Archives of Clinical & Experimental Surgery

Original Article

Arch Clin Exp Surg 2016;5:13-20

doi:10.5455/aces.20150813034247

Impact of surgical procedure artefacts on the hemodynamic parameters of an isoflurane-anesthetized swine cardiopulmonary bypass model

Paul Gavra[1], André Denault[2], Cristian Rosu[2], Louis Perrault[2], France Varin[1]

ABSTRACT

Objectives: This study quantifies cardiopulmonary bypass preparation artefacts on mean systemic arterial pressures (mAP), mean pulmonary arterial pressures (mPAP) and their ratio (mAP/mPAP) in order to assess the usefulness of this ratio as a pharmacodynamic marker for pharmacokinetic/pharmacodynamic modeling studies.

Materials and Methods: Fifteen anesthetized swine were monitored every minute before initiation of cardiopulmonary bypass. Percent relative changes from pre-artefact values (Δ%) were used during anesthesia induction and stabilization (Δ% minute-1 reduction rates). In addition, in some animals, amplitude and duration were recorded for the following procedures: sternotomy, pulmonary artery catheter installation, purse-string sutures and cardiac cannulations.

Results: Isoflurane 5% anesthesia induction effect on mAP, lasted on average 5.3±2.0 minutes at 5.9±1.9 Δ% minute-1. Isoflurane 2% anesthesia stabilization effect on mAP lasted on average 36.0±8.0 min at 0.8±0.9 Δ% minute-1. During stabilization, no change in mAP/mPAP was observed (p=0.68). Average amplitudes of artefacts on mAP were 30-50 Δ%; almost twice those observed for mPAP and mAP/mPAP for the same manipulations (p<0.05). Pulmonary artery catheter installation artefacts lasted longer than those of other procedures (p<0.05). Average artefact duration was 4.5±2.5 minutes (n=160).

Conclusions: In isoflurane-anesthetized swine, mAP/mPAP ratio remains constant during anesthesia stabilization, unlike mAP and mPAP individually. Moreover, the ratio shows potential as a pharmacodynamic biomarker for pharmacokinetic/pharmacodynamic studies involving CPB.

Key words: *Cardiopulmonary bypass, anesthesia, surgical artefacts, mAP/mPAP, swine*

Abbreviations: *AI: 5% isoflurane anesthesia induction, AS: 2% isoflurane anesthesia stabilization, CC: cardiac cannulations, CPB: cardiopulmonary bypass, ECG: electrocardiogram, mAP: mean systemic arterial pressure, mPAP: mean pulmonary arterial pressure, PAC: pulmonary artery catheter, PSS: purse-string sutures, S: sternotomy*

Introduction

Every year, worldwide, 1-1.25 million adult cardiac surgeries are performed [1], the majority of these requiring a cardiopulmonary bypass (CPB). Surgical preparations for this procedure are associated with physical stress, and during, lungs and heart are bypassed and neither is perfused. At the end of surgery, the patient is weaned from CPB and normal circulation is restored. Upon weaning from CPB, pulmonary reperfusion syndrome can cause pulmonary hypertension [2] which, in turn, might be associated not only with difficult weaning but also with right ventricular

Author affiliations : *[1]Faculty of Pharmacy, Université de Montréal, Montréal, Canada [2]Montreal Heart Institute, Montréal, Canada*
Correspondence : *France Varin, Faculty of Pharmacy, Université de Montréal, Montréal, Canada. e-mail: france.varin@umontreal.ca*
Received / Accepted : *July 21, 2015 / July 25, 2015*

dysfunction and a poor post-surgery prognosis [3, 4]. Consequently, treatment and prevention of pulmonary hypertension would be expected to reduce the severity of pulmonary reperfusion syndrome.

