Role of the focused ultrasound examinations in the perioperative patient safety

PhD thesis

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1. INTRODUCTION

The activity of the anaesthesiologist is not limited to intraoperative anaesthesia. Apart of providing optimal conditions for the surgical procedure, the main objective of the discipline is to optimize postoperative outcome and reduce mortality and morbidity.

The incidence of infectious and septic complications is followed by those of cardiovascular and pulmonary complications.

I focused my thesis on two special forms and an ultrasound-based approach of their risk assessment and prevention: hypotension associated to general anaesthesia and postoperative pulmonary complications (PPCs).

Albeit the definition of the intraoperative hypotension is not uniform in literature, abundance of reports underlines its negative impact on postoperative outcome, irrespective of the choice and cut-off of mean arterial or systolic pressure. Undesirable effects consist of myocardial injury, renal failure, and 30 days or one year mortality. Special attention should be paid on cases of postinduction hypotension (0-20 minutes of anaesthesia). In such circumstances, the level of the decrease of blood pressure is determined by the agents administered to induce and maintain anaesthesia and the early compensational capacity of the patients, latter, a function of actual physiological state, comorbidities and especially, preload.

Although, the definition of postoperative pulmonary complications is also heterogenous, the *European Perioperative Clinical Outcome – EPCO* is a good compass and describes a composite of respiratory tract infections, pneumonia, atelectasis, bronchospasm, pleural effusion, respiratory failure, aspiration pneumonitis or pneumothorax. These conditions are especially harmful in the postoperative period and can worsen the outcome by prolonged hospital stay, more frequent intensive care admission and higher mortality.

Consequently, the prediction and risk assessment of both above mentioned postoperative syndromes are vital and validated scoring systems have been developed. However, the available models: *HEART Score* for the prediction of hypotension associated to general anaesthesia and ARISCAT (*Assess Respiratory Risk in Surgical Patients in Catalonia)* Score for PPCs rely mostly on such conditions, like age and comorbidities, which are not or limitedly (e.g., therapy of chronic conditions, duration of the surgical procedure) modifiable by the anaesthesiologist. Challenges concerning fluid balance have utmost importance in provoking postinduction hypotension, Loss of body fluids, especially before urgent surgical procedures, can be profound even before surgery and fluid replacement is the most common and effective way to treat hypotension. On the other hand, extreme fluid replacement therapy is revealed as a risk factor of organ dysfunction and mortality, underlying the importance of correct estimate of preoperative preload.

With regards to PPCs, we have no reliable method predicting PPCs in the early postoperative period to allow for risk-oriented therapy plan.

Point of care ultrasound is becoming widespread in anaesthesiology and intensive care and is a promising tool for these challenges. Focused cardiac ultrasound (FoCUS) is a validated tool of the examination and monitoring of haemodynamic state in the perioperative timeframe. Measurement of the diameter of the inferior vena cava and its collapsibility following spontaneous ventilation (IVCCI) are methods of the assessment of preload and fluid responsibility. Its preoperative evaluation is an upcoming possibility.

Thoracic and lung ultrasound are effective methods of the detection of all PPCs, and sensitivity is higher specificity is appropriate when compared to conventional chest radiography.

Qualitative lung ultrasound score (LUS) relies on the characteristic appearance of different artefact profiles following the level of the deaeration of the lung tissue and allow for a non-invasive estimation. Special version for the perioperative period has been described. B-lines, comet-tailed artefacts have important role, they appear in the interstitial pathologies of the lung and their number has a good correlation to the severity of the underlying condition (e.g., pulmonary oedema, ARDS)

2. OBJECTIVES

- In our first research, our objective was finding evidence regarding whether preoperative IVCCI≥50% could identify patients at high risk for hypotension associated with general anaesthesia in an otherwise haemodynamically stable population.
- Additionally, we decided to evaluate the 50% value of IVCCI as a diagnostic cut-off value in the prediction of our clinical endpoint.
- The aim of the second study was to evaluate the role of the lung aeration score measured on definite timepoints of the first 24 h after major abdominal surgery in the prediction of developing PPCs.
- We targeted to identify the ideal time-point and cut-off, able to predict this clinical endpoint
- Characterisation of these cut-offs were also among our objectives.

3. METHODS

To complete our objectives, we performed two observational studies.

