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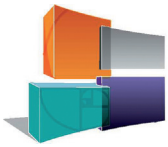

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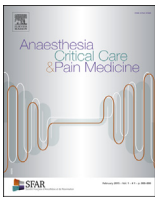

Original Article

Etomidate-induced hypotension: a pathophysiological approach using arterial elastance

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ABSTRACT

Introduction: Anaesthesia frequently induces hypotension. Several recent studies have analysed arterial elastance (Ea) in order to describe clinical variations of mean arterial pressure (MAP). The objective of the study was to assess Ea to explain MAP variation following etomidate induction.

Methods: We conducted a prospective single-centre study. Inclusion criteria were patients undergoing elective cardiac surgery with invasive blood pressure monitoring. Ea was expressed as Pes/SV (Pes: end systolic pressure, SV: stroke volume). Cardiac index (CI), peripheral vascular resistance (PVR) and arterial compliance (C) was compared before and 2 minutes after etomidate induction. Arterial hypotension was defined as a decrease greater than 15% of the baseline MAP.

Results: Of the 45 patients included, 24 (53%) had a preserved MAP and 21 (47%) had an etomidate-induced hypotension. Ea was similar before induction and decreased in the decreased MAP group 2 minutes after induction (2.0 mmHg.ml-1 [1.7-2.4] vs 1.4 mmHg.ml-1 [0.9-1.9]; p = 0.001). Arterial compliance (C) increased in the decreased MAP group 2 minutes after induction (0.8 ml. mmHg-1 [0.6-1.0] vs 0.5 ml. mmHg-1 [0.4-0.6], $p < 0.0001$). No significant change in CI or PVR was observed between patients with or without etomidate-induced hypotension.

Conclusion: Etomidate-induced hypotension was associated to a decrease in Ea. Ea variations can mainly be explained by induced changes in arterial compliance.

Background

Mean arterial pressure (MAP) is a main determinant of tissue perfusion. A decrease in MAP is associated with adverse postoperative outcomes [1]. Several studies have reported associations with postoperative morbidity [2]. Pulse pressure less than 53 mmHg increases the risk factor of excess morbidity after major surgery [3]. It was recently reported better outcomes when MAP was preserved within a 10% variation of the reference value[4]. Maintaining MAP at a subnormal level remains a main goal to achieve during anaesthesia.

Routine use of etomidate for anaesthesia induction reveals that decrease in MAP is not always observed. Although that variation

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might be in relation with difference in volume load or sympathetic stimulation between patients, changes in arterial elastance (Ea) could be more accurate to describe MAP variation. Ea is the ratio of end systolic pressure to stroke volume. It reflects the volume-pressure loop work in the left ventricle. To achieve the maximal transfer of energy from the left ventricle to the arterial system, both ventricle elastance and Ea must be similar [5]. Ea is a reflection of arterial tone variation. Sunagawa et al obtained multiples Ea values when arterial compliance (C) and peripheral vascular resistance (PVR) were modified whereas left ventricle work is preserved [6] [7]. He estimated that Ea can be approximated from the peripheral vascular resistance and arterial compliance. Thus, by analysis Ea, components of blood pressure can be accurately understood. Ea decreases with PVR decrease and when compliance increases. In cardiovascular disease, Ea is increased mainly due to increase in PVR whereas, in healthy population, exercise practice preserves compliance and Ea at normal value [8] [9].

To avoid hypotension during anaesthesia, Ea could be used as an index reflecting the arterial tone associated to MAP decrease. To our knowledge, Ea variation induced by etomidate was not reported before.

We aimed to assess arterial tone by assessing Ea following etomidate-induced hypotension.

Methods

Ethical approval

The study protocol was approved by the local independent ethics committee (reference 2015-A00765-44) on the 26th of November 2015. The present report was drafted in line with the STROBE statement for cohort studies[10]. The study complied with the Declaration of Helsinki on ethical principles for medical research involving human subjects. All patients provided written, informed consent prior inclusion to the study.

Study population

A prospective, observational study was performed in Amiens University Hospital's cardio- thoracic ICU over a six-month period from November 2016 to February 2017. The main inclusion criteria were patients undergoing elective general anaesthesia with intra-arterial blood pressure monitoring prior to induction. The main exclusion criteria were as follows: age under 18 years, atrial fibrillation, no echo cardiac echogenicity, presence of a pacemaker.

