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A mathematical model of dP/dt max for the evaluation of the dynamic control of heart contractility in septic shock

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Abstract*— *Objective: **Septic shock (SS) patients often show elevated heart rate (HR) despite resuscitation and this condition is considered an early manifestation of myocardial dysfunction, due to an impairment of autonomic nervous system (ANS). We aimed at proposing a mathematical model to assess the autonomic control of ventricular contractility (VC) and HR to track changes in heart functionality during SS and resuscitation.** ***Methods:*** **We analyzed beat-to-beat variability of maximum positive time derivative of left ventricular pressure (dP/dt max), heart period (HP) and aortic blood pressure (ABP). We identified the transfer functions relating fluctuations in ABP and HP to dP/dt max to characterize the static and dynamic properties of the arterial baroreflex and the force-frequency relation mechanisms, respectively. Standard indices of autonomic dysfunction have also been considered, as HR variability (HRV) and baroreflex sensitivity (BRS).** ***Results:*** **During baseline the baroreflex is predominant in controlling VC with a gain value of -5.8 (-7.5,-3) s^{-1}, compared to -1.2 (-1.9,-0.5) mmHg/s ms^{-1} of the force-frequency autoregulation. During shock both mechanisms increase their extent in VC control (higher gains and slightly faster dynamics for the baroreflex). After resuscitation the physiological control of VC is not restored and all the animals still exhibit high HR and reduced HRV and BRS.** ***Conclusion:*** **A condition of cardiovascular inefficiency is persistent after resuscitation and this could be due to an autonomic dysfunction.** ***Significance:*** **The ANS in SS patients is crucial to restore homeostasis. Our model could be used to evaluate the efficacy of treatments on VC and relating control mechanisms.**

***Index Terms*—autonomic nervous system, beat-to-beat variability, septic shock, resuscitation, ventricular contractility, bioelectronic medicine**

I. Introduction

TACHYCARDIA and increased ventricular contractility are fundamental compensatory mechanisms in conditions of cardiovascular stress such as sepsis and septic shock. During the progression of septic shock, overwhelming inflammation leads to vasodilation and capillary leakage, which alter cardiac output (CO) by preload reduction, and a massive sympathetic activation is usually elicited in the physiological attempt to maintain vital perfusion. Thus, tachycardia and increased contractility, usually observed in septic patients, are classically considered as the main mechanisms in order to compensate a fall in preload [1], [2].

Current clinical guidelines for resuscitation of shocked patients recommend the administration of fluids in order to restore the circulating blood volume and vasopressors in order to maintain a mean arterial pressure higher than 65 mmHg; central venous oxygen saturation is monitored to be higher than 70% together with an antibiotic therapy to counteract the underlying source of infection [3]–[5]. In addition to these therapies, inotropes are administered to increase CO, if its value is still under a physiological threshold. As a result, it's common to have supranormal values of both heart rate (HR) and CO persisting even after correction of hypovolemia and hypotension, but the current clinical practice doesn't consider this condition deserving appropriate intervention.

To date only few studies have evaluated tachycardia as a mortality factor in patients suffering from septic shock [6]–[8], but they all found that high HR is an independent risk factor for increased mortality, similarly to many other clinical pathologies [9]–[13].

The underlying mechanism of such persistent tachycardia could be an altered chronotropic response, due to an impairment of the sympathetic nervous system (SNS) and, in particular, of SNS mediated organs interactions [14]. In fact, it is now well understood that some septic shock patients may suffer from a protracted and overshooting stimulation of the SNS, which may exceed in time and scope the beneficial short-term compensatory effect, leading to several adverse effects, such as prolonged tachycardia [7], [15]–[17]. The duration of the positive effect of sympathetic stimulation depends on organ vulnerability to adrenergic overstimulation, for instance the heart, which is abundant of β adrenergic receptors, has to be considered as the main target of this sympathetic overstimulation [16]. Moreover, beside the physiological endogenous release of chatecolamines, the high doses of exogenous chatecolamines due to aggressive therapy with dobutamine or norepinephrine, further increase HR and the risk of cardiac failure [18]. For these reasons, in septic shock, tachycardia persisting after adequate volume resuscitation indicates an altered chronotropic response and can be considered as an early manifestation of myocardial dysfunction [14].

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At present, most of scientific research into cardiac impairment in septic shock and multiorgan dysfunction syndrome (MODS) focuses on myocardial depression due to bacterial toxins and inflammatory mediators [19], [20]. However, recent studies show that a crucial issue in sepsis is not only the myocardial depression, but also the impaired regulation of cardiac function due to alterations of cardiovascular autonomic nervous system (ANS).

Clinically, autonomic dysfunction can be quantified by heart rate variability (HRV) and baroreflex sensitivity (BRS) [23]–[27]. Several previous studies demonstrated that a reduction in HRV is one of the best predictors of death in critically ill patients [21]; among these, patients with septic shock and elevated HR have been shown to have also a reduced HRV, indicating an extreme attenuation of the vagal tone [26].

In this study, we focused on the autonomic control of cardiac contractility and HR during a controlled experiment of septic shock and resuscitation. In particular, we aimed 1) to propose a model able to separately characterize the static and dynamic control of ventricular contractility mediated by the autonomic arterial baroreflex and by the force-frequency autoregulation and 2) to determine how these control mechanisms are altered during septic shock or recovered after resuscitation. Both of these mechanisms may occur simultaneously and importantly contribute to the modulation of CO. For example, in response to a fall in arterial blood pressure (BP), a baroreflex-mediated sympathoexcitation is supposed to occur, which will increase the inotropic state. At the same time the concurrent tachycardia could also increase the inotropic state independently via the force-frequency relation (or Bowditch effect) [28]. To our knowledge, no previous study has evaluated the static and dynamic control of ventricular contractility in septic shock condition.