1st study: Role of inferior vena cava collapsibility index in the prediction of hypotension associated with general anaesthesia

Duration of the study: from 26/07/2016 to 30/10/2028. Location: 1st Department of Surgery, Semmelweis University: Registration number of the ethics approval: SE TUKEB 144/2016.

Patients

We enrolled elective, premedicated (RASS 0- –1) surgical patients if their planned surgery was performed under general anaesthesia with endotracheal intubation. Exclusion criteria were hypotension (>90 mmHg), uncontrolled hypertension (>180 mmHg or known phaeochromocytoma), not detectable IVCCI or measurement with limitation in evaluation (dyspnoea, decompensated heart failure, pulmonary arterial pressure >40 mmHg), patients prone to extreme risk associated to hypotensive events (ASA >3, significant stenosis of the carotid artery, significant valve pathology).

Demographic data (sex, age, height, weight), ASA class, relevant comorbidities were recorded.

Study design

Eligible patients were screened using ultrasonography within 30 minutes before surgery. The inferior vena cava was identified, and characteristics were recorded in the dorsal recumbent position under light sedation (RASS 0- -1) and spontaneous breathing. Two groups were formed according to the measured IVCCI: the *collapsing* group characterized by IVCCI≥50% (CI+) and the *noncollapsing* group (CI-) (in whom the IVCCI was< 50%)**.** This level was arbitrarily set with regard to the results in previously published literature verifying that IVCCI values between 40 and 50% are predictive for volume responsiveness in different clinical settings**.**

Vital signs were recorded before protocolled anaesthesia induction (HR, systolic and diastolic blood pressure, MAP). Two minutes after drug administration but before intubating the trachea, the identic vital signs were measured again. The immediate postinduction hemodynamic response was characterized. Hypotensive events were recorded if the systolic blood pressure dropped below 90 mmHg or a ≥ 30% drop in initial systolic pressure was observed.

Ultrasonographic measurements of the inferior vena cava

Ultrasound scans were performed by one of four adequately trained anaesthesiologists, following the guideline of the *ESC (European Society of Cardiology)* from subxiphoid (Fig.1) or transhepatic view in case of imaging difficulties. A device equipped with a convex probe of 5 MHz was used.

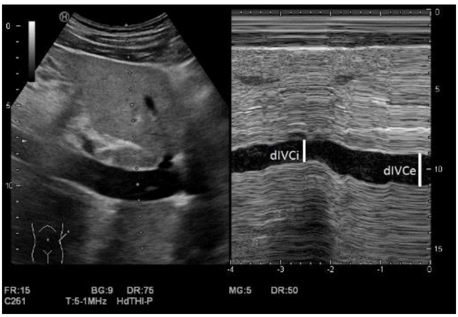

Figure 1: Typical ultrasound image of the inferior vena cava (left). M-mode image represents high respiratory collapsibility. (dIVCe = IVC diameter in expiration, dIVCi = IVC diameter in inspiration)

Anaesthesiologic practice

We provided anaesthesia four our patients following our institutional standards. Clear fluid intake was allowed until 2 hours before surgery except the cases where surgical diagnosis or comorbidities made full stomach probable. Routine premedication using 0,25-0,5 mg of alprazolam was given 1 hour before surgery. Regular cardiovascular medication of the patients was maintained on their established routine, except for diuretics and ACEi-s, which were withdrawn.

Standards of patient monitoring were tailored by needs of the patients' physiologic state and extent of the surgery, no extra methods were introduced. All patients were monitored continuously using ECG, pulse oximetry and capnography starting from the beginning of manual ventilation with the oscillometric or invasive measurement of the blood pressure. We recorded the vital signs measured immediately before induction and 2 minutes later, otherwise they were obtained at 5 min intervals.

To induce general anesthesia, our institutional standard practice of using fentanyl (1–2 μg/kg), propofol (1,5–2 mg/kg) and nondepolarizing muscle relaxants (rocuronium or cis-atracurium) according to age, weight, chronic organ function and the needs of the surgery was not changed for study purposes. Data describing preoperative fluid therapy, doses of drugs used for induction of anaesthesia, and type of the planned surgery were collected in both groups.

2nd study: The role of ultrasonographic lung ultrasound score (LUS) in the prediction of postoperative pulmonary complications

Duration of the study: from 25/08/2019 to 24/07/2020. Location: Semmelweis University, 1st Department of Surgery and Interventional Gastroenterology. Registration number of the ethics approval: SE RKEB 158/2019.

