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Applied cardiovascular physiology in theatre: measuring the cardiovascular effects of propofol anaesthesia

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Cardiovascular homeostasis is a complex and beautiful interplay between the functional differences between various vascular circuits in the body and their tissue's metabolic demand, the physical nature of the endothelial barrier to fluid flux, the circulating blood volume, and reflex-mediated autonomic tone. When at rest, as occurs during anaesthesia, basal metabolic demand is both constant and low. Thus, impairments in autoregulation or sudden decreases in blood volume, as may happen during surgery, are thankfully less detrimental to tissue wellness than might otherwise be the case under conditions of metabolic stress. However, such physiologic reserve though comforting to the anaesthetist and forgiving to the patient, has clearly defined limits. Anaesthesia by its nature decreases central nervous system activity and by default, impairs autonomic responsiveness and at high enough concentrations impairs vascular tone and cardiac contractility. These concepts form the basis for anaesthetic selection in specific patient groups. But mostly all these considerations have focused on the left ventricle (LV) and arterial tone, ignoring venous return by simply placating it with increased fluid resuscitation, vasopressor infusion and/or decreased concentration of anaesthesia if the patient becomes hypodynamic.

However, the circulation is much more interactive in its components defining cardiac output than those described by left ventricular preload and contractility and arterial pressure and arterial vasomotor tone. Fundamental principles of cardiovascular physiology, as originally described by Guyton and colleagues[1] more than 50 yr ago,[1] identified venous return as the primary determinant of cardiac output and that LV function is remarkably insensitive in defining this level of flow, only the required backpressures needed for that flow. We collectively argued these points relative to cardiopulmonary bypass surgery in a physiologic commentary.[2] Until recently, just knowing that venous return was the primary determinant of cardiac output did little to help the bedside clinician manage complex and changing surgical patients. One understood that mean circulatory filling pressure (Pmcf) was the best surrogate for effective circulating blood volume, but its measure and its own determinants were difficult to ascertain at the bedside and nearly impossible to measure repeatedly over time. The effective circulating blood volume represents a balancing act between total circulating blood volume, blood flow distribution amongst various organs with varying degrees of capacitance and unstressed volume, and the resistance to venous return (RVR), which has more of a conductance determinant to its value that actual physical resistive.[3] Importantly, multiple lines of investigation have led to the development of several methods to quantify Pmcf at the bedside using only arterial pressure, central venous pressure (CVP), and cardiac output. A detailed review of these various techniques is found elsewhere.[4] However, presently three techniques are readily available and can be used for the bedside assessment of venous return.

The first approach uses an analogue estimate of Pmcf by assuming a constant proportion of compliance and resistances within the arterial and venous circuit.[5] We recently validated this breath-by-breath analogue approach in a canine model during normal and endotoxic shock state.[6] Using this analogue approach Cecconi and colleagues[7] examined the effect of fluid boluses on Pmcf, the driving pressure for venous return (Pmcf-CVP), and cardiac output in a large postoperative surgical patient population. They showed that fluid loading universally increased Pmcf, if only transiently, and unaltered RVR. However, for cardiac output to increase the driving pressure for venous return also needed to increase. Thus, if fluid loading did not increase cardiac output, CVP increased, whereas in those whose cardiac output increased CVP remained stable. The observation that volume loading does not alter RVR has been known for more than 30 yr,[8] and is the basis for increases in CVP during fluid loading being a 'stopping rule' for fluid infusion therapy.[9]

The second method used is the end-inspiratory pause technique wherein several small end-inspiratory hold manoeuvres are done for 10–15 s each at 5, 7.5, 10 and 15 cm H_2O airway pressure and the resultant steady state Pra, cardiac output values are used to construct the venous return curve.[10] This technique was validated in postoperative cardiac surgery patients[11] and remains the standard technique by which to validate other estimates of Pmcf.

The final approach is to measure the stop flow radial arterial pressure from an indwelling arterial catheter 15 to 20 s after total limb occlusion by rapid inflation of a proximal sphygmomanometer cuff.[12] This approach is attractive because it only requires a simple measure of radial arterial pressure. Geerts and colleagues[13] defined the cardiovascular effects of dobutamine in a porcine model using this approach. Importantly, they identified that dobutamine, a known vasodilator, not only decreased Pmcf but also decreased RVR, such that cardiac output did not decrease as much as would have otherwise been the case if only Pmcf had decreased. And in responsive heart failure patients who are not hypovolemic, the associated decrease in CVP resulted in the expected increase in cardiac output. These data underscore the central role that RVR has in defining cardiac output under conditions in which vasomotor tone varies.

