Severe sepsis and septic shock in patients with pre-existing non-cardiac pulmonary hypertension: contemporary management and outcomes

Mykola V Tsapenko, Vitaly Herasevich, Girish K Mour, Arseniy V Tsapenko, Thomas B O Comfere, Sunil V Mankad, Rodrigo Cartin-Ceba, Ognjen Gajic and Robert C Albright

ABSTRACT

Objective: To review treatment and outcomes of septic shock in patients with pulmonary hypertension (PH) managed at a tertiary care institution.

Design, setting and patients: We identified consecutive patients with non-cardiac PH (non-Group 2 in the World Health Organization classification) who were treated for septic shock in four intensive care units at a tertiary care institution between July 2004 and July 2007. Patients with a left ventricular ejection fraction < 50%, diastolic dysfunction, pericardial effusion or significant valve disease were excluded. Descriptive statistics were used to analyse the data.

Main outcome measures: Hospital mortality, duration of vasopressor and ventilatory support, length of hospital and ICU stay.

Results: The final group for analysis comprised 82 patients. The major causes of PH were chronic obstructive pulmonary disease, interstitial lung disease and portopulmonary hypertension. PH was mild in 46 patients (56%), moderate in 21 (26%) and severe in 15 (18%). Vasopressor treatment was initiated in 69 patients (84%) within the first 48 hours: noradrenaline was most commonly used (53 patients, 65%), and 51 patients (62%) were treated with more than one agent. Sixty-seven patients (82%) were mechanically ventilated, and 33 (40%) required renal replacement therapy. Forty-three patients (52%) survived to hospital discharge; 23 (28%) remained alive at 1 year. Hospital mortality increased with severity of PH: 28% in mild, 67% in moderate and 80% in severe PH. Non-survivors were more likely to have plateau pressures beyond 30 cm H_2O while mechanically ventilated within the first 48 hours in the ICU (56% v 29%, $P = 0.03$), to develop atrial fibrillation (AF) (46% v 12%, $P < 0.001$), and to require longer vasopressor support (mean, 5.3 v 2.6 days, $P = 0.003$). In a multivariate logistic regression analysis, severity of PH (odds ratio [OR], 1.55; 95% CI, 1.04–2.46; $P = 0.04$), new-onset AF (OR, 6.51; 95% CI, 2.24–22.07; $P < 0.001$) and longer duration of vasopressor support (OR, 1.15; 95% CI, 1.03–1.34; $P = 0.04$) were associated with increased hospital mortality.

Conclusions: The severity of PH, new-onset AF, and longer vasopressor support were associated with poor outcomes in patients with PH who developed severe sepsis and septic shock.

Crit Care Resusc 2013; 15: 103–109

Management of patients with pulmonary hypertension (PH) complicated by severe sepsis or septic shock is a clinical challenge and often associated with high mortality. Patients with chronic PH usually have multiple comorbidities and predisposing factors, which make them more vulnerable to acute conditions and explain their decreased survival of an acute illness.[1,2] The level of chronic compromise of the pulmonary circulation also significantly affects the chances of survival after an acute cardiovascular event[3] or surgical procedure.[4] In the setting of an acute illness, patients with chronic PH often deteriorate rapidly and die from progressive right ventricular (RV) failure (49%), progressive respiratory failure (18%) or sudden cardiac death (17%).[3] Cardiopulmonary resuscitation, even when attempted in the hospital setting, is rarely successful in this group of patients.[2,3]

Sepsis and associated acute lung injury may lead to acute elevation of pulmonary arterial pressure (PAP), even in previously healthy people.[5,6] Acute vasodilatation in the setting of sepsis often precipitates life-threatening low systemic vascular resistance, which, when combined with

Abbreviations

AF	Atrial fibrillation
AKI	Acute kidney injury
APACHE	Acute Physiology and Chronic Health Evaluation
CVVH	Continuous venovenous haemofiltration
ECHO	Echocardiography
EGDT	Early goal-directed therapy
PAP	Pulmonary arterial pressure
PEEP	Positive end-expiratory pressure
PH	Pulmonary hypertension
RHC	Right heart catheterisation
RRT	Renal replacement therapy
RV	Right ventricular
RVSP	Right ventricular systolic pressure
SBP	Systolic blood pressure

dramatically elevated pulmonary artery filling pressures, makes standard resuscitative strategies fraught with potential complications.