Patients

Subjects were ≥ 18 years, ASA 2 or 3 classified patients, who were scheduled for elective major abdominal surgery under general anaesthesia with endotracheal intubation on predetermined weekdays. Major surgery was defined as predicted duration of ≥120 min, expected need for postoperative intensive therapy or high dependency care. The prediction of the operation time and booking for ICU/HDU beds depended on the judgement of the attending surgeons and anaesthesiologists. Our exclusion criteria included preceding surgery within 30 days, history of lung resection, need for oxygen therapy at rest or ventilatory support at surgical admission, presence of active respiratory tract infection or thoracotomy as part of the current surgery.

Baseline characteristics such as basic demographic data, comorbidity data were recorded: COPD, hypertension, congestive heart failure (irrespective of EF, following ESC guidelines), diabetes (regardless of aetiology or treatment type), smoking status. Haemoglobin level and creatinine were also collected, and we recorded the initial levels of peripheral oxygen saturation.

Data of intraoperative management

These included the incisional site, type and duration of surgery, dose of intraoperative fluid therapy, estimated fluid balance in the operating room and epidural use. ARISCAT score, a cumulative determinant of PPC risk was also calculated.

Thoracic and lung ultrasound protocol

Ultrasonographic scans were performed by one of four adequately trained independent anaesthesiologists who had at least 2 years of experience in the field.

All examinations were performed using the same ultrasound machine (Hitachi Aloka Noblus, Hitachi Healthcare, Tokyo, Japan). As first choice, a linear transducer of 10–3 MHz was selected using the uniform settings of 7.5 MHz without tissue harmonic imaging. In particular cases, the ultrasonographer could choose a convex probe of 5 MHz to obtain images from obese patients.

Twelve fields of the thorax were scanned defined by the mamillar lines horizontally, the anterior and posterior axillary lines vertically. We performed latero-lateral scanning in at least two interspaces of each field with longitudinal probe position. LUS values (0-1) were determined by the ultrasound images based on literature references (works by *Silvia Mongodi*, modified and optimised to perioperative settings by *Audrey Monastesse*) and a value from a scale with a maximum of 36 point was given as detailed in Table 1. Images or clips were archived for offline validation.

These ’modified’ LUS calculations were performed before surgery (LUS 0h) and repeated between 30 min and 1 hour after surgery (LUS 1h) and 24 hours later. (LUS 24h).

Table 1: Calculation of LUS

LUS	*Original criteria*	*Modified criteria*
0	A-profile, max. 2 B-lines	Conform to original criteria
1	≥3 well separated B-lines/interspace	Original criteria OR One or multiple small subpleural atelectasis with regular pleural line.
2	Multiple coalescent (confluent) B-lines	Original criteria OR multiple small subpleural atelectasis separated with irregular pleural line
3	Tissue-like pattern / complete loss of aeration	Original criteria or subpleural atelectasis ≥1 × 2 cm

Anaesthesiologic practice

Anaesthesia protocol was similar to that of described for the previous study. Intraoperative ventilation used protective parameters with tidal volumes of 6-8 ml/kg based on ideal body weight, an FiO_2 of 0,4, a respiratory rate sufficient to maintain normocapnia and a PEEP=5 cmH_2O. Episodes of intraoperative desaturation (SpO2 < 95% or > 3% decrease from initial) were managed as follows: standardized recruitment manoeuvre of manual inflation, incremental elevation of PEEP, the additional increase of FiO_2 was optional. Patients were extubated either in the operating room following the end of the surgery or in the intensive care where after a spontaneous breathing trial.

Follow-up for PPCs

The follow-up period lasted 7 days postoperatively for the PPCs according to EPCO definitions extended with pulmonary oedema and need for reintubation. A clinician unaware of the patients' LUS values identified them based on clinical and radiographic records. A PPC+ and a PPC- group were formed. We documented the earliest or the most representative diagnosis.

Statistical considerations

For calculation of the sample sizes, a type one error of 0.05 and a required power of 0.80 were set. In the first study the decrease of the systolic blood pressure, in the second one, the between-group differences of LUS values were the values of interest.

For comparisons, we used Student's two-sample t-test and the Mann-Whitney U test in the case of continuous variables, while for nominal variables, χ^2 test or Fisher's exact test were used, where appropriate. Shapiro-Wilk W test challenged normality.

