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Reducing tachycardia in septic shock patients: do esmolol and ivabradine have a chronotropic effect only?

Marta Carrara, Arianna Niccolò, Antoine Herpain, Manuela Ferrario, *Member, IEEE*

***Abstract*— An elevated heart rate (HR) often persists in resuscitated septic shock patients, increasing the risk of mortality. Several drugs for HR control, such as esmolol and ivabradine, have been tested in the recent years, but their benefit on the overall cardiovascular system is still under investigation. The aim of this study is to investigate the hemodynamic effects of the two drugs in a protocol of polymicrobial septic shock and resuscitation, mainly focusing on the vascular function. Twelve pigs were divided into three experimental groups: the esmolol-treated group (n=4), the ivabradine-treated group (n=5) and the control group (n=3). The characteristic arterial time constant τ was computed on aortic arterial pressure (AoP), together with estimates of total arterial compliance and peripheral resistance. Power spectral analysis of aortic and radial diastolic BP oscillations was performed to estimate the sympathetic autonomic control of vascular tone. Septic shock induced a severe cardiac and vascular disarray, only partially resolved by resuscitation. The administration of esmolol, but not ivabradine, was beneficial both for cardiac and vascular function, thereby its adjunction to standard therapies could help to improve patient's condition and optimize the resuscitation strategies.**

***Clinical Relevance*—This study shows a potential beneficial effect of esmolol on the arterial tree**

I. Introduction

A persisting elevated heart rate (HR) is often observed in resuscitated septic shock patients, despite fluids and vasopressors, administered according to the current guidelines, has been successful in restoring a condition of adequate circulating volume, pressure and oxygenation. This uncontrolled tachycardia is clinically considered a sign of early septic myocardial depression and it resulted an independent risk factor for increased mortality [1]. The triggering source of this condition could be a protracted and overwhelming adrenergic stress at cardiac level, which exceeds in time and scope the beneficial short-term compensatory effects [2].

Recently, several pharmacological treatments have been tested to lower the persisting high HR, and only esmolol demonstrated so far a potential benefit in one clinical trial on septic shock [3].

Esmolol is a cardioselective β1-adrenoreceptors antagonist, which acts as a sympathetic blocker, thereby lowering the HR and limiting the adverse effects related to the sympathetic overstimulation. Ivabradine specifically inhibits the pacemaker I_f current of the sinoatrial node, thus, it directly acts only on the HR without acting on any adrenergic receptors, and thus on ventricular contractility or vascular tone [4].

Based on the underlying mechanisms of non-compensatory tachycardia, i.e. a high sympathetic stress, β-blockers theoretically are the treatment of choice; however, their negative inotropic action and their hypotensive side effect, preclude the use in many critically patients. For these reasons, ivabradine has recently gained a lot of attention and its beneficial effects have been tested in one limited clinical trial and preclinical researches, although no consistent results have been achieved yet. In particular, no associated beneficial effects were observed in hemodynamics, lactatemia, vascular responsiveness to vasopressors and circulating levels of pro/anti-inflammatory cytokines [5], [6]. On the other side, a some experimental evidence indicates that esmolol could exert systemic anti-inflammatory and beneficial effects on vascular tone, even if administered at low doses, avoiding the hypotensive side effect [7].

The aim of this study is to investigate the hemodynamic effects of the two drugs at the vascular level in a protocol of porcine polymicrobial septic shock and resuscitation, in the attempt to investigate possible hemodynamic indices and markers of vascular function.

II. Material and Methods

A. Experimental protocol

We performed a controlled experimental study in the Experimental Laboratory of Intensive Care (LA1230336), at the Université Libre de Bruxelles. The local animal ethics committee approved the present study.

