Y. Le Tulzo
P. Seguin
A. Gacouin
C. Camus
E. Suprin
I. Jouannic
R. Thomas

Effects of epinephrine on right ventricular function in patients with severe septic shock and right ventricular failure: a preliminary descriptive study

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Y. Le Tulzo (✉) · P. Seguin · A. Gacouin ·
C. Camus · E. Suprin · I. Jouannic ·
R. Thomas
Service de Réanimation Médicale
et Maladies Infectieuses,
CHRU de Rennes, Hôpital Pontchaillou,
2 rue Henri Le Guilloux,
F-35033 Rennes Cedex 09, France
FAX: +33(2)9928 4164

Abstract *Objective:* To recognize patients with unresponsive septic shock and right ventricular (RV) failure and to evaluate the effects of epinephrine on RV performance in these patients.

Design: Prospective descriptive study.

Setting: Medical intensive care unit.

Subjects: 14 consecutive patients in septic shock unresponsive to fluid loading, dopamine, and dobutamine.

Interventions: Evaluation of RV function by thermodilution with a pulmonary artery catheter equipped with a rapid-response thermistor. Measurements were obtained before and during epinephrine infusion to achieve a systolic arterial pressure ≥ 90 mmHg or a mean ar-

terial pressure (MAP) ≥ 70 mmHg.

Results: At the time of inclusion in the study the hemodynamic pattern in the 14 patients was as follows: (MAP) 58 ± 14 mmHg, systemic vascular resistance (SVR) 1046 ± 437 dyne $\cdot$ s $\cdot$ cm $^{-5}$ $\cdot$ m $^{-2}$, pulmonary artery occlusion pressure (PAOP) 14 ± 4 mmHg, mean pulmonary artery pressure (MPAP) 24 ± 4 mmHg, right arterial pressure (RAP) 11 ± 4 mmHg, cardiac index (CI) 4 ± 1.7 l/min per m 2 . During epinephrine infusion, MAP, CI and stroke volume index (SVI) were increased (27%, $p < 0.01$; 20%, $p < 0.01$; 15%, $p < 0.05$, respectively). There was no change in PAOP, SVR or heart rate. Seven patients (group A) had marked RV failure defined by both RV dilation [RV end-diastolic volume index (RVEDVI) > 92 ml/m 2] and low RV ejection factor (RVEF) ($< 52\%$) and 7 did not (group B). Group A had a lower baseline RVEF than group B (24 ± 7 vs $45 \pm 9\%$, $p < 0.05$), a higher RVEDVI (134 ± 28 vs 79 ± 17 ml/m 2 , $p < 0.01$), and a higher RVES (systolic) VI (103 ± 30 vs 43 ± 11 ml/m 2 , $p < 0.01$). The other hemodynamics, especially RAP and RV stroke work index (RVSWI) were no different in the two groups and did not predict RV dysfunction. In

group A, epinephrine infusion improved RVEF (25%, $p < 0.05$) by a reduction in RVESVI (-8% , $p < 0.05$) without any change in RVEDVI or in RAP, in spite of a rise in MPAP (11%, $p < 0.05$). A rise in RVSWI (76%, $p < 0.05$), SVI (23%, $p < 0.05$), and CI (24%, $p < 0.05$) was also achieved. An upward vertical shift of the Frank-Starling relationship RVSWI/RVEDVI and an upward shift to the left of the pressure volume relationship pulmonary artery peak pressure/RVESVI was observed only in the group with RV failure following treatment with epinephrine. In group B (without RV failure), RV parameters were not modified by epinephrine.

Conclusion: In patients with severe septic shock, RV dysfunction was identified by the use of an RVEF pulmonary artery catheter and was improved by epinephrine by means of an improvement in RV contractility.

Key words Septic shock · Epinephrine · Right ventricular function · Thermodilution method · Right ventricular ejection fraction · Right ventricular dysfunction

Introduction

The main hemodynamic disturbances of septic shock include decreased systemic vascular resistance, hypovolemia, tachycardia, and elevated cardiac output after volume loading, despite left [1] and right [2] ventricular dysfunction. In addition to appropriate antimicrobial therapy and surgery as needed, the treatment of septic shock is based on volume expansion and infusion of catecholamines such as dopamine, dobutamine [3–5], and norepinephrine [6]. Epinephrine administration has been shown to increase arterial pressure, left ventricular stroke work cardiac index, and oxygen transport, without an excessive increase in systemic vascular resistance or worsening of cardiac performance. This improvement with epinephrine therapy was found in patients in whom therapy with dopamine, or dopamine and dobutamine combined, had failed [7–9]. Improvement in these physiologic parameters was also reported when epinephrine was used as a first-line agent [10]. Although right ventricular dysfunction is frequently documented in septic shock [2, 11–17] and could be considered as a prognostic factor [14, 18], few studies have reported therapeutic interventions such as fluid loading [13, 17] or the use of catecholamines [18, 19], and no study has investigated the effects of or the possible advantage of epinephrine on right ventricular dysfunction.