Although these patients are generally considered to pose a clinical challenge and have a high risk of death, formal clinical studies evaluating the management and outcome of patients with PH complicated by severe sepsis are lacking,[7] particularly in the era of early goal-directed therapy (EGDT).

We reviewed contemporary treatment and outcomes of septic shock, as well as the use of specific treatment strategies in managing this condition, in patients with PH treated at a tertiary care institution.

Methods

Patient selection

We identified consecutive patients with an established diagnosis of non-cardiac PH (ie, non-Group 2 PH in the World Health Organization classification) who were treated for severe sepsis and septic shock in four intensive care units at a tertiary care institution between July 2004 and July 2007. The study ICUs were a medical ICU (24 beds), a medical–surgical ICU (18 beds), a cardiovascular ICU (20 beds) and a thoracic–vascular surgery ICU (20 beds). Patients with a left ventricular ejection fraction < 50%, diastolic dysfunction (more than grade 1 of 4), pericardial effusion or significant (mitral or aortic) valve disease were excluded. The study was approved by Mayo Clinic Institutional Review Board.

Definitions and data collection

The presence of PH and its severity were determined by standard criteria[8,9] based on patients' clinical data and test results. All patients had an established objective diagnosis of PH, using either right heart catheterisation (RHC) or echocardiography (ECHO), at least 1 month before the hospitalisation for septic shock. Multiple recent studies have demonstrated that ECHO can be successfully used in patients with different classes of PH[10-12] to evaluate and estimate PAP, although RHC is still considered a gold standard to establish the diagnosis. There is also evidence that mean PAP can be accurately estimated by using systolic PAP only.[13-15] However, there is no widely adopted classification of PH severity based on ECHO criteria or systolic PAP only. As not all of the patients underwent RHC to diagnose PH, we compared direct measurements of the PAP obtained by RHC with estimated values of right ventricular systolic pressure (RVSP) obtained by Doppler ECHO in those patients who underwent both studies. Based on the results ($r^2 = 0.74$, $P < 0.05$), we used the following RVSP by Doppler ECHO criteria to define severity of pre-existing PH:

- mild PH: RVSP 40–60 mmHg or 1/3–1/2 of systemic systolic blood pressure (SBP);
- moderate PH: RVSP 60–80 mmHg or 1/2–2/3 of systemic SBP;
- severe PH: RVSP > 80 mmHg or > 2/3 of systemic SBP.

The diagnosis of septic shock was based on standard criteria: persistent hypotension (mean arterial pressure < 65 mmHg or SBP < 90 mmHg) after fluid resuscitation (volume > 20 mL/kg crystalloid bolus and/or necessitating use of vasopressors) in patients with coexisting criteria for sepsis.[16] Serial blood pressure recordings from arterial lines (or non-invasive cuff readings before the arterial line was placed) starting from the time of onset of septic shock were obtained from the electronic information system and scanned records. To accurately determine the total duration of vasopressor-untreated hypotension in the first 48 hours, we collected individual start and stop times for each vasopressor and subsequently calculated the time intervals devoid of vasopressor therapy, as well as duration of treatment with each vasoactive agent. Similarly, we collected individual start and stop times of ventilator support and calculated the time intervals for this therapeutic modality within the first 48 hours of septic shock management.

RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease) criteria were applied to diagnose acute kidney injury (AKI).[17] Patients with pre-existing end-stage renal disease were excluded from analysis of AKI. Continuous venovenous haemofiltration (CVVH) was the only modality used for renal replacement therapy (RRT) within the first 48 hours for AKI complicating septic shock management.

Acute Physiology and Chronic Health Evaluation (APACHE) III-predicted mortality was calculated based on the worst values obtained from the institutional APACHE III database during the first 24 hours after ICU admission. Recordings from monitors, electronic information systems and medication administration records provided the rest of the data for the study. This allowed for calculation of the duration of each studied parameter with a precision of less than 10 minutes. Electrocardiography criteria were used to establish diagnosis of new-onset atrial fibrillation (AF). Beyond the initial 48 hours of septic shock management, all patients were followed up to discharge from the hospital or death. Mechanical ventilation in intubated patients was managed according to lung protective strategy (including tidal volume, 6 mL/kg; plateau pressure < 30 cm H_2O). Duration of ventilator support or treatment with vasopressors during the whole hospital stay was rounded to half a day (in 12-hour intervals) and is presented in days for the final analysis.

