Reduction of Intra-abdominal Hypertension Is Associated with Increase of Cardiac Output in Critically Ill Patients Undergoing Mechanical Ventilation

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ABSTRACT

Objective: To demonstrate the relationship between intra-abdominal hypertension (IAH) and cardiac output (CO) in mechanically ventilated (MV), critically ill patients. Material and methods: This was a single-center, prospective study performed between January and April 2016, on 30 mechanically ventilated patients (mean age 67.3 ± 11.9 years), admitted in the Intensive Care Unit (ICU) of the Emergency County Hospital of Tîrgu Mureș, Romania, who underwent measurements of intra-abdominal pressure (IAP). Patients were divided into two groups: group 1 – IAP <12 mmHg (n = 21) and group 2 – IAP >12 mmHg (n = 9). In 23 patients who survived at least 3 days post inclusion, the variation of CO and IAP between baseline and day 3 was calculated, in order to assess the variation of IAP in relation to the hemodynamic status. Results: IAP was 8.52 ± 1.59 mmHg in group 1 and 19.88 ± 8.05 mmHg in group 2 (p < 0.0001). CO was significantly higher in group 1 than in the group with IAH: 6.96 ± 2.07 mmHg (95% CI 6.01–7.9) vs. 4.57 ± 1.23 mmHg (95% CI 3.62–5.52) (p = 0.003). Linear regression demonstrated an inverse correlation between CO and IAP (r = 0.48, p = 0.007). Serial measurements of CO and IAP proved that whenever accomplished, the decrease of IAP was associated with a significant increase in CO (p = 0.02). Conclusions: CO is significantly correlated with IAP in mechanically ventilated patients, and IAH reduction is associated with increase of CO in these critically ill cases.

Keywords: stroke volume, cardiac output, intra-abdominal hypertension, intra-abdominal pressure, mechanical ventilation

INTRODUCTION

Intra-abdominal hypertension (IAH), defined as an increase of the intra-abdominal pressure (IAP) above 12 mmHg, is frequently encountered in critically ill patients who are subjected to mechanical ventilation.1 According to the World Society of Abdominal Compartment Syndrome, the normal values for IAP...
range between 10 and 12 mmHg, while IAH is defined as an increase of the IAP above 12 mmHg.\(^2\)

IAH is frequently elevated in critically ill patients, and it has been proved that IAH in mechanically ventilated patients is associated with a significantly higher length of stay in intensive care units (ICU) and ICU mortality, a higher incidence of organ dysfunction, and a longer duration of mechanical ventilation.\(^3\)

The most severe form of IAH is represented by abdominal compartment syndrome, which is a devastating condition that occurs when intra-abdominal pressure exceeds 20 mmHg, being encountered in 20–30% of critically ill patients.\(^4\) Prospective epidemiological studies reported the presence of IAH in 50.5% of mechanically ventilated patients admitted in ICUs and the presence of abdominal compartment syndrome in 8% of the same population.\(^5\)

Abdominal compartment syndrome represents the final stage of a severe condition characterized by an increase in IAP to a degree that compromises the regional blood flow in vital abdominal organs.\(^6\) Abdominal compartment syndrome is considered nowadays a life-threatening condition, being associated with significant deterioration in cardiac, renal, and respiratory function.\(^4\) Therefore, in mechanically ventilated patients, all the necessary therapeutic measures should be undertaken in order to prevent the progression of IAH to more severe stages and abdominal compartment syndrome.

Cardiac output (CO) is the most reliable expression of cardiac performance, and an appropriate CO is essential for maintaining organ perfusion in critically ill patients. However, in many ventilated patients, CO is decreased due to inappropriate fluid therapy, hypovolemia, or cardiogenic shock, and the development of IAH can lead to further progressive deterioration of the clinical condition in these critical cases.