Twelve pigs of both sex (39-52 Kg) were instrumented, and successively allowed to rest for ~2 hours, after which the first baseline measurements and blood samples were taken (baseline, T1). Sepsis was induced by the intraperitoneal instillation of autologous feces (similarly to the protocol described in [8]). During septic shock onset, fluid maintenance was limited until the animal reached a severe condition of hypotension (mean arterial pressure (MAP) goal of 45-50 mmHg for one hour). The end of this period was used as reference for septic shock condition (T2). Immediately after a full fluid resuscitation was initiated with both crystalloid and colloid perfusions, to reach an arterial pulse pressure variation <12% (which was kept for the entire experiment duration). After 120 min of hemodynamic stabilization, defined by a

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stable MAP and no further increase in cardiac output (CO), additional hemodynamic measurements and blood samples were taken (time point T3). The animals were then subdivided into three experimental groups: the ivabradine-treated group (n=5), the esmolol-treated group (n=4) and the control group (n=3). The two treated groups received the drug, i.e. esmolol or ivabradine, at incremental doses until reaching the target of HR 80-90 bpm for one hour, which was defined as time point T4. 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 (time point T5). Animal were then euthanized with a potassium chloride injection and an overdose of thiopental.

B. Signal preprocessing

The arterial pressure was continuously recorded in the ascending aorta (5F pressure catheter, Transonic System Europe, The Netherlands) and in the radial artery (fluid filled catheter, TrueWave®, Edwards, USA). Each pressure signal was then exported to an A/D recording station (Notocord Hem, Notocord, France) with high temporal resolution (250-500Hz).

At each time point, stationary pressure signal segments (~15-min) were selected. The time series of systolic (SAP) and diastolic (DAP) pressures, MAP, pulse pressures (PP=SAP-DAP), and heart period (HP), surrogate of RR-intervals, were extracted using standard algorithms. An adaptive filter was then applied and each time series was resampled at 2Hz (see [8], [9]). These pre-processed time series were then subdivided into 3-min 50% overlapping windows. Each window was detrended using a high-order polynomial function and stationarity was verified (KPSS test). Except for the time constant τ described in the following, the final indices are the average of the ones obtained from each 3-min window. CO (L min^{-1}) and stroke volume SV (mL) were continuously monitored by a pulmonary artery catheter (CCO®, Edwards, USA).

C. The Windkessel time constant τ

According to the 2-element Windkessel model, the time constant τ of the arterial tree can be computed as $\tau = TPR * AC$, were TPR is the total peripheral resistance, and AC is the total arterial compliance. We estimated τ on the aortic arterial pressure (AoP) over long time intervals (6-min 50% overlapping windows) following the method proposed by Mukkamala and colleagues [10]. AC was further independently estimated as AC=SV/PP, and TPR was computed as TPR=MAP/CO, according to the Windkessel model.

D. Spectral analysis

The power spectrum of DAP series was used to quantify the normalized low frequency power (LFu), which represents the relative power in the low frequency (LF, 0.04–0.15 Hz) band and it is computed as the LF power divided by the total power without the very low frequency component (VLF, 0-004Hz). LF oscillations of DAP series are meant to be mainly associated to the sympathetic ANS control of peripheral resistance.

III. RESULTS

Table I reports the values of the clinical and hemodynamic parameters of the three groups of animals. As expected, septic shock (T2) induced a low SV and consequently a low CO, and a condition of severe hypotension; a compensatory tachycardia was also observed in all pigs. The resuscitation with fluids (T3) was partially able to restore a condition of adequate circulating volume (increased CO and SV), MAP around 60 mmHg and oxygenation (SvO2 ≥ 65%). The administered drugs were successful in lowering the HR until the target (80-90 bpm), whereas the control group still exhibited a persistent tachycardia at T4. Interestingly, the noradrenaline administration (T5) induced a further elevation of HR in the control, not completely antagonized in the ivabradine group, whereas the HR of the esmolol group was still maintained lower than 90 bpm thanks to a constant increase in the dosage.

