Effect of intra-abdominal hypertension on left ventricular relaxation: a preliminary animal study

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Background. In the intensive care unit, intra-abdominal hypertension (IAH) is a frequently encountered, life-threatening condition. The aim of this animal study was to evaluate the effect of IAH on left ventricular (LV) relaxation (i.e. the active phase of diastole).

Methods. Seven male rabbits were anaesthetized before mechanical ventilation. A 20 mm Hg increase in intra-abdominal pressure (IAP) was then induced by intraperitoneal infusion of 1.5% glycine solution. Haemodynamic parameters were recorded and the relaxation time constant tau (considered to be the best index of left ventricle relaxation) was calculated. All haemodynamic measurements were recorded at baseline and then after induction of IAH.

Results. A 20 mm Hg increase in IAP was not followed by a significant change in arterial pressure, but was associated with increases in central venous pressure (from 2 [2 to 6] to 7 [7 to 12] mm Hg, P = 0.03), LV end-diastolic pressure (from 7 [6–8] to 15 [11–19] mm Hg, P = 0.04) and the relaxation time constant tau (from 16 [14–18] to 43 [34–52] ms, P = 0.048).

Conclusions. In this animal study, a 20 mm Hg increase in IAP impaired LV relaxation. Further studies are necessary to identify the causes of this impairment.

Keywords: abdominal compartment syndrome; diastolic function; haemodynamic; intra-abdominal hypertension

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Editor’s key points

- Raised intra-abdominal pressure can be life threatening in critically ill patients.
- In this study using rabbits, the effect of increasing abdominal pressure on diastolic function was measured.
- A clinically relevant increase in abdominal pressure impaired left ventricular relaxation.
- The mechanism requires further investigation.

Intra-abdominal hypertension (IAH) is frequently encountered in intensive care units (ICU) and can cause multiple organ failure.1 2 The haemodynamic impairment is complex and only partially understood.3–5 Several studies have described impairments in venous return, whereas others have reported increased systemic vascular resistance or right ventricular dysfunction.3–5 However, no data are available concerning the potential impairment of left ventricular (LV) diastolic function by high intra-abdominal pressure (IAP). In the ICU, fluid infusion is the front-line therapy for patients with haemodynamic instability due to abdominal compartment syndrome. Nevertheless, in the event of LV diastolic dysfunction, fluid infusion could lead to pulmonary oedema. As increases in both systemic vascular resistance and right ventricular dysfunction could impair LV diastolic function, we hypothesized that the latter would be impaired by IAH. The aim of this preliminary animal study was to evaluate the effect of IAH on LV relaxation (the active, ATP-dependent component of diastole6–7). We therefore studied the effect of IAH on the relaxation time constant tau, which is considered to be the best index of LV relaxation.6–8

Methods

Animal preparation

The experimental protocol was performed in seven male New Zealand white rabbits after approval by an institutional animal care committee.

After an overnight fasting with unrestricted access to water, s.c. premedication with ketamine (25 mg kg⁻¹) was performed. Then, the animals were anaesthetized by continuous infusion of midazolam (1 mg kg⁻¹ h⁻¹) and sufentanil (10 μg kg⁻¹ h⁻¹) through the marginal vein of the right ear. Adequacy of anaesthesia was evaluated by the lack of response to an ear pinch. Tracheostomy was performed to allow insertion of a tracheal cannula. The animals were then administered pancuronium bromide (2 mg⁻¹ kg⁻¹ h⁻¹) and were ventilated in a volume-controlled mode with an inspiratory oxygen fraction of 1.0 and a tidal volume of 10 ml kg⁻¹. We decided to ventilate the animals without positive end-expiratory pressure, in order to avoid this technique’s potentially confounding effect on the volume status and on the right heart. The respiratory rate was adjusted (55–65 min⁻¹).