Outcome measures and statistical analysis

Outcome measures included hospital and 1-year mortality, duration of ventilatory support, length of hospital stay and length of ICU stay. Descriptive statistics included demographic data, major comorbidities, main causes and severity of PH, and use of specific treatment strategies including mechanical ventilation, pulmonary artery catheterisation, RRT, intravenous fluid administration and vasoactive medications. All data were summarised separately and are presented as means with standard deviations, medians with interquartile ranges, or numbers of patients with percentages. We used the Wilcoxon rank-sum test to compare continuous baseline characteristics and outcomes, and the Fisher exact test for binary predictors and outcomes. To supplement these analyses, we used multiple linear regression (continuous outcomes) or logistic regression (binary outcomes) as appropriate to test for differences in outcomes between the patient groups. Stepwise multivariate regression models were examined to assess the independent effects of variables of interest on hospital mortality. For all statistical tests, a two-tailed P value < 0.05 was considered statistically significant. We calculated 95% confidence intervals where appropriate. JMP statistical software (version 8.0; SAS Institute) was used for all data analysis.

Results

We identified 213 consecutive ICU patients with established pre-existing non-cardiac PH who were treated for septic shock. After applying exclusion criteria during review of their medical records, 82 patients were included in the final analysis.

The major cause of PH (Figure 1) was chronic obstructive pulmonary disease (24 patients, 29%), followed by interstitial lung disease (14, 17%), end-stage liver disease (ie, portopulmonary hypertension; 12, 15%) and sleep-disordered breathing or obesity (11, 13%). Only four patients had idiopathic PH, and 12 patients had more than one aetiological factor involved in the development of PH. PH was classified as mild in 46 patients (56%), moderate in 21 (26%) and severe in 15 (18%).

Of the 82 patients, 43 (52%) survived to hospital discharge; 23 (28%) remained alive at 1 year. The baseline characteristics (Table 1) of those who survived to discharge and those who did not were similar, except for higher APACHE III scores in the non-survivors (Table 1) and in the degree of PH. Hospital mortality increased with severity of PH: 28% in mild PH, 67% in moderate PH, and 80% in severe PH. Most survivors had mild PH (33, 77%) followed by moderate (7, 16%) and severe (3, 7%) PH. Among the 39 non-survivors, severity of pre-existing PH was represented almost equally: 13 (33%) had mild PH, 14 (36%) moderate and 12 (31%) severe PH (Figure 2).

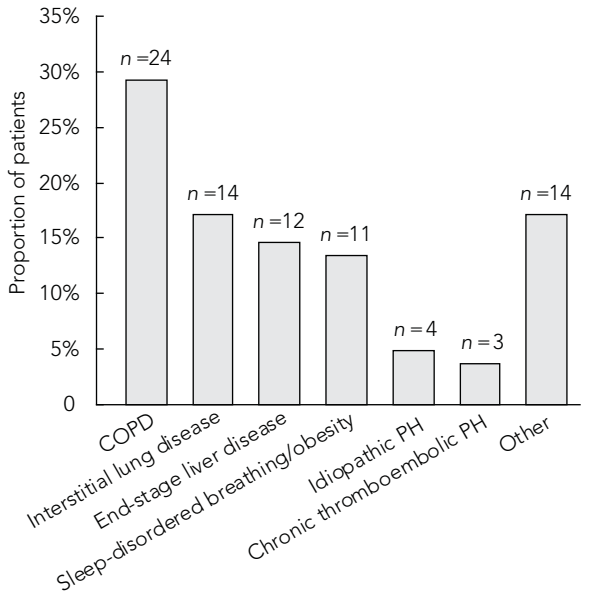
Table 2 shows the comparison of treatments used in survivors and non-survivors. All but 13 patients (84%) required initiation of vasopressor treatment within the first 48 hours of admission: noradrenaline was the most commonly used agent (53 patients, 65%), followed by vasopressin (in most cases as a second agent at a standard dose of 0.04 unit/min) (43, 52%) and dopamine (22, 27%); 51 patients (62%) were treated with more than one agent. Non-survivors had a longer duration of vasopressor support, more frequent use of a pulmonary artery catheter, and a higher incidence of new-onset AF with rapid ventricular response (Table 2A).