Cardiac index and stroke volume

Transthoracic echocardiography (CX50 Ultrasound System and S5-1 Sector Array Transducer, Philips Medical System, Suresnes, France) was performed by a physician using standards views based in accordance in current guidelines [11]. Left ventricular ejection fraction (LVEF) by the visual method on the 4-chamber view [12]. Stroke volume (SV) was measured by velocity time integral by pulse Doppler in the left ventricular outflow tract on a 5-chamber view. The velocity time integral was averaged on five measurements. The area of the chamber was calculated from a single diameter of the outflow tract on the parasternal large axis. Cardiac index (l. min^{-1}. m^{-2}) was calculated based on SV and heart rate. The measurements were saved for off line calculation and interpretation by one experimented cardiologist. In our centre, the intra observer variability was 3 ± 1 % [13].

Blood pressure monitoring, peripheral vascular resistance, calculation of arterial elastance

Systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP) and pulse pressure (PP) were measured using an invasive radial arterial line. Heart rate was measured using a continuous 3 lines electrocardiogram. Cardiac length cycle (T) was estimated using the following formula T (seconds) = 60/HR. Arterial elastance (Ea) was estimated using the formula Ea ($mmHg.ml^{-1}$) = Pes/SV. Pes is the end systolic pressure in the left ventricle estimated from SAP as Pes (mmHg) = 0.9*SAP [14]. Corrected (cEa) is the Ea adjustment to length cycle expressed as following cEa = Ea/T. Corrected peripheral vascular resistance (PVR) to T ratio was calculated using the formula cPVR ($mmHg.min.l^{-1}$) = (MAP/CO)/T. Arterial compliance (C) was expressed as follows C (ml. min^{-1}. m^{-2}) =SV/PP.

To synchronise PP and SV, arterial blood pressure was continuously reported on the echocardiography screen.

Patients with less than 15% MAP variation were allocated to the "preserved MAP" group and patients with greater than 15% MAP variation 2 minutes after induction compared to baseline were allocated to the "etomidate-induced hypotension" group.

Study procedure

On arrival in the operating room, all patients were monitored by continuous three-lead electrocardiogram, pulse oximetry saturation and invasive blood pressure via a radial arterial line. According to our centre's usual practice, patients did not receive any premedication. Standardised general anaesthesia consisted of intravenous sufentanil 0.3 $\mu g.kg^{-1}$ and etomidate 0.4 $mg.kg^{-1}$. Titration of hypnotics and opioids was based on the bispectral index (Covidien, Boulder, CO, USA). No neuromuscular block drug was administered before the repeated measurements at 2 minutes following induction. Neither vasopressor nor fluid challenge were administered during the study procedure. Average SV and PP were determined on three measures and Ea was calculated as described above.

Baseline measures were performed before anaesthetic induction during spontaneous breathing without positive pressure ventilation. After pre-oxygenation, anaesthesia induction was initiated and repeated measures were performed under apnoea without intubation or manual ventilation.

Statistics

In the absence of data on compliance, resistance and Ea with etomidate, a convenient sample size of 45 patients was defined. Data area expressed as median [interquartile range] or numbers (percentage). The distribution of variables was assessed using Kolmogorov-Smirnov test. Comparisons were performed by Mann-Whitney test, Chi-square or Fisher's exact test as appropriate. A linear regression model was used to describe the effect of compliance, peripheral vascular resistance and Ea. All statistical analyses were performed with SPSS® software (version 24, IBM® SPSS®). The limit of statistical significance was $p < 0.05$.

Results

Demographic data (Table 1)

Forty-five patients were included: MAP decreased at anaesthesia induction in 21 patients (47%) and did not decrease in 24 (53%) patients.

Demographic data were similar in the two groups, apart from older age in the decreased MAP group (Table 1). LVEF and etomidate dose were similar in the two groups.

*Haemodynamic data (*Table 2*)*

HR was similar before induction, but increased in the preserved MAP group compared to the etomidate-induced hypotension group (82 bpm [74-85] vs 67 bpm [61-72], respectively; p = 0.004). CI was similar before induction in the preserved MAP and the etomidate-induced hypotension groups (2.2 $l.min^{-1}$. m^{-2} [1.9-2.7]

Table 1
Patients characteristics. Data are expressed as median [interquartile range] or numbers (percentage). MAP: mean arterial pressure; BMI: body mass index; CABG: coronary bypass graft; LVEF: left ventricular ejection fraction. Variables are compared by Mann-Whitney test, Chi-square or Fischer's exact test, as appropriate.