Vasopressor agents such as norepinephrine increase global vasomotor tone, increasing arterial tone, arterial pressure, Pmcf and the RVR. The resultant change in cardiac output is a function of LV contractile reserve. In healthy patients with preserved contractility who can tolerate the increase in arterial pressure without dilating, cardiac output increases, whereas in those who cannot, cardiac output reduces.[14] Similarly, in septic pressor-dependent patients undergoing weaning from vasopressor support, the decreasing norepinephrine concentrations are associated with both a decrease in Pmcf and RVR, such that cardiac output usually remains constant.[15] These findings are relevant to anaesthetists because removing vasopressors may be similar to adding anaesthetics, as both should decrease basal vasomotor tone. In sepsis this is most likely because of decreased sympathomimetic activity and in general anaesthesia as a result of decreased central sympathetic output.

All these interactions form the basis for the recent study by de Wit and colleagues[16] who studied the effect of increasing doses of propofol during surgery on global haemodynamics. They studied three doses of propofol approximating low, medium and high infusion rates that correspond to mean BIS scores of 52, 39 and 29, respectively. Not surprisingly, they showed that as propofol dose increased arterial resistance and arterial pressure decreased. However, both cardiac output and CVP were unchanged. Similarly, with the reduction in LV afterload, both pulse pressure variation and stroke volume variation increased. Not surprisingly, Pmcf also decreased with increasing doses of propofol, probably as a result of an increase in unstressed circulatory volume, as the arterial vasodilation caused blood to perfusion increasing more vascular beds. Why then did cardiac output not decrease? Because if all that happened was a decrease in stressed volume decreasing Pmcf, cardiac output should decrease. Or for that matter, why did cardiac output not go up if CVP remained constant and LV afterload decreased? Ignoring the reality that CVP does not reflect volume responsiveness,[17] it would otherwise be surprising to see that propofol had such a minimal effect of cardiac output. The reason is that RVR also decreased as more parallel venous circuits were opened, increasing vascular conductance. In fact, the decrease in RVR paralleled the decrease in arterial tone, that when coupled with no change in LV contractility cause cardiac output to remain constant. These findings underscore the complex and important interactions that anaesthetics have with the circulation and how by not measuring the determinants of cardiovascular function the bedside anaesthetist may both misunderstand and mistreat their patients. It also adds new meaning to the phrase 'balanced anaesthesia.'

Now that we have the tools necessary to apply the knowledge already known about cardiovascular physiology in theatre, it will be very interesting to see how other general and regional anaesthetics alter cardiovascular function, and do so across patients with varying degrees of cardiovascular reserve.

Declaration of interest

LiDCO Ltd, Edwards LifeSciences: consultant.

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Monitoring consciousness under anaesthesia: the 21st century isolated forearm technique

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The isolated forearm technique (IFT), first introduced by Tunstall[1] for short term use during Caesarean section, was modified by the author[2] and subsequently used successfully with many neuromuscular blocking agents(curare, alcuronium, fazadinium, atracurium, vecuronium) for longer operations. However, with the longer lasting muscle relaxants (pancuronium, rocuronium), the recommended intubation doses generally result in paralysis of the hand when the tourniquet is released.[3 4] With an intubating dose of rocuronium (0.3 mg kg^{-1}),[5] half that usually recommended, and judicious top-up dose titration, given only as required for surgical requirements, the author (I.F.R.) has used the IFT successfully during total i.v. anaesthesia (TIVA/TCI) for women undergoing radical hysterectomy. Nevertheless, when using the recommended intubating dose of rocuronium, the subsequent paralysis of the isolated hand after cuff deflation is a major obstacle to using the IFT. In this issue of the journal an intriguing 'proof of concept' study suggests the possibility that this obstacle to the use of the IFT with rocuronium can be overcome.[6]

The authors of the study[6] call their technique the reversed IFT (rIFT). Instead of using a tourniquet to prevent the arm muscles being blocked by rocuronium the authors, using the principle of a Bier's block with dilute sugammadex, antagonized the paralysis already present in one arm. When the tourniquet was deflated 15 min later, the arm remained unparalysed and there was no significant change in the muscle relaxation in the rest of the body. It is also worth noting that the authors observed no significant complications, with only minor bruising in three patients. In the author's (IFR) experience, bruising and nipping from the NIBP cuff is more of an issue than any problem noted with the padded IFT cuff (Fig. 1A and B).