Although there was no significant difference between survivors and non-survivors in fluid administration within the first 48 hours of ICU admission, survivors demonstrated better response with higher urine output (Table 2A). After excluding patients with end-stage renal disease, 56 of 76 patients (74%) developed criteria for AKI. There was no significant difference between survivors and non-survivors with respect to AKI incidence or timing of RRT initiation within the first 48 hours in the ICU (Table 2A). RRT (in the form of CVVH) was necessary for management of 33 patients (40%): 28 with AKI (11 of them with pre-existing chronic kidney disease, Stage 3–5) and five with end-stage renal disease. Use of RRT did not influence their survival.

Sixty-seven patients (82%) required initiation of mechanical ventilation within the first 48 hours, with non-survivors developing respiratory failure earlier in the course of septic shock (Table 2B). Non-survivors were more hypoxic and tended to require higher and increasing oxygen supplementation within the first 48 hours after admission. Although applied positive end-expiratory pressure (PEEP) and resultant plateau pressure were not significantly different between survivors and non-survivors who required mechanical ventilation within the first 24 hours of admission, a further increase in plateau pressure beyond 30 cm H_2O for at least 1 hour within the first 48 hours was observed in significantly more non-survivors (56%) than survivors (29%) (Table 2B).

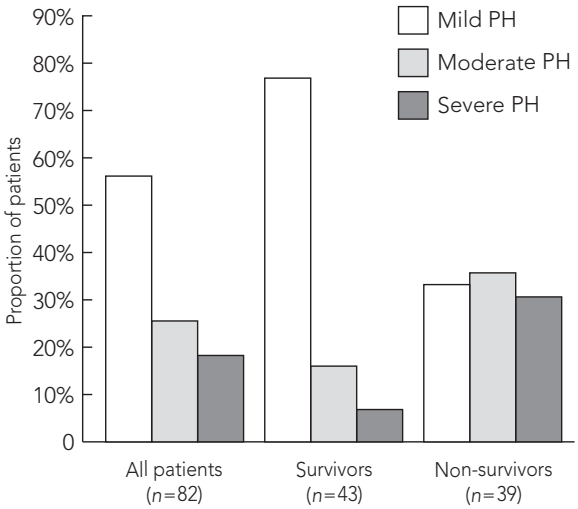
After adjusting for APACHE III score at admission, the severity of pre-existing PH was confirmed to be a significant factor affecting survival to hospital discharge in this patient population (Table 3). Separate logistic regression analysis also demonstrated a strong association of new-onset AF (odds ratio [OR], 6.51; 95% CI, 2.24–22.07; $P < 0.001$) and longer duration of vasopressor support (OR, 1.15; 95% CI, 1.03–1.34; $P = 0.04$) with increased hospital mortality in this patient population.

Figure 1. Causes of pulmonary hypertension (PH) in all patients



COPD = chronic obstructive pulmonary disease.

Figure 2. Severity of pulmonary hypertension (PH) among all patients, and those who did and did not survive to hospital discharge



Discussion

In this retrospective case series, we reviewed the contemporary treatment and outcomes of patients with arterial PH complicated by septic shock. The overall mortality was high and was associated with the severity of PH at baseline, APACHE III score, duration of vasopressor use, and development of AF with rapid ventricular response.

We found the mortality from septic shock among patients with mild PH to be comparable with that of the general population presenting with septic shock.[18,19] Mortality was significantly higher in patients with moderate and severe PH. This may suggest that patients with mild PH could be treated successfully with typical interventions applied to the general population (eg, EGDT). However, our study raises questions about whether aggressive fluid resuscitation (and standard EGDT) shows a benefit for patients with septic shock who had pre-existing moderate to severe

Table 1. Patient characteristics at baseline for all patients, and those who did and did not survive to hospital discharge