II. Materials and Methods

A. Study design and experimental procedure

We performed a controlled experimental study on a large animal model of septic shock induced by a polymicrobial peritonitis on adult swines in the Experimental Laboratory of Intensive Care (LA1230336), at the Université Libre de Bruxelles. The local animal ethics committee (Comité Ethique du Bien-Être Animal) approved the present study (protocol 641 N) and we followed the EU Directive 2010/63/EU for animal experiments and the ARRIVE guidelines for animal research.

Six pigs of both sex (age 4 to 6 months, weight 43.8 ± 3.9 kg expressed as mean ± standard deviation) were obtained from a local farm (BE 400108–48). Animals were fasted for 18 h prior to the start of the experiment with free access to water. Details on the instrumentation and experiment preparation can be found in the supplemental material. After instrumentation, the animals were allowed to rest for approximately 2 hours after which the first baseline measurements and blood samples were taken (baseline, T1). Sepsis was induced by the intraperitoneal instillation, via the two abdominal drains, of 3g/kg of autologous feces collected in the cage, filtered and diluted in 300ml of glucose 10%. During septic shock onset, fluid maintenance was reduced to 1 ml/kg/h until the mean arterial blood pressure (MBP) has decreased below 50 mmHg. Thereafter, fluid maintenance perfusion was moderately increased to keep the animal alive for one more hour of severe hypotension (MBP goal between 45 and 50 mmHg), in order to consolidate the peripheral hypoperfusion and the multiple organ failure. At the end of this period, a second time point T2 was defined as reference for septic shock condition. Immediately after a series of hemodynamic measurements and blood samples, a full fluid resuscitation was initiated with both the same rate of the balanced crystalloid perfusion and an additional colloid perfusion (Geloplasma, Fresenius Kabi, France), aiming to reach a pulse pressure variation <12%. After 120 min of hemodynamic stabilization, defined by a stable MBP and no further increase in CO, additional hemodynamic measurements and blood samples were taken again (T3, end of first resuscitation). Finally, a vasopressor therapy was administered, with a continuous infusion of norepinephrine at a fixed dose of 0,3 µg/kg/min for one hour, after which the last series of hemodynamic measurements and blood samples were taken again (T4, end of full resuscitation). Animal were then euthanized with a potassium chloride injection and an overdose of thiopental.

Two out of six animals were immediately fully resuscitated with vasopressors because of the severity of the distributive shock, therefore the measurements at time point T3 are missing. For this reason, in the following we refer only to baseline (T1), shock (T2) and to fully resuscitation (T4) period.

At each time point, arterial blood samples were collected and EDTA-plasma isolated for laboratory analyses after immediate refrigerated centrifugation. In addition, hemoglobin concentration, blood lactate and electrolyte concentrations were measured (Cobas b-123, Roche, Switzerland). Further laboratory blood analyses were performed, such as cardiac troponin.

B. Hemodynamic data acquisition and preprocessing

Aortic blood pressure (ABP) and left ventricular pressure (LVP) were continuously recorded during the experiment. At each time point stationary segments of 15-minute length on average were selected. Time series of systolic (SAP), diastolic (DAP) and mean (MAP) aortic pressure were obtained from ABP waveform using standard algorithms [29], [30]. The time series of heart period (HP) was obtained from the ABP waveform by computing the time difference between consecutive onsets of ABP beats and considered as a surrogate of the RR-intervals time series. The maximum of positive time derivative of LVP (dP/dt max) was derived on a beat-to-beat basis from LVP recording and it was taken as an indirect measure of ventricular contractility. An adaptive filter was then applied to the time series in order to remove outliers and irregularities [31] and each time series was finally resampled at 2 Hz by means of zero-order hold techniques. The pre-processed time series were then subdivided into 3-min 50% overlapping windows and each window was detrended using a

high-order polynomial function in order to guarantee stationarity further verified using the Kwiatkowski–Phillips–Schmidt–Shin (KPSS) statistical test. All the indices obtained from each 3-min window were averaged and considered for successive statistical comparisons.

C. Ventricular contractility model

The black-box model implemented to study the control of ventricular contractility by the arterial baroreflex mechanism and the force-frequency autoregulation is depicted in Fig. 1.

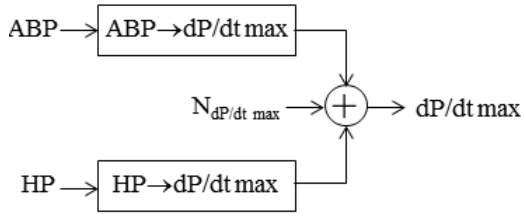

Fig 1. Block diagram for identification of the transfer functions relating fluctuations in aortic blood pressure (ABP) to dP/dt max (ABP→dP/dt max) and fluctuations in heart period (HP), surrogate of the heart rate variability to dP/dt max (HP→dP/dt max) from spontaneous beat-to-beat ABP, HP and dP/dt max variability. $N_{dP/dt\ max}$ represents the residual variability in dP/dt max not accounted for by the ABP and HP fluctuations.