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to obtain a baseline arterial $P_{CO_2}$ of 30–40 mm Hg. An air-filled balloon was placed in the oesophagus to monitor oesophageal pressure. A fluid-filled catheter was introduced into the femoral artery to measure blood pressure. The tip of this catheter was placed in the abdominal aorta, near to the renal arteries. The right common carotid artery was cannulated in the neck, in order to introduce a Millar Mikro-Tip catheter (Millar Instruments Inc., Houston, USA) into the LV. The position of the catheter tip was confirmed by observing the blood pressure profile. The right jugular vein was cannulated with a fluid-filled catheter, in order to measure central venous pressure (CVP). Body temperature was maintained at 38.5–39°C with a heating pad. Two fluid-filled catheters were inserted directly into the peritoneum (one for monitoring IAP and the other for infusing 1.5% glycine solution). The first catheter was connected via rigid tubing to a mercury manometer and zeroed near the mid-axillary line.

**Measurements and calculations**

Blood pressure, CVP, plateau pressure, oesophageal pressure, IAP and LV pressure (LVP) were recorded. The maximum rate of LVP increase during isovolumic contraction ($dLVP_{max}/dt$), an index of LV contractility, and the LV relaxation time constant tau were calculated by the data acquisition system (emka TECHNOLOGIES France, Paris, France). The time constant tau was calculated by considering the exponential decline of LV pressure during isovolumic relaxation, according to the derivative method described by Weiss and colleagues (Fig. 1). All measurements and calculations were made at the end of expiration.

**Study protocol**

Following instrumentation, a 1 h stabilization period was observed. The ventilation parameters were held constant throughout the study protocol. All haemodynamic data were recorded at baseline. The abdominal cavity was then filled with a (non-absorbable) glycine solution, in order to obtain a 20 mm Hg increase in IAP. After a further 1 h stabilization period, all haemodynamic data were again recorded. A stable blood sodium concentration was used as a guide to the absence of glycine absorption. All pressure measurements were performed continuously and averaged over 10 consecutive cardiac cycles. Data from baseline and IAH (IAP = baseline + 20 mm Hg) conditions were compared.

**Statistical analysis**

All results are expressed as the median [interquartile range] and (full range). A Wilcoxon rank-sum test was used to compare data. The threshold for statistical significance was set to $P < 0.05$.

**Results**

The animals’ median body weight was 3048 [2978–3118] g and the median age was 72 [50–107] days.

The baseline and IAH conditions did not differ significantly in terms of the heart rate or arterial pressure (Table 1). The plateau pressure increased significantly (from 23 [18–28] cm H$_2$O at baseline to 34 [27–42] cm H$_2$O with IAH; $P = 0.04$), whereas oesophageal pressure did not vary significantly (from 2.8 [1.5–4] cm H$_2$O at baseline to 3.9 [2–4.5] cm H$_2$O with IAH; $P = 0.22$). Significant increases in CVP and LV end-diastolic pressure (LVEDP) were also observed (Table 1). The relaxation time constant tau increased significantly with IAH (from 16 [13–19] at baseline to 43 [25–63] ms with IAH; $P = 0.048$). The value of $dLVP_{max}/dt$ was lower with IAH, but the difference vs baseline was not statistically significant (Table 1).

**Discussion**

The present study’s most important finding was the significant increase in the relaxation time constant tau with IAH.

Isovolumic relaxation (the early phase of diastole) can be quantified by measuring LVP and calculating the peak instantaneous rate of LVP decline. Nevertheless, this index is highly dependent on the aortic pressure. Since the LVP decline is assumed to be exponential over time, $dLVP/dt$ can be expressed as an exponential equation. When the natural log of LVP is plotted vs time, a straight line is obtained. The slope of this linear relation is called $A$. The tau time constant can then be calculated and equals $-1/A^8$ (Fig. 1). Tau is considered to be the best index of relaxation and so an increase in this parameter will reflect impaired relaxation. Here, the sharp observed increase in tau indicates that IAH impairs LV relaxation in this animal model. In two previous human studies, the effect of IAH on diastolic function was monitored with echocardiography. Alfonsi and colleagues studied 15 patients during laparoscopic aortic surgery, whereas Russo and colleagues studied 10 patients during laparoscopic hysterectomy. Using echocardiography, the researchers found that an increase in IAP decreased the $E/A$ ratio for mitral flow and the peak velocity of the $E$ wave and increased the $E$ wave deceleration time and the isovolumetric relaxation time. Both groups concluded that LV diastolic function was impaired by IAH. However, the fact that the indices used in these studies are highly dependent on loading conditions weakens the researchers’ conclusions. The mitral annulus diastolic peak velocity $E’$ (which can be investigated with Tissue Doppler Imaging) is less dependent on loading conditions and well correlated with tau, but it was not measured as an index of LV diastolic function in the two aforementioned studies.