As rocuronium is now a commonly used neuromuscular blocking agent, the principal merit of the rIFT lies in its potential to minimize restrictions on the intubating dose of rocuronium, as the paralysis in one arm can be antagonized. Alternatively, the authors suggest that the rIFT can be used 'instantly, whenever the depth of anaesthesia becomes unclear' allowing a direct assessment of the patient's conscious state. However, as described, there is a major limitation with the rIFT as there is no possibility of monitoring consciousness during the early stages of anaesthesia: induction, intubation and stabilization of the patient. Even excluding drug errors and syringe swaps, induction of anaesthesia accounts for half the cases of AAWR and, during the maintenance phase of anaesthesia, 40% of AAWR cases occurred at skin incision.[7] Thus, for a more appropriate use of the rIFT, the normal IFT should be used from the start of anaesthesia and, after deflation of the tourniquet, if the hand becomes very weak or paralysed as a result of rocuronium, then is the time for the rIFT.

For various, mostly unjustified, reasons[8] the IFT is rarely used, with one UK activity survey indicating that it was used in only five (0.03%) patients,[9] yet it has the potential to address many of the issues raised in the NAP5 report,[7] ranging from simple clinical utility to more complex research protocols.

Examples of these are:

1. As outlined above, a high proportion of AAWR occur during induction and the early maintenance phase of anaesthesia. A specific problem was patients regaining consciousness, unknown to the anaesthetist, during difficult airway management. Addressing these issues offers a simple introduction to the IFT – use the IFT during this early phase of anaesthesia, but when the time comes to deflate the cuff, continue the procedure using one's normal anaesthetic and clinical monitoring. Even without continuing the formal IFT technique, direct assessment of the patient's responsiveness to command can be made for as long as the arm remains unparalysed.
2. At the end of the procedure, the anaesthetist often faces a dilemma. The surgeon may request additional muscle relaxation to close the abdomen but, at the same time, the anaesthetist wishes the patient to regain consciousness quickly. These conflicting requirements are probably the reason why almost 25% of AAWR cases occur at this time, with 85% of them causing distress to the patient.[7] The IFT is the most reliable method of monitoring conscious levels accurately at this stage of surgery, allowing anaesthetic concentrations to be reduced to a minimum in the presence of full muscle relaxation: average wake up times are 3–4 min after antagonism of the neuromuscular blocking agent.[10 11]

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CARDIOVASCULAR

The effect of propofol on haemodynamics: cardiac output, venous return, mean systemic filling pressure, and vascular resistances†

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Abstract

Background: Although arterial hypotension occurs frequently with propofol use in humans, its effects on intravascular volume and vascular capacitance are uncertain. We hypothesized that propofol decreases vascular capacitance and therefore decreases stressed volume.

Methods: Cardiac output (CO) was measured using Modelflow® in 17 adult subjects after upper abdominal surgery. Mean systemic filling pressure (MSFP) and vascular resistances were calculated using venous return curves constructed by measuring steady-state arterial and venous pressures and CO during inspiratory hold manoeuvres at increasing plateau pressures. Measurements were performed at three incremental levels of targeted blood propofol concentrations.

Results: Mean blood propofol concentrations for the three targeted levels were 3.0, 4.5, and 6.5 μg ml^{-1}. Mean arterial pressure, central venous pressure, MSFP, venous return pressure, Rv, systemic arterial resistance, and resistance of the systemic circulation decreased, stroke volume variation increased, and CO was not significantly different as propofol concentration increased.

Conclusions: An increase in propofol concentration within the therapeutic range causes a decrease in vascular stressed volume without a change in CO. The absence of an effect of propofol on CO can be explained by the balance between the decrease in effective, or stressed, volume (as determined by MSFP), the decrease in resistance for venous return, and slightly improved heart function.

Clinical trial registration: Netherlands Trial Register: NTR2486.