The transfer function ABP→dP/dt max represents the arterial baroreflex control of ventricular contractility, the transfer function HP→dP/dt max represents the control of the contractility by the force-frequency autoregulation. The perturbing noise source $N_{dP/dt\ max}$ represents the residual variability in dP/dt max not described by these two mechanisms, including estimation errors, noise or other mechanisms such as the cardiopulmonary baroreflex.

The mathematical representation of the block diagram consists in the following autoregressive exogenous dual-input model:

$$\frac{dP}{dt}\max(n) = \sum_{i=1}^{p} a_i * \frac{dP}{dt}\max(n-i) + \sum_{i=s1}^{q} b_i * ABP(n-i) + \sum_{i=s2}^{r} c_i * HP(n-i) + W_{\frac{dP}{dt}\max}(n) \quad (1)$$

where n is the discrete time, the coefficients a_i, b_i, and c_i are the unknown parameters to be estimated, $W_{dP/dt\ max}$ is the uncorrelated noise input of the model, p, q, and r define the model orders. Granger causality among the cardiovascular time series was verified before computation of the model [32]. The optimal model orders p, q, r were determined by minimizing the minimum description length (MDL) criterion on the overall population and were fixed to be equal to 2, *s1* and *s2*, respectively, where *s1*, *s2* are the input delays. The input delays were optimized at each time point T1, T2, T4 in order to obtain an impulse response and gain value which are in agreement with the physiology for each pig for both the transfer functions, i.e. with the first peak as negative. From our recursive analyses, the optimal set of values is the following: *s1*=3, *s2*=3 at baseline (T1), *s1*=2, *s2*=3 after development of septic shock (T2) and *s1*=6, *s2*=3 after full resuscitation with fluids and vasopressors (T4). Therefore, the model becomes the following at each time point:

$$\mathrm{T1}: \frac{dP}{dt}\max(n) = \sum_{i=1}^{2} a_i * \frac{dP}{dt}\max(n-i) + \sum_{i=3}^{3} b_i * ABP(n-i) + \sum_{i=3}^{3} c_i * HP(n-i) + W_{\frac{dP}{dt}\max}(n) \quad (2)$$

$$\mathrm{T2}: \frac{dP}{dt}\max(n) = \sum_{i=1}^{2} a_i * \frac{dP}{dt}\max(n-i) + \sum_{i=2}^{2} b_i * ABP(n-i) + \sum_{i=3}^{3} c_i * HP(n-i) + W_{\frac{dP}{dt}\max}(n) \quad (3)$$

$$\mathrm{T4}: \frac{dP}{dt}\max(n) = \sum_{i=1}^{2} a_i * \frac{dP}{dt}\max(n-i) + \sum_{i=6}^{6} b_i * ABP(n-i) + \sum_{i=3}^{3} c_i * HP(n-i) + W_{\frac{dP}{dt}\max}(n) \quad (4)$$

Once the model orders were fixed, the parameters a_i, b_i, and c_i were estimated from the stationary zero-mean fluctuations time series of ABP, HP and dP/dt max by using the standard least-square minimization procedure.

Fig. 2 shows an example of the impulse response of the baroreflex transfer function with a physiological shape: a fast negative peak followed by a smaller subsequent overshoot. The negative early phase is consistent with the autonomic-mediated baroreflex dynamics, representing the rapid decrease in ventricular contractility that follows an increase in ABP. The area of the impulse response is expected to be negative according to this physiological interpretation, which means a negative static gain value of the baroreflex transfer function. Thus, dP/dt max would decrease (increase) in the steady state in response to a step increase (decrease) in mean ABP, as a result of the arterial baroreflex, in case of a stable HP.

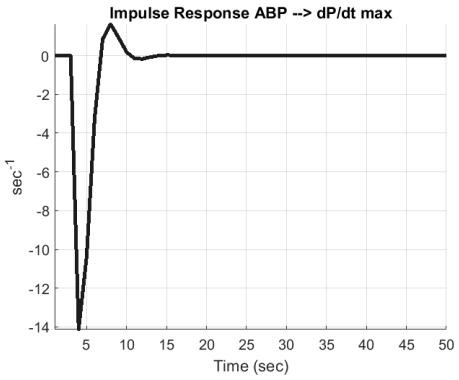

Fig. 2. Impulse response of the baroreflex transfer function ABP→dP/dt max at baseline.

The dynamic of the force-frequency transfer function is similar: the impulse response shows a fast negative peak followed by a smaller subsequent overshoot. The static gain is expected to be negative, such as dP/dt max would decrease (increase) in the steady state in response to a step increase (decrease) in HP, due to the force-frequency autoregulation supposing any change in the mean ABP.

The model was assumed to be linear, thus a complete characterization of the dynamics of the arterial baroreflex and the force-frequency relation mechanisms were obtained from their respective impulse responses. In particular, we computed the following parameters for each transfer function:

- Rise time (t_{rise}), the time it takes for the step response to rise from 10% to 90% of the steady-state response.
- Settling time (t_{set}), the time it takes for the error $|y(t) - y_{final}|$ between the step response y(t) and the steady-state response y_{final} to fall within 2% of y_{final}.
- Peak time (t_{peak}), the time at which the peak of the step response occurs.
- Static gain (G), final value of the step response y_{final}, i.e. the area of the impulse response.