The aim of the present study was to investigate the immediate effects of epinephrine on right ventricular function in patients with septic shock resistant to dopamine and dobutamine. We hypothesized that the use of the right ventricular ejection fraction catheter [20] in these unresponsive patients with septic shock might allow the definition of a relevant subset of patients with right ventricular failure in whom epinephrine could be expected to improve right ventricular performance.

Materials and methods

Patients and entry criteria

All the patients in this study were in septic shock, as defined by: (a) clinical evidence of serious infection; (b) presence of a sepsis syndrome with two of the following criteria: fever or hypothermia (temperature $> 38^{\circ}$ or $< 36.6^{\circ}\text{C}$), heart rate $> 90/\text{min}$, respiratory rate $> 20/\text{min}$ or partial pressure of carbon dioxide in arterial blood < 32 torr, white blood cell count $> 12\,000/\text{mm}^3$ or $< 4\,000/\text{mm}^3$; (c) at least two of the following criteria of persistent septic shock: systolic arterial pressure (SAP) < 90 mmHg, mean arterial pressure (MAP) < 60 mmHg, urine output < 20 ml/h, in spite of volume expansion and dopamine infusion at a minimum rate of $10\text{ }\mu\text{g/kg per min}$.

Briefly, our usual protocol for the treatment of septic shock is to ensure that patients receive adequate antimicrobial therapy and surgery as needed. Supplemental oxygen was administered to maintain an arterial oxygen saturation above 95 % and mechanical ventilation was used when necessary. Hemodynamic parameters

were routinely monitored via a pulmonary artery catheter. After volume expansion to achieve a right atrial pressure (RAP) ≥ 8 mmHg and a pulmonary arterial occlusion pressure (PAOP) between 12 and 15 mmHg, dopamine was started at an initial rate of $5\text{ }\mu\text{g/kg per min}$ and progressively increased. Dobutamine was used if the cardiac index was $< 4\text{ l/min per m}^2$ but was discontinued if SAP decreased by 20 mmHg.

Once the criteria of septic shock resistant to our conventional treatment were met, epinephrine was started according to the judgment of the physician in charge of the patient, especially avoiding patients with a recent history of coronary artery disease or cardiac arrhythmia. Epinephrine was administered via a central venous catheter at an initial infusion rate of $0.1\text{ }\mu\text{g/kg per min}$ and progressively increased in increments of $0.1\text{ }\mu\text{g/kg per min}$ to obtain an SAP ≥ 90 mmHg or an MAP ≥ 70 mmHg. When an adequate rate was established to maintain blood pressure, the epinephrine infusion was kept constant. During the study period, no volume expanders was given, and the infusion rates of dopamine and dobutamine as well as the ventilator setting were not modified (in particular, mechanical ventilation was not started or modified between the measurements). The hemodynamic measurements were performed before and during epinephrine infusion, immediately following stabilization, and within 2 h after epinephrine was started. After the second set of measurements, epinephrine and other vasoactive agents were continued as judged by the physician in charge of the patient, but no further measurements for the study were made.

Patients with moderate or severe tricuspid regurgitation [21], assessed by echo Doppler examination, were not eligible for the study.