	All patients (*n* = 82)	Survivors (*n* = 43)	Non-survivors (*n* = 39)	*P**
Age (years), median (IQR)	72.3 (62.3–81.8)	69.8 (57.5–82.7)	73.5 (66.4–80.8)	0.39
Female	47 (57%)	27 (63%)	20 (51%)	0.29
Body mass index (kg/m^2), median (IQR)	26.6 (23–31.5)	26.1 (21.9–30.9)	27.5 (23.2–32.6)	0.36
APACHE III score, median (IQR)	94 (73.5–116.5)	87 (66.8–107.5)	105 (80.5–123)	0.03
Coronary artery disease	40 (49%)	19 (44%)	21 (54%)	0.31
Arterial hypertension	59 (72%)	31 (72%)	28 (72%)	0.37
Diabetes mellitus	32 (39%)	15 (35%)	17 (44%)	0.97
Chronic kidney disease	27 (33%)	12 (28%)	15 (38%)	0.16
End-stage renal disease	6 (7%)	3 (7%)	3 (7%)	0.89
Atrial fibrillation	22 (27%)	13 (30%)	9 (23%)	0.46
Patent foramen ovale	7 (9%)	5 (12%)	2 (5%)	0.34
Immunosuppression	20 (24%)	11 (26%)	9 (23%)	0.79

IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. * Survivors v non-survivors.

Table 2. Hospital course and management in all patients, and those who did and did not survive to hospital discharge

	All patients ($n=82$)	Survivors ($n=43$)	Non-survivors ($n=39$)	P*
A. Haemodynamic and intravascular volume parameters				
Days in ICU, mean (SD)	10.8 (11.1)	11.2 (12.9)	10.3 (8.9)	0.80
Mean arterial pressure < 60 mmHg, hours within first 48 h, mean (SD)	7.3 (8.1)	6.3 (6.8)	8.4 (9.2)	0.46
Pulmonary artery catheter placed	28 (34.1%)	11 (25.6%)	17 (43.6%)	0.03
Vasopressor treatment, hours within first 48 h, mean (SD)	26.9 (18.8)	23.4 (18.6)	30.8 (18.4)	0.09
Days of vasopressor treatment, mean (SD)	3.9 (5.3)	2.6 (3.8)	5.3 (6.2)	0.003
Elevated cardiac markers within first 48 h	57 (69.5%)	28 (65.1%)	29 (74.3%)	0.16
Developed AF with rapid ventricular response during ICU stay	23 (28%)	5 (11.6%)	18 (46.2%)	< 0.001
Fluid balance, litres for the first 48 h, mean (SD)	8.2 (6.6)	7.4 (4.9)	9.3 (8.2)	0.80
Urine output, total litres for the first 48 h, mean (SD)	2.4 (2.1)	2.9 (2.3)	1.8 (1.6)	0.04
Developed acute kidney injury in first 48 h (excluding ESRD patients)	56 (74%)	27 (68%)	29 (81%)	0.93
Required renal replacement therapy	33 (40%)	14 (33%)	19 (49%)	0.22
Continuous renal replacement therapy started within first 24 h	16 (20%)	7 (16%)	9 (23%)	0.62
Liver function tests abnormal within first 48 h	28 (34.1%)	11 (25.6%)	17 (43.6%)	0.08
B. Mechanical ventilation and oxygenation parameters				
Mechanical ventilation, hours within first 48 h, mean (SD)	26.6 (21.4)	22.5 (21.9)	31.1 (20.1)	0.05
Blood O_2 saturation < 90% for > 1 h within first 24 h	15 (18.3%)	5 (11.6%)	10 (25.6%)	0.10
FIO_2, highest for > 1 h within first 24 h, median (IQR)	0.8 (0.45–1) ($n=72$)	0.7 (0.35–1) ($n=36$)	1.0 (0.5–1) ($n=36$)	0.07
PEEP, highest cm H_2O for > 1 h within first 24 h,† mean (SD)	9.1 (4.2) ($n=46$)	9.1 (4.0) ($n=20$)	9.1 (4.3) ($n=26$)	0.96
Plateau pressure, highest cm H_2O for > 1 h within first 24 h,† mean (SD)	25.1 (7.2) ($n=46$)	24.1 (6.9) ($n=20$)	25.9 (7.6) ($n=26$)	0.61
Plateau pressure > 30 cm H_2O for > 1 h within first 48 h	27/62 (43.6%)	8/28 (28.6%)	19/34 (55.9%)	0.03
Days on ventilatory support, mean (SD)	7.3 (9.8)	7.2 (11.7)	7.4 (7.3)	0.14
FIO_2 increased within first 48 h	14/78 (17.9%)	4/40 (10%)	10/38 (26.3%)	0.06
PEEP increased within first 48 h	11/62 (17.7%)	3/28 (10.7%)	8/34 (23.5%)	0.18
Plateau pressure increased within first 48 h	10/62 (16.2%)	6/28 (21.4%)	4/34 (11.8%)	0.30

ICU = intensive care unit. AF = atrial fibrillation. ESRD = end-stage renal disease. FIO_2 = fraction of inspired oxygen. PEEP = positive end-expiratory pressure.
* Survivors v non-survivors. † Among those patients started on mechanical ventilation within the first 24 hours of ICU admission and ventilated for > 2 hours.