Moreover, the two studies were performed in patients undergoing laparoscopic surgery and carbon dioxide insufflation. This gas can induce its own circulatory effects. In an animal study, Mann and colleagues have demonstrated that insufflation of carbon dioxide (but not argon) to an IAP of 15 mm Hg induced vasopressin release and thus an increase in systemic vascular resistance. We avoided these limitations by filling the peritoneum with fluid and using a gold-standard method to evaluate LV relaxation.

In the present study, the observed impairment in ventricular relaxation may have had several causes. First, relaxation...
is an energy-consuming process and is thus affected by myocardial ischaemia. The potential presence of IAH-induced heart ischaemia requires further investigation. Secondly, contraction and relaxation are intimately coupled and so a change in the former could affect the latter. The peak rate of increase in ventricular pressure during systole \(\frac{dLVP_{\text{max}}}{dt}\) is markedly influenced by acute changes in contractility but does not depend on afterload changes. The decrease in \(\frac{dLVP_{\text{max}}}{dt}\) observed in our animal model was not significant; this was probably due to the small sample size. It is therefore difficult to draw reliable conclusions concerning impaired contractility. Nevertheless, some animal and human studies have reported IAH-induced LV systolic dysfunction. However, other animal and human studies did not show evidence of impaired contractility. Thirdly, an acute increase in LV afterload could lead to impaired relaxation. Several studies have shown that IAH results in elevated circulating levels of renin, aldosterone,
A decrease in lung compliance caused by an upward dissection of the diaphragm could have increased the right ventricular afterload.\textsuperscript{5,11,17} The fact that the observed increase in plateau pressure was not accompanied by a change in tidal volume suggests that the observed increase in plateau pressure was not caused by a change in tidal volume suggesting that lung and/or chest wall compliance was lower during IAH.\textsuperscript{11,17} A decrease in lung compliance caused by an upward displacement of the diaphragm could have increased the right ventricular afterload.\textsuperscript{5,11,17} We also found that oesophageal pressure at end-expiration remained stable whilst CVP and LVEDP increased with IAH. This increase of left and right filling pressures (CVP and LVEDP) was probably not due to pressure transmission but to blood shift from the abdomen to the thorax. These results are in line with those of an animal study with the same IAP.\textsuperscript{17} However, other researchers have found an increase in oesophageal pressure, albeit at higher IAP levels\textsuperscript{18,19} or in a lung injury context.\textsuperscript{17}

In the present study, we increased the IAP by 20 mm Hg. We did not measure the exact baseline IAP which may have created some bias. However, previous studies showed that the baseline value of IAP in rabbits is close to zero (between 0 and 2 mm Hg) and lower than that in humans because the rabbit’s abdominal compliance is higher.\textsuperscript{20} We considered the baseline IAP to be zero and added 20 mm Hg because abdominal compartment syndrome (a life-threatening condition) was defined by the World Society of Abdominal Compartment Syndrome Consensus Conference as ‘a sustained IAP > 20 mm Hg that is associated with new organ dysfunction/failure’.\textsuperscript{2}

One of the limitations of the present study relates to the anatomical differences between rabbits and humans. As a quadruped, the rabbit has less developed anterior muscles, which leads to higher abdominal compliance.\textsuperscript{20} Moreover, the rabbit’s anatomical proportions are close to those of young human infants (i.e. a small thorax and a large abdomen) whilst larger mammals, like pigs, are more close to adults. Hence, some authors emphasize the value of the rabbit model in investigating the physiological effects of IAP on infants.\textsuperscript{21} Despite important differences between human and rabbit heart regarding the position in the thorax, the percentage of body weight (higher for humans) or heart rate,\textsuperscript{22} the rabbit as a model to study human heart function has several advantages over other mammals because the composition of sarcomeric proteins and the sarcolemmic reticulum contribution to calcium elimination are similar.\textsuperscript{23} Another important limitation is the lack of mechanistic evidence. In fact, this study should be considered as a preliminary study that enabled the formulation of hypotheses for investigation in further studies using right heart catheterization or Doppler echocardiographic examination. Nevertheless, physicians who care for patients with IAH must always bear in mind that these patients have impaired LV diastolic function. Indeed, fluid therapy—the front-line therapy in patients with shock and IAH—should be administered with care so as to avoid possible harmful effects on lung function.

