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RELATIONSHIP BETWEEN PROPOFOL PHARMACOKINETIC VARIATION AND HAEMODYNAMIC CHANGES DURING ANAESTHESIA INDUCTION AND KNEE-CHEST POSITIONING IN SURGICAL PATIENTS WITH PROPOFOL TCI ANAESTHESIA

Ph.D. Thesis
Mención de "Doctor Internacional"

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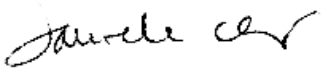
RELACIÓN ENTRE LA FARMACOCINÉTICA Y LOS CAMBIOS HEMODINÁMICOS DURANTE LA INDUCCIÓN Y POSICIONAMIENTO EN PACIENTES QUIRÚRGICOS ANESTESIADOS CON PROPOFOL

Thesis submitted for the degree of Doctor in Neuroscience

"Mención de doctorado internacional"

by

Daniela de Mascarenhas Chaló



SALAMANCA, 2020

Los abajo firmantes, Dra. Dª Consuelo Sancho Sánchez y Dr. D. Antonio Jesús Álvarez-Morujo Suárez, Profesores de la Universidad de Salamanca y miembros del Instituto de Neurociencias de Castilla y León

CERTIFICAN:

Que el presente trabajo titulado **"*RELACIÓN ENTRE LA FARMACOCINÉTICA Y LOS CAMBIOS HEMODINAMICOS DURANTE LA INDUCCIÓN Y POSICIONAMIENTO EN PACIENTES QUIRÚRGICOS ANESTESIADOS CON PROPOFOL*"**, ha sido realizado bajo su dirección por Dña. Daniela de Mascarenhas Chaló, y reúne las condiciones necesarias de calidad y rigor científico para su exposición pública y defensa con el fin de optar al título de Doctor por la Universidad de Salamanca.

En Salamanca, 25 de Septiembre de 2020

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… my tutors, their perseverance and patience
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… my children, my heart
…. and my husband, my fortress, my love.

"The value of experience is not in seeing much, but in seeing wisely."

"One of the first duties of the physician is to educate the masses not to take medicine"

Sir William Osler

ORIGINAL PUBLICATIONS

La presente tesis doctoral corresponde a un compendio de 3 trabajos aceptados previamente para publicación, que se especifican a continuación:

1. **PROPOFOL TCI REDUCTIONS DO NOT ATTENUATE SIGNIFICANT FALLS IN CARDIAC OUTPUT ASSOCIATED WITH ANESTHESIA INDUCTION AND KNEE-CHEST POSITIONING IN SPINAL SURGERY**

   Daniela Chaló, MD,*† Sara Pedrosa, MD,† Pedro Amorim, MD,‡ Sónia Gouveia, PhD,§ and Consuelo Sancho, PhD*

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2. EFFECT OF HEMODYNAMIC CHANGES IN PLASMA PROPOFOL CONCENTRATIONS ASSOCIATED WITH KNEE-CHEST POSITION IN SPINAL SURGERY: A PROSPECTIVE STUDY

Daniela Chalo [1, 2], Sara Pedrosa [2], Pedro Amorim[3], Aura Silva [4], Paula Guedes[4], Rui Correia [5], Sonia Gouveia [6, 7] and Consuelo Sancho[8]

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3. DESIGN OF AN INTERFACE FOR TEACHING CARDIOVASCULAR PHYSIOLOGY TO ANESTHESIA CLINICIANS WITH A PATIENT SIMULATOR CONNECTED TO A MINIMALLY INVASIVE CARDIAC OUTPUT MONITOR (LiDCO *rapid*®)

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INDEX

ABREVIATIONS

BIS: bispectral index

BMI: body mass index

Ce: effect-site concentration

CI: cardiac index

Cm: measured concentration

Cp: plasma concentration

CO: cardiac output

Dia: invasive diastolic pressure

ECG: electrocardiogram

EEG: electroencephalogram

GABA: γ -aminobutyric acid

HD: haemodynamic

HR: heart rate

IV: intravenous

KC: knee-chest position

LOC: loss of consciousness

MAP: mean arterial pressure

MDPE: median prediction error

MDAPE: median absolute performance error

PAC: pulmonary arterial catheter

PE: prediction error

Pk: pharmacokinetic

PPV: pulse pressure variation

SVV: stroke volume variation

SV: stroke volume

SVI: stroke volume index

SVR: systemic vascular resistance

Sys: invasive systolic pressure

TCI: target-controlled infusion

TOF: train of four

INTRODUCTION

Anaesthesia and patient outcomes

For long years, it was thought that anaesthetic management did not influence patient's outcome. Surgical morbidity and long-term mortality were attributed to patient's comorbidity, malignance of the disease, risk infection and type of surgery. Nowadays, there is an increasing evidence that intraoperative anaesthetic management can influence long-term patient outcomes[1–6]. In the last two decades, surgical mortality rates have been falling and, in part, this is due to a huge improvement in anaesthesia related factors and safety. For an anaesthesiologist, perioperative care is no longer the simple fact of administrating the anaesthetic drug and maintaining the patient "asleep". Direct-guided fluid therapy[7,8], maintaining intraoperative normothermia, minimizing blood transfusion and avoiding low mean arterial pressure and deep hypnotic level are additional procedures the anaesthesiologist is responsible for and that will probably improve patient's outcome and decrease surgical mortality[9,10].

Hypotension after induction of anaesthesia is quite common and more prevalent during the late post-induction period and before skin incision (5-10 minutes after), generally thought to be clinically irrelevant[11]. Nowadays, there is some evidence that small haemodynamic changes, such as hypotension, even for small periods, are associated with poor patient outcomes, because they have the potential to cause an ischemia–reperfusion injury which may be manifested as dysfunction of any vital organ, like acute kidney and myocardial injury[3]. Intra-operative management of hypotension is usually guided by conventional monitoring (systolic blood pressure and MAP) but these parameters could mask low levels of blood flow and oxygen delivery, even for short periods, leading to major surgical complications and longer hospital stays[2,5].

Pharmacokinetics and pharmacodynamics of propofol

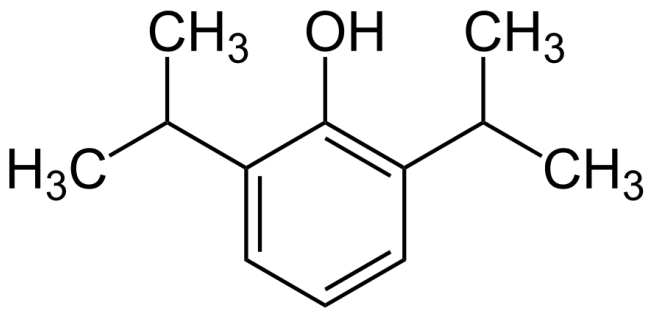

Figure 1: Propofol chemical structure: $C_{12}H_{18}O$.
(Wikipedia)

Since its introduction in clinical practice, the most commonly used intravenous (IV) anaesthetic is propofol[14], an alkylphenol (2,6-diisopropylphenol) currently formulated in a lipid emulsion. Propofol provides rapid onset and offset with context-sensitive decrement times of approximately 10 minutes when infused for less than 3 hours and of less than 40 minutes when infused for up to 8 hours. This "context-sensitive" drug half-life depends on a complex interaction between the rate of drug redistribution, the amount of drug accumulated in fat and the drug`s metabolism. Its mechanism of action is likely the enhancement of γ -aminobutyric acid ($GABA_A$)- induced chloride currents. Propofol causes a dose-dependent decrease in arterial blood pressure through a decrease in cardiac output and systemic vascular resistance[15,16]; propofol also seems to decrease the reflex baroreceptor and reduces sympathetic nerve activity[17,18], and produces moderate respiratory depression. A unique action of propofol is its antiemetic effect, even at concentrations less than those producing sedation. The metabolites of propofol are thought to be inactive and undergo renal elimination. Because clearance of propofol (>1.5 L/minute) ($30ml/min^{-1}/kg^{-1}$) exceeds hepatic blood flow, extrahepatic metabolism or extrarenal elimination may occur[19]. Extrahepatic metabolism has been confirmed during the anhepatic phase of patients receiving a transplanted liver with the determination of propofol metabolites after propofol administration in the absence of liver tissue. The most important

extrahepatic site of propofol metabolism is the kidney. Renal metabolism of propofol accounts for up to 30% of propofol clearance, and this explains the rapid clearance of propofol, which exceeds liver blood flow. The lungs also may play a role in extrahepatic propofol metabolism. In humans, a 20% to 30% decrease in propofol concentration measured across the lung exists with a higher concentration of the metabolite 2,6-diisopropyl 1,4-quinol on the arterial side of the circulation[20,21].

In general anaesthesia, patient inter-individual variability to predict the individual hypnotic drugs requirements or recovery time is still an interesting issue[22]. Some of the factors that influence the pharmacokinetics are well known since the 1990s, such as age, weight, gender and some physiologic parameters. After the publication of the human genome in 2003, pharmacogenetics has become an interesting instrument to understand genes and proteins variations, transforming the actual medicine in a personalised medicine[23]. There are some genes and polymorphisms that can alter hypnotic drugs pharmacodynamics.

Pharmacokinetic models were developed to facilitate anaesthesia maintenance to drive infusion pumps, estimating plasmatic concentrations and effect-site concentrations using complex pharmacokinetic and pharmacodynamic models. In many clinical applications, propofol is administrated using target-controlled infusion (TCI) techniques and has proven to be satisfactorily accurate during anaesthesia[24–27].

Although not perfect, Schnider's pharmacokinetic (Pk) model was the recommended to be used for TCI and advisory displays in *Masui et al*[28] who compared the performance of three compartmental and one physiologically based recirculatory pharmacokinetic model for propofol: Schnider, Marsh, Schüttler and Upton, respectively. The two commonly used and commercially available Pk models in clinical practice in adults are the Schnider and Marsh. The first one, based on arterial blood sampling after intravenous bolus followed by continuous infusion in volunteers, uses as covariates of the metabolic clearance: age, height, lean body mass and total body weight[29]; it can be an advantage over the Marsh model, for

older patients, because it adjusts the dose and the infusion rate according to the patient's age. In contrast, the Marsh model derives from the Pk variables of *Gepts et al*[30] and sets compartmental volumes proportional to weight. Recently, this model showed some benefits in obese patients adjusting the body weight instead of using total body weight[21].

As indicated above, propofol Pk models incorporate covariates as age, weight and height but not physiological parameters as cardiac output (CO) variation. We know that anaesthesia induction and maintenance with propofol will probably cause arterial hypotension and, consequently, cardiac output variation[14,15,17].

Upton and Ludbrook[31] developed a propofol Pk model based on a recirculatory and physiologically system. Recently, there were some modifications to Upton model with two assumptions: first, the parameter cardiac output varies with weight and second, also cardiac output decreases with age[32]. In theory, the Upton model would predict the effect of common haemodynamic disturbances such as congestive heart failure, severe blood loss, dehydration and other high and low cardiac output states but more studies are required to fine tune its performance, namely in the first minutes of infusion.

The effect of cardiac output variation and the propofol pharmacokinetics was also being studied by Upton and Ludbrook[33], that reported an inverse relationship between CO and propofol concentrations after a short propofol infusion in an ovine model. Myburgh[34] observed the same relationship during longer propofol infusions in high-CO state induced with catecholamine infusion also in ovine. Kurita[35] confirmed, in a swine model, that propofol plasma concentrations were inversely correlated to changes in CO during constant infusion. It must be highlighted that most of the published studies were performed in animal models, with no studies in humans. Recently, Keyl[36] found that Schnider's Pk model markedly underestimated propofol plasma concentrations in patients with impaired left ventricular function. It can be speculated that the difference between the predicted and measured propofol

concentration in patients with lower CO is most likely related to a decrease in total propofol clearance, but data is still needed to correlate CO or liver blood flow and plasma clearance of propofol[37].

Knee-chest positioning, a prone position variant

Some surgical positioning, such as prone and knee-chest (KC) position (Figure 2), seems to change haemodynamic parameters and influence anaesthesia drugs pharmacokinetics, reducing propofol requirements[38–42].

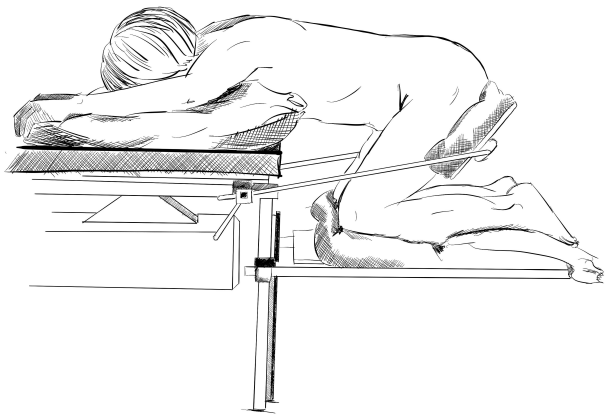

Figure 2: Knee-chest surgical position, a variant from the prone position.

(original drawing by *Henrique Chaló*)

A study in awake volunteers reported a 15% to 20% reduction in CO after the knee-chest position[43], likely related to a decrease in venous return due to blood sequestration in lower limbs.

Some years ago, we presented an observational retrospective study[44] in consecutive patients selected from data basis in neurosurgery. All patients submitted to craniotomy for tumour surgery in either supine or prone position were included. In our study, patients in the prone position required less propofol concentrations.

Prone position and its variants had been developed as a result of the requirement for surgical access. It has been studied since the 1930s and extensively described by Anderton[45] and Edgcombe[46] who recognized physiological changes and associated complications. Some of the physiological changes are cardiovascular, as decreased cardiac output and inferior vena cava obstruction and respiratory, as changes in lung volumes and abnormal distribution of pulmonary blood flow and ventilation.

The effects of the prone position and its variants on cerebral blood flow and cerebral oxygenation are also not well quantified[47]. Although cerebral oxygenation in anesthetized patients in the prone position can be maintained within safe margins, there is evidence of impairment of autoregulation[48], and this might be reflected in low bispectral index (BIS) values.

Major complications associated to prone position are: injuries in the central nervous system, as injuries from arterial occlusion, injuries from venous occlusion, air entrainment, cervical spine injury and undiagnosed space-occupying lesions; injuries to the peripheral nervous system, as peripheral nerve injury; pressure injuries; ophthalmic injury and embolic complications[47,49,50]. Accordingly to these changes and complications, soon there were many devices developed for patients submitted to surgery in prone position, with the purpose to attenuate these deleterious effects, such as specific body mattress; pelvic and shoulder supports; head and neck supports and protection for the face devices; and abdominal frames and mattress[51].

The knee-chest position is currently used in a very large number of surgical procedures. Anaesthesiologists must be prepared to anticipate and minimize predictable risks, like intraoperative hypotension periods due to cardiac output reduction to critical ischemic levels. Positioning patients in KC position following anaesthesia induction further reduces venous return and cardiac output.

Technology and monitoring advances

In the last 30 years, perioperative technology devices had a great progress, such as depth of anaesthesia and cerebral and tissue oxygen monitoring and minimally invasive cardiac output monitors[12,52,53]. Despite these technological advances, occult low levels of blood flow and oxygen delivery still happen in high-risk surgical patients.

Monitoring of hypnotic depth of anaesthesia using digital processing techniques applied to the electroencephalogram (EEG), such as Bispectral Index monitor, is used worldwide to guide anaesthesia maintenance in high-risk patients. It is well known that elderly patients and patients with important comorbidities require less anaesthetic drugs than healthy young patients, therefore BIS monitoring is clinically useful to titrate anaesthetic drugs and avoid awareness risk in these patients[54].

For long years, pulmonary arterial catheter (PAC) was considered the gold standard for cardiac output monitoring in critically ill patients during anaesthesia procedures and intensive care units. The recent trend in cardiac output monitoring is minimally invasive such as arterial pulse contour and pulse power analysis methods. It is an easily and accurate alternative to PAC, as the minimally invasive devices have been compared with innumerable studies to PAC and compared to each other[55–57]. Clinical benefit of monitoring haemodynamic (HD) parameters in high-risk patients is widely known, as arterial pressure variations might not reflect cardiac output, tissue perfusion pressure and oxygen delivery. The objectives of HD monitoring are to assess and optimize cardiac function, in order to achieve and maintain adequate tissue perfusion, guiding fluid therapy and cardiovascular drugs. Also, study of the arterial pressure tracing serve not only to predict but also to assess the fluid response with pulse pressure variation (PPV) and stroke volume variation (SSV) parameters in ventilated patients[58]. Cyclic changes in intrathoracic pressure during respiratory cycle may influence ventricular filling when stroke volume is preload dependent. PPV and SSV are useful parameters consisting in locating patients in the Frank Starling curve,

namely when this reaches the plateau and fluids are given but there is no further increase in stroke volume.

LiDCO *rapid*® (LiDCO Ltd., Cambridge, UK) [13,59–61] is a minimally invasive cardiac output monitor based on the principle that the stroke volume can be tracked continuously by analysis of the arterial pressure waveform, as this is a result of an interaction between stroke volume and the vascular structure. Pulse CO technique uses a standard peripheral arterial line to extract a pulse wave (the systolic and the diastolic part of the pressure curve) based on the assumption of mass/power conservation in a system, when there is a linear relationship between net power and net flow in the vascular system. The harmonic waveform analysis, because of its wave reflections in the vascular system, require an autocorrelation to determine the "change of power" caused by the heart[55]. The first LiDCO monitor used a lithium indicator dilution to calibrate the system, but latest LiDCO *rapid*® does not require external calibration and had demonstrated to be a clinical reliable continuous cardiac output monitor. There are many studies and reviews comparing this CO monitor to PAC and comparing to other minimally invasive CO monitors and results are satisfactory. Although, the utility of this kind of monitors is the patient' s trend evaluation when anaesthesiologist may determinate baseline values, a minimally invasive CO monitor could be connected to the patient any time of the surgery or during the postoperative period. Vincent and Fagnoul[62] wrote "*The main reason why reliable cardiac output monitoring can be useful during surgery is to be able to establish a baseline for high-risk patients in whom complications, such as hypoxemia, tachycardia or oliguria, arise after the immediate postoperative period, and therapeutic interventions become more complex*". Introducing a CO monitor when patient complications had already happened can be disappointing and usefulness, despite some authors would argue that there would still be helpful to manage them.