ROC curves with AUC estimation by Wilcoxon's method, and the standard error according to the method by DeLong described the diagnostical characteristics.

Variables with plausible impact on the clinical endpoints were entered into a forward stepwise logistic regression model building approach. For internal validation, a bootstrap method was used with 200 computer-generated samples. For the calculations we used Excel for Office 365, StatsDirect 3.1.20 and Dell Statistica 13 softwares.

4. RESULTS

Results of the 1st study

Population characteristics

A total of 102 patients were recruited. We had to exclude 19 previously eligible patients due to inadequately visualized IVC (7 cases), a lack of adherence to the protocol (8 cases), a lack of data (2 cases) or a change in anaesthesiologic management to ineligible methods (2 cases). Twenty patients were evaluated in the CI+ group and 63 in the CI+ group.

Table 2: baseline population characteristics in the CI+ and CI- groups

Variable	***Collapsible (CI+) group (N = 20)***	***Non-collapsible (CI-) group (N = 63)***	***P value***
Age, years, median (IQR)	69 (60.5-77)	61 (51-82)	**0.0066**
Male sex, N (%)	7 (35.0%)	29 (46.0%)	0.3858
BMI, kg/m^2	24.15±3.04	26.48±4.94	0.0505
ASA 3, N (%)	9 (45.0%)	16 (25.4%)	0.0959
COPD, N (%)	2 (10.0%)	7 (11.1%)	0.9999
Hypertension, N (%)	14 (70.0%)	36 (57.1%)	0.3060
Peripheral arterial disease, N (%)	3 (15.0%)	4 (6.4%)	0.3510
Diabetes, any type, N (%)	4 (20.0%)	12 (19.1%)	0.9999
Preoperative fluid intake, ml (IQR)	700 (500-1400)	600 (100-1200)	0.1438
Baseline systolic pressure, mmHg	147±16	143±17	0.3218
IVC diameter in expiration, mm	17±3	18±4	0.2031
Propofol dose for induction, mg/kg	1.77±0.15	1.81±0.16	0.3756

Baseline characteristics are summarized in Table 2. Mean age of CI+ group was higher than that of CI- patients and this difference was significant. In other terms the groups did not seem different. The rate of major surgery was 75,0% and 65,5%, respectively. (p=0,5848).

Haemodynamic changes

The mean postinduction decrease in systolic pressure in the CI+ group was 53.8±15.3 mmHg, which was significantly higher than the 35.8±18.1 mmHg observed among CI- patients (P=0.0001)), see Figure 2. The same phenomenon was present in the case of a relative decrease in systolic pressures: CI+ patients had a mean of 36.4 ± 9.1%, while this was 24.7±11.3% in the CI- group (P<0.0001).

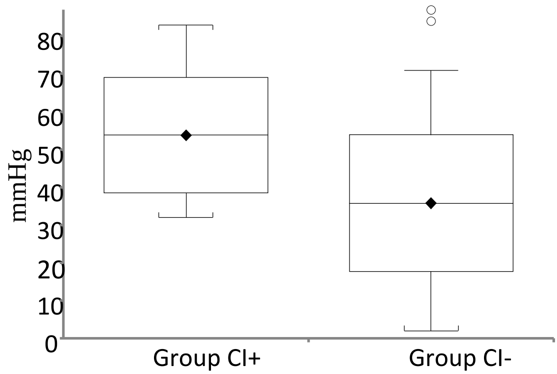

Figure 2: Decrease in systolic pressure after the induction of anaesthesia measured in the study groups (mmHg; mean, SD, CI95%, outliers)

Meanwhile, no difference was detectable in heart rate decrease, as CI+ patients presented a median of only 4 bpm (0 bpm–9.5 bpm), and 1 bpm (− 3 bpm–7 bpm) was observed among CI- patients (P=0.1901).

Performance characteristics of IVCCI

ROC curve is depicted as Figure 3 and its analysis resulted an area under the (AUC) of 64,8% (CI95% 52,1–77,5%).