TABLE I. CLINICAL AND HEMODYNAMIC (AORTIC) DATA AT EACH TIME POINT FOR CONTROL, ESMOLOL AND IVABRADINE GROUP

		CTR	ESM	IVB
HR	T1	60.2 (59.9,80.8)	78.3 (71,86.7)	79.7 (70.1,81.8)
	T2	121 (118,122.5)*	132 (124,153.5)**	137 (134,145)°**
	T3	113 (112.8,113.8)	118 (110.1,124.7)	123 (108.7,147)*
	T4	106.6 (103.3,110)	89.9 (85.4,95.4)	91 (86.6,94.1)§
	T5	119 (113.7,139.6)	87.4 (83.8,94.2)°	100.4 (91,105.4)
CO	T1	3.6 (3.5,4.5)	4.5 (3.6,5.4)	4.1 (3.4,4.4)
	T2	3.3 (3.3,.3)$^{n=1}$	3.1 (2.7,3.5)$^{n=2}$	2.2 (2.1,3)
	T3	4.8 (4.6,6.3)	5.6 (5.3,6.8)	4.9 (4.2,7.1)§
	T4	4.4 (4.3,6.2)	4.1 (3.9,5.2)	4.8 (4,5.5)
	T5	6.7 (6.4,8.7)	5.5 (4.9,6)	6.5 (5.7,6.7)§§
SV	T1	56.7 (55,59.7)	59.2 (50.7,62.6)	49.5 (47.9,55.3)
	T2	28 (28,28)$^{n=1}$	23.9 (19.5,28.2)$^{n=2}$	16.5 (15.9,20.1)
	T3	42.5 (40.8,56)	46.6 (44.9,59.3)	40.2 (38.9,45.9)
	T4	42 (39.9,58.2)	47.1 (44.6,55.1)	52.9 (47,59.7)§
	T5	56.4 (56.1,62.1)	60.9 (55.3,67)	64.4 (56.9,66.7)§§
MAP	T1	63.4 (62.5,72.8)	74.6 (67.9,80)	77.1 (67.1,83.5)
	T2	44.7 (43.9,45.9)	44.8 (35.8,52.6)*	47.3 (46.3,51)**
	T3	62.3 (62.2,65.9)	65.1 (54.6,68.6)	58.4 (55.9,64.3)
	T4	58 (57.8,60.7)	56.4 (48,60.3)	54.5 (50.5,56.7)*
	T5	61.7 (60,73.2)	61 (53.3,67.4)	61.9 (53.9,70.2)
DAP	T1	52.2 (47.9,59.5)	59.5 (52.3,65.1)	58.9 (52,68)
	T2	35.4 (33.7,35.8)	31.6 (22.9,39)**	36.5 (34.9,37.9)*
	T3	48.7 (48.1,50.2)	46.3 (35,52.9)	43.6 (39.5,44.6)
	T4	45.5 (44.6,45.9)	39.3 (32.4,45.2)	38.1 (31.6,38.8)*
	T5	42.7 (40,52.3)	41.6 (34.2,47.5)	36.8 (30.8,44.4)
SAP	T1	78.7 (76.6,86.6)	90.1 (82.1,94.2)	94.3 (78.6,98.7)
	T2	61.6 (60.4,64.8)	63.2 (55.4,72.2)	68.7 (62.1,73.9)
	T3	82.4 (72.8,86.2)	88.3 (78.6,90.3)	83.2 (77,90.6)
	T4	78.2(75.1,81.3)	79 (71.4,83.8)	84.8 (76.1,88.5)
	T5	90.2 (89.4,99.1)	88.4 (80.4,95)§	113 (106,115)§§
PP	T1	27.4 (26.7,28.9)	29.7 (28.4,30.6)	30.3 (27.7,35.1)
	T2	28.4 (25.1,30)	32.6 (31.6,34.1)	34.8 (26.5,36)
	T3	34.6 (31.8,36.2)	39.2 (37.2,43.8)	42.1 (36.2,47.7)
	T4	33.9 (29.8,35.7)	37.9 (36,41.5)	46.6 (44.4,51.3)°
	T5	46.6 (46.5,49.9)*	46.8 (46.2,47.4)*	72.8 (69,76.2)#*§§
SvO_2	T1	64 (55.8,72.3)	62.5 (57,65.5)	63 (61,64)
	T2	NaN	NaN	NaN
	T3	74 (68,77)	70 (65,73)	64 (63.3,64.8)$^{n=3}$
	T4	70 (64.8,73)	56 (52,59.5)	65 (58.5,66)
	T5	73 (72.3,74.5)	62 (58.5,66)°	70 (65.5,71.5)$^{n=4}$
Lac	T1	0.9 (0.9,0.9)	1 (0.9,1.4)	0.9 (0.9,0.9)
	T2	NaN	NaN	NaN
	T3	0.9 (0.9,1.13)	1.1 (0.9,1.45)	1.2 (0.98,1.65)$^{n=3}$
	T4	1.1 (0.95,1.25)	1.3 (1,1.6)	1.35 (0.9,2.25)$^{n=4}$
	T5	1.8 (1.35,2.03)	1.85 (1.2,2.5)	1.9 (1.45,2.95)$^{n=3}$