To better understand pulmonary hypertension and/or potential pharmacological treatment avenues, adult swine CPB models have been developed [5, 6]. They have provided insight into key hemodynamic parameters, such as the mean systemic arterial pressure (mAP) and mean pulmonary arterial pressure (mPAP). The ratio of these two measures (mAP/mPAP) has been suggested to act a biomarker for both pulmonary hypertension severity and selective pulmonary drug effects [7] which makes it an excellent candidate for pharmacokinetic/pharmacodynamic (PK/PD) relationship modeling. Monitoring of the mAP/mPAP ratio identifies conditions where mPAP decreases while mAP remains constant, thus indicating both the drug's local pulmonary effect and its lack of systemic hypotension. This ratio is already being used in human cardiac surgery as it has been recognized as a significant predictor of post-operative outcome [8]. Most importantly, this ratio was also found not to be influenced by the induction and maintenance of general anesthesia in cardiac patients [9]. The ratio has been also correlated with intraventricular septal curvature which is a marker of the consequence of pulmonary hypertension [1]. The ratio was found to be the best hemodynamic predictor of post-CPB circulatory failure [9]. Finally the mAP/mPAP ratio increases significantly in situation where inhaled agents are successful in treating pulmonary hypertension and right heart failure [2-4], thereby strenghtening its utility as a possible PK/PD descriptive tool.

Prophylactic interventions, such as nebulized drugs, are currently being investigated as potential treatment options for pulmonary hypertension [6, 7, 10]. These are administered before the beginning of CPB to exert their preventive antihypertensive effect locally on the lungs. However, as the drug is administered within time-constrained operating room conditions, their acute pharmacological effects often coincide with CPB preparation artefacts that, resultantly, affect the ratio. Monitoring and quantifying the changes in the ratio by surgical artefacts, in the absence of any drug, is necessary in the view of interpreting a PK/PD relationship obtained in the presence of both preparation artefacts and drug effects. Moreover, knowledge of artefact duration is important in order to properly design PK/PD protocols. Such a study is practically infeasible in surgical patients. Hence, the adult swine CPB model was used to replicate human CPB preparations e.g. isoflurane anesthesia induction (AI), anesthesia stabilization (AS) as well as surgical procedures: sternotomy, pulmonary artery catheter (PAC) installation, cardiac cannulations (CC) and purse-string suturing (PSS). This particular study was undertaken to quantify the amplitude and duration of the CPB preparation-related mAP, mPAP and ratio artefacts in a swine CPB model. The overall goal is to provide a better understanding of how CPB-related preparations affect mAP and mPAP values and more importantly, their ratio, a potential biomarker to be used in PK/PD modeling of medication intended for pulmonary hypertension.

Material and Methods

Animals

This observational study was performed on fifteen 3-month old castrated male 35 kg Landrace swine undergoing two separate research projects. The experimental procedures were approved by the institutional Animal Care Committee (*Comité de déontologie animale de l'Institut de cardiologie de Montréal*) in accordance with the recommendations and guidelines on the care and use of laboratory animals issued by the Canadian Council on Animals (Institutional Committee Numbers: 2010-73-2, 2010-73-3).

Animal preparation

Prior to entry to the operating room, animals were sedated with 2.2 mg kg^{-1} xylazine (Boeringer Ingelheim, Burlington, Ont, Canada) and 33-44 mg kg^{-1} ketamine hydrochloride (Ayerst Veterinary Laboratories, Guelph, Ont, Canada) intramuscularly. General anesthesia was induced with 5% isoflurane (AI) (Abbott Laboratories Limited, St-Laurent, QC, Canada) using mask ventilation. The animals were then intubated and ventilated at 15-18 breaths per minute and 6-8 mL kg^{-1} using a 0.66 inspired oxygen fraction. Subsequently, electrocardiogram (ECG) electrodes, an oxygen sensor and a rectal thermometer were installed. Under aseptic conditions, the left femoral artery and the right femoral vein were cannulated to install the mAP sensor and

a central venous catheter, respectively. Cannulations were also performed on the internal right carotid and the external and internal right jugular veins. Isoflurane concentration was then lowered to 2% for anesthesia maintenance, marking the start of the AS period. A median sternotomy followed by a sternal retraction was then performed. A pulmonary arterial catheter (PAC, Edward Life Sciences, Irving, Ca, USA) was next positioned in the pulmonary artery through the internal right jugular vein cannula to monitor mPAP. Correct positioning of the PAC was confirmed using pressure-waveform identification. Heparin was then given at 300 IU kg^{-1} (Leo Pharma, Inc, Ajax, Ont, Canada) preceding surgical manipulations.

CPB surgical manipulations

In the first protocol, animals (n=4) were scheduled to undergo coronary bypass procedures. Hemodynamic data collection was stopped after the AS period. Therefore, only AI, AS and PAC installation measures were available from these animals.