Anaesthesiology education and simulation training

Active learning strategies and simulation technologies are already used with medical students[63,64] and residents[65] and their benefits and advantages on students' learning cognitive and behavioural skills are well recognised[66,67]. Simulation-based learning can also be helpful to develop healthcare professional's knowledge, skills and attitudes while protecting patients from unnecessary risks[68]. Anesthesiologists pioneered the use of patient simulators in training programs all over the world[69,70].

Cardiovascular physiology can be simulated in mannequins but is limited to the simulator monitor curves, missing some important data that today is known as essential to fluid management in high-risk patients. This tool is important to train basic cardiovascular physiology but also haemodynamic variations during anaesthesia phases: induction, positioning, controlled hypotension and other surgical conditions associated with haemodynamic compromise (orthopaedic surgery, vascular surgery, major abdominal surgery).

Anaesthesiologists and other healthcare professionals should be trained on their own monitors, so they can interpret easily their parameters and provide a better and safer healthcare[71–73]. A connection between a patient simulator and anaesthesia monitors, like LiDCO *rapid*®, seems to be the best way to practice clinical scenarios.

In summary…

…despite these great advances in patient monitoring, there are several surgical procedures in high-risk patients where low blood flow (cerebral and coronary) occurs, and may be undetected[4]. That is the reason why we decided to study the haemodynamic changes during anaesthesia induction and knee-chest positioning in neurosurgical patients and its influence in propofol pharmacokinetic variation in a TCI and BIS guided anaesthesia.

HYPOTHESIS AND OBJECTIVES

Hypothesis

The hypothesis of this study is that the fall in arterial blood pressure and cardiac output following induction and after positioning could be attenuated by reducing the propofol target concentrations administered trough target-controlled infusion anaesthesia in neurosurgical patients scheduled for lumbar spinal surgery in the knee-chest position.

We also hypothesized that propofol effect-site and plasmatic concentrations predicted by Schnider pharmacokinetic model would not be accurate when HD changes occurred, especially, after knee-chest positioning. Predicted propofol plasmatic concentration would differ from measured propofol concentration more than 30%, in knee-chest position.

Objectives

The primary objective of this study was to assess whether reductions in propofol target concentrations applied immediately following loss of consciousness and immediately before positioning, would attenuate the HD changes associated with induction itself and knee-chest positioning. The haemodynamic changes were quantified by a minimally invasive cardiac output monitor, LiDCO *rapid*®.

We design two different anaesthesia maintenance protocols to evaluate if protocolled reductions in propofol would attenuate the HD changes:

- In a first set of patients (Phase 1), no propofol target concentration reductions were protocoled and the falls in cardiac output following induction and knee-chest positioning were quantified. Anaesthesia was guided by depth of hypnosis (BIS) and clinical parameters and propofol effect-site concentrations were manually modified by the anaesthesiologist.
- In a second set of patients (Phase 2), two propofol target concentration reductions, based on the data from the first set of patients, were applied.

The secondary objective was to investigate the variation in propofol plasmatic concentrations, predicted by Schnider pharmacokinetic model, after LOC and, especially, after KC positioning, which represent anaesthesia periods with clinical relevant HD changes, and correlate them with measured propofol concentrations.

Another learning aim was to develop an interface that would connect the patient simulator to the cardiac output monitor, LiDCO *rapid*®, for training anaesthesiologists in clinical scenarios associated with haemodynamic compromise in simulation models.

METHODOLOGY

A two-phase prospective cohort study of patients scheduled for lumbar spinal surgery in KC position was conducted following the Research Ethics Board (REB) approval and informed signed consent.

A power analysis was conducted based on an expected CO variation between supine and KC position of 30%[38] and an expected attenuation of 50% in the cardiac output fall, and the calculated number of patients to include in the study was 20 subjects.

Exclusion criteria were: severe ischemic heart disease, congestive heart failure, atrial fibrillation or flutter, Body Mass Index (BMI)>35, Glasgow Coma Scale<15 or dementia disease, history of drug abuse or addiction and patients who were administered pre-operative midazolam. A careful physical examination was performed on each patient to exclude potentially difficult airway, ischemic peripheral arterial disease with Allen's test and all patients were weighted using the same scale.

Anaesthesia, Monitoring and Equipment

Once arrived at the operating room, all patients received a crystalloid intravenous infusion at 400mL/h till the end of anaesthesia induction and maintained at 200mL/h throughout the surgery.

The standard monitored parameters in all patients were heart rate, ECG, peripheral arterial oxygen saturation measured by pulse oximetry, invasive blood pressure, depth of anaesthesia with bispectral index™ (BIS™ brain monitoring, Medtronic, USA), peripheral body temperature and neuromuscular block monitoring with train of four stimulation (TOF) on the right hand.

A left radial artery catheter was placed with local anaesthesia before induction and LiDCO *rapid*® was connected to collect haemodynamic data every second:

- Cardiac output (CO),
- Cardiac index (CI),
- Stroke volume (SV),
- Stroke volume index (SVI),
- Systemic vascular resistance (SVR),
- Invasive systolic pressure (Sys),
- Mean arterial pressure (MAP),
- Invasive diastolic pressure (Dia),
- Heart rate (HR),
- Pulse pressure variation (PPV)
- Stroke volume variation (SVV).

This CO monitor does not require any calibration. In a separate computer, RugLoopII© software was used to drive the remifentanil and propofol pumps (Alaris™ Asena, BD, UK) and to collect data every 5'', connected to the patient monitor (Aisys®, GE Healthcare, USA).

At this moment, we collected the first blood sample called "**Baseline**", free of drugs or "**Moment 0**" and recorded all clinical and HD parameters described previously. Then, anaesthesia induction started with remifentanil (20 μ g/ml) by TCI to achieve and maintain an effect-site concentration target (Ce) of 2,5ng/ml (Minto pharmacokinetic Pk model). Propofol (1%) was then started at 200ml/h until loss of consciousness (LOC). LOC was considered when the patient failed to open his/her eyes following name calling and tapping on the forehead. At the moment of LOC, propofol infusion was stopped and the estimated effect-site concentration of propofol was noted. Schnider's Pk model was used. The pump was then switched to TCI mode.

From this moment on, the anaesthesia protocol in patients from phase 1 and phase 2 was different, as explained in detail below in figure 3.

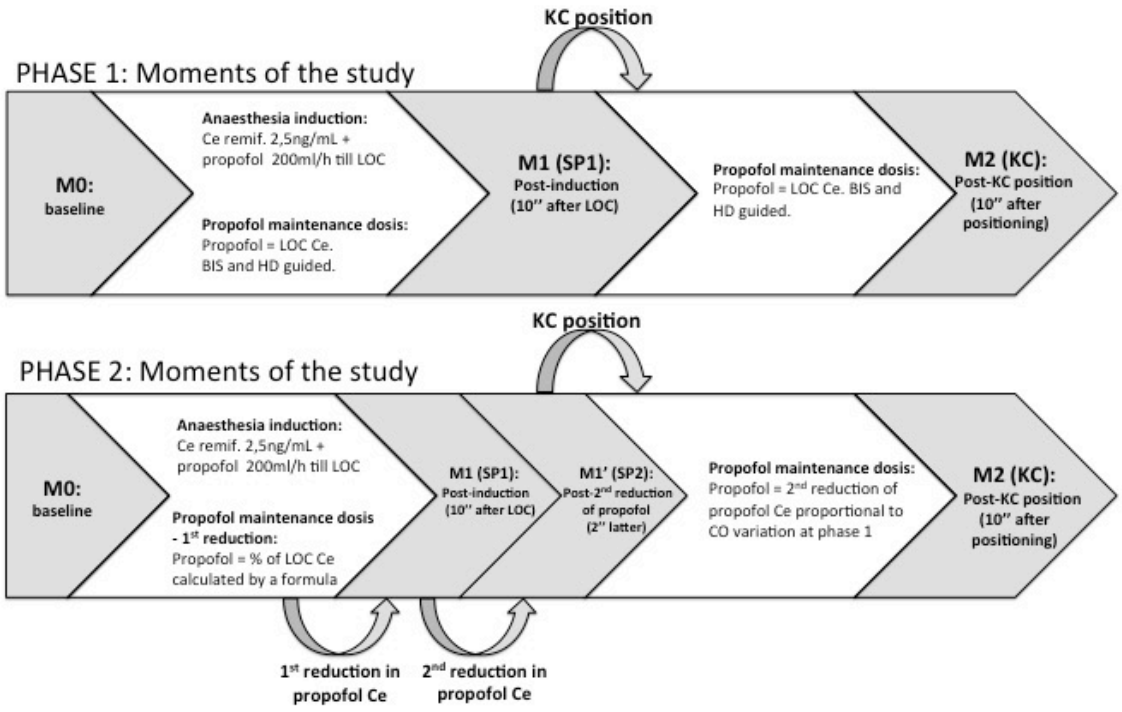

Figure 3: Moments of the study: Phase 1, three moments were registered; Phase 2, four moments were considered.

Experimental protocol

PHASE 1 (P1): "*maintain propofol*"

After LOC, propofol concentration was switched to TCI at a target Ce equal to the Ce at LOC. Maintenance of anaesthesia was guided by BIS (40-60) and HD parameters. Tracheal intubation was accomplished after the muscle relaxant administration (rocuronium 0,6mg/kg) and patients were mechanically ventilated with an O_2/air mixture to achieve SpO_2> 98%, tidal volume (~8ml/kg) and respiratory rate adjusted to normocapnic end-tidal CO_2. Remifentanil Ce was switched to 1ng/ml between intubation and surgical incision. Ephedrine boluses (5mg) were allowed when CO or SYS decreased more than 30% from baseline.

The second blood sample was collected 10 minutes after LOC (**Moment 1 or SP1**) and then patients were positioned in KC position carefully, paying attention to all the compression points and using a ProneView® platform for the head. All the monitoring and anaesthetics infusions were continued.

The third blood sample was collected and parameters were registered 10 minutes after performing KC position, before incision (**Moment 2 or KC**).

During this phase, two blood samples were collected:

Moment 1 or SP1: 10 minutes after LOC, with the patient in supine and drugs in steady-state;
Moment 2 or KC: 10 minutes after KC positioning (KC), with drugs in steady-state.

Before collecting the blood samples, HD parameters and BIS values were registered. At this point, the phase 1 study was completed.

PHASE 2 (P2): "*reduce propofol*"

After LOC, propofol concentration was switched to TCI mode at a Ce target calculated using a formula developed by our group[74] that relates the Ce of LOC with the Ce that results in maintaining BIS between 40 and 60:

Propofol reduction (%) = 100 – (95.2-7.6 * Prop Ce at LOC).

Tracheal intubation and ventilation were performed as described in phase 1. Remifentanil target Ce was changed to 1ng/ml between intubation and surgical incision.

The second blood sample was collected 10 minutes after LOC (**Moment 1 or SP1**). A second reduction of propofol Ce was performed with the same magnitude as the CO variation observed on P1 patients and, 2 minutes later, the third blood sample was collected (**Moment 1' or SP2**). Afterwards, patients were placed in KC position as described in P1. Ten minutes after KC positioning and before incision, the fourth blood sample was collected (**Moment 2 or KC**).

During this phase, three blood samples were collected:

Moment 1 or SP1: 10 minutes after LOC, patient in supine and drugs in steady-state;
Moment 1' or SP2: 2 minutes after the second propofol reduction, patient in supine and drugs in steady-state;
Moment 2 or KC: 10 minutes after KC positioning, drugs in steady-state.

Before collecting the blood samples, HD parameters and BIS values were registered. At this point, the phase 2 study was completed.

Plasma propofol sampling

During the study period, 3 ml arterial blood samples were collected from the left radial artery into heparin containing tubes for propofol and propofol metabolites quantification in the plasma according to the protocol. After blood collection the plasma was separated through centrifugation at 3000 rpm during 15 minutes and was immediately placed at -77ºC and stored until analysis. Propofol plasma concentrations as well as its free metabolites (quinol and quinone) were determined by gas chromatography mass spectrometry according to Guitton *et al*[75] with some adjustments, as described in Silva *et al*[76].

Briefly, 50 μl internal standard thymol solution (0.01 mg/ml) and 1 ml water were added to 0.5-ml aliquot serum or propofol calibration standards. To this solution, 0.5 ml borate buffer (pH 9) was added and mixed by inversion. Then, 300 μl chloroform: ethylacetate (70:30, v:v) were added and mixed for 20 min at 50 rpm, after which 1 l organic phase solution was injected into the gas chromatography-mass spectrometry injector in splitless mode at 250°C. The quantification of propofol was performed in a Varian CP-3800 gas chromatograph (Varian, Walnut Creek, CA) equipped with an ion trap mass detector (Varian Saturn 4000). The chromatographic column was a Varian Factor Four ms (30 m × 0.25 mm × 0.25 μm). The column temperature was programmed to 100°C (1 min), 15°C/min until 300°C (10 min). The detection of propofol and thymol was conducted in Full Scan mode, and the quantification performed by monitoring the characteristic mass-to-charge ratio (m/z) fragments of each molecule: for propofol, the m/z used were 178 and 163, and for thymol, the m/z used were 150 and 135. The retention times for each compound were, respectively, 5.6 and 5.0 min.

For the calibration curve, the non-conjugated metabolites were chemically synthesized since these compounds are not commercially available. The purified metabolites (> 95%) were subsequently used as GC-MS standards.

Pharmacokinetic model performance

The accuracy and bias of models predictions were calculated from differences between measured (Cm) and predicted (Cp) propofol concentration for each individual patient, as the prediction error (PE), defined as:

PE= 100x(Cm-Cp)/Cp

Median prediction error (MDPE) represents the median bias of the model and median absolute performance error (MDAPE) represents the median accuracy of the prediction, calculated for each moment and each phase. In literature, values for MDPE less than 20% (-20 to 20%) and MDAPE between 20-40% are considered an acceptable performance for the Pk model [22,28].

Connection between the patient simulator and the LiDCO rapid®

To connect the patient simulator to the haemodynamic monitor, firstly we had to assess both systems and design a communication channel between them. LiDCO monitor accepts as an input an analogue voltage varying between 0V and 5V and that every volt is directly proportional to a blood pressure (mmHg) value ranging from 0 mmHg (0V) to 500 mmHg (5V). A Raspberry Pi 0 (Rpi0) with a WIFI chip integrated was needed and added to a digital analogue converter connected to the board. We designed a system that allowed us to collect, interpret and modify data, and feed it to the LiDCO *rapid*® monitor. We had developed a Python® script with three independent threads and a circular buffer to handle the data transmission between both systems.

Statistical data analysis

Data was collected from LiDCO *rapid*® and RugLoopII© equipments which acquired data independently and with different sampling frequencies. Therefore, synchronization between data from both equipments was mandatory for this study. Dedicated software was developed in Matlab® for this task. The delay between LiDCO *rapid*® and RugLoopII© series was estimated by the lag of the maximum cross-correlation value between Sys acquired with both equipments. The optimum resampling of the RugLoopII© down to the same temporal basis as the LiDCO *rapid*® was that achieving the highest maximum cross-correlation value. The data synchronization was successful in all recordings as normalized cross-correlations between Sys time series acquired by both equipments were above 0,9 for all recordings (n=20). For data analysis, 1-minute duration windows were considered around each of the above defined study moments and the average of the observed values was computed for each window. The statistical analysis considered a full factorial model in a two-way mixed ANOVA analysis to compare the mean differences of the measured variables, considering the main effect "Moment" (between-subjects), the main effect "Phase" (within-subjects) and their interactions. The normality assumption was tested by Shapiro-Wilk test of normality and the sphericity assumption was investigated by the Mauchly's Test of sphericity. A p-value lower than 5% was considered as statistically significant.

Further post-hoc testing (ANOVA and t-test with Bonferroni correction) was conducted to compare "Moments" and "Phases". The assumption of homogeneity of variances was investigated with Levene's test. Alternative non-parametric testing (Friedman, Wilcoxon Signed-Rank and Mann-Whitney U) were also conducted in order to investigate impact for any deviation from the assumptions of the parametric tests. In this analysis, the statistical conclusions at 5% level from parametric and non-

parametric tests were concordant. Results per moment/phase are expressed as mean ± standard deviation (S.D.). All statistical analyses were conducted in SPSS® software (v25).

RESULTS

In this chapter, there will be presented the abstracts of the publications that resulted from the clinical investigation to the actual doctoral thesis, in spanish language, as required by the "*Comisión de Doctorado y Posgrado, 15 de febrero de 2013*".

The three articles are presented in the Appendices Section, at the end of this document.

ARTICLE 1: **(APPENDIX A)**

PROPOFOL TCI REDUCTIONS DO NOT ATTENUATE SIGNIFICANT FALLS IN CARDIAC OUTPUT ASSOCIATED WITH ANESTHESIA INDUCTION AND KNEE-CHEST POSITIONING IN SPINAL SURGERY

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RESUMEN

Introducción: La inducción anestésica está asociada a grandes variaciones hemodinámicas, incluso cuando es realizada a través de una perfusión guiada por concentraciones en el órgano diana (TCI, *Target Controlled Infusion*), en este caso, el cerebro, utilizando modelos farmacocinéticos (Pk). El posicionamiento quirúrgico en genupectoral provoca igualmente alteraciones cardiovasculares, en especial, diminución del gasto cardiaco (GC). Hoy en día, se cree que éstas variaciones podrían tener impacto en el resultado clínico del paciente y deberían ser evitadas.