PH. It is unclear what ideal haemodynamic and metabolic targets yield optimal survival in this complex population.[20] These questions are yet to be answered, and further studies are needed.

Table 3. Multivariate logistic regression analysis of hospital mortality

	Unit odds ratio (95% CI)	P
Age at the time of event, years	0.99 (0.95–1.03)	0.51
Male	1.40 (0.47–4.29)	0.55
Severity of pulmonary hypertension (each 10 mmHg elevation of right ventricular systolic pressure above 40 mmHg)	1.55 (1.04–2.46)	0.04
APACHE III score (each 10-point change)	1.08 (0.89–1.31)	0.46

APACHE = Acute Physiology and Chronic Health Evaluation.

As use of EGDT has demonstrated significant reduction of mortality in patients with severe sepsis and septic shock,[21] this set of recommendations has been endorsed by the Institute for Healthcare Improvement and has now become the standard therapy in sepsis management (eg, Surviving Sepsis Campaign sepsis bundle).[22] As a result, the Surviving Sepsis Campaign was associated with sustained continuous quality improvement in sepsis care[19] in the general population, as well as in some specific population groups.[23] However, despite implementation of the sepsis bundle in patients with pre-existing PH who developed severe sepsis and septic shock, mortality remained very high in our study.

Interestingly, we found that while non-survivors tended to have AF as a comorbidity less frequently than did survivors, they were more prone to develop new-onset AF with rapid ventricular response. This is consistent with observations that new-onset AF is a frequent (5.9%–31%) complication in patients with sepsis[24-26] and more common

in patients with septic shock than in patients with severe sepsis alone.[24,27] New-onset AF is independently associated with increased mortality in this patient population.[25,26] Controversy continues as to whether new-onset AF reflects the severity of the disease[25,27] or is triggered by more severe systemic inflammation;[24] likely both are true. Understanding the nature and mechanisms involved in the development of AF in patients with sepsis is very important, as our ability to control the AF, rather than the incidence of new-onset AF itself, appears to be more important for patient survival.[24]

Based on our data, we hypothesise that the very high incidence of AF with rapid ventricular response observed in patients with pre-existing PH and septic shock could be due to a "volume-overwhelmed" right ventricle. This situation is likely caused by the inability of the right heart and pulmonary vasculature to adequately accommodate aggressive fluid administration superimposed on an already pressure-compromised pulmonary circulation, as well as on developing reversible sepsis-related myocardial dysfunction, which has been observed in 64% of patients with severe sepsis and septic shock.[28] Overdistended myocardium resulting from intrinsic disease, heart failure or acute volume overload is highly arrhythmogenic and could be responsible for sudden onset of AF.[29] Multiple mechanisms are involved in this arrhythmogenesis, including development of areas of focal increased myocardial activity, single or multiple re-entry circuit formation under the influence of intrinsic abnormalities of the myocardium, higher sympathetic stimulation and pulmonary vascular congestion.[29-31] Most of the mechanisms are observed in patients with septic shock and associated high cardiac output state, particularly if they have compromised cardiac function.[25] Even in the absence of structural heart disease, acute volume overload can cause cardiac arrhythmia.[32]

In our study, we observed periods of increased plateau pressure above 30 cm H_2O within the first 48 hours of admission in the majority of non-survivors who were initiated on mechanical ventilation. Without significant underlying changes in applied PEEP, this could reflect worsening in lung compliance, likely due to pulmonary congestion as a result of volume overload and/or worsening of left ventricular function.