With the second protocol, animals (n=11) were scheduled to undergo CPB. Two PSS were placed on the aorta and one on the right atrium. The sutures were followed by aortic and subsequently atrial cannulation using 22F and 29/29F double-staged cannulas (DLP, Inc, Grand Rapids, Mich, USA), respectively. Once surgical manipulations were complete, CPB was initiated and data acquisition stopped.

Hemodynamic measurements

The mAP and mPAP were monitored at one minute intervals using a Solar® 8000M patient monitor (Marquette, Milwaukee, WI, USA), printed at the end of each experiment using a PRN50 digital writer (Marquette, Milwaukee, WI, USA). AI and AS periods were determined using mAP pressure reduction rates (% $minute^{-1}$). The AI period was considered to start at the beginning of mask ventilation (before mAP signal acquisition) and to end when isoflurane was changed from 5 to 2%. The time between 5% isoflurane induction and mAP signal acquisition was kept as short as possible but was dependent on cannulation time. The AI pressure reduction rate was calculated as follows:

$$\text{Equation 1: } AI\ rate = \frac{\frac{mmHg_I - mmHg_L}{mmHg_I} \times 100}{T_{mmHg_L} - T_{mmHg_I}}$$

where $mmHg_I$ is the initial mAP pressure value obtained at time T_{mmHgI} after signal acquisition and $mmHg_L$ is the last value of the AI period obtained at time T_{mmHgL}.

The beginning of the AS period corresponds to the moment where isoflurane was reduced from 5% to 2%. A constant mAP (within 5%) for more than 4 minutes was considered indicative of the AS period's end. Consistent patterns of pulmonary pressure decreases during the AS period were sometimes not available as they depended on how many trials were made before successful installation of the PAC. When PAC installation time was longer than the stabilization timeframe, pulmonary artery pressure was already stabilized under 2% isoflurane anesthesia conditions (n=9) leaving five animals for mPAP AS rate determination. The AS pressure reduction rates for mAP and mPAP were calculated similarly to the AI rates using Equation 1. During the AS period, care was taken to compute the mPAP rate using pressures at times devoid of any surgical interference.

For CPB-related surgical procedures, times corresponding to the beginning and end of each procedure were noted during surgery. Because sternotomy was carried out before installation of the PAC, mPAP data for it were not available. The amplitude of the artefact (Δ) expressed as a percent relative change from pre-artefact value (Δ%) of each surgical procedure was calculated for the mAP, mPAP and ratio, as follows:

$$\text{Equation 2: } \Delta\ \% = \frac{mmHg_S - mmHg_{PS}}{mmHg_{PS}} \times 100$$

where $mmHg_S$ is the maximum pressure value recorded during a surgical stress and $mmHg_{PS}$ is either the pre-artefact (PSS, CC) or post-artefact (PAC) pressure value. Pre-artefact values were recorded one minute before beginning the procedure while post-artefact values were taken down at the end of the PAC installation artefact. The PAC installation artefact ended when mAP pressures either showed a return to anterior reduction rates or were constant (within 5% variation) for more than 4 minutes. Post-artefact pressure values were used to calculate PAC installation artefact as no mPAP pre-artefact values were available.

For each surgical procedure, duration of the hemodynamic artefact was calculated as the difference be-

tween the onset time of the artefact and the time of return to its pre-artefact value. The beginning and end of each surgical procedure was also noted. To mimic an operating-room setting, all procedures were carried out without deliberate pause for return to pre-artefact value. For each animal, 3 PSS and 2 CC were performed. PSS were performed at short time intervals and thus occasionally generating merged pressure spikes. Merged pressure spikes were counted as a single PSS.

Statistical analysis

Descriptive statistics are presented as mean ± standard deviation. Changes in amplitude (Δ%) and durations of artefacts (min) on the hemodynamic parameters, mAP, mPAP and ratio, for each surgical manipulation were compared using SPSS 16.0.1 (SPSS Inc, Chicago, Il, USA). First, normality of distribution of data was assessed by means of the Shapiro-Wilk test. In comparisons involving all three hemodynamic parameters, normally distributed values were analyzed using one-way analyses of variance (ANOVA) and followed by Tukey's post-hoc test. Non-normally distributed data were analyzed using the Kruskal-Wallis test followed by the Mann-Whitney U test. Non-paired t-tests or Mann-Whitney U tests preceded by Levene variance tests were performed for mAP versus mPAP AS durations and also for ratios during versus after AS. Statistical significance was set at $p<0.05$.