Measurement protocol

Cardiac pressures were measured at end-expiration via a pulmonary artery catheter equipped with a rapid-response thermistor (model 93A 431 H 7.5 F, Baxter-Edwards, Santa Ana, Calif., USA). The atrial port was positioned 2 cm proximal to the tricuspid valve by advancing the catheter until a ventricular pressure tracing was obtained and then pulling back 2 cm. The final correct position of the catheter in the pulmonary artery was verified by chest X-ray. A stable heart rate and absence of arrhythmia were verified on continuous electrocardiographic monitoring. Cardiac output and right ventricular ejection fraction (RVEF) values were obtained by thermodilution via a computer (RVEF I computer, Baxter-Edwards) as previously described [20, 22]. Thermodilution curves were plotted to detect artifacts. The cardiac output and ejection fraction were determined using three random 10-ml aliquots of iced 5 % dextrose in water (CO-set system, Baxter-Edwards Critical Care) and the mean values were calculated. Using thermodilution cardiac output and thermodilution curve computerization, the following parameters were calculated: cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR), left and right ventricular stroke work index (LVSWI, RVSWI), right end-diastolic and end-systolic volume index (RVEDVI, RVESVI) [20]. Systemic arterial pressures were measured via an intra-arterial catheter. This study was approved by the Human Ethical Committee of the French Society of Critical Care Medicine.

Interpretation of the results and statistical analysis

Right ventricular failure was defined by both an increase in RVEDVI over 92 ml/m^2 and a decrease in RVEF below 52 % [22].

Table 1 Characteristics of the patients

Patient No.	Sex	Age	SAPS score	Outcome	Diagnosis	Site of culture	Microorganism	Dopamine/dobutamine ($\mu\text{g/kg per min}$)	Epinephrine ($\mu\text{g/kg per min}$)
1	F	60	22	Alive	Pyelonephritis	Blood, urine	<i>Escherichia coli</i>	25/0	0.30
2	M	82	22	Died	Pneumonia	Blood, respiratory tract	<i>E. coli</i>	10/0	0.20
3	F	74	21	Died	Colitis	Blood	<i>E. coli</i>	10/8	0.50
4	M	82	29	Died	Pneumonia	Respiratory tract	<i>Streptococcus pneumoniae</i>	10/5	0.40
5	M	76	27	Alive	Cholecystitis	Blood, bile	<i>Enterobacter agglomerans</i>	20/20	0.50
6	M	62	22	Died	Colitis	Blood	<i>E. coli</i>	10/10	0.50
7	M	52	21	Died	Pneumonia	Respiratory tract	<i>Pseudomonas aeruginosa</i>	15/10	0.50
8	F	80	25	Alive	Cholecystitis	Blood, bile	<i>E. coli</i> , <i>Klebsiella pneumoniae</i>	10/40	0.50
9	M	70	14	Alive	Cellulitis	Blood, subcutaneous tissue	<i>Streptococcus</i> group A	10/0	0.40
10	M	35	22	Alive	Purpura fulminans	None	Not isolated	10/25	0.20
11	M	82	25	Died	Bowel necrosis	None	Not isolated	12/0	0.10
12	M	82	22	Died	Pneumonia	Respiratory tract	<i>S. pneumoniae</i>	20/0	0.50
13	M	71	19	Died	Pneumonia	Blood, respiratory tract	<i>E. coli</i> , <i>Legionella</i> P.	18/12	0.30
14	M	70	22	Died	Not established	Blood	<i>Candida albicans</i>	10/0	1.0

(SAPS Simplified Acute Physiology Score at admission to ICU)

Values before and during epinephrine infusion were reported as mean $\pm$ one standard deviation. The statistical significance of differences between basal data and those obtained during epinephrine infusion was analyzed using the Wilcoxon matched pairs signed rank test. Differences between groups were compared using the Mann-Whitney U test. A *p* value of < 0.05 was considered significant. The relationships between quantitative values were examined by linear regression analysis.

Results

Characteristics of patients

The study, which extended over 23 months, included 14 consecutive patients with a mean age of 70 ± 14 years. The clinical characteristics of the 14 patients are shown in Table 1. The mean Simplified Acute Physiology Score (SAPS) [23] was 22 ± 4 . The duration of shock before the study was 18 ± 30 h. Microbiological documentation was obtained for all patients, except 2 (purpura fulminans, bowel ischemia) who had previously received antimicrobial therapy. Eleven patients were receiving mechanical ventilation at the time of entry into the study. Infusion rates of vasoactive agents are reported in Table 1. In 8 cases dobutamine was added to dopamine.

The dose of epinephrine infused during the study ranged from 0.1 to 1 $\mu\text{g/kg per min}$. A long-lasting reversal of arterial hypotension was achieved in 8 patients (60%), but 3 of them died of multiple organ failure within 30 days following the onset of septic shock. Despite a transitory improvement, 6 other patients died of refractory shock. Thus, the overall mortality related to septic shock was 64%.