HR=heart rate [bpm], CO=cardiac output [L/min], SV=stroke volume [mL], MAP=aortic mean arterial pressure [mmHg], DAP=diastolic aortic pressure [mmHg], SAP=systolic aortic pressure [mmHg], PP=aortic pulse pressure [mmHg], SvO2=mixed venous oxygen saturation [%], Lac=lactate [mmol/L]. 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). Mann-Whitney U test: °p<0.05 with respect to CTR, #p<0.05 with respect to ESM at the specified time point.

We may speculate that the sympatho-inhibitory effect of esmolol partly prevented the direct adrenergic stimulation of

β1 receptors by noradrenaline. Of note, an increase of aortic PP was induced by shock in all the animals, and it was further exacerbated by resuscitation; in particular, the ivabradine group presented a significantly larger increase of PP with respect to the other two groups, following the administration of the drug (time points T4 and T5) and a greater compensation by an increase in SV than in the esmolol group.

Fig 1 shows the relationship between aortic and radial PP, highlighting a phenomenon of peripheral vascular decoupling induced by septic shock, i.e. an inversion of the physiological PP amplification from central to peripheral vessels. Although all the three groups showed an increased aortic PP after therapy compared to baseline, only the esmolol-treated group was found to have a resolution of the vascular decoupling at T5, with a radial PP higher than the aortic PP. On the contrary, the ivabradine-treated group still exhibited a non-physiological relationship between the two PP values, similar to shock condition (T2).

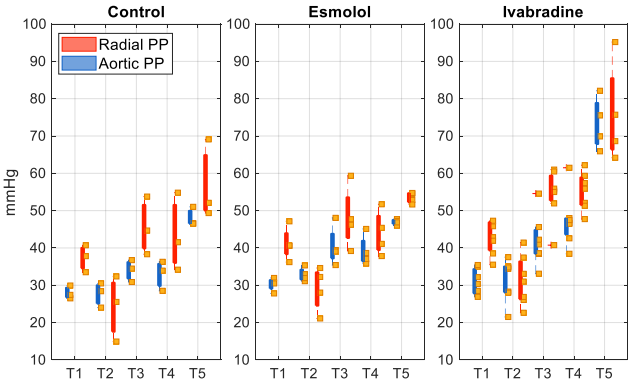

Figure 1. Peripheral vascular decoupling

Table II presents the values of AC, TPR and the characteristic time constant τ computed from aortic BP. Septic shock is known to induce an increase of arterial stiffness [11], mainly aortic, and we observed a significant decrease of AC in all the animals. After fluids and drugs administration (T3 and T4) AC was partially recovered, although still lower than baseline. It is noteworthy to notice that only the ivabradine-treated animals presented a further decrease of AC at T5, which was significantly lower than the esmolol-treated group.

