Shock, Publish Ahead of Print

DOI : 10.1097/SHK.0000000000001085

Non-invasive assessment of intra-abdominal pressure using ultrasound guided tonometry – a proof-of-concept study

Bloch Andreas [1], Glas Michael [1], Kohler Andreas [2], Baumann Ulrich[3], Jakob Stephan M[1]

1) Department of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland

2) Department for Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern,Switzerland

3) Vein Press GmbH, Muensingen, Switzerland

Corresponding Author:

Andreas Bloch, MD

Department of Intensive Care Medicine

Inselspital, University Hospital Bern

CH-3010 Bern, Switzerland

phone: +41-31-632-5073

fax: +41-31-632-4100

e-mail: andreas.bloch@insel.ch

Conflicts of Interest and Source of Funding

Andreas Bloch received a restricted grant from the foundation for research in anesthesia and intensive care medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland. Ulrich Baumann is owner of the VeinPresscompany (VeinPress GmbH, Muensingen, Switzerland). He was involved in the acquisition of data and in the revision of the manuscript but not in the analysis and interpretation of the data nor in the writing of the manuscript. The other authors have disclosed that they do not have any potential conflicts of interest.

Abstract

Background: Intra-abdominal hypertension jeopardizes abdominal organ perfusion and venous return. Contemporary recognition of elevated intra-abdominal pressure (IAP) plays a crucial role in reducing mortality and morbidity. We evaluated ultrasound guided tonometry in this context hypothesizing that the vertical chamber diameter of this device inversely correlates with intra-abdominal pressure.

Methods: IAP was increased in six 5 mmHg steps to 40 mmHg by instillation of normal saline into the peritoneal cavity of eight anesthetized pigs.Liver and renal blood flows (ultrasound transit time), intra-vesical, intra-peritoneal andend-inspiratory plateau pressures were recorded. For ultrasound-based assessment of intra-abdominal pressure(ultrasound guided tonometry), a pressure transducing, compressible chamber was fixed at the tip of a linear ultrasound probe, and the system was applied on the abdominal wall using different pre-determined levels of external pressure. At each IAP level (reference: intra-vesical pressure), two investigators measured the vertical diameter of this chamber.

Results: All abdominal flows decreased (by 39% to 58%), and end-inspiratory plateau pressure increased from 15mbar (14-17 mbar) to 38mbar (33-42 mbar)(median, range) with increasing IAP (all $p<0.01$). Vertical chamber diameter decreased from 14.9 (14.6-15.2)mm to12.8 (12.4-13.4) mmwith increasing IAP. Coefficients of variations between and within observers regarding change of the vertical tonometry chamber diameter were small (all<4%), and the resultswere independent of the externallyapplied pressure level on the ultrasound probe. Correlation of IAP and vertical pressure chamber distance was highly significant (r: -1, p: 0.0004). Ultrasound guided tonometry could discriminate between normal (baseline) pressure and 15 mmHg, between 15 and 25mmHg) and between 25 and 40 mmHg IAP(all $p\leq0.18$).Similar results were obtained for end-inspiratory plateau pressures.

Conclusions:In our model, values obtained by ultrasound guided tonometrycorrelated significantly with intra-abdominal pressures. The method was able to discriminate between normal, moderately and markedly increased IAPvalues.

Keywords

Intra-abdominal hypertension, abdominal compartment syndrome, ultrasound-guided tonometry, non-invasive intra-abdominal pressure measurement, end-inspiratory plateau pressure

Introduction

Intra-abdominal hypertension has a high prevalence among critically ill patients and is known to be an independent predictor of mortality (1-3). Since the causesfor raised intra-abdominal pressure (IAP) are diverse and the association between risk factors and presence of intra-abdominal hypertension is variable, it seems reasonable to screen ICU patientswith risk factors for elevated IAP(1, 2).

Ultrasound is routinely used and recommended in critically ill patients with abdominal problems (4-6). It has previously been demonstrated that ultrasound can also be used for non-invasive pressure estimation, for instance in central veins (7-9), in arteries [(10)], and in the brain [(11, 12)

Ultrasound guided tonometry is a non-invasive pressure measurement technique. An opaque chamber,filled with an ultrasound-translucent mixture of fluids, is attached to a linear ultrasound probe. This chamber is connected to a manometer and the applied pressure on the chamber is continuously displayed on a monitor.