Basal hemodynamic characteristics

The hemodynamic patterns before epinephrine infusion are shown in Table 2: arterial pressure and SVR were low. CI was preserved by tachycardia despite a low SVI. LVSWI was low, despite normal left ventricular filling pressure as reflected by a normal PAOP. Global right ventricular characteristics were as follows: RVEF was low with high RVEDVI and RVESVI and RVSWI was low despite almost normal RAP and pulmonary hypertension. Seven patients had marked RV failure defined by both low RVEF ($< 52\%$) and RV dilation ($\text{RVEDVI} > 92 \text{ ml/m}^2$) and are defined as group A. Patients ($n = 7$) without RV failure are designated as group B. Basal characteristics of the two groups are

Table 2 Hemodynamic variables before (control) and during epinephrine infusion in 14 patients in refractory septic shock (mean $\pm$ SD)

Variables	Control	Epinephrine	Significance
RVEF (%)	35 $\pm$ 13	37 $\pm$ 11	NS
RVEDVI (ml/m ²)	107 $\pm$ 36	112 $\pm$ 32	NS
RVESVI (ml/m ²)	73 $\pm$ 38	73 $\pm$ 32	NS
RVSWI (g/m ²)	6.4 $\pm$ 4	9 $\pm$ 4	$p < 0.01$
RAP (mmHg)	11 $\pm$ 4	10 $\pm$ 3	NS
MPAP (mmHg)	24 $\pm$ 4	27 $\pm$ 5	$p < 0.05$
MAP (mmHg)	58 $\pm$ 14	74 $\pm$ 16	$p < 0.05$
PAOP (mmHg)	14 $\pm$ 4	13 $\pm$ 3	NS
SVR (dyne $\cdot$ s $\cdot$ cm ⁻⁵ $\cdot$ m ⁻²)	1046 $\pm$ 437	1150 $\pm$ 437	NS
SVI (ml/m ²)	34 $\pm$ 9	39 $\pm$ 10	$p < 0.05$
LVSWI (g/m ²)	21 $\pm$ 7	35 $\pm$ 13	$p < 0.01$
CI (l/min per m ²)	4 $\pm$ 1.7	4.8 $\pm$ 1.9	$p < 0.01$
HR (beats/min)	117 $\pm$ 24	119 $\pm$ 24	NS

NS: not significant

Table 3. General characteristics of patients in group A (with RV failure) and group B (without RV failure). Values are mean $\pm$ SD or numbers (NS not significant)

Variables	Group A (n = 7)	Group B (n = 7)	Significance
SAPS	21 $\pm$ 4	24 $\pm$ 3	NS
Mortality	5/7	4/7	NS
Previous pulmonary disease	3/7	2/7	NS
Mechanical ventilation	6/7	5/7	NS
Positive end-expiratory pressure $\geq$ 5	1/7	3/7	NS
Use of dobutamine	3/7	5/7	NS
Epinephrine infusion rate (μ g/kg per min)	.4 $\pm$.3	.4 $\pm$.1	NS
RVEF (%)	24 $\pm$ 7	45 $\pm$ 9	$p < 0.05$
RVEDVI (ml/m ²)	134 $\pm$ 28	79 $\pm$ 17	$p < 0.05$

summarized in tables 3 and 4. Patients with RV failure had lower baseline RVEF, higher RVEDVI, and higher RVESVI than those with preserved RV function. In contrast, the two groups were no different with respect to the other hemodynamic or respiratory characteristics, pre-existing pulmonary disease, therapeutic intervention, or mortality (Table 3). We did not observe any relationship between RVEDVI and pulmonary artery pressure in groups A and B.

Hemodynamic parameters during epinephrine infusion

In all patients epinephrine infusion significantly increased MAP, CI, SVI, and LVSWI (27%, $p < 0.01$; 20%, $p < 0.01$; 15%, $p < 0.05$; 66%, $p < 0.01$, respectively without any change in SVR, heart rate, or PAOP.

There was a rise in RVSWI (33% $p < 0.01$) and in mean pulmonary artery pressure (12.5% $p < 0.05$) but no significant change in RVEF, RVEDVI, RAP, or RVESVI (Table 2). Overall, mean urine output improved (9 $\pm$ 17 to 28 $\pm$ 39 ml/h, $p < 0.05$), although 7 patients remained anuric.