Mechanical ventilation leads to significant changes in the intra-thoracic pressure and consequently alters the left ventricular preload. The interrelation between intra-thoracic pressure, ventricular preload, and IAP is extremely complex, being demonstrated that the respiratory variation of stroke volume is able to predict fluid responsiveness in patients with increased IAP.\(^7\)

It has been proved that in hypovolemic patients, IAH is associated with a significant increase in the parameters reflecting ventricular preload.\(^8\)\(^,\)\(^9\) At the same time, ventricular preload is highly susceptible to the variations of intra-thoracic pressures resulting from mechanical ventilation.\(^7\) As ventricular preload in one of the major determinants of CO, at the same time being influenced by the parameters related to mechanical ventilation, a direct correlation should exist between CO and mechanical ventilation parameters.\(^7\) However, the correlation between IAP and CO in mechanically ventilated severely ill patients has not been elucidated so far.

The role of functional hemodynamic monitoring in critically ill patients has been well established, and the relation between functional hemodynamic parameters and IAH has been demonstrated.\(^7\)\(^–\)\(^9\) Such a functional hemodynamic monitoring includes the assessment of variable hemodynamic parameters such as stroke volume variation and pulse pressure variation. It has been clearly demonstrated that these parameters can predict fluid responsiveness in mechanically ventilated patients, based on the complex relationship between intra-thoracic pressure and intra-abdominal pressure.\(^7\) However, while the relationship between the variation of stroke volume and intra-abdominal pressure has been well documented, little is known about the correlation between IAP and parameters reflecting the global hemodynamic status, such as CO.

The aim of this study was to demonstrate the relationship between CO and IAP in mechanically ventilated critically ill patients and at the same time to demonstrate that the reduction of IAP is associated with the increase of CO in these critical cases.

**PATIENTS AND METHODS**

**Study population**

The study enrolled 30 mechanically ventilated and sedated patients (76.19% males, mean age 67.3 ± 11.9 years, 95% CI 62.9–71.8) admitted in the Intensive Care Unit of the Emergency Clinical County Hospital of Tîrgu Mureș, Romania, between January 2016 and April 2016 for severe abdominal pathology. There were no cases of sepsis in the study lot, and none of the patients required vasopressor support. All patients had comparable ventilator settings.

Clinical, biological, and hemodynamic parameters were compared in 21 patients with normal values of intra-abdominal pressure (IAP <12 mmHg, group 1) and 9 patients with increased values of IAP (IAP >12 mmHg, group 2). The cut-off value of 12 mmHg for defining the IAH was selected according to the value established in the definition released by the World Society of Abdominal Compartment Syndrome.\(^2\)

The study was approved by the ethics committee of the Emergency Clinical County Hospital of Tîrgu Mureș, Romania, and all the investigations were in accordance with the Declaration of Helsinki.
Data collection

In all patients, clinical and laboratory data were collected at enrollment and analyzed (including age, weight, height, gender, blood pressure, urea, creatinine and creatinine clearance, glomerular filtration rate, neutrophil gelatinase-associated lipocalin (NGAL), blood count, central venous pressure, pH). The severity scores APACHE II (Acute Physiology and Chronic Health Evaluation Score), SOFA (Sequential Organ Failure Assessment Score), and SAPS (Simplified Acute Physiology Score) were calculated based on clinical and laboratory data. Parameters reflecting hemodynamic and volemic status such as global end-diastolic blood volume (GEDV), extra-vascular lung water index (EVLWi), and stroke volume variation (SVV) were also collected and analyzed.

Measurements

Determination of IAP was performed daily, on three consecutive days, with the patient on semi-recumbent position, using the AbViser device (ConvaTec, Salt Lake City, USA) and an urethro-vesical catheter (Nelaton type, Shanghai Med SRL, Shanghai, China). Measurements were performed after the injection of 20 mL of saline solution in the urethro-vesical catheter, followed by catheter occlusion with a dedicated valve, and were displayed on the device monitor.