By applying constant external pressure to the skin, the vertical diameter of this chamber is expected to decrease once intra-abdominal pressure rises.

The objective of this proof-of-concept study was to determine the accuracy and reliability of this technique to measure intra-abdominal pressure compared to the gold standard. We hypothesized that the vertical diameter of the ultrasound chamber is inversely correlated with the intra-abdominal pressuremeasured by an intra-vesical catheter. Since IAP is in part transmitted to the thoracic space, we investigated also whether changes in end-inspiratory airway pressure reflect the respective changes in IAP.

Materials and Methods

The study compiled with the Swiss national guidelines for the Care and Use of Laboratory Animals, National Academy of Sciences,1996, and was performed with the approval of the Commission of Animal Experimentation of Canton Bern, Switzerland (approval number BE 16/14).

The study group consisted of 8domestic pigs. Pigs were chosen because of their size which allowed instrumentation similar to that in use for humans.Considerations for sample size can be found in the statistics section. Three days prior to the experiment the animals were admitted to the local animal hospital where they were examined by a veterinarian. Prior to the experiment they were fasted overnight but had free access to water.

In compliance with the three R principle, the same group of pigs were subject to three different, unrelated studies, all involving ultrasound. First, a study investigatingintracompartimental pressure in both lower legs was conducted. After a stabilisation phase and establishment of a second baseline, the present study on abdominal pressure was conducted. Finally, a study on brain perfusion during increased intracranial pressure was performed. The results from the two studies involving leg compartment and increasing intra-cranial pressure will be reported separately.

Anesthesia, Surgery and Monitoring

The animals (weight 39.5 kg, range 39-42 kg)were premedicated with 20mg/kg ketamine and 2mg/kg xylazine intramuscularly, followed by the cannulation of an ear vein. After administration of 0.5mg/kg midazolam and 0.02mg/kg atropine, the pigs were orally intubated. They were ventilated using a volume-controlled mode (Servo-I, Maquet Critical Care, Solna, Sweden) with tidal volumes of 8mL/kg, a positive end-expiratory pressure of

5mmHg and a FiO2 of 30%, aiming for a paO2 above 90mmHg. The respiratory rate was adjusted to maintain arterial pH between 7.35 and 7.45 .

Following intubation, the animals received 1.5g of cefuroxime as an antibiotic prophylaxis prior to surgery. The anesthesia was maintained using propofol (4-8mg/kg/hr) and fentanyl (5-10 mcg/kg/hr),and the depth was controlled by repeatedly testing the response to nose pinch. Additional injections of fentanyl (50 μg) were given as needed. Muscle relaxation was maintained with rocuronium infusionduring the study measurements (0.5mg/kg/h) to ensure absence ofabdominal muscle contractions as recommended by practice guidelines(13-15).

Intravascular catheters were surgically placed in the left internal carotid artery for invasive blood pressure measurement and in the left internal jugular vein for central venous access.

After midline laparotomy, a Foley urinary catheter was placed surgically into the bladder. Ultrasonic transit time flow-probes (Transonic Systems Inc., Ithaca, NY USA) of compatible size were placed around the portal vein, the common hepatic artery and the right renal artery, respectively. A 8.5 French introducer sheath was placed transcutaneously with the tip next to the hepatoduodenal ligament for intra-peritoneal pressuremeasurement. A 20 French chest tube was placed transcutaneously into the peritoneal cavity for subsequentinstillation of warmed fluids to increase pressure. Finally, the abdominal wall was closed tightly with running suture so that the intraperitoneal cavity was sealed.

Hemodynamic and respiratory monitoring

Electrocardiogram (ECG) and oxygen saturation (pulse oximetry, attached to the tail) were continuously monitored. Arterial pressure (MAP) and central venous pressure (CVP) were recorded with pressure transducers (xtrans®, Codan Medical, Germany) which were calibrated using a water scale and zeroed at atrium level before the measurements. All pressure tracings were continuously displayed on a multi-modular monitor (S/5 Critical Care

Monitor®; Datex-Ohmeda, GE Healthcare, Helsinki, Finland) and subsequently displayed and recordedas two minute median values in a clinical information system (Centricity Critical Care, GE Healthcare).

