Physiologic Patients' Response to Fluid Administration in Intensive Care Unit

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Abstract

Introduction: *Cardiovascular instability is common in intensive care unit (ICU) patients. Although aggressive fluid administration is the cornerstone of resuscitation, it has been associated with higher mortality and morbidity and its effects on the cardiovascular system have not been fully explored.* ***Goal:*** *This study aims at characterizing the response to fluid intervention of survived ICU patients without other ongoing treatments.* ***Methods:*** *Before and after the first administration of fluids, one hour of electrocardiogram and arterial blood pressure recordings were extracted from 51 patients (MIMIC-III database, PhysioNet). Induced changes in cardiovascular and autonomic indices were assessed from beat-to-beat analysis and by applying a point process framework for the time-varying estimation of the proposed indices.* ***Results:*** *After fluid therapy initiation the following significant trends were observed: reduction in systolic pressure (μ_{SBP} : p <0.001), decrease in RR interval (μ_{RR} : p =0.010), increase in RR variance (σ^2_{RR} : p <0.001), baroreflex ($G_{SBP->RR,LF}$: p <0.001), and RR and SBP low frequency powers ($S_{RR,LF}$: p <0.001, $S_{SBP,LF}$: p=0.006).* ***Conclusions:*** *Results point to an increased functionality of autonomic control as suggested by increased baroreflex feedback and higher low frequency power after fluid administration.*

1. Introduction

Hemodynamic instability is often referred to as an alteration in effective circulating volume, cardiac function, and/or vascular tone. Hemodynamic instability is common in patients presenting to intensive care unit (ICU) and it can be also a major contributive factor to organ failure due to a mismatch between oxygen delivery and demand [1]. Large volume fluid resuscitation has been considered the cornerstone of hemodynamic resuscitation [2]. The main rationale for administering fluids is the need for circulatory stabilization during shock states [3,4]. In fact, the expected response to a fluid challenge is an increase in stroke volume induced by an increase in systemic filling pressure and venous return [5], with a consequent increase in cardiac index, which relates heart performances to the size of the individual. However, aggressive fluid resuscitation showed an association with observed worse outcomes mainly because of a fluid overload inducing intra-abdominal hypertension and consequent renal dysfunction, thus leaving the optimal strategy for fluid management still largely debated [5,6]. To our knowledge, there is a lack of studies assessing the effectiveness of fluid therapies, the induced physiological changes, and their associations with main clinical outcomes. Indeed, only a few studies explored the physiologic variations induced by fluid challenges, mainly focusing on principal cardiovascular indices like cardiac output, stroke volume and heart rate [6, 7]. Recently, passive leg raising-induced changes in cardiac output showed good ability in predicting the response of cardiac output to volume expansion in adults with acute circulatory failure [8].

Heart rate variability (HRV) reflects the ability of autonomic activity to regulate and modulate the rhythm of the sinoatrial node, and therefore the way in which heart rate is regulated by the parasympathetic and sympathetic branches of the autonomic nervous system. HRV association with autonomic nervous system was assessed through several procedures designed to induce variations in blood pressure like tilt-rest, head down tilt bed rest and lower body negative pressure [9, 10]. Indeed, central volume changes are among the major drivers for cardiac activity modulation induced by the autonomic nervous system (ANS) therefore, their effects on ANS are at the base of the potential of HRV indices in determining response to fluid administration as well as showing the associations of these indices with patients' outcomes. The usefulness of HRV measures was already assessed by Foroutan et al. that explored the role of HRV as an endpoint index for resuscitation in trauma patients [11], by Porta et al. which investigated the association between HRV and ICU patients' mortality [12] as well as by Ferrario et al., which explored the correlation between fluid overload in chronic kidney disease patients on hemodialysis and HRV measures [13].

The goal of this study is to characterize the induced

* L.L. is partially supported by the NIH grant 5R01 EB017205

changes in heart rate variability indices of survived ICU patients.

2. Methods

2.1. Study Design and Cohort Selection

The dataset used in this study was extracted from the MIMIC-III database [14], a publicly available database on PhysioNet [15] collecting both clinical data from the electronic health records and physiological waveforms recordings of patients admitted to the intensive care unit at the Beth Israel Deaconess Medical Center in Boston, MA.

A subset of 10,282 patients whose clinical data were matched with the recorded physiological vital sign waveforms was our starting population. Clinical data were recorded with two distinct systems, Philips CareVue Clinical Information System and iMDsoft MetaVision ICU, referred to as Carevue and Metavision. Data used in this study were extracted from the Metavision system.