	Preserved MAP (n = 24)	**Etomidate-induced hypotension (n = 21)**	**P value**
Age (years)	**60 [54-69]** *	**67 [61-72]** *	0.034
Male gender (n; %)	19 (79)	13 (62)	0.202
BMI (kg m^{-2})	27 [25–30]	27 [23–29]	0.255
Medical history			
Diabetes	9 (38)	6 (29)	0.526
Hypertension	18 (75)	15 (71)	0.787
Smoking	14 (58)	16 (76)	0.852
Coronary disease	15 (63)	11 (52)	0.570
Stroke	4 (17)	2 (10)	0.670
Usual treatment (n; %)			
ACE inhibitor	12 (50)	9 (43)	0.632
Beta blocker	16 (67)	13 (62)	0.739
Calcium channel	4 (17)	8 (38)	0.105
Diuretic	5 (21)	8 (38)	0.202
Type of surgery			
CABG	10 (42)	7 (33)	
Valve replacement	8 (33)	8 (39)	0.954
Combined	6 (25)	6 (29)	
LVEF (%)	60 [55-70]	63 [55-66]	0.956
EUROscore (%)	4 [2–7]	5 [2-8.5]	0.217
Anesthesia protocol			
Etomidate (mg kg^{-1})	0.48 [0.39-0.53]	0.43 [0.39-0.53]	0.306
Sufentanil (µg kg^{-1})	0.40 [0.35-0.47]	0.44 [0.36-0.51]	0.767

vs 2.3 $l.min^{-1}$. m^{-2} [1.9-3.1], respectively; p = 0.777) and did not vary after induction (2.2 $ml.min^{-1}$. m^{-2} [1.9-2.9] and 2.3 $ml.min^{-1}$. m^{-2} [1.8-3.1] for the preserved MAP and the etomidate-induced hypotension groups, respectively; p = 0.777).

Comparison of arterial elastance (Ea), peripheral vascular resistance (PVR) and arterial compliance (C) between preserved MAP and etomidate-induced hypotension *groups (*Table 2 *and* Fig. 1*)*

Ea was similar in the two groups before induction (1.8 $mmHg.m^{-2}$. ml^{-1} [1.5-2.1] and 1.9 $mmHg.m^{-2}$. ml^{-1} [1.3-2.3]; p = 0.682), but decreased after induction in the etomidate-induced hypotension group (2.0 $mmHg.ml^{-1}$ [1.7-2.4] vs 1.4 $mmHg.ml^{-1}$ [1.0-1.9]; p = 0.001). C increased following anaesthesia induction in etomidate-induced hypotension group compared to the preserved MAP group (0.8 [0.6-1.0] vs 0.5 [0.4-0.6], respectively; $p < 0.0001$). cPVR decreased in both groups after induction without any differences between groups (15 $mmHg.min.l^{-1}$ [12–19] vs 15 $mmHg.min.l^{-1}$ [11–20], respectively; p = 0.525).

Ea variation related to arterial compliance (C) and peripheral vascular resistance (cPVR) (Fig. 2)

Using partial linear regression model, the regression could explain most observed Ea according to cPVR with $R^2 = 0.697$ ($p < 0.001$).

Using partial linear regression model, the regression could explain most observed Ea according to C with $R^2 = 0.681$ ($p < 0.001$).

Discussion

Arterial hypotension occurred in 47% of patients after etomidate induction. Arterial elastance decreased in patients with etomidate-induced hypotension. Resistance decreased in both groups whereas compliance was higher in the etomidate-induced hypotension group only.

To analyse Ea variations in our population, we used the 2 compartments model of Windkessel. This model is based on the principle that pulse pressure is determined by compliance of large arteries and resistance of small arteries. Thus, analysis of Ea therefore provides an assessment of both components. Ea can decrease when compliance increases or when resistance decreases. In the present cohort, compliance increased and resistance decreased in the decreased MAP group, resulting in a decrease in Ea. In the light of these findings, multilinear regression was performed to assess the proportion of C and PVR in effective Ea (Fig. 2).

The analysis suggests decrease in MAP is in relation with excess arterial compliance.