Key words: anaesthetics, intravenous; cardiac output; propofol; vascular capacitance

Propofol, one of the most widely used i.v. hypnotic drugs, is used for induction and maintenance of general anaesthesia, procedural sedation, and sedation in the intensive care unit. Its rapid onset, fast recovery, and low rate of nausea and vomiting make propofol the sedative drug of choice in many situations.[1] Use of propofol is, however, accompanied by a decrease in arterial blood pressure and systemic vascular resistance.[2–5] The effect of propofol on cardiac output (CO) is uncertain, with reports varying from no effect[4] to a significant decrease.[3 5–7] Venodilation is an important component of the decrease in systemic vascular

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Editor's key points

- Therapeutic doses of propofol reduce arterial pressure and systemic vascular resistance, but the effect of propofol on cardiac output is uncertain.
- Measurements of mean systemic filling pressure in human subjects at three propofol blood concentrations showed no effect on cardiac output.
- Propofol-induced hypotension results from a reduction in stressed volume attributable to reduced venous and arterial resistance with no change in cardiac output.

resistance, as shown, for example, in a study measuring forearm venous compliance.[8] Nonetheless, the effects of propofol on intravascular volume and vascular capacitance have not yet been explored in humans.

Recently, a method was described to measure mean systemic filling pressure (MSFP) in patients with intact circulation after cardiothoracic surgery.[9] The MSFP is the pressure that exists in the systemic circulation during a no-flow state. It reflects the distending pressure generated by stressed volume (the volume that stresses the vessel walls, thus generating pressure). Given that MSFP is equal to capillary pressure, it is the driving pressure in venous return, and it allows calculation of the arterial and venous components of systemic vascular resistance.[10] Venous return is equal to the difference between MSFP and central venous pressure (CVP) divided by the venous resistance.

We determined the MSFP in humans to gain a better understanding of the contribution of changes in intravascular volume and vascular capacitance to the haemodynamic effects of propofol. Based on previous studies, we hypothesized that propofol decreases vascular capacitance and therefore decreases stressed volume.

Methods

Patients

Seventeen postsurgical patients after elective open oesophageal resection or pancreaticoduodenectomy were enrolled after approval by the Leiden University medical ethics committee (reference P10.067) and registration at the Netherlands Trial Register (reference NTR2486). Informed consent was obtained at least 1 day before surgery. Patients with symptomatic peripheral vascular disease or pulmonary disease, aberrant cardiovascular anatomy, significant valvular regurgitation, or severe arrhythmias were excluded.

Before surgery, an epidural catheter was inserted, but local anaesthetics were not administered until after termination of the study. General anaesthesia was induced with target-controlled infusion (TCI) of propofol (Marsh model using a Module DPS Orchestra pump on a Primea IS base, Fresenius Vial, Brézins, France), continuous infusion of remifentanil, and bolus administration of atracurium or rocuronium, according to hospital standards. During surgery, a central venous catheter was inserted under ultrasound guidance, and an arterial catheter was inserted in the radial artery. The patient's lungs were mechanically ventilated in a volume-controlled mode adjusted to achieve normocapnia with tidal volumes of 8–10 ml kg^{-1} and a respiratory rate of 12–14 breaths min^{-1}. The fraction of inspired oxygen ($F_{I_{O_2}}$) was maintained at 0.4, and a PEEP of 5 cm H_2O was applied. Haemodynamic stability was achieved using fluids (normal saline and lactated Ringer's solutions) and catecholamines (ephedrine, norepinephrine).

Measurements

Systemic arterial blood pressure (P_a) was monitored via a 20 gauge, 3.8 cm radial arterial catheter connected to a pressure transducer (PX600F; Edwards Lifesciences, Irvine, CA, USA). Central venous pressure was measured with a catheter inserted through the right internal jugular vein (MultiCath 3 venous catheter; Vigon GmbH & Co., Aachen, Germany) connected to a pressure transducer. The catheter tip position was checked with a chest radiograph. Both transducers were referenced to the intersection of the anterior axillary line and the fifth intercostal space. Airway pressure (P_{vent}) was measured at the entrance of the tracheal tube. Standard ECG leads were used to monitor heart rate (HR). Cerebral activity was measured using bispectral index (BIS®; Model A 2000, Aspect Medical Systems, Natick, MA, USA). Beat-to-beat cardiac output was obtained by Modelflow® (CO) pulse contour analysis (BMEYE, Amsterdam, The Netherlands) as previously described.[11–13] Measurements were recorded for offline analysis at a sample frequency of 100 Hz and 0.2 mm Hg resolution.