Results

A typical progression of surgery and the hemodynamic changes associated with isoflurane induction and stabilization is represented in Figure 1 and with the different manipulations in Figure 2. The animal "n" differed between hemodynamic parameters as well as between surgical procedures. For the second protocol, complications were observed in 2 out of 11 animals: one died immediately after sternotomy during the AS period and the other did not tolerate prolonged isoflurane anesthesia (data recording ended after the AS period and before surgical manipulations).

During the AI period, only mAP was available as the PAC had yet to be installed. Mean elapsed time between beginning of induction and mAP signal acquisition was 16±10 minutes (n=15) and first recorded values for mAP averaged 89±31 mmHg. The AI period lasted on average 5±2 minutes (n=8), during which a reduction in mAP was observed at a rate of 5.9±1.9 Δ% minute^{-1}. In 6 animals, the preparations were too lengthy to determine the AI rate as these animals had already reached the AS period when first recorded data was available.

The AS period was found to be of similar durations (p=0.077) for systemic and pulmonary pressures, respectively, at 36±8.0 (n=11) and 25.0±14 (n=5) min after mAP signal acquisition. Based on the length of the

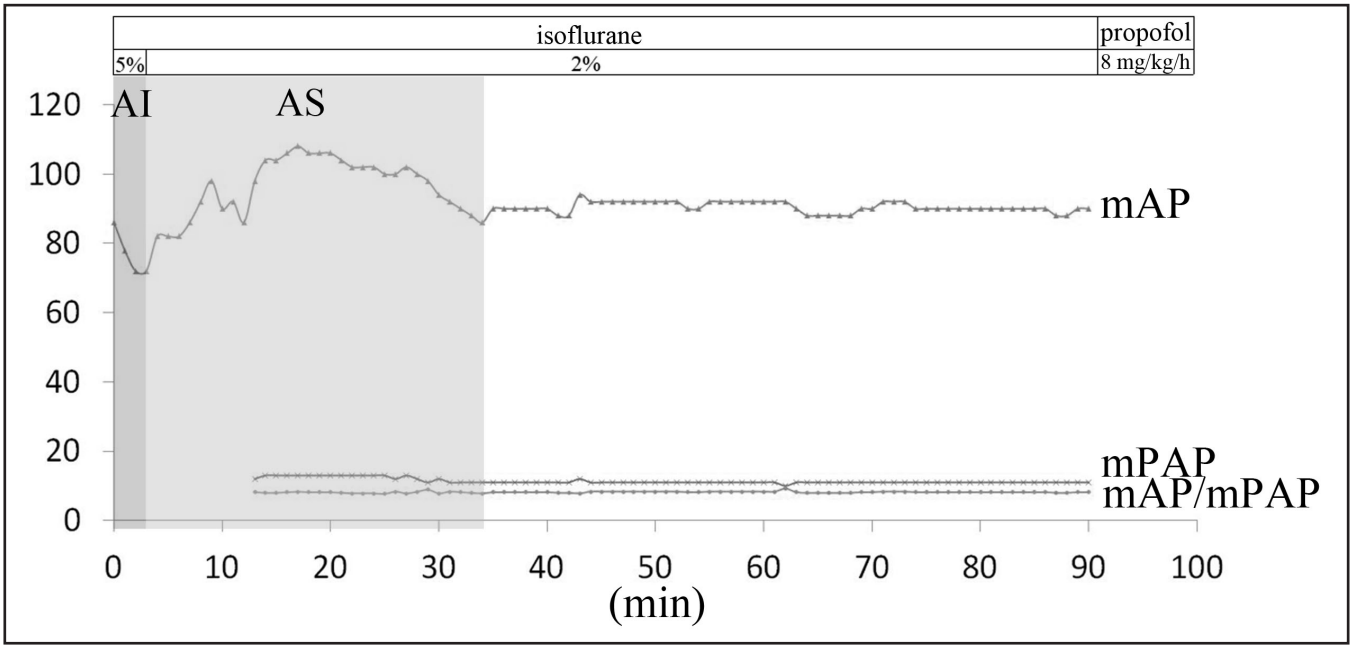

Figure 1. Changes in mean systemic arterial pressure in mmHg (mAP), mean pulmonary arterial pressure (mPAP) and mean systemic arterial pressure over the mean pulmonary arterial pressure ratio (mAP/mPAP) during anesthesia induction with 5% isoflurane (AI) and anesthesia stabilization with 2% isoflurane (AS) in a swine from the first protocol.