The main effect of epinephrine was on right ventricular performance in patients with baseline RV failure (group A, Table 4): epinephrine improved RVEF (25%, $p < 0.05$) through a reduction of RVESVI (-8%, $p < 0.05$). A significant increase in CI (24%, $p < 0.05$), SVI (23%, $p < 0.05$), and subsequently in RVSWI (76%, $p < 0.05$) was observed. These changes occurred without a significant change in RVEDVI or in RAP and despite a significant increase in mean pulmonary artery pressure (11%, $p < 0.05$) and in pulmonary artery peak pressure (15%, $p < 0.05$). When a Frank-Starling relationship for the right ventricle was constructed by plotting RVSWI, as an index of ventricular performance, against RVEDVI, as an index of right ventricular preload, a significant upward vertical shift in the relationship was observed (Fig. 1). A significant upward shift to the left of the pressure volume relationship was also found when the pulmonary artery peak pressure was plotted against RVESVI (Fig. 2).

In patients without RV failure (group B), RV parameters remained unchanged during epinephrine administration.

Discussion

In this paper we describe the effects of epinephrine on RV function in severe septic shock. Because there is no consensus about the use of epinephrine as a primary agent in this situation, epinephrine was introduced in to our therapeutic protocol as a second-line agent. We limited the concomitant confounding effect of other baseline inotropes, such as dopamine and dobutamine, by maintaining infusions of these agents at a fixed rate during the protocol. Although the observed mortality (64%) was lower than that predicted by SAPS (> 80%) [23], the study does not allow any conclusions to be drawn about a possible beneficial effect of epinephrine on mortality.

As others have suggested [2, 12, 15, 18], we chose RVEF and the relation between RVSWI and RVEDVI (preload) as indicators of global RV performance. The relation between pulmonary artery peak pressure and RVESVI was considered to be an indicator of RV contractility: although there is some controversy as to the actual end of RV systole [24, 25], using the pulmonary artery - dicrotic notch or peak pulmonary arterial systolic pressure, as an estimate of RV end-systolic pressure, the end-systolic pressure-volume relation has been shown to be load independent and sensitive to

Table 4. Hemodynamic variables before (control) and during epinephrine infusion according to the presence or not of initial right ventricular dysfunction (mean $\pm$ SD)

Variables	Group A (n = 7)		Group B (n = 7)	
	Control	Epinephrine	Control	Epinephrine
RVEDVI (ml/m ²)	134 $\pm$ 28	134 $\pm$ 30	79 $\pm$ 17	89 $\pm$ 13
RVESVI (ml/m ²)	103 $\pm$ 30	95 $\pm$ 31*	43 $\pm$ 11	50 $\pm$ 8
SVI (ml/m ²)	31 $\pm$ 4	38 $\pm$ 7*	36 $\pm$ 11	39 $\pm$ 12
RVEF (%)	24 $\pm$ 7	30 $\pm$ 8*	45 $\pm$ 9	44 $\pm$ 9
CI (l/min per m ²)	3.7 $\pm$.5	4.6 $\pm$.8*	4.2 $\pm$ 2	4.9 $\pm$ 2.5
RAP (mmHg)	12 $\pm$ 3	10 $\pm$ 2	10 $\pm$ 4	10 $\pm$ 4
MPAP (mmHg)	26 $\pm$ 4	29 $\pm$ 6*	23 $\pm$ 3	26 $\pm$ 2
SPAP (mmHg)	33 $\pm$ 9	38 $\pm$ 10*	30 $\pm$ 6	34 $\pm$ 7
RVSWI (g/m ²)	5.5 $\pm$ 3	9.7 $\pm$ 4*	7 $\pm$ 5	8 $\pm$ 4
MAP (mmHg)	60 $\pm$ 18	72 $\pm$ 18	57 $\pm$ 11	76 $\pm$ 15*
PAOP (mmHg)	15 $\pm$ 2	13 $\pm$ 3	13 $\pm$ 5	13 $\pm$ 3
LVSWI (g/m ²)	19 $\pm$ 7	33 $\pm$ 7*	22 $\pm$ 8	36 $\pm$ 16*
SVR (dyne $\cdot$ s $\cdot$ cm ⁻⁵ $\cdot$ m ⁻²)	1069 $\pm$ 572	1092 $\pm$ 433	1024 $\pm$ 293	1209 $\pm$ 468
HR (beats/min)	121 $\pm$ 19	118 $\pm$ 17	114 $\pm$ 30	120 $\pm$ 30