Objetivo: El objetivo de este estudio clínico es evaluar si las reducciones de las

concentraciones cerebrales de propofol aplicadas justo después de la inducción anestésica y antes del posicionamiento en genupectoral atenúan las alteraciones hemodinámicas asociadas.

Métodos: Estudio prospectivo de cohortes realizado en dos fases que ha incluido 20 pacientes propuestos para cirugía de columna lumbar en posicionamiento genupectoral. Los parámetros hemodinámicos se registraron en distintos momentos a través del monitor LiDCO *rapid*® y fueron comparados con el valor basal, antes de la inducción. La inducción se realizó con perfusión de propofol en modo TCI, hasta conseguir la pérdida de consciencia (LOC, loss of consciousness), y fué registrada la concentración cerebral del fármaco. Se diseñaron 2 protocolos de mantenimiento distintos, aplicados después de la inducción anestésica: en la fase 1 (n=9), la concentración cerebral de propofol de mantenimiento es igual a la concentración de LOC. Las variaciones del gasto cardiaco y otros parámetros hemodinámicos provocadas por la inducción y por el posicionamiento en genupectoral fueron cuantificadas. En la fase 2 (n=11), se planificaron 2 reducciones en la concentración cerebral de propofol para el mantenimiento anestésico con el objetivo de atenuar dichas variaciones hemodinámicas. La primera, calculada a través de una fórmula desarrollada por nuestro grupo de investigación, y la segunda reducción, proporcional a las alteraciones del gasto cardiaco cuantificadas en la primera fase.

Resultados: En la fase 1, comparando el GC basal con el GC después de la inducción se observó una reducción significativa del 25.6%; comparando el basal con el post-posicionamiento en genupectoral, la reducción fué todavía más significativa, 38,4%. En la fase 2, comparando el GC basal con el GC después de la inducción también se observó una reducción significativa del 19,8%; el GC post-posicionamiento en genupectoral se redujo significativamente un 46,9%. Entre las dos fases, no se observaron diferencias significativas en el GC ni en los valores del monitor de profundidad anestésica (BIS). Por otra parte, las variaciones del GC y de la presión arterial media no han sido correlacionables. En la fase 2, la concentración

cerebral estimada de propofol y el propofol infundido fueron significativamente menores ($p<0,001$).

Conclusión: En ambas las fases se observó una diminución significativa del gasto cardiaco en todos los momentos, post-inducción y post-posicionamiento. Las reducciones programadas de las concentraciones de propofol se demostraron ineficaces en la atenuación de las variaciones hemodinámicas. El estudio comprueba que el posicionamiento en genupectoral podría ser un factor independiente responsable de estas alteraciones cardiovasculares. En pacientes de alto riesgo se cree que pequeñas variaciones hemodinámicas podrían alterar su desenlace quirúrgico, aumentando la morbimortalidad. Se alerta a los anestesiólogos y se sugiere la utilización de, además de la monitorización estándar, la monitorización de la profundidad anestésica y del gasto cardiaco en pacientes de alto riesgo operados en genupectoral.

ARTICLE 2: (APPENDIX B)

EFFECT OF HEMODYNAMIC CHANGES IN PLASMA PROPOFOL CONCENTRATIONS ASSOCIATED WITH KNEE-CHEST POSITION IN SPINAL SURGERY: A PROSPECTIVE STUDY

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RESUMEN

Introducción: La inducción y mantenimiento de una anestesia intravenosa con propofol puede realizarse a través de una perfusión guiada por concentraciones en el órgano diana (TCI, *Target Controlled Infusion*), en este caso, el cerebro, utilizando modelos farmacocinéticos (Pk). Además de los datos biométricos, existen otras

variables fisiológicas que podrán influenciar la farmacocinética del propofol, como por ejemplo, las variaciones del gasto cardíaco. Algunos posicionamientos quirúrgicos, como es la posición genupectoral, condicionan alteraciones importantes en las variables cardiovasculares, sobre todo, en el gasto cardíaco.

Objetivos: El objetivo de este estudio clínico es evaluar la influencia de las variaciones del gasto cardíaco provocadas por la inducción anestésica y por el posicionamiento en genupectoral en las concentraciones plasmáticas reales de propofol, comparando éstas con las estimadas por el modelo farmacocinético (Pk) de Schnider.

Métodos: Estudio prospectivo de cohortes realizado en dos fases que ha incluido 20 pacientes propuestos para cirugía de columna lumbar en posicionamiento genupectoral. La inducción se realizó con perfusión de propofol en modo TCI, hasta alcanzar la concentración cerebral de pérdida de consciencia (LOC, loss of consciousness) y ésta fue registrada. Se han diseñado 2 protocolos de mantenimiento distintos, aplicados después de la inducción anestésica, ya descritos en la publicación anterior. Las concentraciones plasmáticas de propofol han sido medidas en varios momentos de ambas fases: después de la inducción anestésica y después del posicionamiento, y comparadas con las estimadas por el modelo.

Resultados: En el momento después de la inducción, el modelo Pk de Schnider presenta un buen funcionamiento. Sin embargo, las concentraciones plasmáticas medidas después del posicionamiento, momento de gran variación del gasto cardiaco, han sido subestimadas por el modelo. Las reducciones intencionales en la concentración cerebral de propofol no resultaron como medida de atenuación de las variaciones hemodinámicas. En el momento después del posicionamiento, no se encontró correlación entre las concentraciones plasmáticas reales y las estimadas por el modelo Pk, siendo las reales significativamente superiores ($p=0.013$). Los valores del gasto cardiaco y del monitor de profundidad anestésica (BIS), por el contrario, decrecieron significativamente ($p<0.001$ y $p=0.004$, respectivamente).

Conclusión: El estudio ha demostrado que el modelo de Schnider subestima significativamente las concentraciones plasmáticas de propofol, asociadas a la diminución significativa del gasto cardiaco provocadas por el posicionamiento en genupectoral. Los anestesiólogos deben conocer las variaciones hemodinámicas de los posicionamientos quirúrgicos y, consecuentemente, las alteraciones farmacocinéticas asociadas, intentando minimizar sus efectos. Se reconoce mayor relevancia en pacientes de alto riesgo, sugiriendo la utilización de, además de la monitorización estándar, monitorización de la profundidad anestésica y del gasto cardiaco.

ARTICLE 3: **(APPENDIX 3)**

DESIGN OF AN INTERFACE FOR TEACHING CARDIOVASCULAR PHYSIOLOGY TO ANESTHESIA CLINICIANS WITH A PATIENT SIMULATOR CONNECTED TO A MINIMALLY INVASIVE CARDIAC OUTPUT MONITOR (LiDCO *rapid*®)

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RESUMEN

Introducción: La fisiología cardiovascular puede ser enseñada y simulada con simuladores de alta fidelidad, sin embargo, estará siempre limitada a sus monitores, que no representan algunos de los parámetros hemodinámicos esenciales en el manejo de la fluidoterapia y de la terapia de decisión en pacientes críticos y de alto riesgo quirúrgico.

Objetivo: El objetivo de este estudio fue proyectar e implementar un interfaz de comunicación entre un simulador de paciente y un monitor hemodinámico de gasto cardíaco mínimamente invasivo (LiDCO *rapid*®), esto es, un monitor que se conecta a un paciente real e interpreta la curva de presión arterial para extraer los datos hemodinámicos.

Métodos: Para conectar el simulador del paciente y el monitor hemodinámico, previamente, se ha a obtenido acceso a ambos sistemas y se ha diseñado un canal

de comunicación entre ellos. El monitor LiDCO *rapid*® acepta datos de voltaje analógicos variando entre 0V y 5V, siendo cada volt directamente proporcional al valor de la presión arterial (mmHg), siendo 0 mmHg = 0V y 500mmHg = 5V. Fue necesario desarrollar un conversor digital integrado a un procesador Raspberry Pi 0 (Rpi0) con WIFI conectado al simulador, que permitiera recoger, interpretar y modificar los datos del simulador para trasmitirlos al monitor hemodinámico. Se desarrolló un guión en Python® con tres canales independientes y un regulador circular para controlar los datos entre ambos sistemas.

Resultados: El monitor LiDCO *rapid*® ha recibido e interpretado los datos enviados como si de un paciente real se tratara, estimando así varios parámetros hemodinámicos, como por ejemplo, el gasto cardíaco, volumen sistólico, resistencias vasculares periféricas, variación de presión de pulso y variación de volumen sistólico.

Conclusión: La conexión entre el simulador de paciente y el monitor LiDCO *rapid*® permite a éste, la creación de curvas arteriales y parámetros hemodinámicos para utilizar en escenarios clínicos simulados, donde residentes y adjuntos en anestesiología, así como estudiantes de medicina, podrán simular y practicar casos clínicos de inestabilidad cardiovascular, preparándolos para situaciones semejantes con pacientes reales, en un ambiente seguro y con su propio monitor hemodinámico.

CONCLUSIONS

1. This study presents evidence that there is a relationship between haemodynamic changes and propofol pharmacokinetic variation during anaesthesia induction and knee-chest positioning in propofol target controlled infusion guided anaesthesia.
2. Physicians should be aware that KC positioning is an independent factor to haemodynamic changes and intended reductions in propofol administration, immediately after LOC and before KC positioning, did not attenuate them.
3. Planned propofol reductions did not avoid the underestimation error from Schnider's pharmacokinetic model. Our study showed that measured propofol concentrations, after haemodynamic changes associated to knee-chest position, were much higher than predicted.
4. When placing patients in knee-chest position, bispectral index values decreased and measured propofol concentrations increased. Our results suggest that the cardiac output variation was responsible for the pharmacokinetic phenomenon described above. The increased plasma propofol concentrations may be due to a reduction in propofol distribution or due to reduced hepatic clearance during hypotensive episodes.
5. We could not find a correlation between mean arterial pressure and cardiac output variation, wherefore, mean arterial pressure may not represent an accurate parameter to guide anaesthesia, vasoactive drugs or fluid therapy.
6. In high-risk patients placed in knee-chest position, anaesthesiologists must be aware of these haemodynamic and pharmacokinetic variations and, in addiction to standard monitoring, the use of depth of anaesthesia and cardiac output monitors may be considered to detect serious haemodynamic changes, to guide therapy and to minimize predictable risks.

7. The connection between the patient simulator and the CO monitor (LiDCO *rapid®)* was developed and tested. Further work is planned, in an educational area with a simulation program, to prepare anaesthesiologists and surgical teams to a structured and careful approach to surgical patients in knee-chest position and high-risk patients.

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OTHER WORKS RESULTING FROM THE STUDY

A. ORAL PRESENTATIONS AND POSTERS

Oral presentations

Several presentations were made in many portuguese Anaesthesiology Departments presenting the haemodynamic monitor LiDCO *Rapid*® to anaesthesiologists and nurses, regarding principles of haemodynamic monitoring and cardiovascular physiology.

Posters

1. "Avaliação da alteração do débito cardíaco através do LiDCO *Rapid*® durante a indução anestésica e o posicionamento cirúrgico"
Chaló D, Gouveia S, Amorim P
Portuguese Society of Anaesthesiology (SPA) Annual Meeting, March 2011, Portugal.

2. "Hemodynamic changes and propofol correlations during induction and knee-chest position in propofol and remifentanil TCI guided anesthesia"
Chaló D, Gouveia S, Silva A, Guedes P, Amorim P
American Society of Anesthesiology (ASA) Annual Meeting, October 2011, EUA.

3. "Hemodynamic Changes During Induction and Knee-Chest Positioning in Propofol and Remifentanil TCI Guided Anesthesia – How to compensate these changes?"
Chaló D, Pedrosa S, Gouveia S, Amorim P
American Society of Anesthesiology (ASA) Annual Meeting, October 2015, EUA.

4. "Inconsistent correlation between MAP and cardiac output during anaesthesia induction and patient positioning"
Chaló D, Pedrosa S, Gouveia S, Amorim P
Euroanaesthesia 2018, The European Anaesthaesiology congress, Denmark.

5. "Non-invasive haemodynamic monitor in high fidelity patient simulator to facilitate learning of cardiovascular parameters to anaesthesia residents"

Chaló D, Marques J, Mendes H, Sancho C

SESAM 2019 Annual Meeting, Society for Simulation in Europe, Scotland

B. EDUCATIONAL PROGRAM

Courses / Workshops

1. "1st Postgraduate course for actualization in haemodynamic monitoring"

Oral presentation: "Introduction to LiDCO"

Instructor: Practical Clinical Cases in pigs

Faculty of Medicine – University of Lisbon, Lisbon, Portugal, 2012

2. Workshop "Principles of Haemodynamic monitoring"

Oral presentation: "Introduction to LiDCO"

Instructor: Practical Clinical Cases

"O Norte da Anestesia" - International Anaesthesiology Congress, Oporto, Portugal, 2013

3. Workshop "Principles of Haemodynamic monitoring"

Instructor: Practical Clinical Cases

"O Norte da Anestesia" - International Anaesthesiology Congress, Oporto, Portugal, 2017

4. Workshop "Principles of Haemodynamic monitoring"

Instructor: Practical Clinical Cases

"O Norte da Anestesia" - International Anaesthesiology Congress, Oporto, Portugal, 2019

5. "Simulation workshop in advanced anaesthesia monitoring – from backstage to the clinical practice"

Coordinators: Daniela Chaló and Pedro Amorim

Annual meeting "Jornadas de Anestesiologia ao Centro IV"

SIMULA- Simulation Clinical Centre of Aveiro University, Aveiro, Portugal, 2018

6. **"Prone Positioning Masterclass: become an expert"**

Coordination: Victor Oliveira and Jan Cernovsky

Oral presentation: "Challenging clinical cases in prone position"

Instructor: Practical Clinical Cases

CUF - Viseu Private Hospital, Viseu, Portugal, 2019

LIST OF APPENDICES

Propofol TCI Reductions Do Not Attenuate Significant Falls in Cardiac Output Associated With Anesthesia Induction and Knee-Chest Positioning in Spinal Surgery

Daniela Chaló, MD,† Sara Pedrosa, MD,† Pedro Amorim, MD,‡ Sónia Gouveia, PhD,§ and Consuelo Sancho, PhD**

Background: Induction of anesthesia and the knee-chest position are associated with hemodynamic changes that may impact patient outcomes. The aim of this study was to assess whether planned reductions in target-controlled infusion propofol concentrations attenuate the hemodynamic changes associated with anesthesia induction and knee-chest position.

Materilas and Methods: A total of 20 patients scheduled for elective lumbar spinal surgery in the knee-chest position were included. In addition to standard anesthesia monitoring, bispectral index and noninvasive cardiac output (CO) monitoring were undertaken. The study was carried out in 2 parts. In phase 1, target-controlled infusion propofol anesthesia was adjusted to maintain BIS 40 to 60. In phase 2, there were 2 planned reductions in propofol target concentration: (1) immediately after loss of consciousness—reduction calculated using a predefined formula, and (2) before positioning—reduction equal to the average percentage decrease in CO after knee-chest position in phase 1. Changes from baseline in CO and other hemodynamic variables following induction of anesthesia and knee-chest positioning were compared.

Results: Induction of anesthesia led to decreases of 25.6% and 19.8% in CO from baseline in phases 1 and 2, respectively ($P<0.01$). Knee-chest positioning resulted in a further decrease such that the total in CO reduction from baseline to 10 minutes after positioning was 38.4% and 46.9% in phases 1 and 2, respectively ($P<0.01$). There was no difference in CO changes between phases 1 and 2, despite the planned reductions in propofol during phase 2. There was no significant correlation between changes in CO and mean arterial pressure.

Conclusions: Planned reductions in propofol concentration do not attenuate anesthesia induction and knee-chest position-related decreases in CO. The knee-chest position is an independent risk factor for decrease in CO. Minimally invasive CO monitors may aid in the detection of clinically relevant hemodynamic changes and guide management in anesthetized patients in the knee-chest position.

Key Words: cardiac output, anesthesia induction, spinal surgery, knee-chest position, hemodynamic variation, propofol TCI anesthesia, minimally invasive CO monitors

(*J Neurosurg Anesthesiol* 2020;32:147–155)

Induction of anesthesia is associated with important hemodynamic changes, but previous studies have mostly been limited to assessment of blood pressure effects.[1–3] In recent years there have been significant technological advances in perioperative monitoring,[4] particularly in the development of minimally invasive cardiac output (CO) monitors such as the LIDCO *rapid* (LiDCO Ltd, Cambridge, UK).[5–11] Unlike previous devices, the LIDCO *rapid* requires neither lithium dilution nor calibration; it uses nomograms based on an individual patient's biometrics to estimate CO and stroke volume. This technology has seldom been used to assess comprehensive hemodynamic changes during anesthesia-induced loss of consciousness (LOC).[12,13] Modern target-controlled infusion (TCI) systems allow more precise titration of induction and maintenance of intravenous anesthesia, as well as modeling of plasma and cerebral drug concentrations.[14,15] Together, these technological advances allow a more accurate

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and comprehensive assessment of the hemodynamic changes associated with induction of anesthesia and patient positioning.

Even short durations of arterial hypotension during anesthesia, and the subsequent ischemia-reperfusion, have been associated with acute kidney injury, cardiac complications, stroke, and increased 30-day and 1-year mortality after noncardiac surgery.[16–18] In procedures where the surgical position may also cause reductions in blood pressure and CO, patients may be exposed to an increased risk of intraoperative hypotension that is sufficient to precipitate critical tissue ischemia.

The knee-chest is a variant of the prone position (Supplementary Digital Content 1, http://links.lww.com/JNA/A96), and it may be a particular problem, as it reduces venous return and CO.[19,20] Physiological changes and complications associated with surgical positioning, including standard prone[21] and knee-chest position, have been studied since the 1930s and extensively reviewed elsewhere.[22,23] The prone position and its variants are currently used in a large number of surgical procedures.[24,25] Anesthesiologists must be aware of the risks that they pose of substantial hemodynamic variation and be prepared to anticipate and minimize such changes.

