk of death is 5 times greater than patients with values higher than this threshold (95%CI 1,7-14,3; *P*=0,003). Results of univariate and multivariate analysis are shown in table 5.

DISCUSSION

The overall mortality was 60%, this result highlights the severity of the clinical conditions in our patient sample. Gender did not seem to influence the prognosis. Similarly comorbidities with effect on cardiovascular system such as hypertension, diabetes and ischemic cardiomyopathy, did not affect the mortality. Although we did not calculate the influence of other concomitant diseases, it seems that the global derangement of cardiovascular system induced by sepsis has a large burden on death risk. At variance BMI showed a positive correlation with prognosis, but, unexpectedly, a BMI over normal limit correlated with a good prognosis.

The novel finding of our study has been the observation that SV detected noninvasively has a positive predictive value in term of mortality, in patients affected by sepsis or septic shock. Our results demonstrated that patients with higher SV showed a significant greater chance of survival when compared with those with a depressed cardiac function. Accordingly, CO and CI, derived in part from SV, have a positive correlation with the outcome.

Also dP/dTmax, considered as an indirect measure of myocardial contractility, shows an interesting significant correlation with mortality, demonstrating how low values might identify patients at high risk for death. It is noteworthy the result concerning the SVR, since we have found that survivors had, in the acute phase of sepsis, lower mean values compared with nonsurvivors, even though in our group the correlation between SVR and the risk of death did not reach the statistical significance.

Taken together these results highlight the relevant role of cardiovascular system in sepsis pathophysiology and the potential usefulness of an early cardiovascular and hemodynamic monitoring.

Overall the most interesting result was the positive association between SV and survival as well as dP/dTmax and survival; this is not surprising since it has been reported that the transition from the systemic inflammatory response syndrome to severe sepsis and septic shock involves, among other, hemodynamic and circulatory abnormalities that result in global tissue hypoxia. It is possible to speculate that subjects with higher SV and higher dP/dTmax retain a cardiovascular function reserve able to counteract the peripheral tissue hypoxia.

The results of the present study, although not definitive due to the relatively limited number of patients, seem to confirm that an efficient myocardial contractility reserve is mandatory to preserve a sufficient perfusion of peripheral circulation and to suggest that SV and dP/dTmax monitoring might help to early stratify the risk of these patients and to plan the best clinical strategy within the ED.

It has also been reported a sepsis induced cardiomyopathy characterized by biventricular impairment of intrinsic myocardial contractility, with a subsequent reduction in left ventricular (LV) ejection fraction and LV stroke work index, that is reversible among survivors patients affected by septic shock[2,14]. Hence, the early stroke volume and hemodynamic monitoring might help to identify these critical patients and to follow the disease's evolution.

Another interesting finding is the role played by low BMI as negative predictive factor both when considered within the univariate analysis and when included in a multivariate analysis with hemodynamic parameters. This is not completely new since previous studies have already shown a protective effect of increased BMI and overweight on mortality rate in patients affected by sepsis and septic shock[16,17,18]. Pathophysiological mechanisms supporting these findings have not been defined; contrasting results have been reported concerning a possible protective effect in sepsis exerted by leptin, a hormone highly involved in the pathophysiology of obesity[19,20]. Alternatively, in our experimental set in which patients are elderly and characterized by several comorbidities, the low BMI might be the expression of malnutrition and cachexia thus representing, per se, a negative predictive factor.

Although noninvasive monitoring through Nexfin is far to replace the invasive monitoring in critical ill patients, it has been shown a good correlation in CO tracking compared with invasive methods[21]. This new noninvasive monitoring appears as an attractive tool for the early evaluation of patients in the ED, able to contribute to the risk stratification of septic patients and useful in the decision to address severe patients toward an intensive care units. Because of the easy application of this method, and its ability to delineate the hemodynamic profile, we suggest its wide application in the early phases of sepsis, since it could represent a bridge between an initial cardiovascular evaluation in the ED and a more accurate and invasive monitoring in the intensive care unit.

LIMITATIONS

Important limitations are represented by comorbidities and administration of drugs that can affect the cardiovascular system, even though these conditions are strictly connected with pathologic conditions, as sepsis and/or shock, and then barely modifiable. Another limitation is represented by the impossibility to monitor with this device patients with repetitive cardiac dysrhythmias, for the reasons explained above.

The lactate values, even though statistically significant, did not show relevant differences between survivors and non survivors; this could reflect the different time in blood gas analysis withdrawal, the different sepsis hemodynamic phases of each patient and the complex lactate's kinesis. Furthermore, although lactate level is an important marker of severity, some patients in septic shock never generate abnormal lactate levels[22]. Anyway, the nonsurvivors lactate values were in that intermediate range reported by literature, which is correlated with an increased risk of adverse outcome[23,24].

CONCLUSION

In summary, the results of our study suggest the use of noninvasive hemodynamic monitoring in the ED setting as a reliable tool for the early risk stratification of patients in sepsis and septic shock, together with other clinical markers.

DISCLOSURE STATEMENT

The authors declare that there is no conflict of interests.