We focused our attention on the first recorded administration of fluid with a valid (not null) recorded fluid amount or infusion rate.We successively included only patients with available both electrocardiographic (ECG) and arterial blood pressure (ABP) recordings. From the resulting 5,604, we considered 2,248 patients with available waveforms recordings both 1 hour before and 1 after the fluid administration. Only waveforms belonging to patients that are not under vasopressor, sedative and mechanical ventilation treatments in the selected time window were considered for this study, resulting in 387 patients, since it is reasonable to assume that other treatments different than fluids may have high influencing and confounding effects on the autonomic activity. In the end, only 54 subjects had good quality signals, of which 3 have been excluded because they died during their hospital stay.

Each patient's set of waveforms was processed with an internally developed automatic annotation software in order to extract the times of R-peak events on the ECG and the times and values of systolic events on the ABP signals. Obtained annotations underwent manual review and correction for missing beats and beats not belonging to sinusal rhythm.

2.2. Cardiovascular Data Modeling and Feature Engineering

The available annotations of R-peaks and corresponding systolic blood pressure (SBP) values were modeled using a closed-loop point-process approach, which allows for the estimation of the HRV and SBP variability spectral indices as well as the estimation of the feedback and feedforward gains describing the underlying regulatory mechanisms for the heart rate and blood pressure control exerted by the ANS. Specifically, the inverse gaussian distribution was used to model the inter-beat-interval times, which was already proved to be a proper model of heartbeat dynamics [16, 17], and whose expected value ($\mu_{RR}(t)$) can be estimated with a bivariate autoregressive (BVAR) model, which also includes the effect of systolic arterial pressure changes, as follows:

$$\mu_{RR}(t) = a_{110} + \sum_{i=1}^{p} a_{11i}(t) RR_{t-i} + \sum_{j=1}^{q} a_{12j}(t) SBP_{t-j} \tag{1}$$

The expected value of the systolic arterial pressure ($\mu_{SBP}(t)$) was estimated in continuous time according to the following BVAR model:

$$\mu_{SBP}(t) = a_{220} + \sum_{i=1}^{r} a_{21i}(t) \mu_{RR,(t-i)} + \sum_{j=1}^{s} a_{22j}(t) SBP_{t-j} \tag{2}$$

where $\mu_{RR,(t-i)}$ represents the average RR interval at the time of the systolic events and the order of the BVAR model p=q=r=s=7 was chosen as the lowest order that allowed a good fitting with the IG distribution, assessed looking at the KS-distance and at the number of points out of 95% confidence intervals of the autocorrelation function of the residuals. The autoregressive parameters a_{11i} and a_{12j} for i,j=0,1,2,..,p were estimated within a point process framework by maximum likelihood estimation. a_{21i} and a_{22j} were estimated through weighted least squares.

Time-varying autospectra ($S_{RR}(t,f)$, $S_{SBP}(t,f)$) were estimated following Barbieri et al. [18]

and baroreflex and feedforward gains were estimated as follows:

$$\begin{aligned} G_{RR \to SBP}(t,f) &= \sqrt{\frac{S_{RR} - |h_{11}|^2 \sigma^2_{RR}}{S_{SBP} - |h_{21}|^2 \sigma^2_{RR}}} \\ G_{SBP \to RR}(t,f) &= \sqrt{\frac{S_{SBP} - |h_{22}|^2 \sigma^2_{SBP}}{S_{RR} - |h_{12}|^2 \sigma^2_{SBP}}} \end{aligned} \tag{3}$$

where σ^2_{RR} and σ^2_{SBP} are the RR and SBP variances and h_{ij} represents the transfer function estimated from the autoregressive coefficients. From the proposed modeling approach, we extracted the following time-varying indices: the average RR interval (μ_{RR}), the average SBP series (μ_{SBP}), σ^2_{RR}, σ^2_{SBP}, the power in the LF and HF bands (LF: 0.04-0.15Hz, HF: 0.15-0.45Hz) of the RR spectrum ($S_{RR,LF}$, $S_{RR,HF}$) and the normalized powers ($S_{RR,LFn}$, $S_{RR,HFn}$), the average power in the LF and HF band of the SBP spectrum ($S_{SBP,LF}$, $S_{SBP,HF}$) and the normalized ones ($S_{SBP,LFn}$, $S_{SBP,HFn}$), the sympatho-vagal balance of the RR spectrum ($S_{RR,LF/HF}$), the average feedforward

Table 1. Population characteristics reported as median (first;third quartiles) or incidence (%) for numeric and categorical features, respectively. VA: vasoactive agents, FA: fluid administration.