CO was determined using the thermodilution method, with a 3 F arterial Piccocatheter inserted percutaneously in the femoral artery and a central venous catheter inserted in the internal jugular vein. The calculation of CO was done using a Pico Plus device (Pulsion, Feldkirchen, Germany), according to the PICCO technique which is based on two physical principles: transpulmonary thermodilution and pulse contour analysis. A cold saline solution (15 mL) was injected by central venous catheter and passed through the right heart, lung, and left heart, being detected by the Picco thermodilution catheter placed in the femoral artery. Upon this thermodilution phase, the monitor was calibrated to perform a continuous hemodynamic monitoring, based on pulse contour analysis. A new calibration was performed just before each IAP measurement to ensure the reliability of CO estimation.

Central venous pressure (CVP) was determined using a 7 F central venous catheterization set, introduced via the internal jugular vein, connected with a standard transducer that measured the CVP, the values being displayed on a monitor.

Hemodynamic parameters (GEDV, EVLWi, and SVV) were determined with the use of the Picco Plus device (Pulsion, Feldkirchen, Germany).

In order to avoid circadian variation, all the measurements were performed in the morning, between 9:00 a.m. and 10:00 a.m. at baseline, and were repeated daily, at the same hour, in 23 patients who survived at least 3 days post inclusion in the study. The variation of CO and IAP between baseline and day 3 was calculated in this subgroup, in order to assess the interrelation between IAP variation and hemodynamic status.

Statistical analysis

All the statistical analyses were performed using the InStat Graph Pad software. Fisher’s exact test (or the Student t-test for age) was used to compare the baseline characteristics of patients in group 1 and group 2. Continuous values were expressed as the mean and standard deviation, and statistical significance was determined using the Mann-Whitney test. Linear regression was used for assessing the correlation between CO and IAP. The statistical significance level was set at an alpha of less than 0.05.

RESULTS

Baseline clinical characteristics

The mean age of the population was 66.5 ± 13.4 years in group 1 and 69.3 ± 7.5 years in group 2 (p = 0.4). The clinical baseline characteristics of the study population showed no significant differences between the groups with respect

| TABLE 1. Baseline characteristics of the study population |
|------------------------------|-------------------------------|-------------------------------|---|
|                              | Group 1 IAP <12 mmHg n = 21 (70.0%) | Group 2 IAP >12 mmHg n = 9 (30.0%) | P value |
| Age, years                   | Mean ± SD 66.5 ± 13.4           | Mean ± SD 69.3 ± 1.75          | 0.4 |
| Gender, male                 | n (%) 16 (76.2)                 | 6 (66.5)                      | 0.6 |
| Weight (kg)                  | Mean ± SD 89.9 ± 17.0           | Mean ± SD 85.8 ± 10.1          | 0.5 |
| Height (cm)                  | Mean ± SD 173.2 ± 5.6           | Mean ± SD 170.2 ± 5.6          | 0.2 |
to age \((p = 0.4)\), gender \((p = 0.6)\), weight \((p = 0.5)\), height
\((p = 0.2)\), blood pressure \((p = 0.7\) for systolic blood pressure,
0.9 for diastolic blood pressure, and 0.3 for mean blood pressure),
and central venous pressure \((p = 0.4)\) (Table 1 and Table 2).

IAP was 8.52 ± 1.59 mmHg in group 1 and 19.88 ± 8.05
mmHg in group 2 \((p < 0.0001)\).

**Biomarkers of organ dysfunction and IAP**

Biomarkers expressing renal function, such as urea, creatinine,
and GFR, showed no statistically significant differences
between the study groups \((p = 0.4\) for urea, 0.2 for creatinine,
and 0.2 for GFR). However, NGAL, a reliable biomarker expressing acute kidney injury,
showed significantly higher values in the group with IAH as compared to
the group with normal IAP (Table 2).