Tidal volume, respiratory rate, PEEP, end-inspiratory plateau pressure and inspired oxygen concentration were continuously monitored and recorded in the same clinical information system.

Intraabdominal pressure monitoring

The intra-vesical pressure was continuously monitored by connecting the intra-vesical catheterto an intra-abdominal pressure device (UnoMeterAbdo Pressure, unomedical, Denmark). As recommended by the manufacturer, 20ml of normal saline were injected into the bladder retrogradly and the pubic bone served as reference level.

The intra-peritoneal pressure was continuously recorded with a pressure transducer (xtrans®, Codan Medical, Germany) which was calibrated using a water scale and zeroed at pubic bone before the measurements.

Ultrasonic transit time Flowmetry

Blood flow in the portal vein, the hepatic artery and the right renal artery was continuously measured with ultrasonic transit time flow-probes which were calibrated before insertion as recommended by the manufacturer. Onlyvalues with a signal quality>75% were used for further analysis. The measurements were averaged over one minute.

Ultrasound guided tonometry “VeinPress”

The VeinPress2014 System consists of a pressure transducing chamber filled with ultrasound translucent oil. The front wall of this chamber was applied to the skin surface, the back side attached to a13–6 MHz linear array ultrasound probe (HFL 38x transducer with a SonoSite

M-Turbo Ultrasound Machine, SonoSiteInc, Bothell, WA, USA) (figure 1). The pressure in the chamber was measured and displayed continuously on a monitorafter having brought the device in contact to the skin using commercially available ultrasound gel and zero adjustment.

Study protocol

After instrumentation was completed, two investigators performed independently ultrasound guided tonometry measurement in the middle of the left lower quadrant of the abdominal wall using three different predefined pressure levels (0mbar, 30mbar and 50mbar). During each pressure application,the vertical diameter of the chamber was measured and the ultrasound loops recorded (figure 1).Of note, the displayed size of the organ chamber diameter on the ultrasound screen was approximately ten times larger than its true size which made it relatively easy to quantify small differences in diameter length.After each examination, the vertical diameter of the chamber in the stored image was re-measured by the respective other investigator, resulting in 4 (online) measurements at each condition.Afterwards, intra-abdominal pressure (reference: intra-vesical pressure) was increasedto 15 mmHg, and then further in 5 mmHg steps to 40 mmHg by infusing warmed normal saline into the peritoneal cavity.At each intra-abdominal pressure level, ultrasound guided tonometry was repeated. Finally, the intra-abdominal pressure was normalized by draining the intra-peritoneal fluid through the thoracic drainage tube.

At each intra-abdominal pressure level, heart rate, arterial and central venous pressure, inspiratory plateau pressure, flows in the renal artery, the hepatic artery and in the portal vein, as well as the intra-vesical and the intra-peritoneal pressure were recorded.After the experiment, each of the two investigators measured the chamber diameters of their own and of the respective other investigator’s images again by using the recorded ultrasound loops, resulting in another 4 (offline) measurements at each condition.This time, the investigators were blinded to IAP level and applied external pressure level.

Sample size and statistical analysis

No data for sample size calculations were available. We hypothesized a moderate to strong correlation (correlation coefficient: 0.8) between the IAP measured intravesically and the respective estimated pressure by ultrasound-guided tonometry. The needed sample size required to detect a significant difference to a correlation coefficient of zero is 8 (with a probability of a type I error (α) of 0.05 and a power (1 - β) of 0.80 (StatsToDo, computer program to calculate sample size requirement for estimating the correlation coefficient).

Despite normal data distribution (Shapiro-Wilk-Test), values are displayed as median and range for better interpretation of data distribution and discrimination between the different intra-abdominal pressure levels. The effect of increasing intra-abdominal pressure on the different measurements was assessed using Friedman, followed by Wilcoxon test. For multiple testing (n=2-3) the statistical significance level was lowered to $p<0.02$. Spearman correlation coefficient and regression analysis with curve fitting was used for identifying the relationship between intra-abdominal pressure and tonometry assessments and end-inspiratory plateau pressure measurements, respectively. Within and between investigator comparisons of the vertical ultrasound chamber diameter were made using coefficients of variation.