Venous return curves were constructed by measuring steady-state P_a, CVP and CO throughout the final 3 s for a set of four 12 s inspiratory hold manoeuvres at increasing P_{vent} plateau pressures of 5, 15, 25, and 35 cm H_2O. The inspiratory hold manoeuvres were separated by 1 min intervals to re-establish baseline haemodynamic steady state. The CVP increases with the increase of P_{vent}, whereas CO and P_a decrease to reach a steady state between 7 and 12 s after initiation of inspiratory hold (Fig. 1). From the steady-state values of CVP and CO during the four inspiratory hold periods, a venous return curve was constructed using linear regression. The inspiratory hold manoeuvres were performed during three sequential, increasing target blood propofol concentrations (propofol C_b), depending on what was haemodynamically (i.e. arterial hypotension) feasible in the individual patient. Haemodynamic measurements were made only after propofol blood–effect site equilibration. Venous propofol blood concentration was determined after collecting samples into test tubes containing potassium oxalate at 6 min after a predicted target propofol concentration had been achieved, and analysed as described.[14]

Data analysis and statistics

The CVP and CO data were fitted by linear regression using a least-squares method for each volume state to define the venous return curve. We defined MSFP by extrapolation to zero flow, assuming that airway pressure does not affect MSFP. We have previously validated this extrapolation in piglets[15–17] and described the technique in postoperative cardiac surgery patients.[9] Total systemic vascular resistance (R_{sys}) was calculated as the ratio of the pressure difference between mean P_a and mean CVP and CO, as follows:

$$R_{sys} = \frac{P_a - CVP}{CO}$$

The resistance downstream to MSFP was taken to reflect the resistance to venous return (R_{vr}) and was calculated as the ratio of the pressure difference between MSFP and CVP and CO, as follows:

$$R_{vr} = \frac{MSFP - CVP}{CO}$$

Systemic arterial resistance (R_a) was taken to be the difference between systemic and venous resistance. The pressure gradient

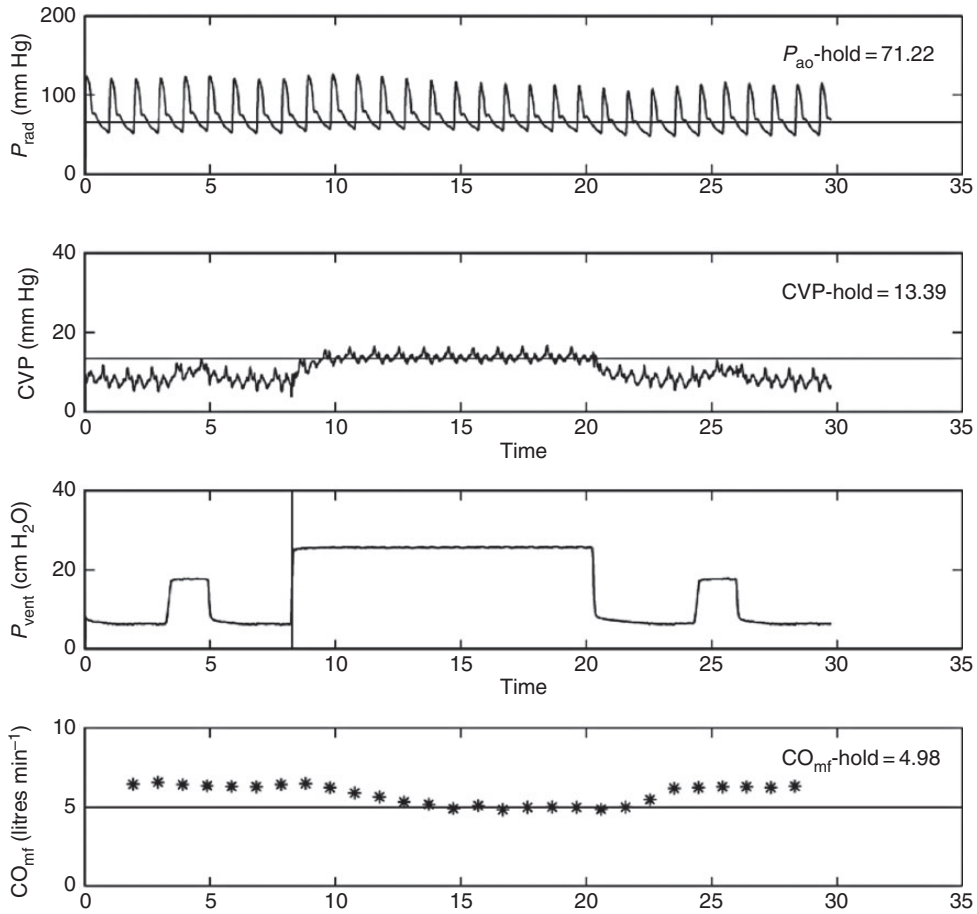

Fig 1 Effects of an inspiratory hold manoeuvre on radial arterial pressure (P_{rad}), central venous pressure (CVP), airway pressure (P_{vent}), and beat-to-beat cardiac output (CO_{mf}).

to venous return (P_{vr}) was defined as the pressure difference between MSFP and CVP.