**Cardiac output and IAP**

There were no statistically significant differences between
the study groups in respect to hemodynamic parameters expressing
global volemic status \((p = 0.07\) for GEDV, \(p =
0.3\) for EVLWI, and \(p = 0.1\) for SVV) (Table 3).

However, mean values of CO were significantly higher
in the group with normal values of IAP than in the group
with IAH (Figure 1). Furthermore, linear regression demonstran-
ed an inverse correlation between CO and IAP \((r =
0.48, p = 0.007)\) (Figure 2), proving that higher values of
IAP are associated with lower values of CO.

Serial measurements of CO proved that each decrease
in IAP (from day 1 to day 2 and from day 2 to day 3) was
associated with a significant increase in CO, the correlation
between IAP decrease and CO increase being statistically
significant \((p = 0.02)\) (Figure 3).

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**TABLE 2.** Clinical and biological characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Group 1 IAP &lt;12 mmHg</th>
<th>Group 2 IAP &gt;12 mmHg</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n = 21 (70.0%)</td>
<td>n = 9 (30.0%)</td>
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<tr>
<td>Systolic arterial pressure (mmHg)</td>
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<tr>
<td>Mean ± SD</td>
<td>110.9 ± 29.6</td>
<td>115.2 ± 31.7</td>
<td>0.7</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>97.4–124.4</td>
<td>89.0–141.1</td>
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<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td></td>
<td></td>
<td>0.9</td>
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<tr>
<td>Mean ± SD</td>
<td>54.5 ± 16.8</td>
<td>55.1 ± 18.3</td>
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<tr>
<td>95% confidence interval</td>
<td>46.8–62.6</td>
<td>41.0–69.2</td>
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<tr>
<td>Central venous pressure (mmHg)</td>
<td></td>
<td></td>
<td>0.3</td>
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<tr>
<td>Mean ± SD</td>
<td>9.9 ± 3.7</td>
<td>11.3 ± 4.0</td>
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<tr>
<td>95% confidence interval</td>
<td>8.1–11.6</td>
<td>8.2–14.4</td>
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<tr>
<td>Urea (mg/dL)</td>
<td></td>
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<td>0.4</td>
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<tr>
<td>Mean ± SD</td>
<td>86.3 ± 38.4</td>
<td>72.6 ± 45.11</td>
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<tr>
<td>95% confidence interval</td>
<td>68.8–103.9</td>
<td>37.9–107.3</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td></td>
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<td>0.2</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.4 ± 0.85</td>
<td>1.1 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>1.0–1.8</td>
<td>0.6–1.6</td>
<td></td>
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<tr>
<td>Creatinine clearance (mL/min)</td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>76.5 ± 37.4</td>
<td>87.6 ± 35.9</td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>58.5–94.6</td>
<td>60.6–115.2</td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate (mL/min/1.73 m²)</td>
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<td></td>
<td>0.2</td>
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<tr>
<td>Mean ± SD</td>
<td>59.4 ± 29.5</td>
<td>78.0 ± 39.67</td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>45.8–72.8</td>
<td>47.5–108.5</td>
<td></td>
</tr>
<tr>
<td>NGAL (ng/mL)</td>
<td></td>
<td></td>
<td>0.02</td>
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<tr>
<td>Mean ± SD</td>
<td>3241 ± 299.0</td>
<td>5717 ± 411.6</td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>203.3–444.9</td>
<td>373.3–770.1</td>
<td></td>
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<tr>
<td>Leucocyte count (*10³/mm³)</td>
<td></td>
<td></td>
<td>0.5</td>
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<tr>
<td>Mean ± SD</td>
<td>12.548 ± 6.074</td>
<td>14.944 ± 11.099</td>
<td></td>
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<tr>
<td>pH</td>
<td></td>
<td></td>
<td>0.1</td>
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<tr>
<td>Mean ± SD</td>
<td>7.3 ± 0.1</td>
<td>7.2 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>7.2–7.3</td>
<td>7.1–7.3</td>
<td></td>
</tr>
</tbody>
</table>
There were no statistically significant differences between the study groups in respect to severity scores. Significantly elevated APACHE II, SOPHA, and SAPS scores were recorded in similar percentages in both groups on day 1, without any major difference between the groups regarding the severity of the condition at baseline (p = 0.4 for APACHE scores >25, p = 0.4 for SOFA scores >10, and p = 1 for SAPS scores >30) (Table 4).