Standard statistical software packages were used for analysis of data (GraphPad Prism 6, GraphPad Software, USA and IBM SPSS Version 21, IBM Corporation, USA).This manuscript adheres to the applicable ARRIVE guidelines.

Results

Systemic hemodynamics and intestinal blood flows

The mean arterial blood pressure increased in all pigs from baseline to the first IAP level andremained stable afterwards. The heart rate was not statistically significantly affected by the IAP levels. The flow in the renal artery decreased gradually over the course of the

pressure stages and increased after the IAP was normalized. The flow in the portal vein and in the hepatic artery increased from baseline to the first IAP level and decreased gradually thereafter. Both flows increased after the IAP was normalized (table 1).

Intra-abdominal flows and pressures

The predefined IAP levels were reached in all animals. Intra-peritoneal pressures increased in parallel with intravesical pressuresbut with a large inter-individual range at each pressure level (Electronic supplement1, http://links.lww.com/SHK/A688).

Renal (r: – 0.9286, p: 0.0022) and portal (r: -.8810, p: 0.0072) flows were inversely correlated with IAP levels, while hepatic artery flow did not correlate (r:-0.5476, p:0.1710). The flow in the renal artery decreased linearly with increased IAP. The blood flow in the hepatic artery decreased after an initial rise at pressure level of 15 mmHg. All flows increased after the IAP normalized.

Ultrasound guided tonometry

Due to technical difficulties the ultrasound analysis of the first pig could not be evaluated, therefore, the analysis of the ultrasound tonometry consists of a population of seven pigs.

Coefficients of variation for within observer variation were2.5% (1.1-3.4%; median, range) andbetween observer 2.5% (0.7-3.5%). Theaverage of the directly measured on-line measurements of the two investigators were used for further analysis.

The measured vertical chamber diameter was 14.8 (14.1-15.5) mmwithout external pressure and decreased with an externally applied pressure of 50 mbar from 14.9 (14.6 -15.2) to 12.8 (12.4-13.4) with increasing IAP($p<0.0001$, Electronic supplement 2, http://links.lww.com/SHK/A689). Since the values for the externally applied pressure of 30 and 50 mbar were comparablethe 50 mbar level values were used for further analysis

(Electronic supplement 2, http://links.lww.com/SHK/A689). Ultrasound-guided tonometry was able to discriminate between normal and increased values (≥15 mmHg, p=0.017), between 15 mmHg and 25 mmHg(p=0.018) and between 25 mmHg and 40 mmHg (p=0.017). However, the method could not discriminate (other) nearby intra-abdominal pressure levels due to overlapping ranges (figure 2).

Correlation of IAP and vertical pressure chamber diameter was highly significant (r: -1, p: 0.0004). However, curve fitting revealed linear in some and quadratic relationship in other animals.

End –inspiratory airway pressure

End-inspiratory airway pressure increased statistically significantly with increasing IAP levels ($p < 0.0001$; r: 1.0, $p < 0.0004$). Due to a linear relationship between IAP and end-inspiratory airway pressure in all animals, prediction of IAP by airway pressure was fairly precise(intravesical pressure mmHg = 2.019*end-inspiratory plateau pressure mmHg-18.46; $r^2=0.9114$) (Electronic supplement 1, http://links.lww.com/SHK/A688).

Discussion

In this proof of concept study values obtained by tonometry guided ultrasound correlated well with increasing IAP. The method was able to discriminate between normal, moderately and markedly increased IAP values. Inbetween, tonometry measurements were overlapping. Since the vertical diameter of the tonometry chamber decreased continually with increasing IAP in every pig, the methodmay also play a role in monitoring the evolution of IAP inindividual subjects. Nevertheless, we do not suggest that ultrasound guided tonometry can replace the established, (semi-) continuous assessment of IAP using urinary bladder pressure. Rather, ultrasound tonometry may be used to decide in what patients urinary bladder pressure measurement should be established.