After confirming a normal distribution of data with the Kolmogorov–Smirnov test, differences in parameters between different propofol concentrations were analysed using Student's paired *t*-tests, with $P<0.05$ considered significant. All values are given as the mean (SD).

Results

Seventeen patients, three women and 14 men, were enrolled. Mean age was 62 (9) yr (range 42–79 yr), mean weight 84 (12) kg, mean height 180 (8) cm and mean body mass index 26 (2.7) kg m^{-2}. All subjects underwent oesophageal resection, except one subject who underwent pancreaticoduodenectomy. One subject was given a low dose of norepinephrine (0.02 μg kg^{-1} min^{-1}) during the entire study interval; all other subjects did not receive vasoactive medication. Subjects had a mean positive fluid balance of 1.85 (1.07) litres (range 0.6–3.8 litres).

Pooled measurements obtained at three increasing propofol concentrations are reported in Table 1. Mean propofol C_b were 3.0 (0.9), 4.5 (1.0), and 6.5 (1.2) μg ml^{-1}. The BIS decreased with increasing propofol C_b to 54 (13), 39 (8), and 29 (7), respectively. Increasing concentrations of propofol led to venous dilatation as venous resistance decreased. Arterial resistance decreased in a similar manner, because the ratio between R_a and R_{vr} did not change significantly. Mean arterial pressure decreased from 82 (12) to 75 (12) and 66 (10) mm Hg, respectively, at the three propofol C_b levels ($P<0.001$). A small but significant increase in HR was found as propofol C_b increased [69 (10), 71 (12), and 73 (11) beats min^{-1}, respectively; $P<0.001$]. Pulse pressure variation increased from 7 (3) to 7 (3) to 11 (5)% at increasing blood propofol levels ($P<0.001$). The MSFP decreased significantly with the increase in propofol C_b (Fig. 2). The pressure to venous return (MSFP minus CVP) also decreased, but the resistance to venous return did too, resulting in no significant change. Therefore, CO did not change significantly despite the increased propofol C_b.

Discussion

We showed that an increase in propofol C_b is associated with a decrease in systemic arterial pressure without a significant change in CO. Venous and total peripheral resistance and MSFP decline with increasing propofol C_b.

Figure 3 shows a venous return curve plotted using the average values of CVP, MSFP, and CO. With increasing propofol concentrations, the venous return curve turns clockwise, which

Table 1 Haemodynamic effects of three doses of propofol administration. BIS, bispectral index; CO, cardiac output; CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure; MSFP, mean systemic filling pressure; PPV, pulse pressure variation; propofol C_b, blood propofol concentration; P_{vr}, pressure difference between MSFP and central venous pressure; R_a, resistance of the arterial circulation; R_{sys}, resistance of the systemic circulation; R_{vr}, resistance for venous return; R_{vr}/R_{sys}, location of MSFP; SVV, stroke volume variation; TCI dose, propofol effect site concentration set on TCI pump; VR slope, slope of the venous return curve. Statistical comparison: P_1, Student's paired *t*-test between propofol concentrations 1 and 2; P_2, Student's paired *t*-test between propofol concentrations 1 and 3