IAP remains a severe clinical condition with potentially devastating impact on patient outcomes.4,10 In ICU units, mechanical ventilation represents one of the major factors predisposing to the development of IAH, which usually results from a complex interaction between multiple factors. Besides the ventilation settings, other factors involved in the pathophysiology of this syndrome could be related to the biological condition of the patient or to the complex...
interaction between intra-thoracic and intra-abdominal pressures, interaction in which the volemic status and the cardiac output play a significant role.

IAH, intra-thoracic pressures, and ventricular preload

While the etiological factors for IAH are well defined, including obesity, insufflation of carbon dioxide during abdominal laparoscopic surgery, excessive fluid accumulation in the abdominal cavity or the presence of ascites, the factors that could be associated with the variation of IAP in different clinical scenarios are less clarified. It has been proved that a high tidal volume and the application of positive end-expiratory pressure during mechanical ventilation are associated with elevation of IAP.\textsuperscript{11–13} The elevated IAP pushes the diaphragm upward, decreasing the compliance of the respiratory system, and leads to increase in the intra-thoracic pressures. At the same time, IAH decreases the venous return from the lower extremities and therefore reduces the cardiac preload and the left ventricular end-diastolic volumes.\textsuperscript{14–16} This is the most probable mechanism via which IAH alters the preload conditions and, as a direct consequence, reduces the CO. In line with these observations, our study demonstrated significantly lower values of CO in the group with IAH (4.57 ± 1.23 L/min vs. 6.96 ± 2.07 L/min, \( p = 0.003 \)), proving that an increased IAP is directly associated with the alteration of hemodynamic status. In this study, the interrelation between CO and IAP was also demonstrated by the inverse correlation between them at linear regression analysis (\( r = 0.48, p = 0.007 \)).

Fluid balance, preload, and IAP

One of the factors that could be associated with the progression of IAH is represented by fluid accumulation in the abdominal cavity, resulting either from excessive fluid administration or from a pathological process in the abdominal cavity (e.g., ascites).
It has been demonstrated that the interaction between IAP and intra-abdominal volume leads to a significant increase in IAP after a relatively small accumulation of fluid or blood in the abdominal cavity.\textsuperscript{1,5} Intra-peritoneal fluid collection, obesity, large amount of intravenous fluid received, and abdominal distention have been identified as significant independent predictors of IAH in patients admitted to the ICU.\textsuperscript{3}

IAH frequently appears in patients who develop an inflammatory process inside the abdominal cavity and can be further exacerbated by the excessive fluid therapy in these cases.\textsuperscript{6} An increase of IAP has been proved to be associated with a significant reduction of the splanchnic blood flow.\textsuperscript{16,17} Intraoperative and postoperative optimization of fluid administration has been proved to be strongly associated with a reduction in mortality in critically ill patients; however, in a study by Liu et al., static preload variables represented by central venous pressure and pulmonary capillary wedge pressure were not able to predict the cardiac response to fluid therapy in patients with IAH.\textsuperscript{7}

Fluid therapy is considered a predisposing factor for IAP increase, as excessive intravenous fluid administration can worsen IAH. At the same time, volemic status is one of the key determinants of cardiac output and is a directly influencing variable of hemodynamic parameters such as the respiratory variation of stroke volume (SVV) or of pulse pressure (PPV).