Given the small between and within observer coefficients of variation, the accuracy and reliability of the vertical chamber assessments seem excellent and cannot account for thehigh variability of measurements at a given IAP level. A potential explanation is the relatively small size of the tonometry chamber with respect to the range of tested IAP. This results in low resolution: with a perfectly linear relationship, each 1 mmHg change in intraperitoneal pressure would have resulted in only ½ mm change in the vertical chamber diameter. In addition, it is conceivable that an altered shape of the chamber and a different amount and composition of fluid inside the chamber may improve precision. However, also differences in the compliance of the abdominal walland in the amount of fluid in the peritoneal cavity at a specific pressure level may have influenced the results(16). These circumstances and different hydrostatic forces in upper abdomen and pelvis may also explain thevariable differences between intra-peritoneal and intra-vesical pressures among the animals. These differences are in agreement with published data in different animal models of increased IAP(16-18).

The nature of an animal study, the relatively small sample sizeand the infusion of muscle relaxants during the measurements may limit the transferability of the results to clinical practice. Nevertheless, studies in humans demonstrate that deep muscle relaxation in comparison with moderate or no muscle relaxation may decreases IAP but not its variability (19-21).The strengths of the method are its non-invasiveness, easy applicability and the high reproducibility of the results.

Given the widespread use and availability of ultrasound in anesthesia, emergency departments, and in the ICU both for diagnostic and therapeutic purposes, we think that ultrasound guided tonometry has the potential as a screening tool in the acute care setting in patients with risk factors for developing increased IAP or abdominal compartment syndrome..

Increasing intra-abdominal pressure is transmitted to the intrathoracic space and therefore affects lung mechanics. By increasing pleural pressure both total lung capacity and lung compliance decrease. This is reflected by changes in the plateau pressure at a given tidal volume(22, 23). In our model, the rise in IAPwas closely tracked by respective changes in plateau pressure. This finding highlights the clinical importance of lung mechanics alsoin circumstances of elevated intra-abdominal pressure and may help to detect and understand the effects of intra-abdominal hypertension on cardio-pulmonary function as well as in guiding ventilator strategies.

The initial increase in blood pressure may present a reaction of the animals to the fluid infusion. The observed changes in portal and renal blood flow were inversely correlated with IAP levels. However blood flow in the hepatic artery was preserved. These findings are in accordance with the literature and underline the importance of hepatic arterial supply for liver perfusion(24-26).

In conclusion,in our model increased IAP can be detected reliably by ultrasound guided tonometry.. Nevertheless, the method will need further development and evaluation in clinical studies.