Table 1 Clinical informations

Subjects	80
Mortality	60%
Mean age ±SD	70.98±15.8 years
Gender	Male=52
	Female=28
Diabetes	22 /80 patients
Hypertension	35/80 patients
Ischaemic cardiomyopathy	18/80 patients
Blood cultures	23/80 positives
	39/80 negatives
	18/80 not available
Use of norepinephrine	14/80

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Table 2 Baseline parameters

Parameters	Mean ± SD	Median (IQR 25- 75)
Sys(mmHg)	103,4±23,5	101,5 (90,2 - 114)
Dia(mmHg)	57,4±10,2	57,5 (51 – 64,7)
Map(mmHg)	74,4±14	74 (65,2 – 82,7)
Hr(bpm)	94,4±17,9	93 (82,2 – 104,5)
CO(L/min)	6,1±2,2	5,8 (4,6 – 7,2)
CI(L/min/m^2)	3,3±1,1	3,2 (2,5 – 4)
SV(ml)	65,1±22,3	60 (48,5 – 78,7)
SVR(dyn*s*cm^{-5})	1172,9±532,5	1042,5(798,5-1414,2)
dP/dT max(mmHg/s)	714,87±373,6	626 (457-932)
pH	7,45±0,08	7,47 (7,42 – 7,5)
Bicarbonate(mEq/L)	24,8±6,0	23,7(20,6 – 27,7)
Lactate(mmol/L)	2,2±1,5	1,9 (1,2 – 2,6)
PCT(ng/ml)	18,4±44,5	2,1(0,49 – 19,3)
SOFA score	5,8±3,6	5,0 (3,0 – 8,0)

All values are expressed as mean ± standard deviation (SD) and median with interquartile range (IQR). Sys: systolic pressure; Dia: diastolic pressure; Map: mean arterial pressure; Hr: heart rate; CO: cardiac output; CI: cardiac index; SV: stroke volume; SVR: systemic vascular resistance; dP/dTmax: left ventricular contractility index; PCT: procalcitonin

Table 3 Clinical differences between survivors and deceased patients

	OUTOCOME	MEAN±SD	P(t-test)
Age (years)	deceased	72,2±17,1	0,39
	survivors	69,1±13,7	
PCT (ng/ml)	deceased	23,1±55,7	0,28
	survivors	11,8±19,4	
SOFA score	deceased	6,9±3,8	0,001
	survivors	4,1±2,7	
BMI (kg/ m^2)	deceased	25,05±4,05	0,014
	survivors	27,7±5,2	
Lactates (mmol/L)	deceased	2,52	0,029
	survivors	1,78	

All values are expressed as mean ±SD. PCT: procalcitonin; BMI: body mass index

Table 4 Cardiovascular parameters of survivors and deceased patients

PARAMETERS	OUTOCOME	MEAN±SD	P(t-test)
Sys (mmHg)	deceased	101,1±26,2	0,28
	survivors	106,9±18,5	
Dia (mmHg)	deceased	58,1±10,8	0,42
	survivors	56,2±9,3	
Map (mmHg)	deceased	74,2±15,84	0,85
	survivors	74,8±11,0	
CO (L/min)	deceased	5,5±1,7	0,005
	survivors	7,0±2,6	
CI (L/min/m^2)	deceased	3,0±0,8	0,004
	survivors	3,8±1,3	
HR (bpm)	deceased	95,9±19,4	0,35
	survivors	92,1±15,4	
SV (ml)	deceased	57,9±16,4	0,001
	survivors	76,0±25,7	
SVR (dyn*s*cm^{-5})	deceased	1282,4±572,3	0,023
	survivors	1008,6±423,6	
dP/dTmax (mmHg/s)	deceased	611,1±332,8	0,002
	survivors	868,8±382,7	

All values are expressed as mean ±SD. Sys: systolic pressure; Dia: diastolic pressure; Map: mean arterial pressure; CO: cardiac output; CI: cardiac index; Hr: heart rate; SV: stroke volume; SVR: systemic vascular resistance; dP/dTmax: left ventricular contractility index

Table 5 Correlation between evaluated variables and death's risk

	HR for death (95% CI)	*p*	HR for death (95% CI)	*p*
Sys	1,0 (0,99-1,03)	0,28	Nc	-
Dia	0,98 (0,94-1,03)	0,42	Nc	-
Map	1,0 (0,97-1,04)	0,85	Nc	-
Hr	1,01 (0,95-1,08)	0,74	Nc	-
SVR	1,0 (0,99-1,0)	0,32	Nc	-
SV	1,25 (1,09-1,43)	0,001	NE	-
CO	1,44 (1,12-1,85)	0,005	Nc	-
CI	2,0 (1,26-3,2)	0,004	Nc	-
dP/dT max	1,1 (1,03-1,18)	0,005	5,9 (2,1-16,5)	0,001
BMI	1,14 (1,02-1,27)	0,021	1,11 (1,0-1,2)	0,05

Sys: systolic pressure; Dia: diastolic pressure; Map: mean arterial pressure; Hr: heart rate; SVR: systemic vascular resistance; SV: stroke volume; CO: cardiac output; CI: cardiac index; dP/dT max: left ventricular contractility index; BMI: body mass index; HR: hazard ratio; Nc: not computed; NE: not entered

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