D. Cardiac baroreflex sensitivity analysis

The cardiac baroreflex, i.e. the ANS control of oscillations in the RR-intervals or HP induced by oscillations in SAP, was estimated via the bivariate model method. Details of the method can be found in [33]. The parameter of interest is the feedback gain, which quantify the cardiac BRS. Granger causality from SAP to HP was verified before computation of the gain [32]. The order of the model was optimized based on the Akaike Information Criterion, ranging from 5 to 15.

E. Heart rate variability and complexity analysis

We assessed HRV by means of linear and non-linear methods [34]. In particular, we computed the root mean square of successive differences between adjacent HP (RMSSD), the standard deviation of successive differences between adjacent HP (SDSD), and the standard deviation of the overall HP time series (SD). Moreover, we calculated the quadratic sample entropy (QSE), in order to investigate the non-linear characteristics of HRV as described in [35], and for this purpose the template length *m* was fixed at 1 and the tolerance *r* was computed as 20% of the standard deviation of the time series.

F. Clinical data

Clinical variables collected at each time point were the following: CO (L min^{-1}), stroke volume SV (mL), temperature T (°C), urine output UO (mL), arterial pH, lactate (mmol L^{-1}), mixed venous oxygen saturation SvO2 (%), base excess BE (mEq L^{-1}), cardiac troponin cTnT (ng/mL), hematocrit Ht (%).

G. Statistical analysis

Friedman test was performed to detect differences in time points across multiple test attempts. In case of significant Friedman test p-value, i.e. < 0.05, we used then the Wilcoxon signed-rank test to assess significant changes among time points within the septic shock group of animals. Significance was considered with a p-value < 0.05. The rise time, settling time and peak time were compared between the two transfer functions ABP→dP/dt max and HP→dP/dt max by means of Mann-Whitney U test.

Parameters values are reported as median (25th, 75th percentile).

III. RESULTS

Fig. 3 shows the median values (25^{th},75^{th} percentile) of MAP, HP and dP/dt max time series at each time point of the experiment. Table I provides the median values (25^{th},75^{th} percentile) of the clinical, laboratory and hemodynamic variables.

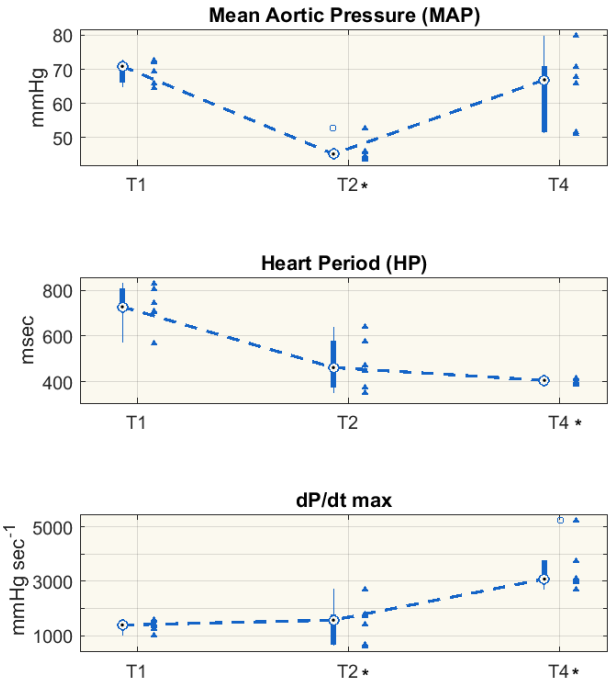

Fig. 3. Distributions (median, 25^{th},75^{th} percentile) of the values at each time point of the following variables: mean aortic pressure (MAP), heart period (HP) and maximum of positive time derivative of left ventricular pressure (dP/dt max). The values relating each pig are marked by blue triangles. T1 = baseline, T2 = after development of septic shock, T4 = after resuscitation with fluids and vasopressors. Wilcoxon signed test: *p-value<0.05 with respect to T1 (Friedman test p-value<0.05).

Septic shock induced a drop in MAP, CO and SV with a compensatory increase in HR (i.e. a fall in HP) and ventricular contractility, as expected. The rise in lactate values at T2 together with the decrease in BE, pH and SvO2 denotes the typical anaerobic cellular metabolism of shock condition. Interestingly, at T4, after the resuscitation with fluids and vasopressors, even if MAP returned to values similar to baseline (except for one pig) all the other clinical variables highlight that the physiological condition of baseline was not completely restored, in particular, HR and dP/dt max further increased with respect to the previous shock condition (Fig. 3).

Cardiac BRS feedback gain [mmHg ms^{-1}] showed a monotonic decreasing trend from T1 to T4: at T1 BRS was 2.4

(1.7,5.3), at T2 decreased to 0.6 (0.3,3.3) and at T4 reached values equal to 0.3 (0.2,0.4).