Volume overload could also be at least partially responsible for resistant haemodynamic instability, systemic hypotension, and acute right and left ventricular failure.[1] Experiments showed that when RV afterload is increased, even a relatively small increase in preload (volume) may result in RV dysfunction, which can develop even with constant pulmonary vascular resistance and a decrease in mean PAP. These observations postulate that high RV filling pressure restores normal haemodynamics only if pulmonary vascular resistance is normal and RV contractility is not markedly reduced.[33]

This study illustrates the dramatic mortality risk that severe PH affords patients with septic shock. Applying all recommended standard EGDT among the population with severe PH may not be as advantageous as when applied to standard critically ill patients without PH. This suggestion could be further supported by the fact that some developed countries do not use protocolised EGDT as routine management of patients with sepsis, yet have been able to achieve comparable or even favourable survival.[34] Moreover, we found a striking incidence of AF and AKI among patients with PH who developed severe sepsis and septic shock. Successful management of the conditions would require a better understanding of the complex haemodynamic changes experienced by patients with severe PH and septic shock. Whether more rapid institution of vasopressors in place of volume resuscitation to improve perfusion among patients with sepsis and PH may be of benefit is a hypothesis worthy of clinical study.

Our study has several important factors limiting the ability to generalise its findings to all patients with PH. Along with the inherent issues surrounding retrospective studies, these limitations include the relatively small sample size and heterogeneous nature of PH, as well as uneven proportions of patients with different severities of the condition. Although all patients had confirmed sustained elevation of PAP by serial ECHO, not all of them underwent RHC to establish the diagnosis and severity of PH. Nonetheless, this study provides important information regarding real-world experience in managing septic shock in patients with pre-existing PH.

In conclusion, our study demonstrated that the severity of PH, development of AF, and longer duration of vasopressor support are associated with an increased mortality risk among patients with pre-existing PH who develop septic shock. Contemporary septic shock management remains associated with high mortality in this patient subset, and further study with respect to optimising clinical strategies among this patient population is required.

Competing interests

None declared.

Author details

Mykola V Tsapenko, Assistant Professor of Medicine[1,2]
Vitaly Herasevich, Assistant Professor of Medicine and Anesthesiology[2,3]
Girish K Mour, Physician[1,2]
Arseniy V Tsapenko, Physician[4]
Thomas B O Comfere, Assistant Professor of Anesthesiology[2,3]
Sunil V Mankad, Associate Professor of Medicine[2,5]
Rodrigo Cartin-Ceba, Assistant Professor of Medicine[1,2]
Ognjen Gajic, Professor of Medicine[1,2]

Robert C Albright, Associate Professor of Medicine[2,6]

1 Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minn, USA.

2 Multidisciplinary Epidemiology and Translational Research in Intensive Care (METRIC), Mayo Clinic, Rochester, Minn, USA.

3 Department of Anesthesiology, Mayo Clinic, Rochester, Minn, USA.

4 Division of Pulmonary and Critical Care Medicine, Brown University, Miriam Hospital, Providence, RI, USA.

5 Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minn, USA.

6 Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minn, USA.

Correspondence: mykolatsapenko@yahoo.com

References

1 Tsapenko MV, Tsapenko AV, Comfere TB, et al. Arterial pulmonary hypertension in noncardiac intensive care unit. *Vasc Health Risk Manag* 2008; 4: 1043-60.

2 Huynh TN, Weigt SS, Sugar CA, et al. Prognostic factors and outcomes of patients with pulmonary hypertension admitted to the intensive care unit. *J Crit Care* 2012; 27: 739.e7-e13.

3 Hoeper MM, Galié N, Murali S, et al. Outcome after cardiopulmonary resuscitation in patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2002; 165: 341-4.

4 Kaw R, Pasupuleti V, Deshpande A, et al. Pulmonary hypertension: an important predictor of outcomes in patients undergoing non-cardiac surgery. *Respir Med* 2011; 105: 619-24.

5 Vieillard-Baron A, Schmitt JM, Augarde R, et al. Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. *Crit Care Med* 2001; 29: 1551-5.

6 Sibbald WJ, Paterson NA, Holliday RL, et al. Pulmonary hypertension in sepsis: measurement by the pulmonary arterial diastolic-pulmonary wedge pressure gradient and the influence of passive and active factors. *Chest* 1978; 73: 583-91.

7 Lahm T, McCaslin CA, Wozniak TC, et al. Medical and surgical treatment of acute right ventricular failure. *J Am Coll Cardiol* 2010; 56: 1435-46.

8 Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54 (1 Suppl): S55-66.

9 Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC); European Respiratory Society (ERS); International Society of Heart and Lung Transplantation (ISHLT); et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; 34: 1219-63.