We have previously observed that lower propofol concentrations are required in patients in the prone position compared with similar individuals in the supine position. Thus, in the present study, we hypothesized that the reduction in blood pressure and CO associated with the knee-chest position could be attenuated by reducing the dose of propofol administered after induction of anesthesia but before positioning. We also hypothesized that the use of TCI propofol would allow more controlled reductions in propofol dose. The main aim of the study was to assess whether reductions in TCI propofol concentrations applied promptly after LOC but before positioning would attenuate the hemodynamic changes associated with anesthesia induction and knee-chest positioning.

MATERIALS AND METHODS

A 2-phase prospective cohort study of patients undergoing elective lumbar spine surgery in the knee-chest position with TCI propofol anesthesia was conducted following Research Ethics Board approval and after receiving written informed consent. Patients with severe ischemic heart disease, congestive cardiac failure, atrial fibrillation or flutter, body mass index $>35\,kg/m^2$, Glasgow Coma Scale <15, dementia, history of drug abuse or addiction, and chronic opioid consumption, and those who were administered preoperative midazolam were excluded.

Anesthesia, Monitoring, and Equipment

All patients received a crystalloid intravenous infusion at 400 mL/h from arrival in the operating room until the end of anesthesia induction, and, thereafter, at 200 mL/h until the end of surgery. Routine monitoring—ECG, heart rate, peripheral arterial oxygen saturation measured by pulse oximetry, invasive blood pressure, bispectral index (BIS brain monitoring; Medtronic, Minneapolis, Minnesota), peripheral body temperature, and neuromuscular block monitoring—was undertaken in all patients. A left radial artery catheter was placed under local anesthesia before induction of anesthesia. The LiDCO *rapid* monitor was connected via this cannula, and the following hemodynamic data were collected every second: CO, cardiac index, stroke volume, stroke volume index, systemic vascular resistance, invasive systolic, diastolic, and mean arterial blood pressure, heart rate, pulse pressure variation, and stroke volume variation. A separate computer connected via the patient monitor (Aisys; GE Healthcare, Chicago, Illinois), RugLoopII software (DEMED website; Temse, Belgium) was used to drive the propofol and remifentanil infusion pumps (Alaris; Asena, BD, UK) and to collect data every 5 minutes.

Immediately before induction of anesthesia, baseline clinical and hemodynamic parameters were recorded; this was defined as moment 0 (M0). Anesthesia was then induced with TCI remifentanil (20 μg/mL) to achieve and maintain an effect-site concentration target (Ce) of 2.5 ng/mL (Minto pharmacokinetic model) and propofol (1%) at 200 mL/h until LOC, determined as the moment when the patient failed to open his/her eyes after being called by name and tapped on the forehead. At the moment of LOC, propofol infusion was stopped, and the estimated Ce noted. The infusion pump was then immediately switched to TCI mode using Schnider's pharmacokinetic model. From this moment onwards, the propofol administration protocols were different during phases 1 and 2. These are outlined in detail below and illustrated in the Figure 1.

Following induction of anesthesia and administration of muscle relaxants (rocuronium, 0.6 mg/kg), all patients were intubated. Mechanical ventilation (tidal volume, 8 mL/kg) with an O_2/air mixture to achieve $SpO_2 > 98\%$ was adjusted to maintain normocapnic end-tidal carbon dioxide. Remifentanil Ce was switched to 1 ng/mL after intubation and before surgical incision. Ephedrine boluses (5 mg) were allowed if CO or systolic blood pressure decreased by $>30\%$ from baseline in all patients.

After placement in the knee-chest position, a ProneView platform was used to support the head, and compression points were carefully protected. All monitoring and anesthetic infusions were continued during positioning.

Experimental Protocol

The study was carried out in 2 parts. In phase 1, the reductions in propofol Ce were not protocolized but targeted to maintain BIS 40 to 60. The reductions in CO following induction of anesthesia and knee-chest positioning were quantified. In a second group of patients—phase 2—two planned reductions in propofol Ce were applied, one immediately after LOC and the other before patient positioning. Hemodynamic variables were compared within individuals and also between the 2 phases. All hemodynamic variables were collected with drugs in

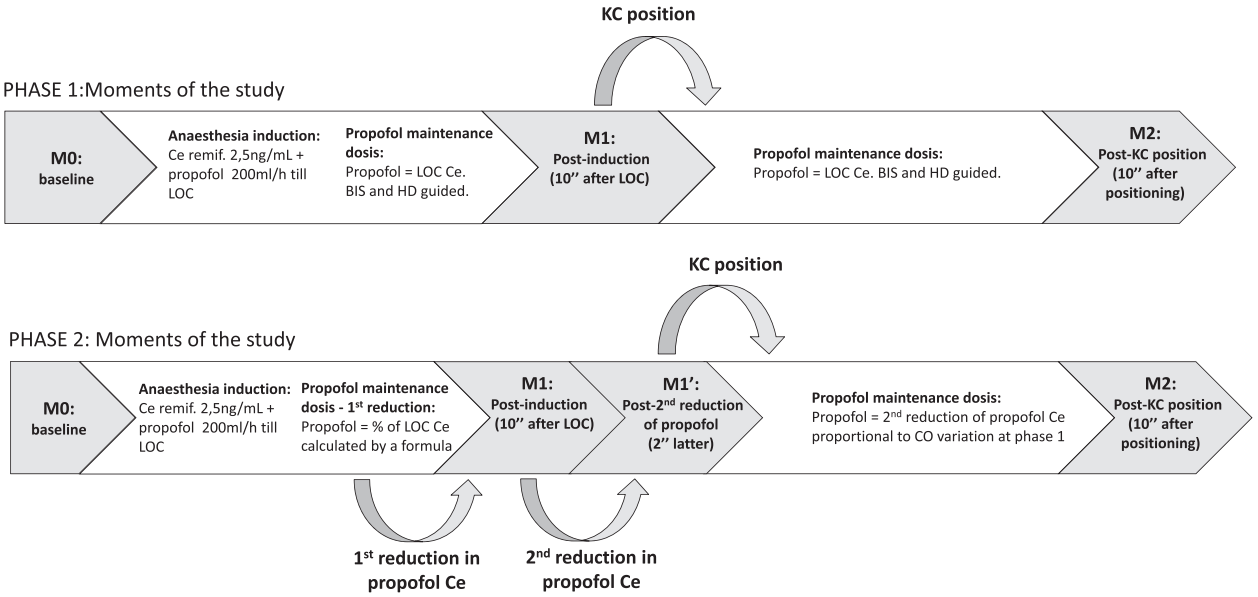

FIGURE 1. Moments of the study. Phase 1 included three moments—M0, M1, and M2. Phase 2 included four moments—M0, M1, M1′, M2. BIS indicates bispectral index; Ce, effect-site concentration; CO, cardiac output; HD, hemodynamic; KC, knee-chest position; LOC, loss of consciousness; remif, remifentanil.

the steady-state and when the signal of the LiDCO *rapid* was quantified as "good."

Phase 1

After LOC, propofol administration was switched to TCI mode at a target Ce equal to the Ce recorded at LOC. Subsequent propofol administration was targeted to maintain BIS 40 to 60 and stable hemodynamic parameters. Data were recorded 10 minutes after LOC (before positioning the patient), and this was defined as moment 1 (M1). Further data were recorded 10 minutes after the patient was placed in the knee-chest position but before skin incision, and this was defined as moment 2 (M2).

Phase 2

In phase 2, propofol was also switched to TCI mode after LOC, but with a lower Ce target than in phase 1, calculated using a formula previously developed by our group (Supplemental Digital Content 2, http://links.lww.com/JNA/A97). This formula relates the Ce at LOC with the Ce that maintains BIS between 40 and 60, as follows:

$$\text{Propofol Reduction}\,(\%) = 0.75\ (100 - [95.2 - 7.6 \times ID]),$$

where ID = induction dose (ie, Ce at LOC)

A second reduction in propofol Ce was implemented after M1. The magnitude of this reduction was equal to the percentage decrease in CO during knee-chest positioning measured in phase 1. Further data were collected 2 minutes after the second reduction in propofol Ce in phase 2, and this was defined as moment M1′ (M1′). As in phase 1, data were recorded 10 minutes after patients were placed in the knee-chest position (M2).

Data Analysis

In phase 1, a decrease in CO between supine and knee-chest positions of 30% was expected on the basis of data from a previous study.[19] In phase 2, we anticipated a reduction of half the CO variation quantified in phase 1, that is, 15%, similar to that in awake volunteers.[26] On the basis of a statistical significance of 5% and power of 80%, the power analysis determined that 20 patients were required.

Data were collected from the LiDCO *rapid* and RugLoopII software independently and at different sampling frequencies. Synchronization between the 2 data sets was, therefore, required before the analysis. Dedicated software was developed in Matlab for this task. The delay between the LiDCO *rapid* and RugLoopII data were estimated by the lag of the maximum cross-correlation value between simultaneous systolic blood pressure values acquired from both sources. The optimum resampling of RugLoopII data were placed in the same timeline as those from the LiDCO *rapid*, achieving the highest maximum cross-correlation value. Data synchronization was successful in all recordings. Normalized cross-correlations between systolic blood pressure time series acquired by both devices were above 0.9 for all recordings. For data analysis, 1-minute duration windows around each of the above-defined study moments were utilized, and the average of the observed values computed for each window.

Statistical analysis incorporated a full factorial model in a 2-way mixed analysis of variance (ANOVA) analysis to compare the mean differences of the measured variables, considering the main effect moment (between subjects), the main effect phase (within subjects), and their interactions. The normality assumption was tested by the Shapiro-Wilk test of normality, and the sphericity

assumption was investigated by the Mauchly's Test of sphericity. Further post hoc testing (ANOVA and *t* test with Bonferroni correction) was conducted to compare moments and phases. The assumption of homogeneity of variances was investigated using Levene's test. Alternative nonparametric testing (Friedman, Wilcoxon Signed-Rank, and Mann-Whitney *U*) was also conducted in order to investigate the impact of any deviation from the assumptions of the parametric tests. In this analysis, the statistical conclusions at the 5% level from parametric and nonparametric tests were concordant. Data for moment and phases are expressed as mean ± SD. All statistical analyses were conducted in SPSS software (version 25) (IBM, New York). *P*-values <0.05 were considered statistically significant.

RESULTS

Twenty patients were included in the study: 9 in phase 1 and 11 in phase 2. Patient demographics and baseline values are shown in Table 1. There were no significant differences in patient demographics or American Society of Anesthesiologists' status between the 2 phases. There was also no statistically significant difference in baseline CO before induction of anesthesia, or in the estimated propofol Ce at LOC between phases 1 and 2.

Phase 1 Results

Anesthesia induction reduced CO by 25.6% (averaged percentage reduction for all patients with respect to the baseline—M0 to M1), from 7.37 ± 1.85 to 5.39 ± 1.33 L/min ($P < 0.01$). Positioning patients from supine to knee-chest caused a further average decrease in CO of 17.2% (M1 to M2), from 5.39 ± 1.33 to 4.39 ± 1.17 L/min ($P = 0.026$). The total decrease in CO from baseline (M0) to after knee-chest positioning (M2) was, on average, 38.4%, from 7.37 ± 1.85 to 4.39 ± 1.17 L/min ($P < 0.01$) (Table 2).

There was no statistically significant association between CO changes and age, weight, sex, initial CO, or propofol Ce at LOC at any moment in phase 1. Systolic, diastolic, and mean arterial blood pressure decreased significantly from baseline at both M1 and M2 ($P < 0.01$). From M0 to M1, on average, systolic blood pressure decreased by 30.7%, diastolic pressure by 28.9%, and mean pressure by 30.3%. From M0 to M2, systolic blood pressure decreased by 42.4%, diastolic pressure by 39%, and mean pressure by 33.1%. Stroke volume was also reduced from baseline (M0) to M1 by 16% and from baseline to M2 by 37% (both $P < 0.01$). Systemic vascular resistance and heart rate decreased from M0 to M1 by 4.4% and 11.7%, respectively, and increased from M1 to M2 by 7.3% and 11.8%, respectively. Pulse pressure and stroke volume variability increased significantly from M1 to M2, from 9% to 21% and 13% to 21%, respectively (Fig. 2). Ephedrine boluses of 5 mg were required in 4 patients: 1 bolus per patient after induction and one bolus after positioning in 2. BIS values did not differ between M1 and M2. Propofol Ce at LOC was 5.03 ± 0.75 μg/mL (Table 1).

TABLE 1. Patients' Demographics and Baseline Values

Characteristics	Phase 1	Phase 2
Age (y)	49.3 ± 8.7	59.7 ± 13.5
Sex (F/M) (n)	6/3	6/5
Height (cm)	161.6 ± 9.0	167.8 ± 12.4
Weight (kg)	70.9 ± 13.9	77.3 ± 11.6
Body mass index (Kg/m^2)	27.0 ± 3.5	27.4 ± 3.0
ASA classification I/II (n)	3/6	2/9
Cardiac output (baseline) (L/min)	7.4 ± 1.8	7.2 ± 2.3
Propofol Ce at LOC (μg/mL)	5.03 ± 0.75	4.34 ± 1.52

Demographics and baseline values of the patients for phase 1 and phase 2. Values are expressed as mean ± SD or number (n).

ASA indicates American Society of Anesthesiologists; Ce, effect-site concentration; LOC, loss of consciousness.

Phase 2 Results

The average decrease in propofol Ce following LOC was 27.5% (maximum decrease 43% (7.0 μg/mL), minimum decrease 19% (2.7 μg/mL). At M1 (10 min after LOC), CO decreased by 19.8% (average percentage of all subjects with respect to the baseline, from M0 to M1), from 7.24 ± 2.34 to 5.64 ± 1.65 L/min ($P < 0.01$). After M1, the planned second reduction in propofol target Ce was 17.2% (the percentage decrease in CO identified during positioning in phase 1). Following this second reduction at M1′, CO was 5.56 ± 1.74 L/min, which was not significantly different from that at M1. From M1′ to M2 (10 min after KC position), CO decreased on average by 31% (from 5.56 ± 1.74 to 3.91 ± 1.89 L/min, $P < 0.01$), and from M0 to M2 by 46.9% (7.24 ± 2.34 to 3.91 ± 1.89 L/min, $P < 0.01$) (Table 2). There was no statistically significant association between CO changes and age, weight, sex, initial CO, or propofol Ce at LOC, at any moment in phase 2. Ephedrine was not administered in any patient.

Systolic, diastolic, and mean blood pressure were decreased significantly from baseline at all moments ($P < 0.01$). From M0 to M1, on average, systolic blood pressure decreased by 22.2%, diastolic blood pressure by 15.1%, and mean pressure by 19%. From M2 to M0, systolic blood pressure decreased by 42.5%, diastolic pressure by 24.6%, and mean pressure by 34.3%. Stroke volume was also reduced significantly from baseline, on average, by 18.6% from M0 to M1, and 47% from M0 to M2 (both $P < 0.01$).

Systemic vascular resistance was slightly increased after induction of anesthesia (by 1.9%) and significantly so (23.9%) after knee-chest positioning ($P < 0.05$). There was no change in heart rate. Changes in pulse pressure variation (26% vs. 29%) and stroke volume variation (23% vs. 24%) after knee-chest positioning were similar (Fig. 3). In phase 2, propofol Ce at LOC was 4.34 ± 1.52 μg/mL (Table 1).

Phase 1 Versus Phase 2 Results

The reduction in CO following induction of anesthesia was not significantly different between phases: a 25.6% reduction during phase 1 and 19.8% during phase 2. There was also no difference in the reductions in CO following the knee-chest position between the 2 phases: 17.2% and 31% in phases 1 and 2, respectively. Only

TABLE 2. Hemodynamic Variables, Bispectral Index Values, and Effect-Site Concentration (Ce) of the Drugs

	Phase 1 (N = 9)					Phase 2 (N = 11)						Two-way ANOVA (*P*)		
Variables (Units)	**Moment 0 (M0)**	**Moment 1 (M1)**	**Moment 2 (M2)**	**Variation M0 to M1 (%)**	**Variation M0 to M2 (%)**	**Moment 0 (M0)**	**Moment 1 (M1)**	**Moment 1′ (M1′)**	**Moment 2 (M2)**	**Variation M0 to M1 (%)**	**Variation M0 to M2 (%)**	**Moment**	**Phase**	**Moment× Phase**
Cardiac output (L/min)	7.4 ± 1.8	5.4 ± 1.3$	4.4 ± 1.2¥	−25.6	−38.4	7.2 ± 2.3	5.6 ± 1.6$	5.6 ± 1.7	3.9 ± 1.9¥#	−19.8	−46.9	< 0.001	0.867	0.514
Cardiac index (L/min/m^2)	4.2 ± 1.0	3.0 ± 0.6$	2.5 ± 0.5¥	−25.6	−38.4	3.9 ± 1.1	3.0 ± 0.9$	3.0 ± 0.8	2.1 ± 1.0¥#	−19.8	−46.9	< 0.001	0.479	0.516
SVR (dynes s/cm^{-5})	1077.4 ± 208.1	1011.2 ± 141.9	1095.1 ± 385.5	−4.4	4.3	1263.0 ± 511.9	1230.2 ± 417.3	1285.8 ± 444.7	1518.3 ± 621.8#	1.9	23.9	0.043	0.133	0.209
Systolic pressure (mm Hg)	153.2 ± 16.4	106.7 ± 18.2$	87.1 ± 13.0¥	−30.7	−42.4	170.1 ± 23.0	131.5 ± 23.1$	129.7 ± 32.2	95.9 ± 24.6¥#	−22.2	−42.5	< 0.001	0.018	0.363
MAP (mm Hg)	105.7 ± 15.5	74.0 ± 14.5$	63.2 ± 10.0¥	−30.3	−39.0	108.4 ± 15.7	86.7 ± 12.0$	89.1 ± 21.7	69.6 ± 14.5¥#	−19.0	−34.3	< 0.001	0.099	0.427
Diastolic pressure (mm Hg)	77.3 ± 13.7	55.0 ± 10.6$	50.6 ± 9.9¥	−28.9	−33.1	75.7 ± 10.1	63.2 ± 7.7$	65.0 ± 14.2	56.0 ± 10.3¥	−15.1	−24.6	< 0.001	0.22	0.246
Stroke volume (mL/beat)	97.0 ± 19.6	81.2 ± 16.6$	59.7 ± 14.8¥,#	−16.0	−37.1	99.8 ± 20.8	81.7 ± 24.0$	76.7 ± 23.9	54.4 ± 24.2¥#	−18.6	−47.0	< 0.001	0.939	0.453
Heart rate (beats/min)	77.0 ± 15.4	66.9 ± 12.4	74.5 ± 13.8	−11.7	−2.5	72.6 ± 18.4	70.5 ± 16.1	73.3 ± 13.1	72.3 ± 15.3	−0.7	1.5	0.035	0.879	0.208
SVV (%)	—	9.4 ± 5.9	21.1 ± 8.6¥	—	—	—	17.1 ± 10.8	23.2 ± 13.3	24.5 ± 9.9	—	—	< 0.001	0.295	0.235
PPV (%)	—	13.6 ± 5.2	27.9 ± 11.2#	—	—	—	20.3 ± 14.6	26.4 ± 15.7	29.2 ± 21.1	—	—	< 0.001	0.636	0.293
BIS	94.0 ± 2.2	61.8 ± 15.2$	42.3 ± 15.1#	−34.2	−55.5	95.3 ± 2.6	49.9 ± 9.8$	46.5 ± 7.5	37.7 ± 8.7¥#	−48.0	−22.7	< 0.001	0.056	0.165
Propofol Ce (μg/mL)	—	3.84 ± 0.63	2.53 ± 0.79#	—	−34.1 (M1 to M2)	—	2.63 ± 0.54	2.47 ± 0.57	2.13 ± 0.47#	—	−19.0 (M1 to M2)	< 0.001	0.018	0.003
Remifentanil Ce (ng/mL)	—	2.36 ± 0.42	1.11 ± 0.35#	—	−51.2 (M1 to M2)	—	1.85 ± 0.66	1.12 ± 0.20	1.15 ± 0.48#	—	−21.3 (M1 to M2)	0.001	0.132	0.107

Results are presented as mean ± SD.