In conclusion, a 20 mm Hg increase in IAP impaired LV relaxation in this animal model of IAH. Further studies are required to investigate the mechanism of the observed impairment in LV relaxation.

**Table 1** Haemodynamic parameters and airway pressures at baseline and with intra-abdominal hypertension (IAH). Results are expressed as the median [interquartile range] and (full range). HR, heart rate; MAP, SAP and DAP, mean, systolic and diastolic arterial pressure; IAP, intra-abdominal pressure; dLVP\textsubscript{max}/dt, maximum rate of increase in left ventricular pressure during isovolumic contraction; LVEDP, left ventricular end-diastolic pressure; CVP, central venous pressure; Tau, relaxation time constant

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>IAH (baseline + 20 mm Hg)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>202 [152–252] (150–255)</td>
<td>166 [116–216] (115–220)</td>
<td>0.60</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>60 [45–75] (44–76)</td>
<td>50 [38–67] (36–70)</td>
<td>0.20</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>72 [61–83] (60–85)</td>
<td>83 [60–103] (58–105)</td>
<td>0.15</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>48 [43–52] (35–60)</td>
<td>41 [30–56] (30–58)</td>
<td>0.45</td>
</tr>
<tr>
<td>dLVP\textsubscript{max}/dt (mm Hg s\textsuperscript{-1})</td>
<td>3590 [3463–3717] (3405–3750)</td>
<td>2111 [2011–2211] (2020–2225)</td>
<td>0.14</td>
</tr>
<tr>
<td>Tau (ms)</td>
<td>16 [14–18] (13–19)</td>
<td>43 [34–52] (31–55)</td>
<td>0.048</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>7 [6–8] (5–9)</td>
<td>15 [11–19] (10–20)</td>
<td>0.04</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>7 [2–2 to 6] (–1 to 7)</td>
<td>7 [–2 to 12] (–1 to 13)</td>
<td>0.03</td>
</tr>
<tr>
<td>Plateau pressure (cm H\textsubscript{2}O)</td>
<td>23 [18–28] (17–29)</td>
<td>34 [27–42] (25–43)</td>
<td>0.04</td>
</tr>
<tr>
<td>Oesophageal pressure (cm H\textsubscript{2}O)</td>
<td>2.8 [1.5–4] (1–5)</td>
<td>3.9 [2–4.5] (1.5–5)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

and catecholamine and thus increases systemic vascular resistance.\textsuperscript{4,5,11,14,15} Fourthly, an acute increase in right ventricular afterload could also impair LV relaxation.\textsuperscript{11,17} The observation that the observed increase in plateau pressure was not accompanied by a change in tidal volume suggests that lung and/or chest wall compliance was lower during IAH.\textsuperscript{11,17} A decrease in lung compliance caused by an upward displacement of the diaphragm could have increased the right ventricular afterload.\textsuperscript{5,11,17} We also found that oesophageal pressure at end-expiration remained stable whilst CVP and LVEDP increased with IAH. This increase of left and right filling pressures (CVP and LVEDP) was probably not due to pressure transmission but to blood shift from the abdomen to the thorax. These results are in line with those of an animal study with the same IAP.\textsuperscript{17} However, other researchers have found an increase in oesophageal pressure, albeit at higher IAP levels\textsuperscript{18,19} or in a lung injury context.\textsuperscript{17}

In conclusion, a 20 mm Hg increase in IAP impaired LV relaxation in this animal model of IAH. Further studies are required to investigate the mechanism of the observed impairment in LV relaxation.

**Declaration of interest**
None declared.

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