10 Er F, Ederer S, Nia AM, et al. Accuracy of Doppler-echocardiographic mean pulmonary artery pressure for diagnosis of pulmonary hypertension. *PLoS One* 2010; 5: e15670.

11 Janda S, Shahidi N, Gin K, Swiston J. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. *Heart* 2011; 97: 612-22.

12 Kuppahally SS, Michaels AD, Tandar A, et al. Can echocardiographic evaluation of cardiopulmonary hemodynamics decrease right heart catheterizations in end-stage heart failure patients awaiting transplantation? *Am J Cardiol* 2010; 106: 1657-62.

13 Pyxaras SA, Pinamonti B, Barbati G, et al. Echocardiographic evaluation of systolic and mean pulmonary artery pressure in the follow-up of patients with pulmonary hypertension. *Eur J Echocardiogr* 2011; 12: 696-701.

14 Aduen JF, Castello R, Daniels JT, et al. Accuracy and precision of three echocardiographic methods for estimating mean pulmonary artery pressure. *Chest* 2011; 139: 347-52.

15 Chemla D, Castelain V, Provencher S, et al. Evaluation of various empirical formulas for estimating mean pulmonary artery pressure by using systolic pulmonary artery pressure in adults. *Chest* 2009; 135: 760-8.

16 Annane D, Bellissant E, Cavaillon JM. Septic shock. *Lancet* 2005; 365: 63-78.

17 Bellomo R, Ronco C, Kellum JA, et al; Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; 8: R204-12.

18 Schramm GE, Kashyap R, Mullon JJ, et al. Septic shock: a multidisciplinary response team and weekly feedback to clinicians improve the process of care and mortality. *Crit Care Med* 2011; 39: 252-8.

19 Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Med* 2010; 36: 222-31.

20 Berisha S, Kastrati A, Goda A, Popa Y. Optimal value of filling pressure in the right side of the heart in acute right ventricular infarction. *Br Heart J* 1990; 63: 98-102.

21 Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345: 1368-77.

22 Dellinger RP, Carlet JM, Masur H, et al; Surviving Sepsis Campaign Management Guidelines Committee. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32: 858-73.

23 El Solh AA, Akinnusi ME, Alsawalha LN, Pineda LA. Outcome of septic shock in older adults after implementation of the sepsis "bundle". *J Am Geriatr Soc* 2008; 56: 272-8.

24 Meierhenrich R, Steinhilber E, Eggermann C, et al. Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. *Crit Care* 2010; 14: R108.

25 Salman S, Bajwa A, Gajic O, Afessa B. Paroxysmal atrial fibrillation in critically ill patients with sepsis. *J Intensive Care Med* 2008; 23: 178-83.

26 Walkey AJ, Wiener RS, Ghobrial JM, et al. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA* 2011; 306: 2248-54.

27 Seguin P, Signouret T, Laviolle B, et al. Incidence and risk factors of atrial fibrillation in a surgical intensive care unit. *Crit Care Med* 2004; 32: 722-6.

28 Pulido JN, Afessa B, Masaki M, et al. Clinical spectrum, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock. *Mayo Clin Proc* 2012; 87: 620-8.

29 Nattel S, Shiroshita-takeshita A, Brundel BJ, Rivard L. Mechanisms of atrial fibrillation: lessons from animal models. *Prog Cardiovasc Dis* 2005; 48: 9-28.

30 Hirose M, Takeishi Y, Miyamoto T, et al. Mechanism for atrial tachyarrhythmia in chronic volume overload-induced dilated atria. *J Cardiovasc Electrophysiol* 2005; 16: 760-9.

31 See VY, Roberts-Thomson KC, Stevenson WG, et al. Atrial arrhythmias after lung transplantation: epidemiology, mechanisms at electrophysiology study, and outcomes. *Circ Arrhythm Electrophysiol* 2009; 2: 504-10.

32 Narayan SM, Drinan DD, Lackey RP, Edman CF. Acute volume overload elevates T-wave alternans magnitude. *J Appl Physiol* 2007; 102: 1462-8.

33 Via G, Braschi A. Pathophysiology of severe pulmonary hypertension in the critically ill patient. *Minerva Anestesiol* 2004; 70: 233-7.

34 Peake SL, Bailey M, Bellomo R, et al; ARISE Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Australasian resuscitation of sepsis evaluation (ARISE): a multicentre, prospective, inception cohort study. *Resuscitation* 2009; 80: 811-8. ❑