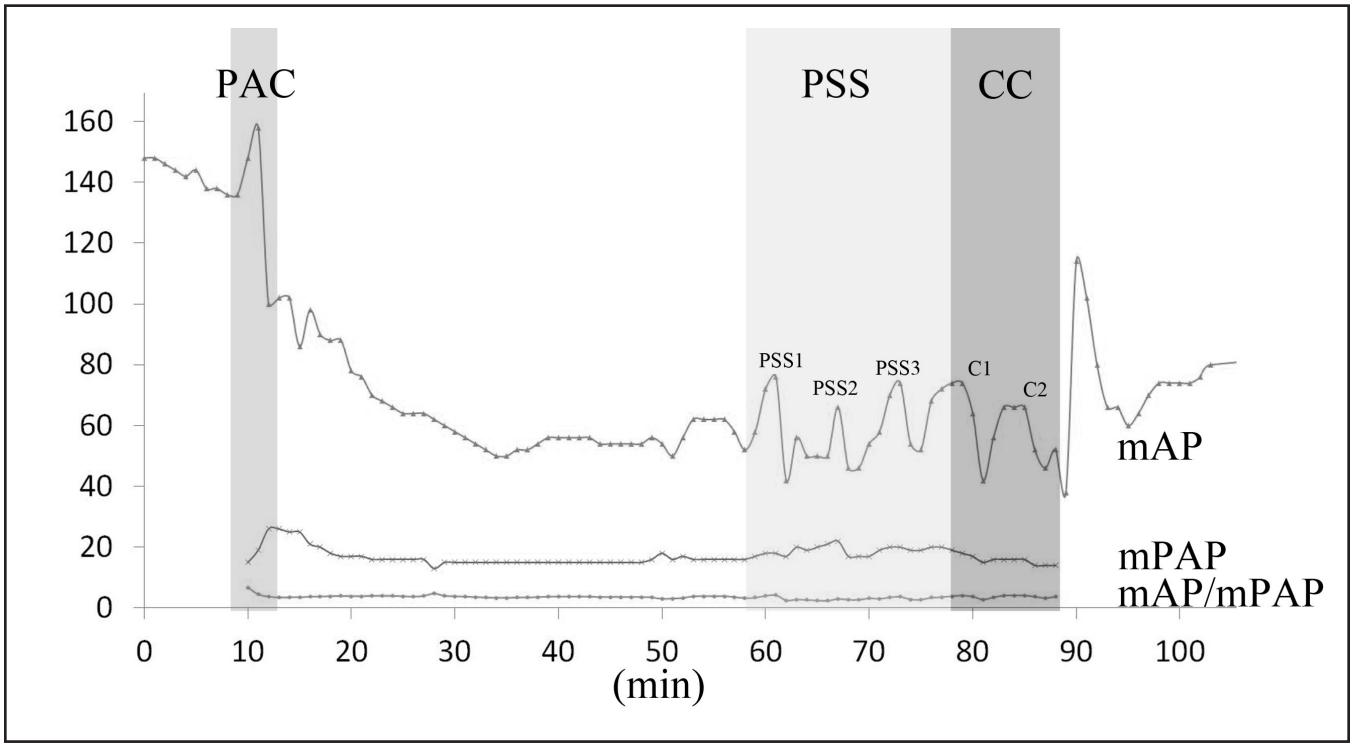

Figure 2. Progression of hemodynamic parameters and surgical procedure artefacts in a swine from the second protocol. Changes in mean systemic arterial pressure in mmHg (mAP), mean pulmonary arterial pressure in mmHg (mPAP) and mean systemic arterial pressure over mean pulmonary arterial pressure ratio (mAP/mPAP) are shown during pulmonary artery catheter (PAC) insertion, purse-string sutures (PSS): PSS1 and PSS2 aortic sutures; PSS3 auricular suture; and cardiac cannulations (CC) C1: aortic cannulation; C2: auricular cannulation.

arterial/venous cannulation procedures and PAC installation, mAP and mPAP rates were characterized in 11 and 5 animals, respectively. Using initial AS pressure values, mAP and mPAP pressure reduction rates were 0.8±0.9 and 0.2±0.2 Δ% min^{-1}, respectively, and there was an overall reduction of 17.6±6.6 (p=0.03) and 17.1±7.1 Δ% (p=0.04) for mAP and mPAP. Beginning and end-AS mean ratio values were similar (p=0.68).