List of abbreviations

CVP Central venous pressure

ECG electrocardiogram

IAP intra-abdominal pressure

MAP mean arterial pressure

PEEP positive end-expiratory pressure

References

1. Malbrain ML, Chiumello D, Pelosi P, Wilmer A, Brienza N, Malcangi V, Bihari D, Innes R, Cohen J, Singer P, Japiassu A, Kurtop E, De Keulenaer BL, Daelemans R, Del Turco M, Cosimini P, Ranieri M, Jacquet L, Laterre PF, and Gattinoni L. Prevalence of intra-abdominal hypertension in critically ill patients: a multicentre epidemiological study. *Intensive Care Med* 30: 822-829, 2004.
2. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A, Regli A, Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olvera C, and Pediatric Guidelines Sub-Committee for the World Society of the Abdominal Compartment S. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med* 39: 1190-1206, 2013.
3. Zhang HY, Liu D, Tang H, Sun SJ, Ai SM, Yang WQ, Jiang DP, and Zhang LY. Study of intra-abdominal hypertension prevalence and awareness level among experienced ICU medical staff. *Mil Med Res* 3: 27, 2016.
4. Frankel HL, Kirkpatrick AW, Elbarbary M, Blaivas M, Desai H, Evans D, Summerfield DT, Slonim A, Breitkreutz R, Price S, Marik PE, Talmor D, and Levitov A. Guidelines for the Appropriate Use of Bedside General and Cardiac Ultrasonography in the Evaluation of Critically Ill Patients-Part I: General Ultrasonography. *Crit Care Med* 43: 2479-2502, 2015.
5. Volpicelli G, Lamorte A, Tullio M, Cardinale L, Giraudo M, Stefanone V, Boero E, Nazerian P, Pozzi R, and Frascisco MF. Point-of-care multiorgan ultrasonography for the evaluation of undifferentiated hypotension in the emergency department. *Intensive Care Med* 39: 1290-1298, 2013.
6. Shokoohi H, Boniface KS, Pourmand A, Liu YT, Davison DL, Hawkins KD, Buhumaid RE, Salimian M, and Yadav K. Bedside Ultrasound Reduces Diagnostic Uncertainty and Guides Resuscitation in Patients With Undifferentiated Hypotension. *Crit Care Med* 43: 2562-2569, 2015.
7. Thalhammer C, Aschwanden M, Odermatt A, Baumann UA, Imfeld S, Bilecen D, Marsch SC, and Jaeger KA. Noninvasive central venous pressure measurement by controlled compression sonography at the forearm. *J Am Coll Cardiol* 50: 1584-1589, 2007.
8. Martin DS, Lee SM, Matz TP, Westby CM, Scott JM, Stenger MB, and Platts SH. Internal jugular pressure increases during parabolic flight. *Physiol Rep* 4, 2016.
9. Baumann UA, Marquis C, Stoupis C, Willenberg TA, Takala J, and Jakob SM. Estimation of central venous pressure by ultrasound. *Resuscitation* 64: 193-199, 2005.
10. Zakrzewski AM and Anthony B. Non-Invasive Blood Pressure Estimation Using Ultrasound and Simple Finite Element Models. *IEEE Trans Biomed Eng*, 2017.
11. Maissan IM, Dirven PJ, Haitsma IK, Hoeks SE, Gommers D, and Stolker RJ. Ultrasonographic measured optic nerve sheath diameter as an accurate and quick monitor for changes in intracranial pressure. *J Neurosurg* 123: 743-747, 2015.
12. Robba C, Cardim D, Tajsic T, Pietersen J, Bulman M, Donnelly J, Lavinio A, Gupta A, Menon DK, Hutchinson PJA, and Czosnyka M. Ultrasound non-invasive measurement of intracranial pressure in neurointensive care: A prospective observational study. *PLoS Med* 14: e1002356, 2017.