TABLE I
CLINICAL AND LABORATORY DATA AT EACH TIME POINT OF THE EXPERIMENT. VALUES ARE REPORTED AS MEDIAN (25TH,75TH) PERCENTILE

	T1	T2	T4
HR	82.5 (74.3,84.8)	129.9 (105.6,159.7)	147.6 (144,150.6) *
SAP	84.8 (79.3,86.6)	64.8 (61.2,69.2)	92.7 (91.8,99.5) §§
DAP	54.7 (51.1,57.5)	33.5 (31.3,35.5) *	43.7 (30.8,44.8)
PAP	20 (16,21)	21 (19,29)	26 (23,33) *
RAP	6.5 (5,8)	6 (4.8,6.5)	8 (6,10)
CO	4.9 (4.3,5.4)	3 (2.5,4.3)	9.4 (8,9.9) §
Lact	0.9 (0.9,0.9)	1.7 (1.3,2.1)	2.45 (1.9,3.1) **
SV	65 (57,66)	23 (20.3,36.5)	64.5 (56,69) §
Ht	27 (25,28.4)	33.5 (28,37)	25.6 (24,30)
BE	8.9 (8.4,11)	5.9 (5.2,5.9) *	5.7 (4.6,7) *
pH	7.48 (7.47,7.49)	7.42 (7.41,7.45)	7.44 (7.41,7.45)
UO	1 (0.53,1.1)	0.1 (0.06,0.45)	0.22 (0.2,0.24)
SvO_2	65 (61,69)	59.5 (53,68)	75 (68,78)
T	38.9 (38.8,39.1)	38.4 (37.7,39.2)	38.8 (38.2,39.1)
cTnT	11 (8,15)	21 (17,25)	35 (26,48) **

HR=heart rate [bpm], SAP=systolic aortic pressure [mmHg], DAP=diastolic aortic pressure [mmHg], PAP=pulmonary arterial pressure [mmHg], RAP=right atrial pressure [mmHg], CO=cardiac output [L min^{-1}], Lact=lactate [mmol L^{-1}], SV=stroke volume [mL], Ht=hematocrit [%], BE=base excess [mol L^{-1}], UO=urine output [L], SvO2=mixed venous oxygen saturation [%], T=temperature [C°], cTnT=cardiac troponin [ng L-1]. T1 = baseline, T2 = after development of septic shock, T4 = after resuscitation with fluids and vasopressors. Wilcoxon signed test: *p<0.05, **p<0.01 with respect to T1, §p-value<0.05, §§p-value<0.01 with respect to T2 (Friedman test p-value<0.05).

TABLE II
HRV AND HR COMPLEXITY INDICES EVALUATED AT EACH TIME POINT. VALUES ARE REPORTED AS MEDIAN (25TH,75TH) PERCENTILE

	T1	T2	T4
RMSSD	66 (55.1,91.4)	37.2 (11.5,93.6)	18.6 (12.6,20.3)
SDSD	3.5 (2.9,4.8)	2 (0.6,4.9)	1 (0.7,1.1)
SD	6.9 (4.6,8.4)	3.4 (1.4,5.4)	1.4 (0.8,1.8)
QSE	1.8 (1.7,2.2)	1.3 (0.4,2.1)	0.8 (0.4,0.9)

RMSSD=root mean square of successive difference [ms], SDSD=standard deviation of successive difference [ms], SD=standard deviation [ms], QSE=quadratic sample entropy
T1=baseline, T2=after development of septic shock, T4=after resuscitation with fluids and vasopressors.

Table II shows the HRV indices. HRV was reduced at T2 and tended to further decrease at T4 (even if not significantly).

Fig. 4 and 5 illustrate the average distribution of the impulse and step responses, respectively.

Table III reports the static and dynamic indices which characterize the two transfer functions ABP→dP/dt max and HP→dP/dt max. The gains of both the transfer functions are negative in agreement with the physiology. We observed an increasing trend in static gains of both the transfer functions from T1 to T4 and a delayed response in the contractility control mechanism mediated by baroreflex (ABP→dP/dt max) at T4, after resuscitation. This suggests that after resuscitation the autonomic-mediated baroreflex mechanism is slower in modulating ventricular contractility in response to a change in BP. A delayed response hints a depressed vagal activity during the resuscitation and this is in line with the results obtained from HRV and BRS analyses previously reported.

TABLE III
STATIC AND DYNAMIC CHARACTERISTICS OF ABP→DP/DT MAX AND HP→DP/DT MAX TRANSFER FUNCTIONS. VALUES ARE REPORTED AS MEDIAN (25TH,75TH) PERCENTILE

		T1	T2	T4
t_{rise}	ABP→dP/dt	0.69 (0.65,0.75)	0.77 (0.64,0.95)	0.6 (0.49,0.67)
	HP→dP/dt	0.65 (0.65,0.67)	0.77 (0.62,0.95)	0.6 (0.48,0.75)
t_{set}	ABP→dP/dt	5.9 (5,6.3)	5.8 (5.4,6.2)	6.2 (5.3,7.7)
	HP→dP/dt	5.9 (5.1,6.3)	6.4 (5.9,7.2)	4.3 (3.8,5)
t_{peak}	ABP→dP/dt	2.5 (2.5,2.6)	2.2 (2,2.5)	3.8 (3.7,3.9) §
	HP→dP/dt	2.5 (2.5,2.5)	2.7 (2.5,3) #	2.3 (2.2,2.5) ##
G	ABP→dP/dt	-5.8 (-7.5,-3)	-13.8 (-16.5,-12)	-21.9 (-30.5,-6)
	HP→dP/dt	-1.2 (-1.9,-0.5)	-13.2 (-43.8,-0.7)	-13.7 (-22.9,-7.8)

t_{rise}=rise time [s], t_{set}=settling time [s], t_{peak}=peak time [s], G=static gain [s^{-1} or mmHg/s ms^{-1}]. T1=baseline, T2=after development of septic shock, T4=after resuscitation with fluids and vasopressors.
Wilcoxon signed test: §p-value<0.05 with respect to T2 (Friedman test p-value<0.05). Mann-Whitney U test: #p-value<0.05, ##p-value<0.01 between ABP→dP/dt max and HP→dP/dt max transfer functions.