* Difference with basal value: $p < 0.05$

Fig 1 In patients in group A with RV failure, when a Frank-Starling relationship for the right ventricle was constructed by plotting RVSWI, as an index of ventricular performance, against RVEDVI, as an index of right ventricular preload, a significant ($p < 0.05$) upward vertical shift was observed after epinephrine infusion. 1 control point, 2 after epinephrine infusion point

changes in RV contractility [26–28]. As few data are available about normal RVEDVI and RVEF values [22], the combination of a high RVEDVI and a low RVEF was chosen to define right ventricular failure. Measurement of right ventricular volume thermodilution is a bedside technique which is reproducible (coefficient of variation near 7%), easily performed, and well correlated with results derived from contrast ventriculography, echocardiography, and radionuclide angiography [14, 15, 18, 20, 29]. Nevertheless, reproducibility of the measurements may still have been affected by the

fact that the study population included patients who were hemodynamically unstable with large right ventricular volumes and tachycardia.

Before the use of epinephrine, the patients had an initial hemodynamic profile characteristic of severe septic shock, with low blood pressure, low stroke volume, and tachycardia. Our data are consistent with previous reports about RV dysfunction in septic shock [2, 12, 13, 15, 18], since 50% of our patients had severe depressed RV function with marked RV dilation and a decrease in RVEF (group A). Interestingly and consistent with the findings of others [2], this dysfunction was only detectable by volume measurements and not by other parameters, such as RAP or RVSWI, which were no different in the two groups.

RV performance may be impaired in septic shock by excessive afterload [11–13]. As in other studies [2, 15, 18], we did not observe any relationship between mean pulmonary artery pressure and RVEDVI in any group. Moreover, there was no difference in the level of pulmonary hypertension between the two groups. Consequently, in this study it is likely that excessive afterload was not the major determinant of RV dilation and failure. The role of myocardial ischemia is another much debated question in septic shock [15, 30, 31] but is unlikely in our study, since the baseline arterial hypotension was the same in both patient groups. Consequently, we can hypothesize that the RV dilation and dysfunction in group A were due to an intrinsic myocardial depression [15, 31].

There are few data on the effects of catecholamines on RV performance in septic shock, and their overall benefit on RV function is not obvious since inotropic stimulation and an increase in systemic blood pressure can be counterbalanced by an increase in RV afterload and a decrease in the RV oxygen supply/demand ratio. In an experimental model of porcine septic shock [30], dobutamine and norepinephrine were shown to im-

Fig 2 In patients in group A with RV failure, when a pressure-volume relationship was constructed by plotting pulmonary artery peak pressure *SPAP* against *RVESVI* as an indicator of inotropic state, a significant ($p < 0.05$) upward shift to the left was observed after epinephrine infusion. 1 control point, 2 after epinephrine infusion point

prove RVEF by a direct inotropic effect and by an increase in the RV oxygen supply/demand ratio, respectively, but in human septic shock neither norepinephrine nor dopamine was able to modify RVEF [18, 19], in

spite of an improvement in systemic blood pressure. In our study, the beneficial effect of epinephrine on RV function was observed solely in patients with previous RV dysfunction (group A): in these patients, the improvement in RVS_{WI}, SVI, and RVEF, in spite of an increase in afterload, occurred without any alteration in preload conditions as evidenced by the stability of RVEDVI (Fig. 1) and of RAP. These facts as well as the displacement upward and to the left of the RV end-systolic volume – pulmonary peak pressure relationship (Fig. 2) suggest that the major factor accounting for RV performance improvement after the administration of epinephrine is an increase in myocardial contractility. Since the increase in arterial pressure during epinephrine challenge was no different in patients with or without RV dysfunction, we hypothesize that the main mechanism for improvement in contractility by epinephrine does not come from the restoration of the RV oxygen supply/demand ratio but from epinephrine's potent inotropic effect [32, 33].

In conclusion, RV monitoring during severe septic shock permits the identification of patients with RV dysfunction who are difficult to identify with usual measurements, such as those for RAP or RVS_{WI}. Administration of epinephrine to these patients improves RV performance with a rise in SVI and RVEF without an increase in RVEDVI via a predominant effect on RV contractility. The role of the beneficial effect of epinephrine on the clinical course of sepsis, and especially on mortality, cannot be predicted from this preliminary study and requires further comparative studies.

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