ANOVA indicates analysis of variance; BIS, bispectral index; MAP, mean arterial pressure; PPV, pulse pressure variation; SVR, systemic vascular resistance; SVV, stroke volume variation.

The significant differences (5% level) were calculated based on repeated measures of ANOVA post hoc pairwise testing with Bonferroni correction. There were no significant differences between M1 and M1′. The percentage of variation is computed as (Mi/Mj−1)×100. For example (M1/M0−1)×100 is the percentage of each variable increase/reduction from M0 to M1. Phase comparison presents the *P*-value of the 2-way ANOVA analysis with regard to between-subjects effect (phase) and the moment(s) exhibiting significant differences at 5% level.

$significant differences between M0 and M1.

¥significant differences between M0 and M2.

#significant differences between M1 and M2.

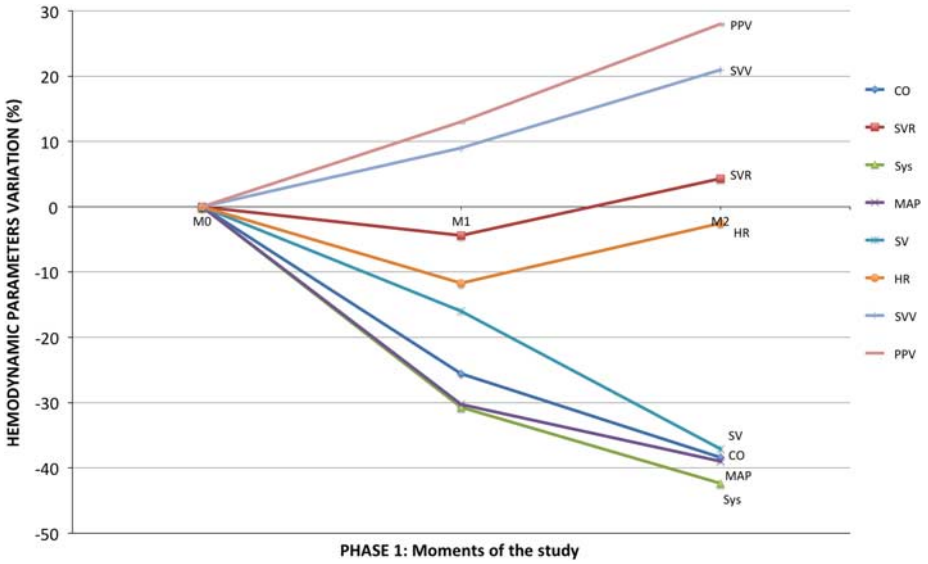

FIGURE 2. Hemodynamic changes (% from baseline) from M0 to M1 and M2 during phase 1. CO indicates cardiac output; HR, heart rate; MAP, mean arterial blood pressure; PPV, pulse pressure variation; SV, stroke volume; SVR, systemic vascular resistance; SVV, stroke volume variation; Sys, invasive systolic blood pressure.

postinduction changes in systolic blood pressure were significantly different between the 2 phases, being higher in phase 2 compared with phase 1 ($P < 0.001$) (Table 2). There was a nonsignificant trend toward higher systemic vascular resistance increases from baseline in phase 2 (Table 2 and Fig. 4). There were no differences in BIS between phases (Table 2).

The relationship between CO and mean arterial pressure variation in both phases of the study were assessed using correlation coefficients: In phase 1, $r = 0.34$ for variation between M0 and M1, and $r = 0.004$ for variation between M0 and M2 (not significant). For phase 2, $r = 0.56$ for variation between M0 and M1 (not significant) and $r = 0.76$ between M0 and M2 ($P < 0.01$).

Comparing drug concentrations between the 2 phases, propofol Ce was significantly lower in phase 2 at M1, but there were no significant differences for remifentanil Ce (Table 2). In order to test for any interaction between age and

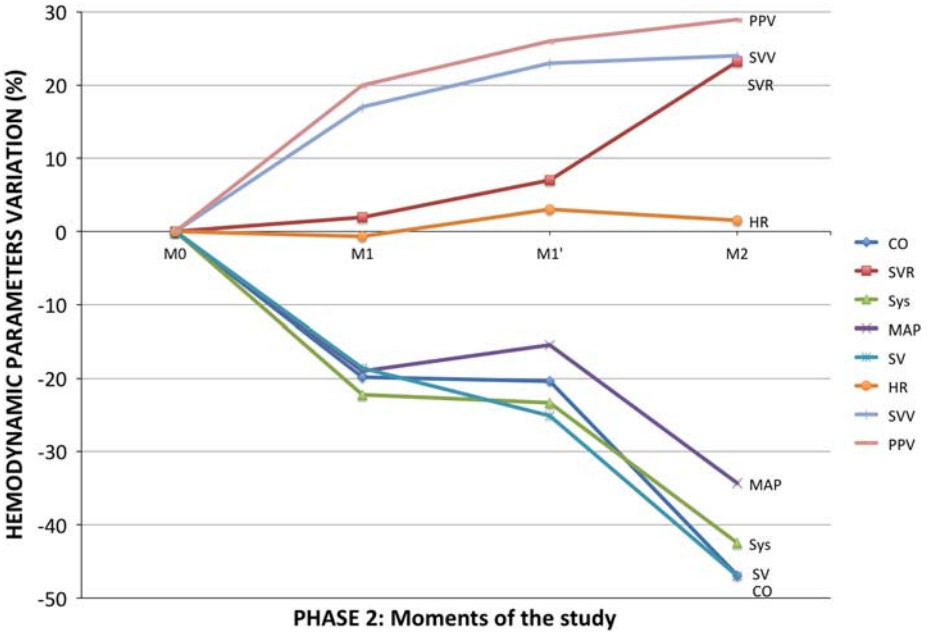

FIGURE 3. Hemodynamic changes (% from baseline) from M0 to M1, M1′, and M2 in phase 2. CO indicates cardiac output; HR, heart rate; MAP, mean arterial blood pressure; PPV, pulse pressure variation; SV, stroke volume; SVR, systemic vascular resistance; SVV, stroke volume variation; Sys, invasive systolic blood pressure.

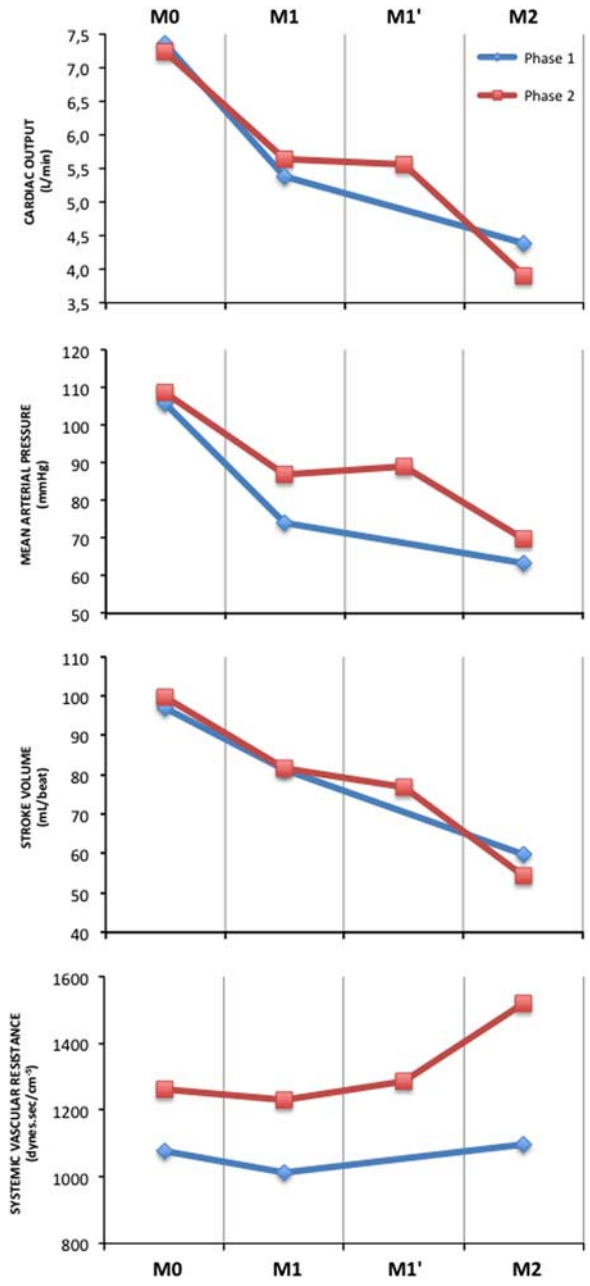

FIGURE 4. Changes in cardiac output, mean arterial pressure, stroke volume, and systemic vascular resistance during phases 1 and 2.

response to changes in propofol Ce, we further considered the ANOVA adjusted for age and found no significant age interaction terms for all the variables reported in Table 2. Furthermore, adjustment for age did not impact the significance of the differences between moments and phases.

DISCUSSION

In this study, induction of anesthesia was associated with significant reductions in CO. In phase 1, CO decreased by 25.6% and, in phase 2, by 19.8% despite the predefined reduction in propofol following LOC. Despite this, systolic blood pressure was higher at M1 (after induction of anesthesia) in phase 2 compared with phase 1 ($P = 0.018$). Hypotension after induction of anesthesia is relatively common, and it is more prevalent during the late postinduction period and before skin incision (5 to 10 min after).[2,13] Although this is often believed to be clinically inconsequential, there is some evidence that even small reductions in blood pressure can be associated with poor patient outcomes.[4,5,27] Intraoperative management of hypotension is usually guided by conventional hemodynamic monitoring (systolic and mean blood pressures), but these variables might not identify low levels of blood flow and oxygen delivery, which, even if time limited, may lead to major perioperative complications and longer hospital lengths of stay.[17,28] In our study, there was no correlation between mean arterial pressure and CO, especially during phase 1. Therefore, it appears that arterial pressure might not be the best variable to guide anesthesia management, and vasoactive drug or fluid therapy.

Placing anesthetized patients in the knee-chest position resulted in further decreases in CO in both phases of our study. It had been expected that the preplanned propofol reduction of 17% before positioning would attenuate any further reduction in CO, but, in the event, it did not, there was a 31% reduction in CO associated with knee-chest positioning in phase 2. Possibly the measured reduction in CO (17%) during knee-chest positioning identified in phase 1, which was the basis for the second planned reduction in propofol Ce during phase 2, was impacted by the ephedrine boluses administered in some patients to maintain blood pressure within predetermined targets. Using an esophageal Doppler in anesthetized patients after knee-chest positioning, Bennarosh et al[19] reported a 35% reduction in CO, although the change after anesthesia induction was not quantified. That study also indicated that propofol target plasma concentrations to maintain BIS values constant were reduced (by 30%), but there was no intervention in the anesthesia protocol. A study in awake volunteers reported a 15% to 20% reduction in CO after the knee-chest position,[26] likely related to a decrease in venous return due to blood sequestration in lower limbs.

In our study, assessment at M1′ in phase 2 allowed us to interpret the hemodynamic changes in more detail. The only intervention between M1′ and M2 was positioning, confirming that the knee-chest position is an independent factor for CO reduction. Our data suggest that this likely occurred because of decreased venous return, because the reduction in stroke volume we observed was not compensated by an increase in heart rate. The absence of a heart rate response may be related to propofol's action on the baroreflex.[1,29] In addition, the changes in systemic vascular resistance in phase 2 were not sufficient to compensate for the decrease in stroke volume.

Pulse pressure variation and stroke volume variation are hemodynamic markers of hypovolemia in mechanically ventilated patients, and they might also be useful in the standard prone or knee-chest positions; Biais et al[30] demonstrated that fluid responsiveness could be predicted

in the prone position. In our study, increases in pulse pressure and stroke volume variations suggest that anesthetized patients in the knee-chest position behave as if they are hypovolemic. Stroke volume decreased from M1 to M2 by 24.6% in phase 1 and by 30.1% in phase 2. We believe that this represents a relative hypovolemia because of reduction in venous return secondary to accumulation of the intravascular volume in the lower extremities. These findings suggest that vasopressor and chronotropic drugs, such as ephedrine, may be the best treatment for the decrease in CO caused by the knee-chest position in anesthetized patients.

As expected, propofol Ce was significantly lower in phase 2 compared with phase 1 because of the planned reductions. There were no differences in remifentanil Ce, BIS values, or hemodynamic parameters except for systolic blood pressure. Thus, we can conclude that, in the knee-chest position, patients may require a lower propofol Ce to maintain anesthesia. Importantly, there were no cases of awareness in our study. These findings suggest that plasma concentrations might be higher than estimated by the models we used,[14,15] and influenced by CO variations, as previously observed by Keyl et al.[31] The increased plasma propofol concentrations may be due to a reduction in propofol distribution or due to reduced hepatic clearance during hypotensive episodes.[32,33] The effects of the prone position and its variants on cerebral blood flow and cerebral oxygenation are also not well quantified.[34] Although cerebral oxygenation in anesthetized patients in the prone position can be maintained within safe margins, there is evidence of impairment of autoregulation,[35] and this might be reflected in low BIS values. However, our hypothesis that reducing propofol Ce promptly after LOC and immediately before knee-chest positioning could attenuate the fall in CO and thereby minimize adverse effects, including cerebral effects, was not supported by the findings of our study.

Nevertheless, our study does confirm that hemodynamic changes in anesthetized patients do not necessarily result from excessive anesthesia, as BIS was similar in both phases. Further, because our study was conducted in healthy patients (American Society of Anesthesiologists classification I and II) scheduled for an elective procedure for either lumbar disc herniation or lumbar spinal canal stenosis, the hemodynamic changes we identified could not be attributed to blood loss, hypovolemia, or cardiac disease. Many authors have highlighted the need to optimize high-risk patients during the perioperative period, guided by advanced hemodynamic monitoring.[5,7,36,37] We believe that anesthetized patients in the knee-chest position could also benefit from such monitoring, including before induction of anesthesia, when it is possible to establish a baseline for trend evaluation during the entire surgical procedure.[38]

The present study has several limitations. The sample size may be considered small. However, the ANOVA analysis was comprehensive, with 3 measures compared in each individual and between the 2 phases. The definition of the moments of data analysis presented quite a challenge, but we defined the 10-minute period of stabilization following induction of anesthesia and KC positioning according to previous literature.[2,19] The fact that this was a nonrandomized study may also be considered a limitation. However, data from phase 1 was essential to quantify the interventions during phase 2. Finally, as this was a short duration study limited to the early intraoperative period, it was not possible to determine whether any of the hemodynamic changes we identified might impact patient outcomes.

CONCLUSIONS

Induction of anesthesia and the knee-chest position are associated with significant reductions in CO. Physicians should be aware that the knee-chest position is an independent risk factor for hemodynamic changes, and that reductions in propofol concentration immediately after LOC and before positioning do not attenuate them. We found no correlation between mean arterial pressure and changes in CO, suggesting that blood pressure alone may not be a useful variable to guide anesthesia management or vasoactive drug or fluid therapy in this context. The use of minimally invasive CO monitors in anesthetized patients may aid in the detection of important hemodynamic changes in the knee-chest position and guide therapy in order to minimize predictable risks. We plan further work using a simulation program to educate clinical teams in a structured approach with regard to the anesthesia management of patients scheduled for surgery in the knee-chest position.