IV. DISCUSSION

To the best of our knowledge, this is the first study that examines the static and dynamic control of ventricular contractility by the arterial baroreflex and force-frequency relation during a controlled experiment of septic shock and resuscitation. By means of a mathematical analysis of spontaneous beat-to-beat variability of the hemodynamic variables, we were able to separately characterize the contribution of the two mechanisms controlling ventricular contractility.

The main findings of this study consist in i) the feasibility of the proposed model; ii) the alteration of left ventricular contractility control mechanisms during shock which persists after resuscitation; iii) the emerging evidence that heart contractility should be considered a new therapeutic target for sepsis resuscitation.

The mechanisms under investigation significantly and independently control contractility with times of response in the order of seconds. Our results showed that the autonomic baroreflex mechanism was predominant at baseline (gain value of ABP→dP/dt max transfer function is higher than the gain of HP→dP/dt max transfer function, Table III). Indeed, as Fig. 4 shows, the impulse response of force-frequency mechanism is pretty negligible. After septic shock has fully developed (T2), both the mechanisms appeared amplified: both gain values were higher, in particular, the force-frequency related gain value increased to become comparable to the baroreflex related one. Interestingly, after resuscitation

(T4) the physiological control of contractility was not restored and both the mechanisms maintained a gain value similar to shock condition or even increased.

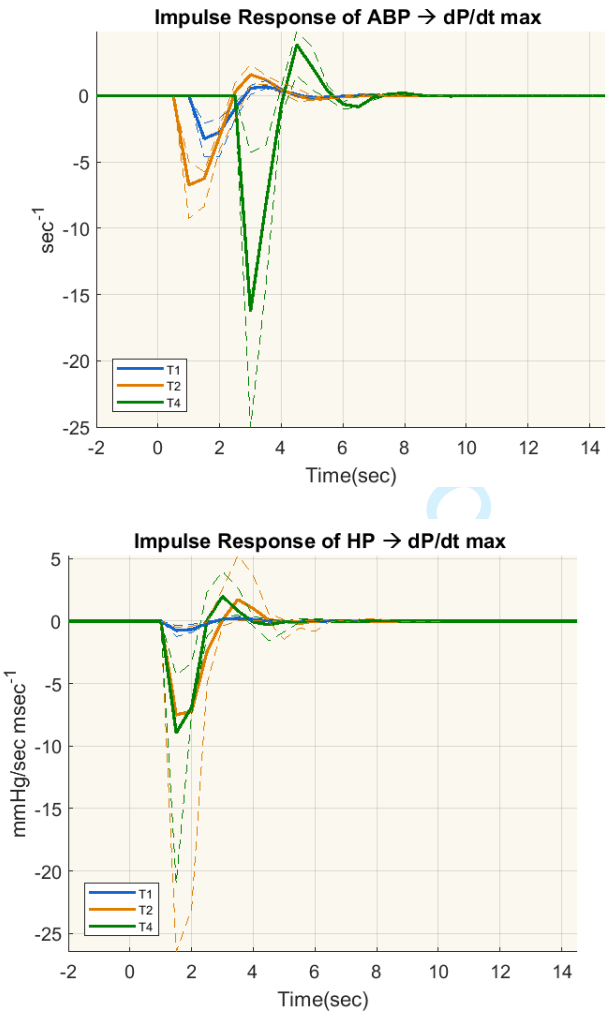

Fig. 4. Median values (25th,75th percentile) of ABP→dP/dt max and HP→dP/dt max impulse responses computed at each time point of the experiment. T1 = baseline, T2 = after development of septic shock, T4 = after resuscitation with fluids and vasopressors.

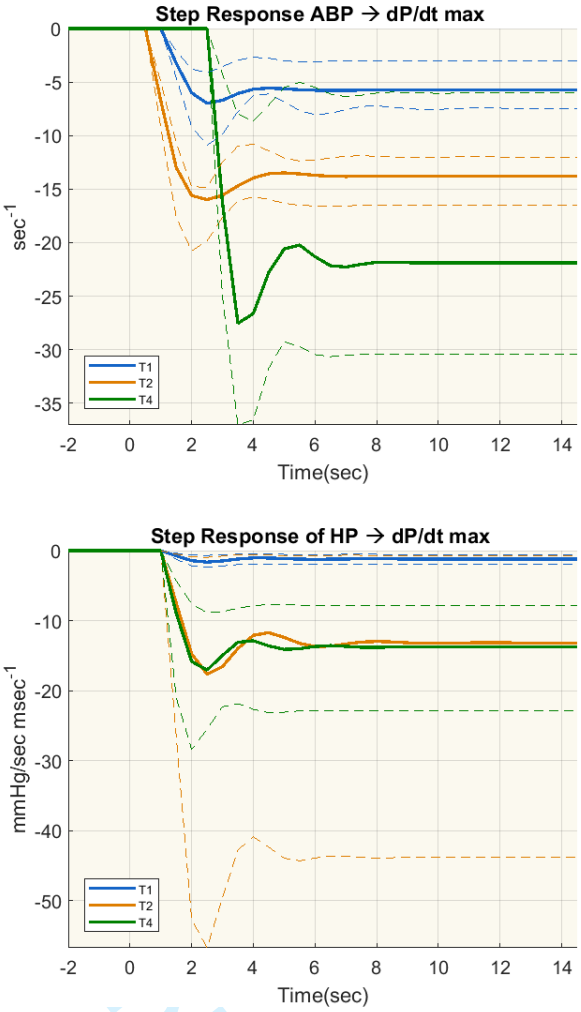

Fig. 5. Median values (25th,75th percentile) of ABP→dP/dt max and HP→dP/dt max step responses computed at each time point of the experiment. T1 = baseline, T2 = after development of septic shock, T4 = after resuscitation with fluids and vasopressors.