Parameter	Propofol concentration 1 (low)		Propofol concentration 2 (middle)			Propofol concentration 3 (high)		
	Mean	SD	Mean	SD	P_1	Mean	SD	P_2
MAP (mm Hg)	82	13	75	12	0.04	66	10	<0.001
HR (beats min^{-1})	69	10	71	12	0.047	73	11	<0.001
CO (litre min^{-1})	5.7	1.2	5.8	1.1	0.77	5.5	1.2	0.34
CVP (mm Hg)	7.8	2.8	7.3	2.9	0.04	7.2	3.0	0.03
MSFP (mm Hg)	27.9	5.4	24.6	4.9	0.01	21.4	4.2	<0.001
VR slope (litre min^{-1} mm Hg^{-1})	−0.31	0.11	−0.30	0.21	0.41	−0.40	0.10	<0.001
P_{vr} (mm Hg)	20.2	5.6	17.2	5.1	0.01	14.2	3.4	<0.001
R_{vr} (mm Hg min litre^{-1})	3.7	1.4	3.1	1.1	0.01	2.6	0.7	<0.001
R_a (mm Hg min litre^{-1})	8.6	3.4	7.5	2.6	0.06	5.8	2.2	<0.001
R_{sys} (mm Hg min litre^{-1})	13.6	4.5	12.1	4.3	0.004	11.0	3.6	0.002
R_{vr}/R_{sys}	0.28	0.07	0.26	0.72	0.31	0.25	0.06	0.12
SVV (%)	6.6	2.2	7.1	2.9	0.48	9.7	3.9	0.002
PPV (%)	7.0	2.9	7.5	2.8	0.45	10.8	4.72	<0.001
TCI dose (μg ml^{-1})	2.9	0.86	4.0	0.80	<0.001	5.4	1.0	<0.001
Propofol C_b (μg ml^{-1})	3.0	0.90	4.5	1.0	<0.001	6.5	1.2	<0.001
BIS	54	13	39	8	<0.001	29	7	<0.001

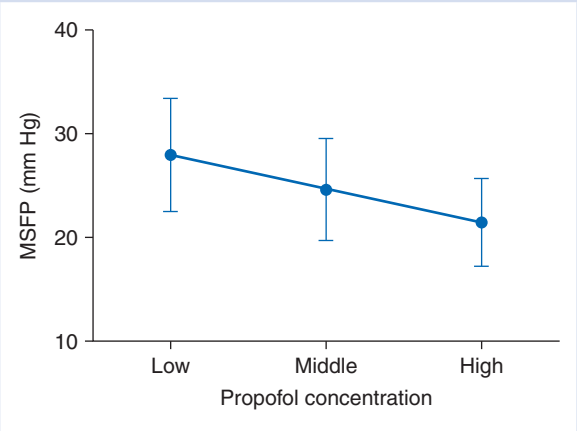

Fig 2 Change in mean systemic filling pressure (MSFP) at increasing blood propofol concentrations.

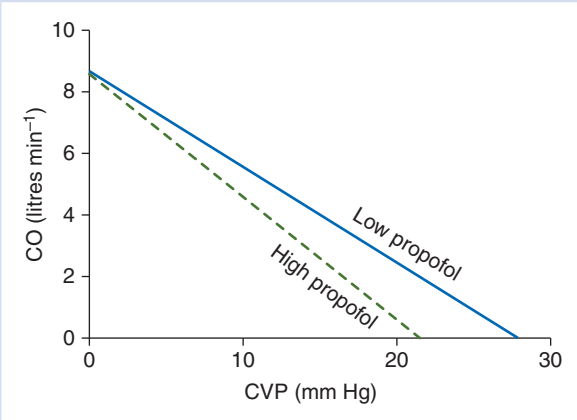

Fig 3 Venous return curve that was plotted using the average values of central venous pressure (CVP), mean systemic filling pressure, and cardiac output (CO), acquired at two increasing propofol concentrations.

is indicated by the decrease in MSFP and the constant value of CO at a CVP of zero. The steeper curve indicates a decrease in R_{vr}, as the slope of the curve equals $1/R_{vr}$.

The decrease in MSFP can be explained by either an increase in systemic vascular compliance or an increase in unstressed volume (the volume in the circulation that does not build up intravascular pressure). Several studies have explored the effect of propofol on the venous circulation. Muzi and colleagues[8] showed a significant increase in forearm venous compliance by occlusive plethysmography during propofol administration. Robinson and colleagues[18] later showed that the effects on forearm venous compliance were similar to the effects of sympathetic denervation by stellate ganglion block. Hoka and colleagues[19] examined the effect of propofol on vascular stressed volume in rats by measuring MSFP. They also showed a dose-dependent decrease in MSFP, but not in rats whose sympathetic nervous system was blocked with hexamethonium, which suggested a propofol-induced inhibition of the sympathetic nervous system. Given that a change in sympathetic activity mainly causes an alteration of stressed volume and not of venous compliance, this also seems to be the case with propofol infusion.