13. Malbrain ML, Cheatham ML, Kirkpatrick A, Sugrue M, Parr M, De Waele J, Balogh Z, Leppaniemi A, Olvera C, Ivatury R, D'Amours S, Wendon J, Hillman K, Johansson K, Kolkman K, and Wilmer A. Results from the International Conference of Experts on Intra-

abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions. *Intensive Care Med* 32: 1722-1732, 2006.
14. Malbrain ML, De Laet IE, De Waele JJ, and Kirkpatrick AW. Intra-abdominal hypertension: definitions, monitoring, interpretation and management. *Best Pract Res Clin Anaesthesiol* 27: 249-270, 2013.
15. Malbrain M. Abdominal compartment syndrome. *F1000 Med Rep* 1, 2009.
16. Gudmundsson FF, Viste A, Gislason H, and Svanes K. Comparison of different methods for measuring intra-abdominal pressure. *Intensive Care Med* 28: 509-514, 2002.
17. Freimann FB, Otvos J, Chopra SS, Vajkoczy P, Wolf S, and Sprung C. Differential pressure in shunt therapy: investigation of position-dependent intraperitoneal pressure in a porcine model. *J Neurosurg Pediatr* 12: 575-581, 2013.
18. Jakob SM, Knuesel R, Tenhunen JJ, Pradl R, and Takala J. Increasing abdominal pressure with and without PEEP: effects on intra-peritoneal, intra-organ and intra-vascular pressures. *BMC Gastroenterol* 10: 70, 2010.
19. Williams MT, Rice I, Ewen SP, and Elliott SM. A comparison of the effect of two anaesthetic techniques on surgical conditions during gynaecological laparoscopy. *Anaesthesia* 58: 574-578, 2003.
20. Koo B-W, Oh A-Y, Seo K-S, Han J-W, Han H-S, and Yoon Y-S. Randomized Clinical Trial of Moderate Versus Deep Neuromuscular Block for Low-Pressure Pneumoperitoneum During Laparoscopic Cholecystectomy. *World J Surg* 40: 2898-2903, 2016.
21. Kim MH, Lee KY, Lee KY, Min BS, and Yoo YC. Maintaining Optimal Surgical Conditions With Low Insufflation Pressures is Possible With Deep Neuromuscular Blockade During Laparoscopic Colorectal Surgery: A Prospective, Randomized, Double-Blind, Parallel-Group Clinical Trial. *Medicine (Baltimore)* 95: e2920, 2016.
22. Kubiak BD, Gatto LA, Jimenez EJ, Silva-Parra H, Snyder KP, Vieau CJ, Barba J, Nasseri-Nik N, Falk JL, and Nieman GF. Plateau and transpulmonary pressure with elevated intra-abdominal pressure or atelectasis. *J Surg Res* 159: e17-24, 2010.
23. Cortes-Puentes GA, Cortes-Puentes LA, Adams AB, Anderson CP, Marini JJ, and Dries DJ. Experimental intra-abdominal hypertension influences airway pressure limits for lung protective mechanical ventilation. *J Trauma Acute Care Surg* 74: 1468-1473, 2013.
24. Pastor CM, Morel DR, Clergue F, Mentha G, and Morel P. Effects of abdominal Co2 insufflation on renal and hepatic blood flows during acute hemorrhage in anesthetized pigs. *Crit Care Med* 29: 1017-1022, 2001.
25. Ferrara G, Kanoore Edul VS, Caminos Eguillor JF, Martins E, Canullan C, Canales HS, Ince C, Estenssoro E, and Dubin A. Effects of norepinephrine on tissue perfusion in a sheep model of intra-abdominal hypertension. *Intensive Care Med Exp* 3: 46, 2015.
26. De Waele JJ, De Laet I, Kirkpatrick AW, and Hoste E. Intra-abdominal Hypertension and Abdominal Compartment Syndrome. *Am J Kidney Dis* 57: 159-169, 2011.