It has been shown that elevated IAP increases the preload parameters in patients with hypovolemia.\textsuperscript{18,19} At the same time, Diaz et al. proved that IAH induction in non-hypovolemic patients significantly increases hemodynamic variables such as SVV and PPV, proving that a direct relation exists between IAP and hemodynamic parameters characterizing cardiac function.\textsuperscript{7} In line with these observations, the present study proves that a direct interaction exists between IAH and CO variation in critically ill patients undergoing mechanical ventilation. However, in the present study we did not record any significant difference of SVV between the study groups (15.0 ± 7.5 vs. 19.5 ± 7.36, p = 0.1), probably because SVV increases especially in hypovolemic conditions, while there were no cases of hypovolemia in the study groups.

**IAH and CO variation**

In an experimental study, Diaz et al. proved that induction of IAH leads to a reduction in cardiac index, in the absence of any significant changes in the blood pressure.\textsuperscript{7} Similarly, our study demonstrates that an inverse correlation exists between IAH and CO in critically ill patients undergoing mechanical ventilation. Furthermore, we also proved that an increase in CO is achievable after correction of IAP. Reduction of IAP from 13.4 mmHg to 11.5 mmHg resulted in a significant increase in CO, from 5.3 L/min to 6.2 L/min (p = 0.02). According to the authors’ knowledge, this is the first study demonstrating that a reduction in IAP could lead to an improvement of CO in critically ill subjects.

**The cause-effect interaction between CO to IAP**

The results of our study could lead to a challenging debate related to the possible cause-effect mechanism between CO and IAP: is the regression of IAP that leads to the improvement of CO via a complex mechanism that involves the amelioration of left ventricular preload conditions following the re-equilibration of the balance between intra-thoracic and intra-abdominal pressures, or is it rather the increase in CO, consecutive to proper fluid administration and hemodynamic improvement, the factor that leads to regression of IAP? While the effect of IAP on CO has been addressed by many studies, the potential effect of CO on IAP determination has not been studied so far. This new hypothesis launched by our study is not clearly answered in the present, and further studies are required in order to elucidate the potential influence of CO on IAP.

**IAH, biomarkers, and severity scores**

At the same time, it was demonstrated that in mechanically
ventilated patients with IAH, the application of an increasing positive end-expiratory pressure is associated with an increased release of inflammatory biomarkers such as interleukin-9 and type III procollagen expression and type II epithelial cell damage. Other studies demonstrated that IAH is associated with the development of acute renal failure in critically ill patients. In line with these results and with our previous experience, we also proved that the levels of NGAL, a biomarker associated with acute renal failure, are increased in patients with IAH compared to the patients with normal IAP. Interestingly, we recorded significantly higher levels of NGAL in patients with IAH (571.7 ± 411.6 vs. 324.1 ± 299.0, p = 0.02), without any significant difference in other serum biomarkers characterizing renal function such as creatinine clearance, GRF, or urea. This could be explained by the fact that NGAL, a complex biomarker, reflects not only the acute renal injury, but also the acute deterioration in cardiac status. In a study by Kirbis et al., a urine NGAL level of 50 ng/mL had a 90% specificity for the diagnosis of acute heart failure, proving that NGAL is a reliable biomarker for predicting the deterioration of cardiac function. Therefore, the elevated levels of NGAL in patients with IAH in the present study could be also attributed to the deterioration of CO, NGAL being more sensitive to the alteration of CO than the other measured parameters.

Interestingly, in this study there was no association between severity scores and IAH, probably because we did not analyze separately the subgroup of patients with severe IAH (>20 mmHg) or with abdominal compartment syndrome, while the high values for severity scores would be expected in this subcategory of severe IAH patients.

CONCLUSIONS

This study demonstrates a complex interaction between CO and IAP in mechanically ventilated critically ill patients. Patients with increased IAP present lower values of CO, and whenever accomplished, the reduction of IAH was associated with a significant increase in CO in this patient population.

CONFLICT OF INTEREST

None declared.

REFERENCES