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Published online 2019 September 24. **Research Article**

Effect of Hemodynamic Changes in Plasma Propofol Concentrations Associated with Knee-Chest Position in Spinal Surgery: A Prospective Study

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Abstract

Background: Anesthesia induction and maintenance with propofol can be guided by target-controlled infusion (TCI) systems using pharmacokinetic (Pk) models. Physiological variables, such as changes in cardiac output (CO), can influence propofol pharmacokinetics. Knee-chest (KC) surgical positioning can result in CO changes.
Objectives: This study aimed to evaluate the relationship between propofol plasma concentration prediction and CO changes after induction and KC positioning.
Methods: This two-phase prospective cohort study included 20 patients scheduled for spinal surgery. Two different TCI anesthesia protocols were administered after induction. In phase I (n = 9), the loss of consciousness (LOC) concentration was set as the propofol target concentration and CO changes following induction and KC positioning were quantified. In phase II (n = 11), based on data from phase I, two reductions in the propofol target concentration on the pump were applied after LOC and before KC positioning. Propofol plasma concentrations were measured at different moments in both phases: after induction and after KC positioning.
Results: Schnider Pk model showed a good performance in predicting propofol concentration after induction; however, after KC positioning, when a significant drop in CO occurred, the measured propofol concentrations were markedly underestimated. Intended reductions in the propofol target concentration did not attenuate HD changes. In the KC position, there was no correlation between the propofol concentration estimated by the Pk model and the measured concentration in plasma, as the latter was much higher ($P = 0.013$) while CO and BIS decreased significantly ($P < 0.001$ and $P = 0.004$, respectively).
Conclusions: Our study showed that the measured propofol plasma concentrations during the KC position were significantly underestimated by the Schnider Pk model and were associated with significant CO decrease. When placing patients in the KC position, anesthesiologists must be aware of pharmacokinetic changes and, in addition to standard monitoring, the use of depth of anesthesia and cardiac output monitors may be considered in high-risk patients.

Keywords: Hemodynamics, Knee-Chest Position, Propofol Pharmacokinetics, Anesthesia, Infusion Pumps

1. Background

Anesthesia induction and maintenance with propofol can be guided by target-controlled infusion (TCI) systems that incorporate a pharmacokinetic (Pk) model into a computer-controlled pump, allowing for intravenous anesthetics titration and targeting plasma and effect-site drug concentrations (1, 2). However, propofol pharmacokinetics can be influenced by changes in physiological variables, such as cardiac output (CO), as propofol is a high-clearance drug. In addition, an increase in the propofol plasma concentration could also result in hemodynamic (HD) changes (3-7). These HD variations can modify the TCI modeling ability to predict propofol concentrations (8) such that up to a 60% precision error can occur as the great-

est bias after induction in the early maintenance phase (9).

Patients' positioning in the knee-chest (KC) position (Figure 1) following anesthesia induction further reduces venous return and CO (10, 11). Physiological changes and complications associated with surgical positions, such as the prone and KC positions, have been studied extensively (12, 13).

Researchers previously observed that patients in the prone position required less propofol than those in the supine position. In the present study, it was hypothesized that predicted propofol effect-site (Ce) and predicted plasma concentrations (Cp) would not be accurate when these HD changes occur, especially after KC positioning (4, 5, 14). It was also hypothesized that applying two different TCI anesthesia protocol reductions in propofol infusion, one performed after induction and the other one before positioning, would reduce the prediction error and attenuate the CO changes.

2. Objectives

The aim of this study was to quantify the variations in propofol plasma concentrations (Cm), both after induction and after KC positioning, and correlate them with Cp by the Schnider Pk model. CO was continuously measured with a minimally invasive CO monitor, LiDCO *rapid*® (15-17) (LiDCO Ltd., Cambridge, UK).

3. Methods

After obtaining the REB approval and written informed consent, we recruited consecutive neurosurgical patients scheduled for lumbar spinal surgery in the KC position. A two-phase prospective observational study was conducted.

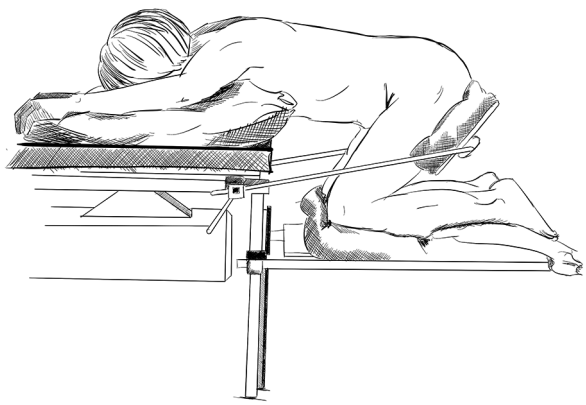

Figure 1. KC surgical position, a variant from the prone position

In the first set of patients (phase I), propofol plasma concentrations were measured and compared with concentrations predicted by the Schnider Pk model and the changes in CO following induction and KC positioning were quantified. In the second set of patients (phase II), based on the data from the first set of patients, two propofol target concentration reductions were planned immediately after anesthesia induction and before positioning.

Propofol plasma concentrations were also measured and compared with predicted and the changes in CO following induction and KC positioning were also quantified, as done in phase I. The exclusion criteria included patients with severe ischemic heart disease, congestive heart failure, atrial fibrillation or flutter, body mass index (BMI) > 35 $kg.m^{-2}$, dementia, history of drug abuse or addiction, and preoperative midazolam. A careful physical examination was performed on each patient to exclude potentially difficult airway and ischemic peripheral arterial disease.

3.1. Anesthesia Protocol

A crystalloid intravenous infusion at 400 $mL.h^{-1}$ was initiated once patients arrived in the operating room, which continued until the end of anesthesia induction and maintained at 200 $mL.h^{-1}$ throughout the surgery. Patients received American Society of Anesthesiologists (ASA) standard monitoring, including depth of anesthesia monitoring with bispectral index™ (BIS™ brain monitoring, Medtronic, USA) and neuromuscular block monitoring with the train of four stimulations on the right hand. Before induction, a left radial artery catheter was placed with local anesthesia to measure invasive blood pressure and LiDCO *rapid*® was connected to collect CO and other hemodynamic parameters every second. This device used the same algorithm as the LIDCO *plus*® system, but it required neither lithium dilution nor calibration, as it used nomograms based on patients biometric parameters to estimate cardiac output and stroke volume. In a separate computer, RugLoopII© software (DEMED website, Temse, Belgium) was used to drive remifentanil and propofol pumps (Alaris™ Asena, BD, UK) and to collect data every five seconds while connected to the patient monitor (Aisys®, GE Healthcare, USA). At this moment, the first blood sample, called "Baseline", which was free of drugs, was collected and all pharmacological and HD parameters were recorded. Anesthesia induction commenced with remifentanil (20 $\mu g.mL^{-1}$) by the TCI mode to achieve a predicted effect-site target concentration (Ce) of 2.5 $ng.mL^{-1}$ (Minto pharmacokinetic model). Propofol (1%) was then started at 200 $mL.h^{-1}$ in the TCI view until the loss of consciousness (LOC). The LOC was considered when the patient failed to open the eyes following name-calling and tapping on the forehead. At the moment of LOC, propofol predicted effect-site concentration (Ce) was noted from RugLoopII© soft-

ware. The propofol protocol in patients from P1 and P2 was different, as explained in detail in the following.

3.2. Experimental Protocol

3.2.1. Phase I (P1)

After LOC, the propofol concentration was switched from the TCI view to the TCI mode with Schnider Pk model at a target concentration equal to the Ce at LOC. Tracheal intubation was accomplished following neuromuscular blocking drug administration (rocuronium 0.6 $mg.kg^{-1}$) and patients' lungs were mechanically ventilated with O_2 and air mixture to achieve SpO_2 of > 98%, tidal volume of 8 $mL.kg^{-1}$, and the respiratory rate adjusted to normocapnia. Remifentanil Ce was reduced to 1 $ng.mL^{-1}$ until surgical incision. Anesthesia maintenance was guided by BIS™ (40-60) and HD parameters by the anesthesiologist. The second blood sample was collected 10 min after LOC and then patients were positioned in the KC position carefully and using a ProneView® platform for the head. The third blood sample was collected and parameters were registered 10 minutes after performing the KC position before incision (Figure 2). At this point, phase I of the study was completed.

3.2.2. Phase II (P2)

After LOC, the propofol concentration was switched from the TCI view to the TCI mode at a Ce target lower than Ce at LOC, calculated using a formula described in detail in supplementary file Appendix 1, which relates the Ce of LOC with the Ce that results in maintaining BIS between 40 and 60.

Tracheal intubation and ventilation settings were similar to phase I. Remifentanil Ce was changed to 1 $ng.mL^{-1}$ until surgical incision. The second blood sample was collected 10 minutes after LOC. A second reduction of propofol Ce was performed with the same magnitude as the CO variation observed in phase I patients and 2 minutes later, the third blood sample was collected. Afterward, patients were placed in the KC position as described in phase I. Ten minutes after KC positioning and before incision, the fourth blood sample was collected (Figure 3). At this point, phase II of the study was completed.

3.3. Plasma Propofol Sampling

During the study period, 3 mL arterial blood samples were collected from the left radial artery into heparin containing tubes for propofol and propofol metabolites quantification in the plasma according to the protocol. The propofol plasma concentration and its free metabolites were determined by gas chromatography mass-spectrometry with some adjustments (18, 19).

The accuracy and bias of model predictions were calculated from differences between propofol Cm and Cp for each individual patient expressed as the prediction error (PE) (3), median prediction error (MDPE), and median absolute performance error (MDAPE). An acceptable performance was characterized by MDPE of less than 20% (-20 to 20%) and MDAPE of 20% - 40%. A model is most accurate when the values of MDPE and MDAPE are close to zero. In TCI, the typical accepted values are 10% to 20% for bias and around 30% for accuracy (20).

3.4. Data Analysis

Data were collected using LiDCO *rapid*® and RugLoopII© software that gathered data independently and with different sampling frequencies; therefore, synchronization between data was mandatory for this study. Dedicated software was developed in Matlab® for the interface. For data analysis, one-minute duration windows were considered around each of the above-defined study moments and the average of the observed values was computed for each window. The statistical analysis was considered as a full factorial model in a two-way mixed ANOVA analysis used to compare the mean differences of the measured variables, considering the main effect "Moment" (within-subjects: same individual at different moments), the main effect "Phase" (between-subjects: different individuals, a group compared to another) and their interactions "Moment × Phase". A P value of < 0.05 was considered statistically significant. Further post hoc testing (ANOVA and *t*-test with Bonferroni correction) was conducted to compare "Moments" and "Phases". The results were expressed as mean ± standard deviation (SD). All statistical analyses were conducted in SPSS® software V. 25 (IBM, New York, USA).

4. Results

Twenty patients (9 in phase I and 11 in phase II) were included in this study. Patients' demographic data are presented in Table 1.

Data concerning the drugs used, HD parameters, and BIS values are reported in Table 2. In phase I, there were no protocolled propofol target reductions; thus, propofol Ce target concentrations were manually modified by the anesthesiologist, guided by BIS and HD parameters (Figure 2). Propofol Ce and Cp were statistically different between all moments ($P < 0.001$) but measured propofol did not show any differences (Table 2).

There were significant HD changes after anesthesia induction and after KC positioning with respect to the baseline in both phases (Figure 4). In phase I, CO fell by 25.6% after induction and 38.4% after KC position, compared to the baseline.

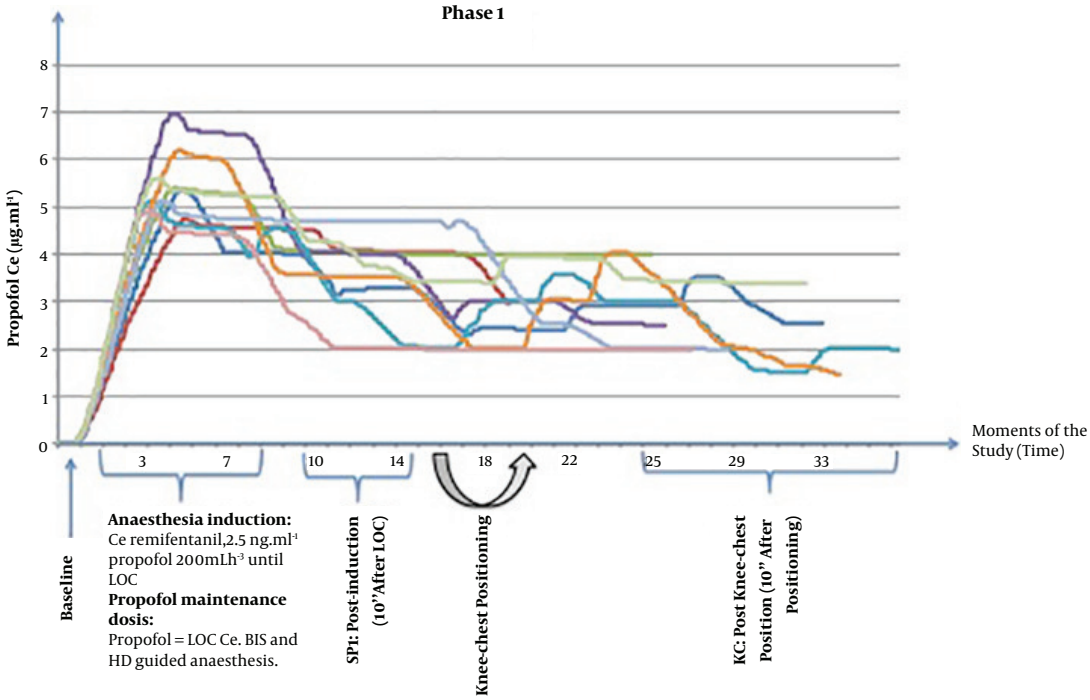

Figure 2. Relationship between propofol effect-site concentration (Ce) (μg.mL^{-1}) and moments of the study (time) in phase I (baseline, SP1, and KC). HD, hemodynamic; LOC, loss of consciousness; KC, knee-chest; SP1, supine.

Table 1. Demographics and Baseline Values of the Subjects in Phase I and Phase II[a]

Characteristics	Phase I	Phase II
Age, y	49.3 ± 8.7	59.7 ± 13.5
Sex (f/m)	6/3	6/5
Height, cm	161.6 ± 9.0	167.8 ± 12.4
Weight, kg	70.9 ± 13.9	77.3 ± 11.6
Body Mass Index, kg.m^{-2}	27.0 ± 3.5	27.4 ± 3.0
ASA classification I/II	3/6	2/9
Cardiac output (baseline), L.min^{-1}	7.4 ± 1.8	7.2 ± 2.3
Propofol Ce at LOC, μg.mL^{-1}	5.03 ± 0.75	4.34 ± 1.52
Time to LOC, min	3.76 ± 0.80	3.05 ± 1.22

Abbreviations: ASA, American Society of Anesthesiologists; LOC, loss of consciousness; Propofol Ce, propofol effect-site concentration.
[a]Values are expressed as No. or mean ± SD.

In phase II, after induction, propofol target Ce was set at a value below the Ce at LOC, based on the formula presented earlier in methods. The average decrease in propofol Ce following LOC was 27.5%, with a maximum of 43% (prop Ce LOC = 7.0 μg.mL^{-1}) and a minimum of 19% (prop Ce LOC = 2.7 μg.mL^{-1}). The second reduction in propofol was performed in all patients that was equal to the CO reduction measured in patients from the phase I following KC positioning (17.2%) (Figure 3). Propofol Ce and Cp were statistically different between all moments, except between SP2 and KC moment (Table 2). Measured propofol showed a statistical difference between SP2 and KC moment (P = 0.013).

In phase II, despite propofol Ce reductions, CO reduced significantly from baseline 46.9%, after induction 19.8% and after KC position 31% (Figure 4). From moment SP1 to moment SP2, HD parameters did not vary.

In both phases, there was no statistical association between CO changes and age, weight, gender, baseline CO, and propofol Ce at LOC (P > 0.05). A correlation was found between baseline CO and propofol requirements for LOC (propofol infused volume until LOC), with statistical significance in phase II (r = 0.76; P = 0.006). Between phases, there were significant differences in propofol Ce (P = 0.005) and propofol Cp (P = 0.015) at the SP1 moment. Propofol infused volume was statistically different between all moments and between phases, except for LOC.

A total of 71 arterial blood samples were obtained, propofol concentrations were measured, and the predicted error was calculated for each patient, as shown in Table 3.

At the SP1 moment, there were no differences between

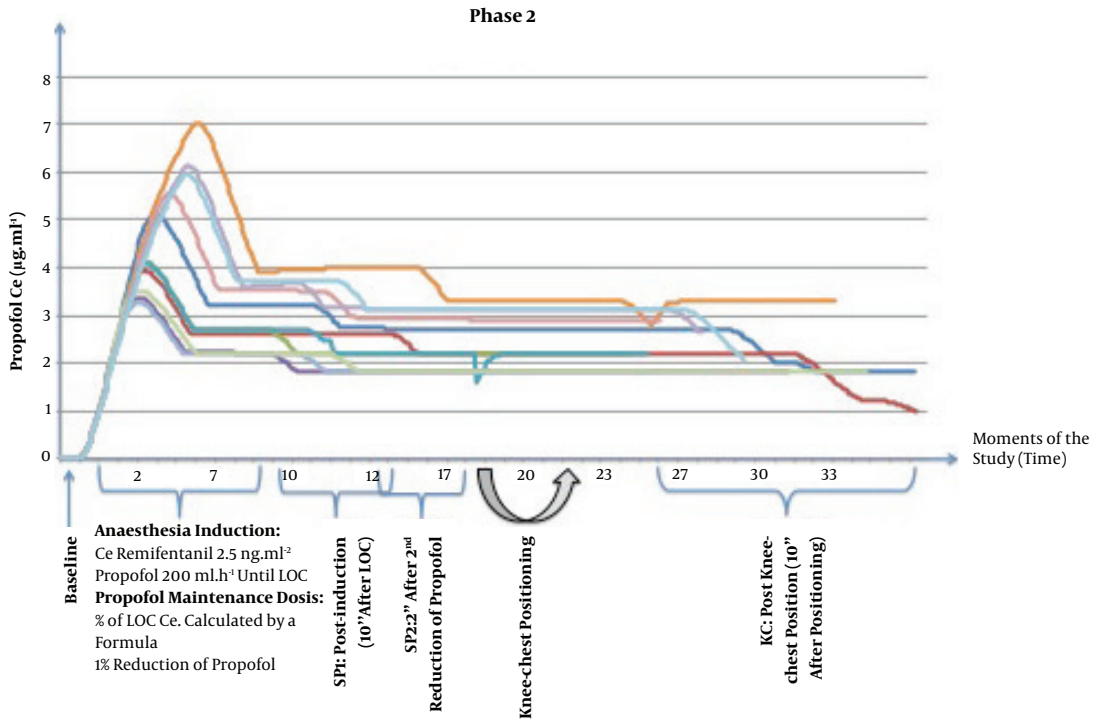

Figure 3. Relationship between propofol effect-site concentrations (Ce) ($\mu g.mL^{-1}$) and moments of the study (time) in phase II (baseline, SP1, SP2 and KC). HD, hemodynamic; LOC, loss of consciousness; KC, knee-chest; SP1, supine; SP2, supine after the second reduction in propofol infusion.