Percent relative change from pre-artefact values and duration of hemodynamic changes caused by each CPB-related surgical procedure are summarized in Table 1. Often, because of the close timing of manipulations, the multiple aortic PSS artefacts translated as only one single hemodynamic artefact for a total of 22.

During sternotomy, Δ% were observed for mAP in only 5 animals and were highly variable (32±37 Δ%). The remaining animals did not show any artefact resulting in any kind of highly variable overall effect (9.9±23 Δ%, n=13).

The artefact amplitudes caused by each surgical manipulation for mAP and mPAP were compared following sternotomy. Mean mAP changes caused by PAC installation were all significantly greater than those observed for mPAP and for the mAP/mPAP ratio($p<0.05$). In contrast, no significant difference was found between mPAP versus ratio Δ% for PAC installation, PSS and CC.

Artefact durations on the hemodynamic parameters were also analyzed. Both PAC installation mAP artefact and ratio artefact lasted significantly longer than PSS and CC artefacts ($p<0.05$). Overall mean artefact duration of all pooled data (all surgical manipulations on all hemodynamic parameters) was 4.5±2.5 minutes (n=160).

Discussion

This study has confirmed that in the swine model, the ratio remains stable during induction and stabilization of general anesthesia as already documented in patients . In addition, the present work has documented both the amplitude and duration of the hemodynamic changes caused by standard CPB-related surgical procedures. These findings should be taken into account in studies that aim to determine drug-related hemodynamic effects in cardiac patients undergoing cardiac surgery with CPB. As such, this information will help not only in designing studies by reducing bias and enabling a better characterization of the net pharmacological effect, but also assist in the analysis of ongoing studies.

Table 1. Hemodynamic mean changes caused by each surgical procedure and their duration.

	Sternotomy (S)	Pulmonary Artery Catheter (PAC)	Purse-string Sutures (PSS)	Cannulations (CC)
mAP (n)	(13)	(13)	(22)	(16)
Δ Pressure (%)	9.9 ± 23	47 ± 33*	41 ± 19#	-34 ± 14†
Artefact duration (min)	6.6 ± 4.6	8.3 ± 3.7‡	4.2 ± 1.7	4.4 ± 1.8
mPAP (n)		(10)	(22)	(16)
Δ Pressure (%)		14 ± 8	21 ± 11	-21 ± 11
Artefact duration (min)		6.0 ± 2.3	3.9 ± 1.4	3.7 ± 1.8
mAP/mPAP (n)		(10)	(22)	(16)
Δ Ratio (%)		22 ± 13	25 ± 14	-25 ± 10
Artefact duration (min)		7.4 ± 4.3††	4.4 ± 1.8	3.7 ± 1.1

Mean changes (Δ), expressed as percentages of pre-artefact values. **mAP:** mean systemic arterial pressure; **mPAP:** mean pulmonary arterial pressure; **mAP/mPAP:** mean systemic arterial pressure over mean pulmonary arterial pressure ratio; **n:** number of animals.

* p = 0.001 and 0.045, mAP vs PAC mPAP and mAP/mPAP Δ%, respectively;
# p = 0.001 and 0.001,mAP vs PSS mPAP and mAP/mPAP Δ%, respectively;
† p = 0.004 and 0.004, mAP vs CC mPAP and mAP/mPAP Δ%, respectively;
‡ p = 0.012 and 0.012, ratio vs PSS and CC mAP artefact duration, respectively;
†† p = 0.001 and 0.001,ratio vs PSS and CC mAP/mPAP artefact duration.

Robitaille et al. [9] showed that, during general anesthesia, patients' systemic and pulmonary pressures decreased proportionally resulting in an unchanged ratio. Their study was conducted in a context of general anesthesia induced by a drug combination of fentanyl/sufentanyl, midazolam and isoflurane. In swine, no change was observed in the ratio during induction and stabilization, thus concurring with their results even with the sole use of isoflurane. As isoflurane is a common anesthetic for this animal species [11], our results can be generalized to a broader range of experimental models. Indeed, in the absence of surgical manipulation, the ratio seems to be a reliable hemodynamic marker that doesn't fluctuate with the degree of anesthesia.