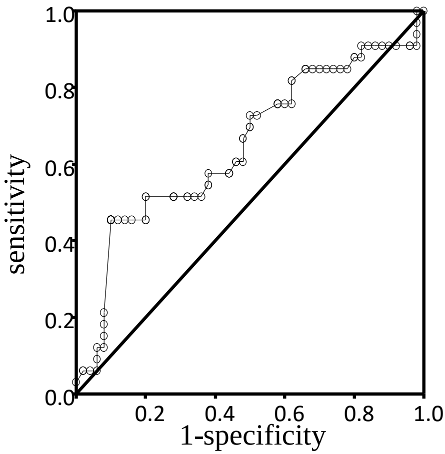

Figure 3: ROC analysis of IVCCI and prediction of hypotension

The maximum of the ROC curve's A *Youden-index* identified the ideal cut-off point at IVCCI=50%, the same level we arbitrarily set based on literature data to distinguish between CI+ and CI- groups. At this level the sensitivity was only 45.5% (95% CI 28.1–63.7%), but the specificity was as high as 90.0% (95% CI 78.2–96.7%). The positive predictive value was 75.0% (95% CI 50.9–91.3%), similarly, the negative predictive value was 71.4% (95% CI 58.7–82.1%) giving a positive likelihood ratio of 4.5 (95% CI 1.8–11.3).

Results of the 2nd study

Population characteristics

A total of 76 patients were enrolled. We had to exclude 9 previously eligible patients. Three of them were reoperated in the observation period, 2 withdrew consent, in 2 cases the follow-up scans were interfered by poor postoperative visualisation conditions, in 2 cases, the surgical plan was changed to a procedure not eligible for inclusion. Finally, 67 subjects were available for analysis: 18 patients in the PPC+ group, 49 were evaluated in the PPC- population. 67.

Table 3. Preoperative variables in the PPC+ and PPC- groups

Variable	***PPC+ N=18***	***PPC- N=49***	***p value***
age, years	68.4±10.2	66.4±9.6	0.4829
male sex, N (%)	11 (61.1)	26 (53.1)	0.5570
ASA 3, N (%)	12 (66.7)	13 (26.5)	**0.0026**
BMI, kg/m^2	26.4±4.6	26.5±5.5	0.9736
COPD, N (%)	5 (27.8)	5 (10.2)	0.1175
Hypertension, N (%)	11 (61.1)	33 (67.4)	0.6337
Chronic heart failure, N (%)	5 (27.8)	6 (12.2)	0.1494
Diabetes, N (%)	2 (11.1)	10 (20.4)	0.4903
Smoking, N (%)	2 (11.1)	5 (10.2)	1.0000
Active non pulmonary infection N (%)	3 (16.7)	6 (12.2)	0.6926
SpO_2 on ambient air, %, median (IQR)	97 (94-99)	98 (96-99)	0.2588
Haemoglobin, g/dl	12,4±2,5	13,0±1,9	0,2892
Creatinine, µmol/l	86,2±31,2	74,2±18,3	0,1408

Preoperative variables were similar in both groups, ASA 3 class was significantly more represented among PPC+ patients. Most of the operational data and characteristics available postoperatively were comparable except ARISCAT scores, significantly higher in the PPC+ group.

Table 4. Operational data and characteristics available postoperatively

Variable	***PPC+ N=18***	***PPC- N=49***	***P value***
Operation time, min, median (IQR)	190 (120-266)	123 (86-177)	0.0619
Surgeries with upper quadrant involvement, N (%)	14 (77.8)	35 (71.4)	0.7597
Upper gastrointestinal tract, N	4	9	
Pancreatic-biliary, N	7	16	
Liver resection, N	3	7	
other, N	0	3	
Surgeries limited to lower quadrants, N (%)	4 (22.2)	14 (28.6)	
colorectal surgery, N	3	12	
other, N	1	2	
laparoscopy, N (%)	1 (5.56)	8 (16.3)	0.4258
epidural catheter, N (%)	6 (33.3)	17 (34.7)	1.0000
Intravenous fluid, ml/kg/h, median (IQR)	10,7 (7.6-16.1)	10.9 (7.9-15.6)	0.9052
Estimated fluid balance, ml/kg, median (IQR)	22.4 (13.1-28.7)	19,1 (13-0-28.7)	0.1925
ARISCAT score	38±12	25±13	**0.0006**

Distribution of the postoperative pulmonary complications

We identified 18 PPCs with the following frequency data: 5 cases (27.8%) of respiratory failure, 2-2 cases of pulmonary oedema, bronchospasm, or respiratory tract infections (11,1%), 7 patients with pleural effusion (with or without atelectasis) (38.9%). There were 8 PPCs present on postoperative day 1.