Table 2. Drug Data, Cardiac Output, and BIS Values for Each Moment and Each Phase[a, b]

Drugs Data and Variables (Units)	Phase I (N = 9)			Phase II (N = 11)				Two-Way ANOVA (P Value)		
	Baseline	SP1	KC	Baseline	SP1	SP2	KC	Moment	Phase	Moment × Phase
Propofol ($\mu g.mL^{-1}$)										
Ce	5.03 ± 0.75 (LOC)	3.84 ± 0.63[c]	2.53 ± 0.79[e]	4.34 ± 1.52 (LOC)	2.92 ± 0.64[c]	2.47 ± 0.57	2.20 ± 0.51[e]	< 0.001*	0.054	0.352
Cp	-	3.83 ± 0.74	2.48 ± 0.86[e]	-	2.97 ± 0.68	2.46 ± 0.58	2.24 ± 0.58[e]	< 0.001*	0.06	0.083
Cm	-	3.61 ± 1.14	3.31 ± 2.11	-	2.96 ± 0.81	2.68 ± 0.72	3.90 ± 1.90[f]	0.455	0.961	0.162
Remifentanil ($ng.mL^{-1}$)										
Ce	-	2.36 ± 0.42	1.11 ± 0.35[e]	-	1.85 ± 0.66	1.12 ± 0.20	1.15 ± 0.48[e]	< 0.001*	0.132	0.107
Propofol Inf. volume (mL)	12.46 ± 2.44 (LOC)	22.53 ± 4.09[c]	37.09 ± 8.07[d, e]	9.63 ± 4.09 (LOC)	15.86 ± 6.10[c]	19.36 ± 6.71	27.15 ± 8.63[d, e, f]	< 0.001*	0.014*	0.034*
BIS	94.0 ± 2.2	61.8 ± 15.2[c]	42.3 ± 15.1[e]	95.3 ± 2.6	49.9 ± 9.8[c]	46.5 ± 7.5	37.7 ± 8.7[d, e]	< 0.001*	0.056	0.165
Cardiac output ($L.min^{-1}$)	7.4 ± 1.8	5.4 ± 1.3[c]	4.4 ± 1.2[d]	7.2 ± 2.3	5.6 ± 1.6[c]	5.6 ± 1.7	3.9 ± 1.9[d, e]	< 0.001*	0.867	0.514

Abbreviations: Ce, effect-site concentration; Cm, measured plasmatic concentration; Cp, predicted plasmatic concentration; Inf., Infused; LOC, loss of consciousness; KC, knee-chest; SP1, supine; SP2, supine after the second reduction in propofol infusion.
[a] Values are expressed as mean ± SD.
[b] The superscripts c, d, e, and f indicate significant differences (5% level) on repeated measures ANOVA post hoc pairwise testing with Bonferroni correction (*).
[c] Significant differences between Baseline and SP1.
[d] Significant differences between Baseline and KC;
[e] Significant differences between SP1 and KC;
[f] Significant differences between SP2 and KC.

Cp and Cm (P = 0.559) and there was a statistical correlation between them (r = 0.640; P = 0.002). At the KC moment, there was an underestimation of propofol plasma concentrations from the Pk model in both phases (34% in phase I and 74% in phase II) (Figure 5). Cp and Cm were statistically different (P = 0.005) and there was no statistical correlation between them (r = 0.374; P = 0.104). In both phases, BIS values did not differ between phases (P = 0.165) (Table 2). There were no cases of patient awareness. Linear regression analysis revealed no statistically significant relation-

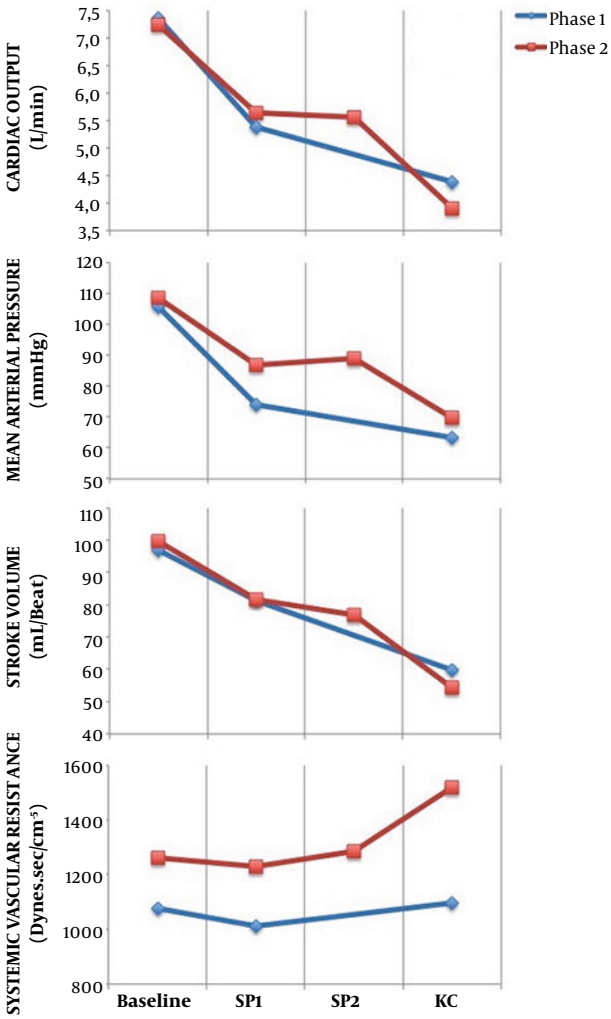

Figure 4. HD changes (cardiac output, mean arterial pressure, stroke volume, and systemic vascular resistance variation) in phase I and phase II.

ship between BIS values and propofol Cm or BIS values and cardiac output at any moment.

5. Discussion

In the present study, a propofol TCI system with Schnider Pk model was used to drive a propofol pump that showed a marked underestimation of plasma propofol levels in patients placed in the KC position. The study also showed that the KC position was associated with significant hemodynamic changes, as a reduction in CO from baseline was observed (Figure 4). After induction, the Schnider Pk model showed a good performance in Cp prediction (Table 3). Also, there was a statistical correlation between Cp and Cm. In the KC position, when the greatest

Table 3. Performance Analysis of the Propofol Schnider Pk Model Expressed in Median Prediction Error (MDPE) and Median Absolute Performance Error (MDAPE) for Each Moment and Phase (%)

Moments	Propofol Pk Model Performance (%)	
	MDPE	MDAPE
Phase I		
SP1	-6% (-49 to 20)	15% (1 to 49)
KC	28% (-35 to 114)	35% (6 to 114)
Phase II		
SP1	13% (-43 to 45)	20% (4 to 45)
SP2	18% (-45 to 56)	32% (0 to 56)
KC	48% (-44 to 270)	48% (6 to 270)

Abbreviations: KC, knee-chest; SP1, supine; SP2, supine after the second reduction in propofol infusion.

CO reduction occurred, Schnider Pk model performance was not accurate, as propofol Cp was not correlated with Cm and it was markedly underestimated by 34% in phase I and 74% in phase II. Also, in the KC position, the MDPE and MDAPE values calculated at this moment did not show a good performance.

In phase II, between moment SP2 and moment KC, when propofol Cp and propofol Ce concentrations were unchanged and the only intervention performed on patients was KC positioning, it was observed an increase in the measured propofol concentrations ($P = 0.013$) and a decrease in BIS values ($P = 0.004$) (Figure 5).

The influence of CO on the pharmacokinetic models to predict propofol plasma concentrations during TCI had already been discussed by some authors (6). It can be speculated that the difference between the predicted and measured propofol concentrations in patients with lower CO is most likely related to a decrease in total propofol clearance, but further data are still needed to correlate CO or liver blood flow and plasma clearance of propofol. Upton et al. (14) reported an inverse relationship between CO and propofol concentrations after a short propofol infusion in an ovine model. Myburgh et al. (8) observed the same relationship during longer propofol infusions in a high-CO state induced by catecholamine infusion in the ovine. Kurita et al. (5) confirmed, in a swine model, that Cp was inversely correlated with changes in CO during constant infusion. We also plotted the relationship between measured Cp and the inverse of CO, but we did not observe any statistical association. It must be highlighted that most of the published studies were performed in animal models, with no studies in humans. Recently, Keyl et al. (4) found that Schnider Pk model markedly underestimated Cp in patients with impaired left ventricular function.

In phase II of our study, we found a statistical correla-

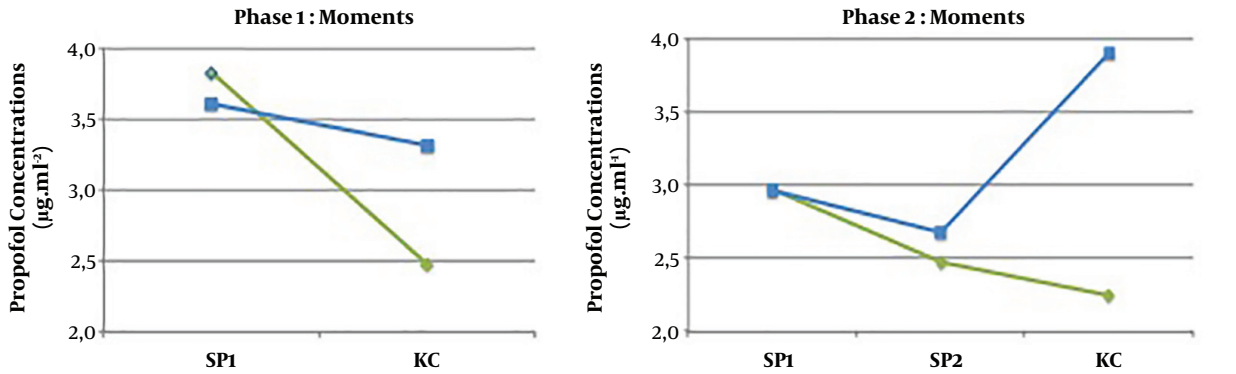

Figure 5. Predicted (green line) and measured (blue line) propofol concentrations ($\mu g.mL^{-1}$) at SP1, SP2 (phase II), and KC moment in both phases. KC, knee-chest; SP1, supine; SP2, supine after the second reduction in propofol infusion.

tion between propofol infused volume until LOC and baseline CO, showing that CO is a determinant to infer the initial concentrations of propofol for anesthesia induction (14).

In the present study, we expected a correlation between propofol infused volume and CO fall. Comparing both phases, propofol consumption (propofol infused volume) was much lower in phase II than in phase I (P = 0.034) (Table 2). Also, patients in both phases did not show differences in BIS values and other parameters; thus we can conclude that patients in the KC position need lower propofol concentrations. Nevertheless, propofol targeted reductions did not attenuate the CO fall when placing patients in the KC position, as the authors previously hypothesized. The results suggest that planned decrements in propofol target Ce did not correspond to a decrease in Cm (Figure 5), as in phase II, after two reductions, the underestimation increased at the KC moment.

Furthermore, hemodynamic changes should be avoided in high-risk patients, even for short periods, as they are associated with poor outcomes (21-23). The present study also showed an important finding that even in ASA 1 and 2 patients, significant HD changes may occur after the KC position.

5.1. Limitations

The present study has several limitations. ANOVA was quite comprehensive, with three measures compared in each individual and between the two groups. However, regarding propofol concentrations, the sample size may be considered small. The definition of the moments of data analysis was a challenge. We defined a 10-minute period stabilization following induction and KC positioning according to the literature (10, 24). The fact that this was a non-randomized study may be considered a limitation. However, we needed data from the first phase to determine the intervention in the second phase.

5.2. Conclusions

Our study showed that the measured propofol concentrations, after hemodynamic changes associated with the KC position, were much higher than the values predicted by Schnider Pk model. Planned propofol reductions did not attenuate the underestimation error from the Pk model. When placing patients in the KC position, BIS values decreased and the measured propofol concentrations increased. Our results suggest that the CO variation was responsible for the pharmacokinetic phenomenon described above. In high-risk patients placed in the KC position, anesthesiologists must be aware of these pharmacokinetic changes and, in addition to standard monitoring, the use of depth of anesthesia and cardiac output monitors may be considered. Further work is planned in an educational area with a simulation program to prepare surgical teams to a structured and careful approach for these patients.

Footnotes

Authors' Contribution: Daniela Chalo, Sara Pedrosa, and Pedro Amorim designed the study. Daniela Chalo, Sara Pedrosa, and Aura Silva collected the data. Daniela Chalo, Aura Silva, and Paula Guedes de Pinho helped in propofol analysis. Sonia Gouveia and Rui Correia conducted the statistical analysis. Daniela Chalo and Sara Pedrosa wrote the manuscript. Pedro Amorim, Rui Correia, Paula Guedes de Pinho, and Consuelo Sancho helped to write and revise the manuscript.

Clinical Trial Registration Code: ClinicalTrials.gov, ID: NCT03961958 registered 22 May 2019.

Conflict of Interests: Authors declare that there is no conflict of interest in this study.

Ethical Approval: This prospective cohort study was approved by the local Research Ethics Board of the Centro Hospitalar do Porto in Oporto, Portugal on the 3rd of July 2009, chaired by Luisa Bernardo: ref. 061/09 (041-DEFI/057-CES).

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Patient Consent: Written and informed consent was requested to all patients.

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Advances in Simulation

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Design of an interface for teaching cardiovascular physiology to anesthesia clinicians with a patient simulator connected to a minimally invasive cardiac output monitor (LiDCO *rapid*®)

Daniela Chaló[1,2,3*], Joana Marques[3,4], Henrique Mendes[5] and Consuelo Sancho[1]

Abstract

Cardiovascular physiology can be simulated in patient simulators but is limited to the simulator monitor curves and parameters, missing some important data that today is known as essential to fluid management and therapeutic decision in critical ill and high-risk surgical patients. Our main objective was to project and implement a unidirectional communication channel between a pre-existing patient simulator and a minimally invasive cardiac output monitor (LiDCO *rapid*®); a monitor that connects to real patients and interprets the arterial wave. To connect the patient simulator to the hemodynamic monitor, firstly, we had to assess both systems and design a communication channel between them. LiDCO monitor accepts as an input an analog voltage varying between 0 V and 5 V and that every volt is directly proportional to a blood pressure (mmHg) value ranging from 0 mmHg (0 V) to 500 mmHg (5 V). A Raspberry Pi 0 (Rpi0) with a WIFI chip integrated was needed and added to a digital analogue converter connected to the board. We designed a system that allowed us to collect, interpret and modify data, and feed it to the LiDCO *rapid*® monitor. We had developed a Python® script with three independent threads and a circular buffer to handle the data transmission between both systems. The LiDCO hemodynamic monitor successfully received data sent from our setup like a real patient arterial wave pulse and interpreted it to estimate several hemodynamic parameters, as cardiac output, stroke volume, systemic vascular resistance, pulse pressure variation, and stroke volume variation. The connection between the patient simulator and the LiDCO monitor is being used to create arterial curves and other hemodynamic parameters for clinical scenarios where residents and anesthesiologists can simulate a variety of unstable hemodynamic conditions, preparing them to face similar situations with real patients in a safe environment and with their own monitors.

Keywords: Clinical simulation, Cardiovascular physiology, Medical education, Healthcare innovation

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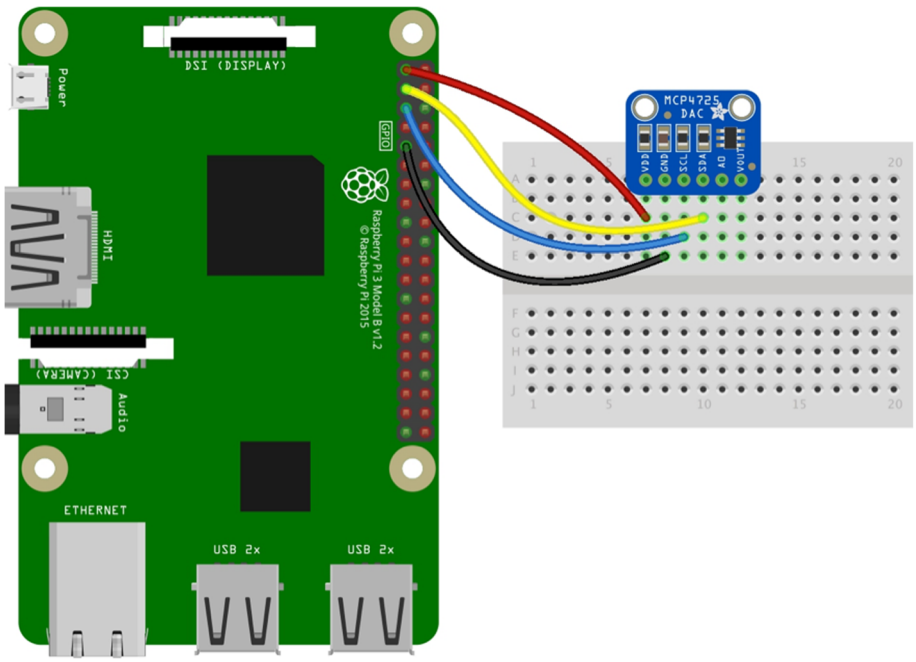

Fig. 1 Diagram connection between the Raspberry Pi and the MCP4725 12-bit DAC

Introduction

Technological advances in medicine are an actual fact and the new generation of anesthesia clinicians must be prepared, since the very beginning of their residence, to use advanced technology in several equipment: monitors and patient ventilators, ultrasound and airway management devices. Also, experienced anesthesiologists need to be updated and must know how to use the new devices and how to teach to younger clinicians and residents. Active learning strategies and simulation technologies are already used with medical students [1, 2] and residents [3], and their benefits and advantages on students' learning cognitive and behavioural skills are well recognised [4, 5]. Simulation-based learning can also be helpful to develop healthcare professional's knowledge, skills, and attitudes while protecting patients from unnecessary risks [6]. Anesthesiologists pioneered the use of patient simulators in training programs all over the world [7, 8]. In Portugal, since 2018, the Anesthesiology Medical Council established a program with recommended courses using simulation as a teaching tool.