Systemic and pulmonary pressures took up to 45 minutes to stabilize after lowering isoflurane from 5 to 2%. Therefore, by utilizing the ratio, it would be possible to start PD data sampling before complete stabilization, resulting in a considerably shorter experimentation time.

Surgery is an acute physical stress known to elicit several endocrine responses, in particular during CPB-related procedures. The sympatho-adrenal response involves physiological vasopressor surges [12] resulting in hypertension and possibly tachycardia [13]. Previous swine studies [14, 15] have documented the evolution of hemodynamic artefacts as well as plasma concentration changes of several biochemical markers of pain and inflammation at pre-determined time points: before, during and after esophageal and inguinal soft tissue surgeries. Potts et al. [12] were able to model and describe individual mAP artefacts as pressure spikes related to vasoactive amine bolus inputs. The present study monitored continuously the hemodynamic parameters during CPB procedures and quantified the amplitude of each hemodynamic change related to a specific surgical artefact in view of calculating their areas under the curve for application in future PK/PD studies.

The results here demonstrate that the amplitude and duration of surgical procedure artefacts on mAP and mPAP differed significantly one from the other. Variations in systemic pressures observed during surgical manipulations were to be expected as they involved surgical stress and, in the case of the PSS and CC, direct contact with the heart and/or aorta. In regards to PAC installation, the ensuing large mAP artefact could be attributed to pulmonary artery contact [16]. The resulting vasoconstriction may explain the high variability observed for mAP artefacts.

Overall, CPB-related surgical procedures caused on average a 40 % mAP change from pre-artefact values, higher than the 20% increase suggested by Potts et al. [12], most probably because of the nature of the stress.

Nursing procedures, such as endotracheal tube suctioning, do not generate as much stress as surgical procedures. The 40 Δ% of mAP is approximately two- fold higher than that observed for mPAP and the ratio. Even though pulmonary pressures usually show very minute variability as a result of their low-pressure nature [17], these results suggest that surgical manipulations do indeed affect pulmonary circulation. Consequently, use of the aforementioned hemodynamic parameters as markers for modeling within 7 minutes of a surgical manipulation would introduce a large vasopressor artefact in the area under the curve of any hemodynamic parameter. If manipulation artefacts are accounted for, the most useful hemodynamic parameter for PK/PD modeling is, in the opinion of the authors, the ratio. It demonstrates minimal amplitude artefacts while still reflecting changes in both mAP and mPAP.

Limitations

Given the observational nature of this study, no attempt was made to modify animal preparation, anesthetic procedures or timing of surgery manipulations. Firstly, lengthy animal CPB-related procedures, especially PAC installation time, resulted in reduced availability of pulmonary data during AS period. Secondly, depending on surgical conditions and/or animal responsiveness, amplitudes and durations of hemodynamic artefacts were greatly variable and sometimes overlapped, inflating the measured artefact and its variance . As this situation is highly representative of intraoperative clinical protocols, it might also be perceived as a strength. Furthermore, animals used in this study were healthy, relatively young adults and without previous surgeries, whereas a typical patient undergoing CPB would be subject to several previous health issues, most notably pre-existing pulmonary hypertension that could certainly affect the hemodynamic reaction to surgical procedures.

Conclusion

Monitoring mAP/mPAP ratios throughout CPB preparations enabled characterization of the amplitude and duration of surgical procedure artefacts. This information is necessary when designing and analyzing data from PD studies involving cardiovascular agents as these artefacts modify the PD biomarker used to assess efficacy. This work also reinforces the use of the ratio as a PD biomarker because, while remaining informative on the pulmonary drug effect, its sensitivity to surgical artefacts appears minimal.