Studies of the pharmacologic effects of etomidate remain controversial. Etomidate is known to be associated with good haemodynamic stability when used for anaesthesia induction and usually does not induce myocardial depression. In the present cohort, SV and CI were similar in the two groups after induction. In a previous study, etomidate was described to decrease CI and MAP at induction [15]. Nevertheless, CI was measured by a minimally invasive cardiac output monitoring device whereas we used echocardiography. The displayed values of that device are displayed from a healthy population, which may not be accurate. About HR, it increased in the normal MAP group, suggesting a mechanism of compensation, whereas HR remained in the same range for the decreased MAP group. No difference in terms of medical history or drug use could explain these differences in HR. The BIS level was also similar suggesting the same hypnotic effect. As others, we found that etomidate can induce a decrease in MAP [15] [16]. Aggarwal et al reported a reduction of MAP after etomidate, but to a lesser extent than that observed with propofol [17]. Skovsted et al showed that etomidate can induce sympathetic tone depression in a rat model [18]. This finding could explain the decrease in arterial tone. Normally, large artery can store wave energy during systole due to its elastic property and return to smaller vessel during diastole. In contrast, when vascular tone is inhibited by the sympathetic system, arterial contraction during diastole is decreased, resulting in changes in pulse pressure. These observations are conceptualised in a two-element Windkessel model [19]: the large artery represents compliance and the small artery represents resistance. Stergiopulos et al reported that compliance and resistance both play a role in MAP and pulse pressure [20]. When assessing each parameter alone, a poor regression was observed with MAP. These authors argued that both resistance and compliance are determinants of arterial pressure.

Nevertheless, the respective contributions of each element on arterial pressure can vary depending on clinical situations. On a population of hypertensive patients, the sensitivity of Ea to a change in resistance was 2.5 times more than a similar change in compliance suggesting a more contribution of small artery in Ea [21]. The same findings were found in another hypertensive population [14]. On a population of healthy men, trained athlete's compliance contributes more in Ea than in sedentary men [22]. Ea variation is related to decreased resistance in patients with aortic valve stenosis during exercise [23]. In the present cohort, compliance was increased following induction of anaesthesia with etomidate. As mentioned before, we can suppose etomidate induced sympathetic inhibition of arterial tone with a larger increase in compliance than a decrease in resistance. To date, compliance variation with etomidate is only reported on a model of monkey with an increase in compliance [24].

As Ea describes arterial tone, bedside Ea could be a valuable index in routine practice. Indeed, MAP variation can be induced by cardiac index, volume load or arterial tone variation. Ea could be associated to MAP interpretation to assess arterial tone and to

Table 2
Hemodynamic variables before and 2 minutes after anesthesia induction. Data are expressed as median [interquartile range]. Preserved MAP MAP variation < 15 %; Etomidate-induced hypotension MAP variation > 15 %; HR heart rate; BIS bispectral index scale; SAP systolic arterial pressure; DAP diastolic arterial pressure; SV stroke volume; CI cardiac index; cPVR peripheral vascular resistance to length cycle ratio; cEa arterial elastance to length cycle ratio. P value: comparisons between the 2 groups.

Variables	Preserved MAP (n = 24)	Etomidate-induced hypotension (n = 21)	P value
HR (bpm)			
Before	62 [56-69]	65 [60-72]	0.524
After	**80 [73-85]** *	**67 [61-73]** *	0.004
BIS			
Before	92 [90-97]	92 [89-97]	0.758
After	41 [33-45]	36 [29-42]	0.145
MAP (mmHg)			
Before	89 [82-96]	91 [86-103]	0.246
After	**95 [85-105]** *	**69 [60-78]** *	<0.0001
SAP (mmHg)			
Before	131 [123-146]	132 [127-160]	0.369
After	**138 [129-153]** *	**99 [86-115]** *	<0.0001
DAP (mmHg)			
Before	64 [60-71]	67 [60-75]	0.198
After	72 [64-79]	52 [47-59]	<0.0001
Pulse pressure (mmHg)			
Before	71 [57-81]	72 [63-81]	0.562
After	**62 [53-82]** *	**47 [39-51]** *	<0.0001
SV (ml)			
Before	71 [57-85]	80 [56-86]	0.691
After	64 [47-72]	64 [51-92]	0.328
CI (ml min^{-1} m^{-2})			
Before	2.2 [1.9-2.7]	2.3 [1.9-3.1]	0.275
After	2.2 [1.9-2.9]	2.3 [1.8-3.1]	0.777
cPVR (mmHg.min.l^{-1})			
Before	19 [15–23]	21 [12–26]	0.682
After	**15** [12–19]	**15** [11–20]	0.525
Arterial compliance (ml $mmHg^{-1}$ m^{-2})			
Before			
After	0.5 [0.4-0.6]	0.5 [0.4-0.7]	0.873
	0.5 [0.4-0.6] *	**0.8 [0.6-1.0]** *	<0.0001
Ea (mmHg m^{-2} ml^{-1})			
Before	1.8 [1.4-2.1]	1.9 [1.3-2.3]	0.682
After	**2.0 [1.7-2.4]** *	**1.4 [1.0-1.9]** *	0.001
cEa (mmHg m^{-2} ml^{-1})			
Before	1.7 [1.4-2.0]	1.7 [1.3-2.0]	0.927
After	**1.5 [1.4-1.9]** *	**1.3 [0.9-1.6]** *	0.023