In recent years, significant progress has been made with perioperative technology, namely, with minimally invasive cardiac output (CO) monitors such as the LIDCO *rapid*® (LiDCO Ltd., Cambridge, UK) [9–11]. This device uses the PulseCO™ algorithm, without calibration, which converts the blood pressure arterial wave to its constituent parts of flow (cardiac output and stroke volume) and systemic vascular resistance (SVR). The PulseCO™ algorithm is scaled to each patient with a nomogram using age, height, and weight. The PulseCO™ algorithm is reliable in unstable patients and in patients on vasoactive drugs. This CO monitor also estimates: cardiac index, stroke volume index, pulse pressure variation (PPV), and stroke volume variation (SVV).

Patient simulators (PS) are an essential tool as part of the methodology in which lifelike situations are simulated and clinicians are exposed to scenarios in a safe environment which later promote self-reflection during the debriefing phase, in order to improve the clinician's knowledge and skills. This patient simulator, METIman® Pre-Hospital (CAE Healthcare), is an advanced pathophysiological simulator that can represent different clinical scenarios, including important variations in hemodynamics, by modifying parameters such as heart contractility, aortic impedance, systemic, and pulmonary vascular resistances. Nevertheless, in most cases, advanced hemodynamic parameters, such as stroke volume, pulse pressure variation (PPV), and stroke volume variation (SVV), are not represented in the simulator's monitors, resulting in a technological limitation. Patient simulators are also limited because of their inability to integrate with real clinical equipment, as minimally invasive cardiac output monitors.

Our main objective in this study was to project and implement an unidirectional communication channel between a pre-existing patient simulator METIman® Pre-Hospital from CAE Healthcare and a minimally invasive cardiac output monitor, LiDCO *rapid*® [12], thus being able to simulate a set of conditions on the patient

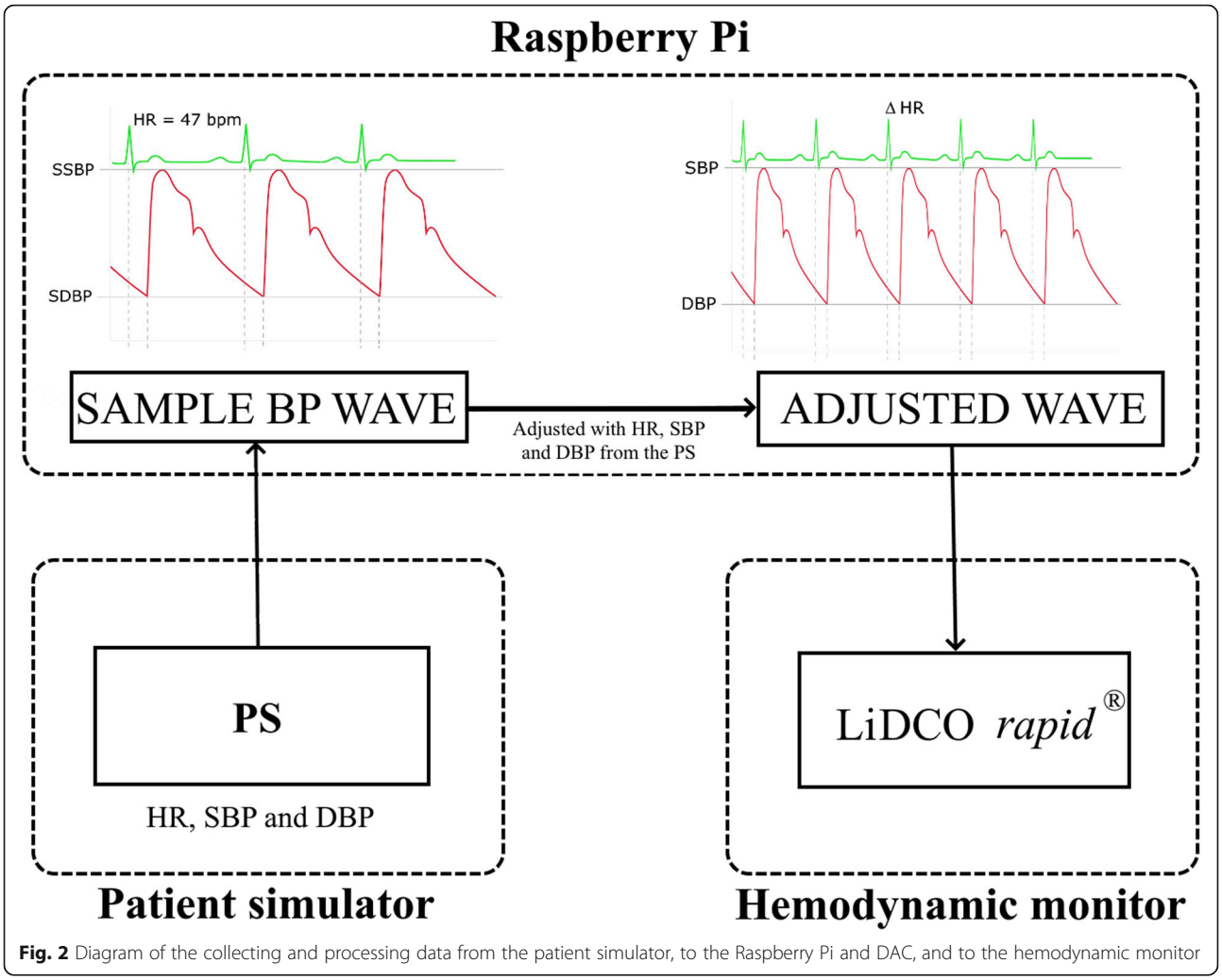

Fig. 2 Diagram of the collecting and processing data from the patient simulator, to the Raspberry Pi and DAC, and to the hemodynamic monitor

simulator and make the LiDCO monitor respond to those same conditions as if a real patient was being monitored. This integration will further allow us to develop clinical scenarios and train clinicians in advanced hemodynamic monitoring using simulation.

Material and methods

To achieve the goal of connecting the patient simulator to the LiDCO *rapid*® monitor, firstly, we had to assess both systems and design a communication channel between them. To perform the hardware integration, we used a Raspberry Pi Zero W®. The Raspberry Pi Zero W® is a small computer on a board that runs a distribution of Linux and can be programmed on demand using Python®. We also used a DAC (digital to analogue converter) board with a MCP4725 12-bit DAC (Fig. 1) [13, 14]. This is an I2C (serial protocol for two-wire interface to connect low-speed devices like microcontrollers) controlled by DAC that can run on a 0–5 V output to generate and send a 0–5 V continuous signal to the LiDCO monitor input. For the connection between the DAC and the monitor, it used a BNC Female Jack Terminal Block compatible with the coaxial input line of the LiDCO monitor. The patient simulator data can be accessed by connecting the Raspberry Pi and the patient simulator control unit over its internal network and doing a SQL (Structured Query Language) request to its main processing unit, obtaining the systolic blood pressure (SBP), diastolic blood pressure (DBP), and the heart rate (HR), values it generates once a second. Alongside, we worked with the LiDCO development team and established that the LiDCO monitor accepts as an input an analog voltage varying between 0 V and 5 V and that every volt is directly proportional to a blood pressure (BP) (mmHg) value ranging from 0 mmHg (0 V) to 500 mmHg (5 V). Therefore, a circuit was designed to allow the Raspberry Pi to collect, interpret, and modify the data from the PS (input) and feed it into the LiDCO monitor (output) (Fig. 2). As the PS did not have a way to export the BP pulse wave values, we created an

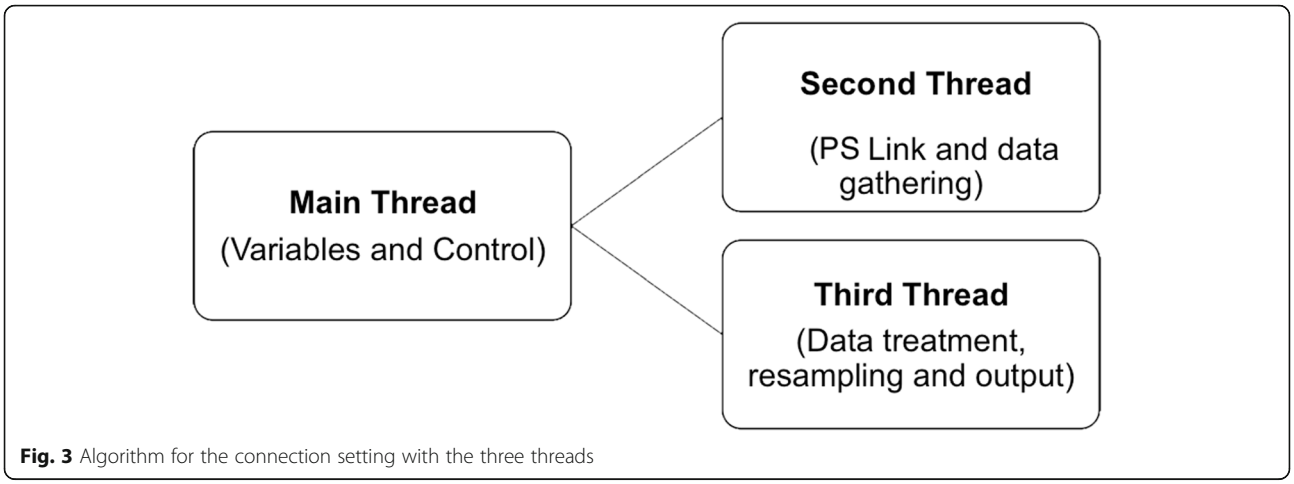

Fig. 3 Algorithm for the connection setting with the three threads

algorithm program in Python®, in which we gathered and normalized the amplitude of a standard BP pulse wave (0 mmHg–1 mmHg) from a real patient and resized it to the value range acquired from the PS (DBP/SBP). The Python® script had three independent threads and a circular buffer to handle the data transmission between both systems. The first thread (main) was responsible for setting some local variables that store function values and to initiate the two secondary threads and the circular buffer. The buffer contains the normalized array with the BP pulse wave information. The second thread connected to the PS query the HR, SBP, and DBP on 1-s intervals making it available to the third thread. The third thread received the buffer BP pulse wave values, performed the necessary calculations, and wrote the final values on the DAC (adjusted to 0–5 V) with an adjusted frequency to match the HR value on the PS (Fig. 3). Variables transmitted from the patient simulator are presented at Table 1.

Results

The communication between the patient simulator and the LiDCO monitor was successfully achieved. Data from the PS (HR, SBP, DBP) was extracted on a frequency of 1/s (1 Hz). This information was processed, resampled, and sent to the LiDCO monitor to be interpreted as if data from a real blood pressure pulse wave was being processed. The LiDCO hemodynamic monitor successfully received and interpreted the data sent from our setup as if it was received from a real patient, as it can be seen in the Electronic Supplementary Material (ESM.1). The interface algorithm used a normalized vector as a reference, i.e., a sample of BP waveform (signal), acquired from a patient without pathology, recorded at 250 Hz and 47 bpm (beats per minute). Then, the signal from the normalized vector was adjusted to the HR and to the BP from the PS, and the amplitude of the maximum signal and minimum signal corresponded to the SBP and to the DBP, respectively (Fig. 4).

Table 1 Output variables transmitted from the PS to the DAC

Variable	Signal type	Units	Inferior limit	Superior limit
HR	Digital (decimal)	bpm	0	350
SBP	Digital (decimal)	mmHg	NA	NA
DBP	Digital (decimal)	mmHg	NA	NA

Discussion

Cardiovascular physiology can be simulated in patient simulators but is limited to the simulator monitor curves and parameters, missing some important data essential to fluid management and goal-directed therapy (GDT) in critically ill and high-risk surgical patients. The purpose of hemodynamic monitoring is to identify variations in cardiovascular parameters and intervene before major complications occur, including organ failure or death. During surgery, fluid therapy should be targeted according to physiological measures and maintained using fluids or vasopressors once normovolemia has been established, so that tissue oxygenation would not be compromised [11, 15].

This tool is important to train not only basic cardiovascular physiology but also hemodynamic variations during anesthesia phases: induction, positioning, controlled hypotension, and other surgical conditions associated with hemodynamic compromise (orthopedic surgery, vascular surgery, major abdominal surgery) [16]. It can also be used to test enhanced recovery after surgery and emergency protocols associated with situations with hemodynamic instability like massive hemorrhage, septic shock, trauma, and obstetric hemorrhage. The implementation of GDT with the use of minimally invasive monitors to guide perioperative practice has become rapidly established and accepted over the last few years, from central venous pressure until stroke volume variation or pulse pressure variation. All minimally invasive

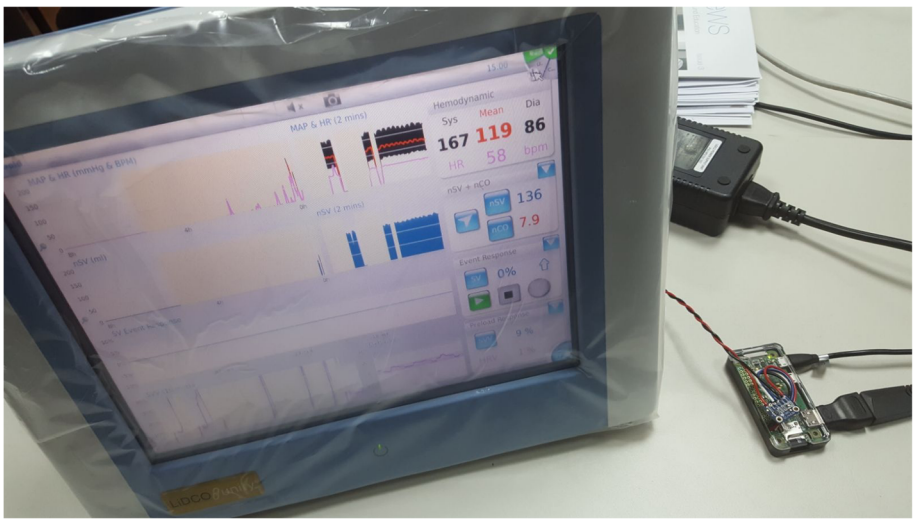

Fig. 4 Connection between the Raspberry Pi and the LiDCO monitor

monitors have different characteristics and layouts, so clinicians should train on their own monitor to be familiar with the parameters and its interpretation, to minimize errors and provide a better and safe healthcare.

Patients with cardiac or vascular pathology can display different hemodynamic curves, especially in those with heart diseases, abnormal contractibility, rhythm conditions, and valve-related pathologies. This fact should be taken into consideration when developing scenarios. There is a limitation related to the fact that we used a normalized vector to simulate the BP waveform, so that can only vary the amplitude of the BP wave and the HR, but not the wave configuration. Despite this limitation, the methodology still has advantages as it requests a few number of parameters from the simulator that can be, in future versions, provided from a control station, allowing the training even without the need of a patient simulator.

Authors also believe the interface could be used with other PS or other monitors. Nevertheless, this possibility is dependent on the ability to communicate with the simulator to request the three variables used (HR, SBP, and DBP). If the PS is different and the transmitted

Fig. 5 Clinical scenario in the simulation center

signal is analog, the approach would be easier, because the only request would be a 0–5 V analog input transmitted from the probe side.

Conclusions

Anesthesiologists should be trained on their own cardiac output monitors, so they can interpret fast and easier their parameters, minimize errors, and provide a better and safe healthcare. The interface between the patient simulator and LiDCO *rapid*® monitor is now being used to teach anesthesiologists and residents with success, allowing a safe environment in a clinical simulation scenario (Fig. 5). In the near future, authors believe that the interface can be developed for other patient simulators, and it can also be used to teach other healthcare providers in an interprofessional educational program.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s41077-020-00134-0.

Additional file 1: Brief video with the blood pressure pulse wave generated by the connection between the patient simulator and the LiDCO monitor

Abbreviations

BP: Blood pressure; CO: Cardiac output; DAC: Digital to analogue converter; DBP: Diastolic blood pressure; ESM: Electronic supplementary material; GDT: Goal-directed therapy; HR: Heart rate; MAP: Mean arterial pressure; NA: Non-applicable; PS: Patient simulator; PPV: Pulse pressure variation; Rpi0: Raspberry Pi 0; SBP: Systolic blood pressure; SQL: Structured query language; SVV: Stroke volume variation

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Ethical approval and consent to participate

This article does not contain any studies with human participants or studies with animals performed by any of the authors.

Authors' contributions

DC, JM, and HM designed the connection. HM developed the interface for the connection. DC, JM, and CS wrote the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare no conflict of interest.

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