Acknowledgements

This research was supported by Fonds de recherche du Québec - Santé (FRQS) and Groupe de recherche universitaire sur le médicament de l'Université de Montréal (GRUM). The authors would like to specifically acknowledge the invaluable help of Marie-Pierre Mathieu and Stéphanie Blanchet from Dr. Perrault's laboratory.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Haddad F, Guihaire J, Skhiri M, Denault AY, Mercier O, Al-Halabi S. Septal curvature is marker of hemodynamic, anatomical, and electromechanical ventricular interdependence in patients with pulmonary arterial hypertension. Echocardiography 2014;31:699-707.
2. St-Pierre P, Deschamps A, Cartier R, Basmadjian A, Denault AY. Inhaled milrinone and epoprostenol in a patient with severe pulmonary hypertension, right ventricular failure and reduced baseline brain saturation value from a left atrial myxoma. J Cardiothorac Vasc Anesth 2014;28:723-9.
3. Laflamme M, Perrault LP, Carrier M, Elmi-Sarabi M, Fortier A, Denault AY. Preliminary experience with combined inhaled milrinone and prostacyclin in cardiac surgical patients with pulmonary hypertension. J Cardiothorac Vasc Anesth 2015;29:38-45.
4. Denault A, Lamarche Y, Rochon A, Jennifer C, Mark L, Jean-Sébastien L, et al. Innovative approaches in the perioperative care of the cardiac surgical patient in the operating room and intensive care unit. Can J Cardiol 2014;30:S459-S477.
5. Hubert M, Salazkin I, Desjardins J, Blaise G. Cardiopulmonary bypass surgery in swine: a research model. J Exp Anim Sci 2003;42:135-49.
6. Fortier S, DeMaria RG, Lamarche Y, Malo O, Denault A, Desjardins F, et al. Inhaled prostacyclin reduces cardiopulmonary bypass-induced pulmonary endothelial dysfunction via increased cyclic adenosine monophosphate levels. J Thorac Cardio-

vasc Surg 2004;128:109-16.
7. Lamarche Y, Malo O, Thorin E, Denault A, Carrier M, Roy J, et al. Inhaled but not intravenous milrinone prevents pulmonary endothelial dysfunction after cardiopulmonary bypass. J Thorac Cardiovasc Surg 2005;130:83-92.
8. Hentschel T, Yin N, Riad A, Habbazettl H, Weimann J, Koster A, et al. Inhalation of the phosphodiesterase-3 inhibitor milrinone attenuates pulmonary hypertension in a rat model of congestive heart failure. Anesthesiology 2007;106:124-31.
9. Robitaille A, Denault AY, Couture P, Belisle S, Fortier A, Guertin MC, et al. Importance of relative pulmonary hypertension in cardiac surgery: the mean systemic-to-pulmonary artery pressure ratio. J Cardiothorac Vasc Anesth 2006;20:331-9.
10. Aubin MC, Laurendeau S, Mommerot A, Lamarche Y, Denault A, Carrier M, et al. Differential effects of inhaled and intravenous sildenafil in the prevention of the pulmonary endothelial dysfunction due to cardiopulmonary bypass. J Cardiovasc Pharmacol 2008;51:11-7.
11. Greene Sa, Benson GJ, Tranquilli WJ, Grimm Ka. Effect of isoflurane, atracurium, fentanyl, and noxious stimulation on bispectral index in pigs. Comp Med 2004;54:397-403.
12. Potts AL, Anderson BJ, Holford NH, Vu TC, Warman GR. Dexmedetomidine hemodynamics in children after cardiac surgery. Paediatr Anaesth 2010;20:425-33.
13. Desborough JP. The stress response to trauma and surgery. Br J Anaesth 2000;85:109-17.
14. Eisold S, Mehrabi A, Konstantinidis L, Mieth M, Hinz U, Kashfi A, et al. Experimental study of cardiorespiratory and stress factors in esophageal surgery using robot-assisted thoracoscopic or open thoracic approach. Arch Surg 2008;143:156-63.
15. Schoffmann G, Winter P, Palme R, Pollak A, Trittenwein G, Golej J. Haemodynamic changes and stress responses of piglets to surgery during total intravenous anaesthesia with propofol and fentanyl. Lab Anim 2009;43:243-8.
16. Moore JP, Hainsworth R, Drinkhill MJ. Phasic negative intrathoracic pressures enhance the vascular responses to stimulation of pulmonary arterial baroreceptors in closed-chest anaesthetized dogs. J Physiol 2004;555:815-24.
17. Kittnar O. Cardiac preload: hemodynamic physiology during thoracic surgery. Curr Opin Anaesthesiol 2011;24:21-3.