TABLE II. EMODYNAMIC AND CLINICAL DATA, TOTAL ARTERIAL COMPLIANCE AND RESISTANCE AT EACH TIME POINT

		CTR	ESM	IVB
AC	T1	2.1 (1.96,2.2)	2 (1.8,2)	1.6 (1.5,1.9)
	T2	1 (1,1)$^{n=1}$	0.7 (0.6,0.9)$^{n=2}$	0.6 (0.4,0.6)**
	T3	1.3 (1.2,1.6)	1.2 (1.2,1.4)*	1 (0.9,1.1)
	T4	1.5 (1.2,1.8)	1.3 (1.2,1.3)	1.1 (0.9,1.2)
	T5	1.2 (1.1,1.3)	1.3 (1.2,1.4)	0.8 (0.8,1)#
TPR	T1	1453 (1161,1620)	1247 (1100,1656)	1614 (1411,1694)
	T2	1061 (1061,1061)$^{n=1}$	1169 (759,1579)$^{n=2}$	1763 (1548,1895)
	T3	1101 (821,1106)	828 (652,1014)*	944 (720,1163)§
	T4	1081 (780,1119)	1000 (770,1200)	950 (818,1097)
	T5	714 (671,765)*	842 (710,1118)	781 (717,932)*§
Tau	T1	1.4 (1.3,1.8)	1.2 (1.1,1.3)	1.2 (1.17,1.4)
	T2	0.73 (0.72,0.8)	0.4 (0.36,0.5)°**	0.6 (0.5,0.7)
	T3	0.7 (0.66,0.8)	0.5 (0.4,0.7)	0.4 (0.3,0.6)
	T4	0.7 (0.66,0.9)	0.7 (0.5,0.9)	0.5 (0.3,0.6)
	T5	0.5 (0.4,0.5)*	0.6 (0.5,0.7)	0.3 (0.3,0.4)#**

AC=total arterial compliance [mL/mmHg], TPR=total peripheral resistance [dyn*s/cm^5]. 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). Mann-Whitney U test: °p<0.05 with respect to CTR, #p<0.05 with respect to ESM at the specified time point.

The TPR values showed a decreasing trend from T1 to the end of the experiment, with a significantly diminished value at T5 compared to baseline, mostly in the ivabradine group. Accordingly, the aortic τ was also decreased by shock and it was not completely restored after resuscitation. The ivabradine-treated animals were characterized by a significantly lower τ with respect to the esmolol-treated pigs at T5.

The values of LFu of aortic and radial DAP oscillations are presented in Fig 2 for ivabradine- and esmolol-treated groups. A depression of LFu power occurred in both groups in shock, in agreement with the fact that sepsis and shock induce a suppression of the physiological sympathetic modulation of the peripheral vascular tone. This condition was only partly recovered after therapy, and in particular, only the esmolol group showed a clear increase of LFu after noradrenaline administration (T5), mostly appreciable in the radial DAP LFu.

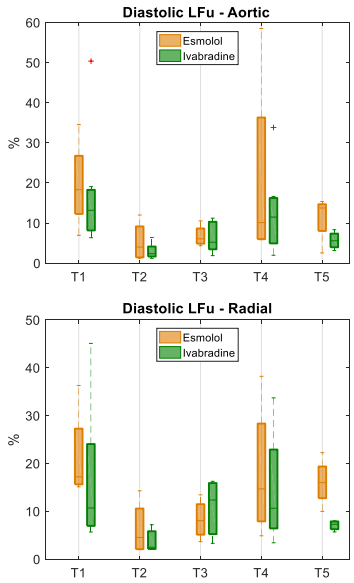

Figure 2. Normalized low frequency (LFu) power of aortic and radial diastolic BP oscillations for ivabradine- and esmolol-treated animals

IV. Discussion and Conclusions

In this study we investigated the hemodynamic effects of esmolol and ivabradine, two cardioselective drugs allowing theoretically to control tachycardia in resuscitated septic shock patients in intensive care. Despite the main effect addresses the HR, other physiological systems, such as the circulation or the inflammatory and immune system, can undergo secondary effects. In particular, β1-adrenoreceptors antagonists like esmolol were found to have an anti-inflammatory action, which could be further beneficial for septic shock subjects.