These results, together with the clinical and laboratory variables, the HRV and the cardiac BRS analysis, highlighted that after resuscitation, i.e. after restoration of circulating volume and blood pressure, the ANS control is still altered and this affects the heart and its functionality. An inefficient heart is prone to long term consequences such as cardiomyopathy or heart failure, which are very common in septic patients.

A. Hemodynamic changes during septic shock (T2)

Septic shock induced a severe hypotension and hypoperfusion as documented by the clinical and laboratory variables reported in Table I. Moreover, an extensive hypovolemia occurred due to massive capillary leakage: the hematocrit increased, due to the higher density of the circulating blood, and CO was dramatically reduced due to low SV. Compensatory mechanisms, like tachycardia, were activated to maintain CO despite a fall in preload.

Urine output decreased near to 0 mL, showing a certain degree of kidneys failure. It is interesting to observe that although HR rose more than 50% from baseline, only a slight increase occurred in ventricular contractility (dP/dt max, Fig. 3). We hypothesized that this could be influenced by reduction in the end diastolic volume. Indeed, it is known that the index dP/dt max decreases per se, if the end diastolic volume decreases, as it is the case in shock condition.

The hemodynamics findings, such as the HRV and HR complexity analysis and the study of the cardiac BRS, suggest a shock-induced autonomic dysfunction by “uncoupling” the continuous physiological communication among vital organs through ANS signaling. In this context, the notion of complexity, as calculated by means of entropy estimates, refers to the regularity/irregularity of the time series, i.e. the degree to which template patterns repeat themselves: repeated

patterns imply regularity and lead to reduced values of entropy. A loss of HR complexity, which means a higher regularity of the HR, is considered a feature of impaired adaptation of the ANS to physiological stress in several cardiovascular pathologies [36]–[38]. Accordingly, our results show that the autonomic modulation of HR in response to acute stress induced by septic shock was severely impaired (Table II), in agreement with literature [21], [26]. Moreover, the cardiac baroreflex is severely depressed during shock; thus, variations in blood pressure were not followed by a physiological adaptation of the HR in order to maintain homeostasis. Our hypothesis, as already proposed in [39], is that the elevated HR prevents any change in HRV and, thus, any adaptation to BP variability.

The ventricular contractility model proposed in this work revealed that both mechanisms, i.e. the baroreflex and the force-frequency autoregulation, increased their extent during shock condition. These results indicate that the combine effect of these mechanisms can significantly increase the level of contractility and thereby importantly aid in maintaining homeostasis during critical conditions such as septic shock. Although a notable rise in the gains was found, minor changes were reported in the dynamic characteristics of the transfer functions (Table III). Only a slight delay in the peak time was observed in the step response of the force-frequency autoregulation related mechanism, and, oppositely, a slight acceleration in the peak time in the step response of the baroreflex mechanism (Table III).

B. Hemodynamic changes after resuscitation (T4)

Clinical guidelines recommend resuscitation with intravascular fluid administration to counteract hypotension and tachycardia [3], [4]. However, as already reported in the literature, septic patients often have a persistent tachycardia even after excluding hypovolemia [7], [15]–[17]. In this study, the animals showed a persistently elevated HR and contractility at T4, confirming what already observed in other septic populations. The reason for this phenomenon has been hypothesized to be an altered chronotropic response, probably related to an impairment of the SNS with disturbances in ANS signaling. Our data fully support this hypothesis. HRV and baroreflex functionality were still suppressed after resuscitation, indicating an ongoing dysfunctionality in autonomic control of BP and HR.

HRV is assumed to be mostly dependent on the parasympathetic outflow to the heart. Moreover, the recovery of baroreflex functionality has also been associated to an increased vagal activity in several pathologies [24], therefore, we could hint a vagal driver of an effective resuscitation [26]. An extensive literature is even pointing at the central role of the vagus nerve as therapeutic target: direct vagus nerve stimulation has been proved to be beneficial in several diseases, including sepsis and shock [40]–[45].

As regard the contractility model, the results suggest that the contractility was maintained elevated by both the baroreflex and the force-frequency relation, as the gain values of the related transfer functions were still similar to shock condition. Moreover, the dynamic characteristics showed a delayed response of the baroreflex mechanism at T4. The peak time increased whereas the one related to the force-frequency meachnism decreased, so to be significantly different (Table III). This suggests that after resuscitation the autonomic-mediated baroreflex mechanism is slower in modulating ventricular contractility in response to a change in BP. A delayed response hints a depressed vagal activity during the resuscitation and this is in line with the results obtained from HRV and BRS analyses previously reported. The persistent increase of the gain related to the force-frequency relation after resuscitation could be also attributed to the overwhelming sympathoexcitation. In fact, it has been demonstrated that this mechanism is influenced by adrenergic stimulation and, in particular, the excitation of beta adrenergic receptors has been shown to produce an important enhancement of the force-frequency influence on myocardial contractility [46].