Figure legends

Figure 1: Lower part: ultrasound-guided tonometry system with opaque, fluid-filled chamber (marked a) and the pressure transducer (marked b). The system is attached to a linear array ultrasound probe (marked c). Left side: baseline IAP, the right side: intra-abdominal pressure of 40mmHg, resulting in decreased chamber diameter (marked d). Upper part: ultrasound pictures demonstrating the vertical chamber diameter at the respective pressure level while applying an external pressure of 50 mbar on to the skin. As illustrated with white lines the vertical diameter is measured from the very top to the most hyperechogenic line which resembles the margin of the chamber.

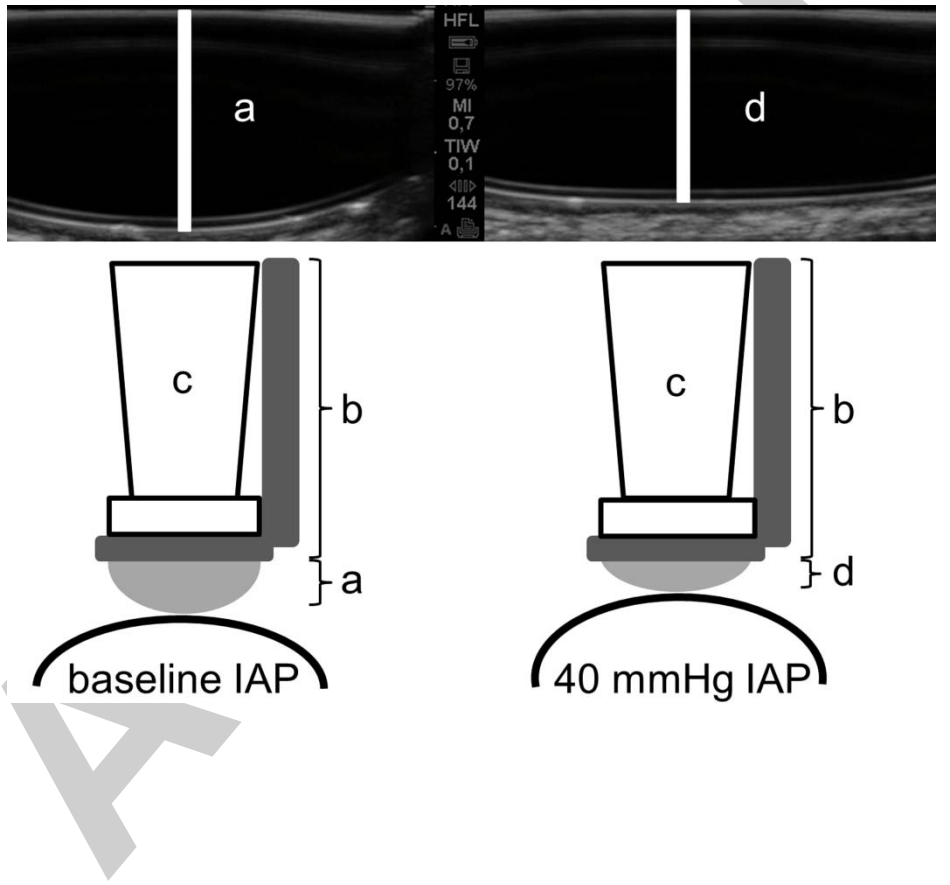
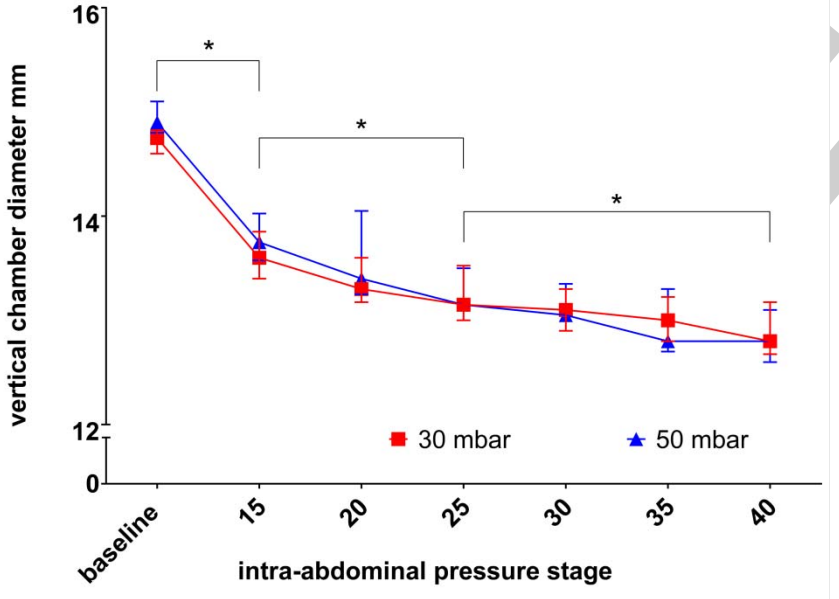


Figure 2: Vertical chamber diameter change over the respective stages for externally applied pressure level of 30 and 50 mbar. Means are displayed. Red resembles a pressure level of 30 mbar and blue 50 mbar. * illustrate significant discrimination after correction for multiple testing ($p < 0.02$)



	heart rate / min	MAP mmHg *	CVP mmHg *	renal flow ml **	hepatic artery flow ml **	portal flow ml **
baseline	83 [78-99]	88 [78-99]	3 [1-4]	354 [274-511]	207 [139-264]	1089 [942-1218]
15mmHg	108 [76-115]	102 [97-112] Δ	5 [2-6]	310 [286-454]	276 [194-412]	1279 [996-1392]
20mmHg	99 [80-107]	101 [94-113]	4 [2-6]	281 [258-456]	250 [168-363]	1035 [901–1226]
25mmHg	96 [76-114]	95 [80-117]	3 [2-5]	239 [227-440]	179 [159-335]	943 [756-1094]
30mmHg	91 [87-142]	95 [85-114]	4 [2-8]	226 [210-416]	145 [107-312]	837 [713-1022]
35mmHg	113 [81-144]	94 [86-112]	4 [2-7]	185 [162-344]	133 [111-290]	669 [616-911]
40mmHg	121 [76-135]	96 [85-107]	4 [2-9]	148 [141-284] Δ	127 [103-257]	594 [589-720] Δ
end	94 [78-97]	95 [81-109]	3 [1-5]	267 [239-460]	160 [86-311]	1096 [953-1102]

Table 1: Hemodynamics and regional blood flows. MAP: mean arterial blood pressure; CVP: central venous pressure; renal flow: flow in the right renal artery; portal flow: flow in the portal vein. Values are median. [interquartilerange].Friedman Test: *$p < 0.05$.**$p < 0.0001$. Wilcoxon Test (between baseline and most aberrant, and end value, respectively: Δ: $p < 0.02$.