Population Characteristics	*Full* 54	*Non-Surivors* 3 (5.6%)	*Survivors* 51 (94.4%)
Age (years)	60 (51;70)	61 (57;76)	60 (50;70)
Length of stay (days)	2 (1;3)	15 (6;16)	2 (1;3)
Sex (F)	27 (50%)	1 (33.3%)	26 (50.9%)
VA need 48 hrs after FA	5 (9.3%)	2 (66.7%)	3 (5.9%)
Urin output (mL)	195 (75;450)	180 (101;409)	200 (76;450)

gain in the LF band ($G_{RR\rightarrow SBP,LF}$), the average feedforward gain in the HF band ($G_{RR\rightarrow SBP,HF}$), the average baroreflex gain in the LF band ($G_{SBP\rightarrow RR,LF}$) and the average baroreflex gain in the HF band ($G_{SBP\rightarrow RR,HF}$). $S_{RR,LFn}$ and $S_{RR,HFn}$ were normalized by the total power minus the power in very low frequency band (VLF: 0.003-0.04Hz) whereas $S_{SBP,LFn}$ and $S_{SBP,HFn}$ were normalized by dividing for the total power. From the resulting time series we extracted 5 minutes averages before (referred to as *PRE* condition) and after (referred to as *POST* condition) fluid administration.

In order to test the presence of a treatment effect we used a Friedman test on the 51 survived subjects on a set of 12 repetitions of features recorded every 5 minutes during *PRE* and *POST* conditions for each patient. Test significance was set to 0.05.

3. Results

The extracted population consisted of 54 patients, of which only 3 died in the ICU. The resulting *Survivors* subset of the population (51 patients) shows 26 (50.9%) females, a median age of 60 (50;70) and a length of stay of 2 (1;3) days, as reported in Table 1.

Table 2 shows the distributions of 60-minute averages of the considered indices in *PRE* and *POST* conditions as median (first;third quartiles) and the resulting p-values obtained through Friedman test. Both average RR and SBP series showed significant treatment effect (respectively, p=0.010 and $p<0.001$), with a decreasing value after the administration. A significant treatment effect with an increase from *PRE* to *POST* conditions was found for σ^2_{RR} ($p<0.001$), RR spectra in both frequency bands ($S_{RR,LF}$: $p<0.001$, $S_{RR,HF}$: $p<0.001$), normalized RR spectrum in LF band ($S_{RR,LFn}$: p=0.008), sympatho-vagal balance ($S_{RR,LF/HF}$: p=0.048), and in SBP spectrum in LF band ($S_{SBP,LF}$: p=0.006). Treatment influenced also the baroreflex gain both in LF and HF bands ($G_{SBP\rightarrow RR,LF}$: $p<0.001$, $G_{SBP\rightarrow RR,HF}$: $p<0.001$), showing an increase in the *POST* condition. A reduction in feedforward gains in both LF ($G_{RR\rightarrow SBP,HF}$: p=0.047) and HF ($G_{RR\rightarrow SBP,HF}$: p=0.039) bands was also observed.

Table 2. Friedman test results on *Survivors* population. For each feature p-values and population median (first;third quartiles) before and after the administration.