Finally, also the clinical variables support the hypothesis of a stress condition unresolved by the resuscitation. Lactate, BE and urine output did not recover to baseline values, hinting a persistent alteration in either tissue perfusion and kidneys functionality even after resuscitation. Interestingly, the SV returned to physiological values (~60 mL) comparable to the baseline ones, but HR and CO were almost doubled (Table I). We can hypothesize that this result indicates a situation of ventricular-arterial uncoupling [47], i.e. a condition where the left ventricle is not able to provide an adequate SV with the lowest possible energetic consumption. Cardiac troponin raised further at T4, suggesting an ongoing cardiomyocytes stress and supporting the idea of a condition deserving clinical attention.

C. Ventricular contractility indexes

We employed dP/dt max as an index of ventricular contractility because it is relatively independent from afterload compared to other indices which are, on the contrary, influenced by cardiac loading [48], [49]. However, the preload level can influence the value of dP/dt max, as it is known that the lower is the end diastolic volume (EDV) the lower will be the value of dP/dt max, and vice versa [48]. For this reason, we verified that the large increase in dP/dt max found at T4 was really due to the altered physiological condition and not artificially generated by the fluid expansion following the resuscitation. Thus, we compared the index with the one normalized with respect to the value of end diastolic volume (EDV), at baseline and after resuscitation. The results showed a significant increase in the preload-adjusted index dP/dt max / EDV from T1 to T4, confirming the validity of our findings: T1, 10.7 (9.2,12.9) mmHg/s mL^{-1}; T4, 28.9 (26,36.4) mmHg/s mL^{-1}. We were not able to perform a similar verification during shock condition since the left ventricle volume (LVV) measure was not available. However, in this case, the effect of a reduction in preload would have had the opposite influence over dP/dt max, leading to a possible underestimation of its

value.

Although the maximal ventricular elastance (E_{max}) is generally recognized as the most specific index of ventricular contractility [50], E_{max} presents several computational limitations mainly due to the recording of the left ventricular volume (LVV), which requires frequent calibrations, e.g. at each time a variation in hematocrit occurs, as its measure depends on impedance properties of blood. The advantage of using dP/dt max instead, lies in its computational ease, since it is derived from LVP only.

D.Model assumptions

We characterized the dynamic ventricular contractility control via the arterial baroreflex and the force-frequency relation through the ABP→dP/dt max and HP→dP/dt max transfer functions, respectively. Thus, we assumed these mechanisms to be linear and time invariant. This hypothesis appeared to be reasonable in the context of this study as the spontaneous hemodynamic fluctuations analyzed were quite small and obtained at rest, similarly to other literature works [50].

Furthermore, the following additional assumptions were made in order to build the dual-input autoregressive exogenous input model as represented by equation (1). First, the transfer functions can be defined by their pole-zero representation, which has been proven to be successful in representing various physiological control systems as reported in [51]. Second, the terms *s1* and *s2* in the model equation were forced to be higher than zero in order to enforce causality, and also higher than one based on the convention used to describe the temporal relationships among the time series: given dP/dt max(n) as the peak of time derivative of the current LVP, HP(n) designated the difference between onset(n+1) and onset(n) on the ABP beat generated by the n^{th} cardiac contraction and MAP(n) was the average ABP value within HP(n). From this assumptions, it derived that MAP(n) cannot influence dP/dt max(n) as the physiological causal relationship has the opposite direction; the same applies also for the relation between HP(n) and dP/dt max(n).

E. Limitations of the study

The main limitation of this study consists in the small sample size, which may be the source of a high variability in the results so to affect the statistical tests. However, we think that the results, which showed evident trends, can still be considered important, even if not statistically significant.

Finally, the unavailability of direct measures of autonomic outflow, such as the cardiac sympathetic nerve activity, did not permit other than a speculation about the autonomic activity at the cardiac level during shock and resuscitation.

V. Conclusion

The proposed analyses gave important insights into the autonomic regulation of ventricular contractility and HR during a protocol of septic shock and resuscitation. Besides clinical variables and standard hemodynamic indices as BRS and HRV, an advanced parametrical model has been proposed to study the static and dynamic properties of two main mechanisms of ventricular contractility control: the autonomic-mediated arterial baroreflex and the force-frequency autoregulation mechanism.

The results highlighted a condition of cardiovascular inefficiency triggered by septic shock which was not resolved after resuscitation. ANS plays a key role to restore the lost homeostasis, and, when its functionality is not successfully recovered, the resuscitation is not effective, as already reported in other recent researches of our group [39], [52]. Moreover, this work is in line with previous studies which observed a persistently elevated cardiac frequency and contractility after resuscitation in septic patients, and explained this phenomenon with an impairment of the ANS [14]. Our results further suggested that this persistent sympathoexcitation could be related to a dysfunction of both the arterial baroreflex and the force-frequency mechanisms.

In conclusion, the proposed models could be valuable tools in assessing the autonomic control mechanisms during shock and resuscitation, and they could be useful to evaluate the effectiveness of treatments, combined with standard clinical measures. In addition, our results support the emerging evidence that heart contractility should be considered a new therapeutic target for sepsis resuscitation.

As final remark, innovative technologies in the field of bioelectronic medicine are growing and they are advocated as the future medicine for the vast majority of diseases. These techniques are based on the direct stimulation of the ANS, in particular of the vagus nerve and clinical trials are ongoing [42]. Our model could be used to evaluate the efficacy of such treatment on LV contractility and relating control mechanisms.

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