The lung ultrasound score (LUS) kinetics

Baseline LUS levels of the PPC+ and PPC- groups were similar. Median LUS 0h values were 1.5 (IQR 1-2) and 1 (IQR 0-2) (p=0.4625) respectively. In the first postoperative hour, both groups had a marked increase resulting in scores of 6.5 (IQR 3–9) and 5 (IQR 3–7). The value tended to be higher among PPC+ patients, but this difference was not significant (p=0.1925). At LUS

24h measurements, a marked contrast was detectable: PPC+ patients showed a prominent and persistent elevation (median 6; IQR 6-10) while, in the PPC- group, LUS 24h values were decreased when compared to LUS 1h levels (median 3; IQR 2-4; p<0.0001). See Fig.4.

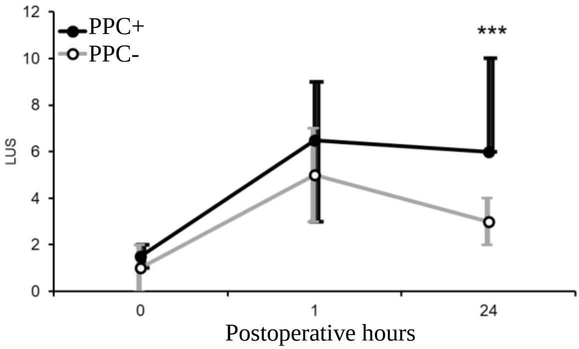

*Figure 4: Lung ultrasound scores at different timepoints in the PPC+ and PPC- groups. Median values with interquartile ranges. ***: p < 0.0001*

Diagnostic performance of LUS 24h

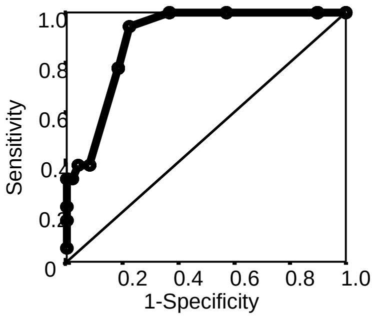

Figure 5: ROC curve of LUS24h in the prediction of PPCs

Based on the previous results LUS values of postoperative 24th hour were examined further and they were plotted for ROC (Fig.5). The area under the curve was 0.8963 (CI95% 0.8253–0.9672) indicating a strong model for prediction. The optimal cut-off value was identified at LUS=5. At this level, the sensitivity was 0.9444 (CI95% 0.7271–0.9986) with 0.7755 specificity (CI95% 0.6338–0.8823). Positive and negative predictive values were calculated as 0.6071 (CI95% 0.4058–0.7850) and 0.9744 (CI95% 0.8652–0.9994), respectively.

Results of the multivariate analysis

In forward stepwise model building creatinine, LUS at 1 h and at 24 h were retained.

Table 5. Odds Ratios of predictors for PPCs retained in the multivariate analysis

Variable	***OR***	***CI95%***	***bootstrap validated CI95%***	***p value***
creatinine	1.04	1.00-1.07	1.00-1.10	**0.0364**
LUS,1h	0.72	0.49-1.60	0.45-1.16	0.0966
LUS, 24h	2.64	1.56-4.50	1.93-4.20	**0.0003**

The 24th postoperative hour's LUS was verified to be an independent and significant risk factor for PPCs. Goodness of fit assessed by Hosmer Lemeshow had a p=0.7804 suggesting good calibration (p=0,7804).

5. CONCLUSION

1. Our first study verified that ultrasound imaging of the inferior vena cava and the measurement of its collapsibility following spontaneous ventilation are easy to integrate methods into the practice of the preoperative anaesthesiologic examination.
2. We demonstrated sufficiently that high collapsibility (at least 50%) of

the diameter of the inferior vena cava following spontaneous ventilation is accompanied with more profound hypotension associated with general anaesthesia.

3. According to our results, this method could predict postinduction hypotension with high specificity but low sensitivity.
4. We were the first to report a 24 hours' quantitative lung ultrasound protocol to follow postoperative pulmonary status.
5. We concluded that persistently high postoperative lung ultrasound score at 24 h identify patients at risk of or in an early phase of postoperative pulmonary complications.
6. This variable was adequately verified to be an independent risk factor of PPCs.

6. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

Publications related to Ph.D dissertation

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