deliver the appropriate therapy management when hypotension occurs. Association between MAP and Ea variations were reported in previous studies to guide norepinephrine weaning. Following cardiac surgery, Ea monitoring could shorten norepinephrine cumulative dose in vasoplegic syndrome [25]. When compared to phenylephrine, norepinephrine preserved better arterial compliance without attenuating the stroke volume[26]. Consequently, norepinephrine might be the most appropriate vasopressor to reverse etomidate-induced hypotension. On contrary, studies on Ea variation following changes in volume load are controversial and requires larger cohorts [27] [28].

Our study presents some limits. The main limit is the difference in HR values between the 2 groups following induction (Table 2). Because calculation of Ea is based on several assumptions that can be influenced by different clinical conditions including HR, we adjusted Ea to cardiac cycle top allow comparisons between groups. We did still have a significant difference between groups. We could not explain the difference in HR between groups. The anaesthetic dose of etomidate and the beta-blocker use was similar (Table 1). We can suppose the volume charge prior to induction was different. However anaesthetic protocol was standardised for all patients: no liquid intake from 0:00 am, no administration of diuretic 24 hours before surgery, no fluid challenge before the induction. We could not evaluate the volume load with surrogate markers as pulse pressure variation or stroke volume variation as no mechanical ventilation was applied in the protocol. However, the impact of fasting was assessed in a previous study without effect on the volume load [29]. No nociceptive stimulation was done, especially no laryngoscopy was performed during the 2 minutes of observation. We also hypothesised sympathetic inhibition could differ between groups but the BIS level was similar. We assumed that changes in MAP following induction were exclusively due to the effect of etomidate.

The older patients had also a lower HR and a lower MAP (Table 1). It reminds that general anaesthesia for elderly patients remains a challenge in every practice. In a national UK survey assessing the morbidity of major surgery, patients over 70 years had higher complications rate [30]. It also reminds that aging is physiological process with hormonal modifications [31]. Elderly patients with eventual adrenal insufficiency could explain the absence of response to stress induced by general anaesthesia with low HR and low MAP.

Concerning measurement of Ea, stroke volume and pulse pressure were obtained by 2 different devices (echocardiography and invasive arterial monitoring), which could lead to a cycle synchronisation error. However, arterial pressure was gated on