Our results show that the severe circulatory derangement induced by polymicrobial septic shock was not completely resolved by the resuscitation maneuvers, as the hemodynamic and clinical variables were not returned to values similar to baseline. However, the administration of esmolol was found to be beneficial not only for the HR, but also for the vascular circulation: the esmolol-treated pigs exhibited a controlled HR even after noradrenaline administration (Table I), a partial resolution of vascular decoupling (Fig 1), an improved AC,

TPR and τ (Table II) with respect to the other groups, and a higher value of LF power of DAP oscillations compared to ivabradine-treated pigs (Fig. 2).

Acute inflammation and sepsis are known to impair endothelial functions and to induce a stiffening of large compliant vessels, such as the aorta [12]. Moreover, a positive correlation between sympathetic excitation and increased arterial stiffness has also been reported [13]. Esmolol does not directly interfere with the sympathetic regulation of vascular tone as it doesn't act on β2 adrenergic receptors expressed at the vessels level, so we may speculate that its anti-inflammatory action could be responsible for the improved AC observed in this group. Moreover, the resolution of the vascular decoupling condition could also be secondary to a decreased inflammatory state; in fact, one of the hypothesis for this PP reversal is a different response of central and peripheral vessels to inflammatory vasoactive substances, such as nitric oxide [12]. Finally, it has been recently demonstrated that esmolol enhances ex-vivo vascular reactivity and increases mRNA and protein expression of α1 adrenoreceptors at the vessels level, thus contributing to improved vascular responsiveness to vasopressors [7]. On the contrary, as expected considering its pharmacologic features, ivabradine was shown not to induce any vascular beneficial effect when tested on the same experimental protocol of a rat CLP-induced septic shock model [6]. Accordingly, our results report that the LF power of DAP oscillations was increased after noradrenaline administration only in the esmolol group; since the LF oscillations of DAP are meant to be mainly associated to the sympathetic autonomic control of peripheral resistance [14], we may infer that esmolol and not ivabradine improves the vascular responsiveness to vasopressors.

In conclusion, our results support the idea that the adjunction of esmolol to standard septic shock management could help to relieve inflammation, control the HR, and increase vascular responsiveness, thereby optimizing drugs administration and improving patient's condition. Fig 3 shows the ABP waveform at each phase of the experiment for one pig from all the groups. The waveform of the esmolol-treated pig after full resuscitation (green line, T5) has a shape more similar to baseline than in the other groups, highlighting a cardiovascular improvement induced by the drug.

Further studies with a larger number of subjects in each experimental group and with direct measures of cardiac and vascular function, will permit to validate the results herein presented and their safety regarding the negative inotropic effect of esmolol.

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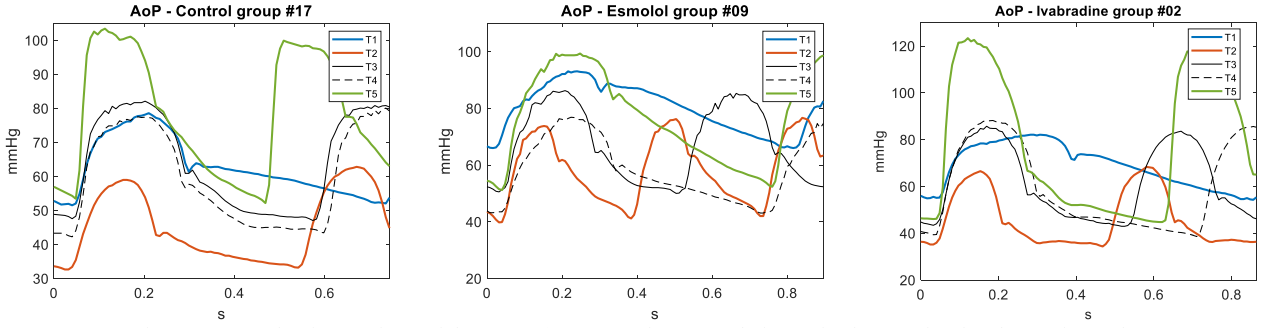

Figure 3. Example of an aortic arterial pressure (AoP) waveform at each time point for one pig of each experimental group