HRV Feature	p-value	*PRE*	*POST*
μ_{RR} [msec]	**0.010**	791.19 (682.7; 896.69)	776.49 (672.28; 878.26)
$S_{RR,LFn}$ [n.u.]	**0.008**	0.35 (0.27; 0.49)	0.36 (0.28; 0.51)
$S_{RR,HFn}$ [n.u.]	0.605	0.27 (0.18; 0.39)	0.29 (0.2; 0.36)
$S_{RR,LF}$ [msec^2]	**<0.001**	837.1 (173.3; 3170.6)	1830.77 (472; 4858.49)
$S_{RR,HF}$ [msec^2]	**<0.001**	207.23 (39.59; 2359.92)	708.74 (55.24; 3155.17)
$S_{RR,LF/HF}$ [n.u.]	**0.048**	8.97 (3.3; 21.57)	11.68 (3.79; 25.55)
$G_{RR\rightarrow SBP,LF}$ [mmHg/msec]	**0.047**	0.38 (0.2; 0.48)	0.32 (0.2; 0.42)
$G_{RR\rightarrow SBP,HF}$ [mmHg/msec]	**0.039**	0.26 (0.18; 0.42)	0.24 (0.16; 0.34)
σ^2_{RR} [msec^2]	**<0.001**	76.46 (35.75; 173.51)	131.08 (33.78; 257.67)
μ_{SBP} [mmHg]	**<0.001**	126.63 (110.48; 141.83)	120.36 (107.38; 137.74)
$S_{SBP,LFn}$ [n.u.]	0.301	0.31 (0.21; 0.39)	0.34 (0.2; 0.4)
$S_{SBP,HFn}$ [n.u.]	0.910	0.24 (0.19; 0.33)	0.25 (0.2; 0.32)
$S_{SBP,LF}$ [mmHg^2]	**0.006**	45.19 (21.08; 125.59)	88.42 (29.15; 171.97)
$S_{SBP,HF}$ [mmHg^2]	0.622	39.91 (17.17; 92.55)	40.71 (16.99; 95.41)
$G_{SBP\rightarrow RR,LF}$ [msec/mmHg]	**<0.001**	3.79 (1.28; 7.12)	4.51 (1.89; 9.24)
$G_{SBP\rightarrow RR,HF}$ [msec/mmHg]	**<0.001**	2.15 (1.22; 7.2)	3.11 (1.09; 10.1)
σ^2_{SBP} [mmHg^2]	0.680	6.18 (3.24; 9.21)	5.68 (3.5; 9.12)

4. Discussions and conclusions

The emerging patients' characteristics show a middle-aged, sex-balanced population with a low mortality rate, indicating a generally healthier condition when compared with the average ICU reports, a feature that can be readily linked to the absence of additional undergoing therapies during the selected two-hour window around fluid administration. The results on the *Survivors* population show a general decrease in RR interval (increase in heart rate) and, interestingly, a reduction in systolic blood pressure. Averaged trends are shown in Figure 1, where a stabilization of the systolic pressure toward healthier values is observed after fluid administration. The general increase in the average high and low frequency powers, normalized low frequency power and sympatho-vagal balance of the RR spectrum after fluid administration suggests an increase in the overall autonomic activity with an imbalance toward the sympathetic branch. These results might be explained considering the observed baroreflex activation. As baroreflex gain increases after the administration, the possibly consequent restoration of autonomic control activity reflects on vasculature tone and control, as further supported by the observed increase in low frequency power of the SBP time series together with a reduction of the feedforward

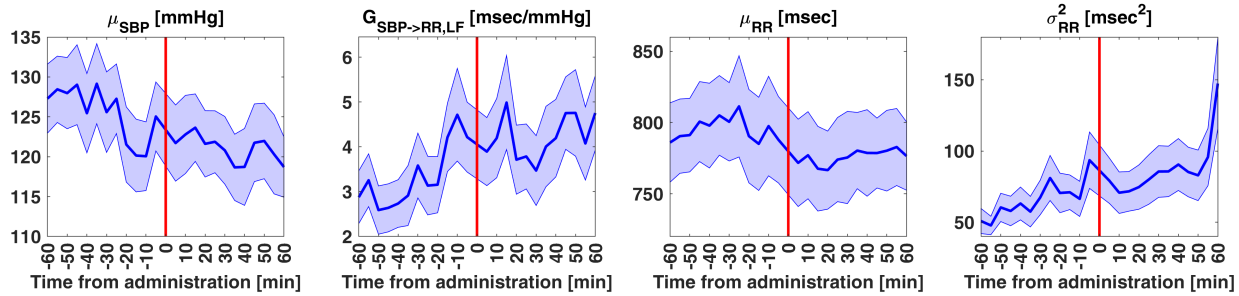

Figure 1. Median trends (± median absolute deviation error) of average systolic pressure, baroreflex gain in the LF band, average RR interval and RR variance around the administration of fluids (red line) for each 5 minutes interval.

gain. In conclusion, results obtained after fluid administration on survivor patients admitted to the ICU point at a possible restoration of autonomic control on both heart and vasculature, thus bringing patients to a more stable health state under the control of a slightly recovered autonomic nervous system activity as also previously observed on a generic surviving ICU population[19]. Our results show that heart rate variability indices could be used in clinical practice as markers for assessing fluid responsiveness and possibly giving timely recommendations to the clinicians about the most appropriate fluid therapy and addressing its effectiveness right after administration.

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