The intersection of a cardiac function curve with the venous return curve reflects steady-state CO (Fig. 4). The increase in SVV at higher propofol concentrations means that the cardiac function curve is steeper at higher propofol C_b. As our data also show that CO remains constant and CVP decreases, this suggests a change in the cardiac function curve. This small enhancement

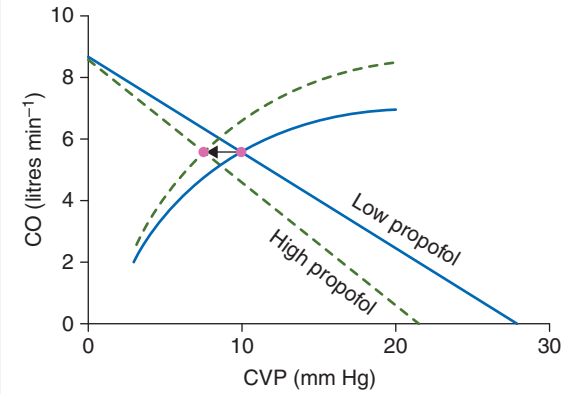

Fig 4 When an estimation of a cardiac function curve is added to the venous return curve, the intersection of both curves reflects steady-state cardiac output (CO). CVP, central venous pressure.

in cardiac function is most probably attributable to a decrease in afterload. This phenomenon is also seen in, for example, septic shock models.[20]

Clinical implications

Several textbooks describe a propofol-induced decrease in CO after an induction dose.[21 22] We show that this does not occur with a wide range of propofol effect site concentrations, as used during the maintenance of anaesthesia or sedation. Rather, propofol appears to produce a dose-dependent decrease in arterial pressure by a decrease in stressed volume without a change in CO. The decrease in stressed volume associated with propofol infusion suggests that hypovolaemic patients will have a more pronounced decrease in arterial blood pressure. It is also likely that fluid loading will have a beneficial effect on propofol-induced hypotension. Patients with congestive heart failure may, however, benefit from the propofol-induced decrease in cardiac preload and afterload, because this will most probably enhance CO and reduce cardiac and pulmonary filling pressures.

Study limitations

Although we performed our study in only 17 subjects, the responses were specific and uniform and reached statistical significance. The propofol C_b that we used in our study protocol (3.0–6.5 μg ml^{-1}) are commonly used during anaesthetic maintenance, as shown by the adequate depth of anaesthesia measured with BIS. After an induction or bolus dose, however, peak plasma propofol concentrations are much higher and may even reach 80–100 μg ml^{-1}.[21] Most research on the haemodynamic effects of propofol has been performed with bolus administration of propofol, which might be a reason for the differences seen in cardiac function compared with our study. Also, co-administration of opioids with propofol infusion could further affect filling pressures and CO.

The propofol C_b used was not the same in each subject included in our study. Given that the aim was to investigate the haemodynamic changes after a change in propofol C_b, we had to choose three separate targets of propofol concentration that were haemodynamically feasible and produced adequate anaesthetic depth in the individual subjects without making alterations in other (i.e. vasoactive) drugs. Nevertheless, propofol C_b and, more importantly, haemodynamic responses proved to be fairly uniform.

The method of measuring MSFP using the inspiratory hold method has never been validated in humans by comparing it with MSFP by total circulatory stop flow.[23] However, measuring MSFP with ventilatory manoeuvres is comparable to MSFP measurements using circulatory stop flow in intact dogs.[24] We think the method used in the present study is a useful and minimally invasive way to investigate haemodynamic pharmacodynamics in patients.

Conclusions

Increases in propofol C_b within the therapeutic range decrease vascular stressed volume without a change in CO. The absence of an effect of propofol on CO can be explained by the balance between the decrease in effective, or stressed, volume (as determined by MSFP), the decrease in resistance for venous return, and slightly improved heart function.

Authors' contributions

Study conception: J.R.J., B.F.G.
Study design: R.B.deW., J.V., J.R.J., J.V., L.P.A., B.F.G.
Data collection: F.deW., A.L.vanV., R.B.deW., J.V., B.F.G.
Analysis of the data: F.deW., A.L.vanV., R.B.deW., J.V., J.R.J., J.V., B.F.G.
Interpretation of the data: F.deW., A.L.vanV., R.B.deW., J.V., J.R.J., J.V., L.P.A., E.deJ., D.P.V., B.F.G.
Drafting the manuscript: F.deW., A.L.vanV., R.B.deW., J.V., J.R.J., J.V., L.P.A., E.deJ., D.P.V., B.F.G.
All authors read and approved the final manuscript.

Declaration of interest

B.F.G. and D.P.V. have performed consultancy work on behalf of their hospital employer for Edwards Lifesciences LLC. The other authors have no conflicts to declare.

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