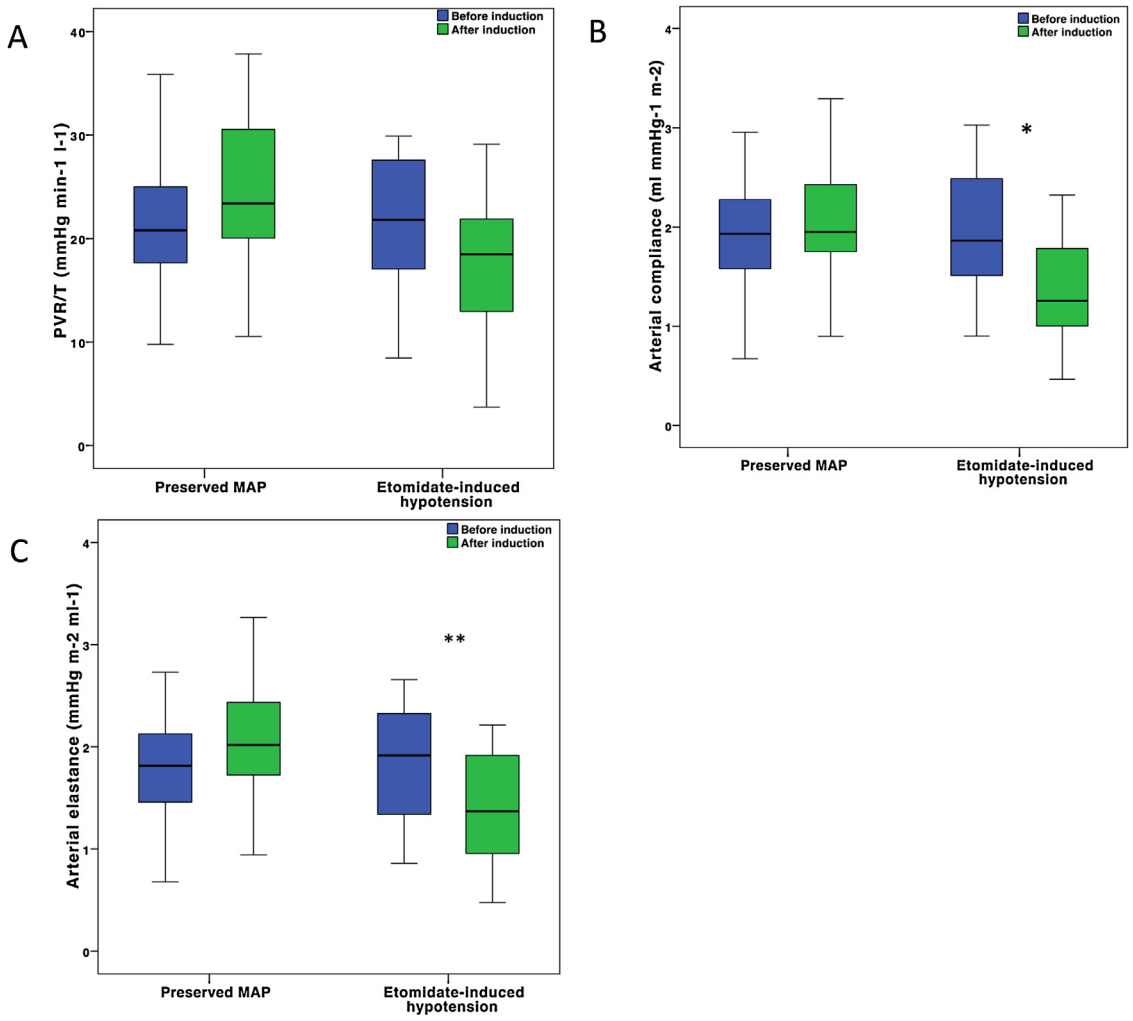

Fig. 1. Comparisons of resistance (A), arterial compliance (B), and elastance (C) between normal MAP and decreased MAP before and after induction. *: P value <0.0001, **: P value at 0.001.

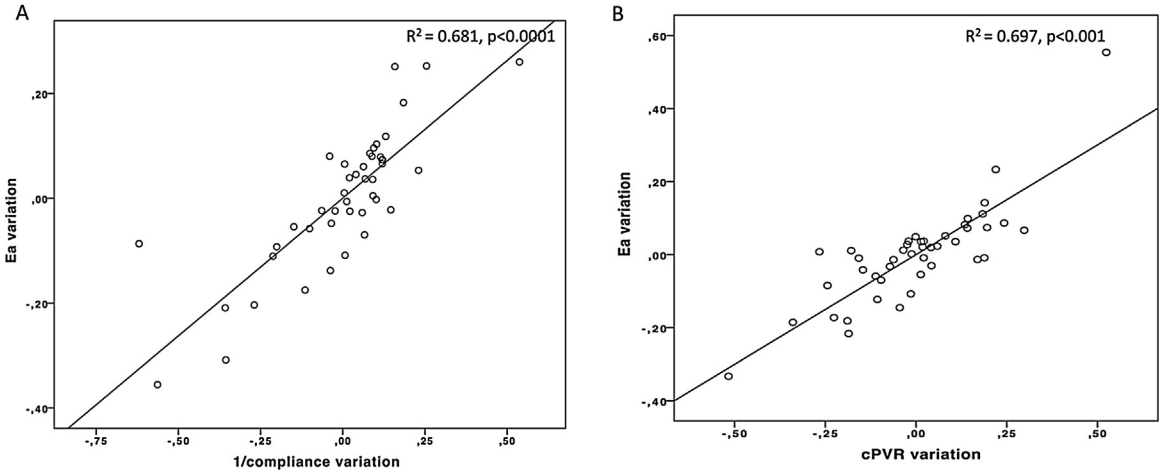

Fig. 2. Effective arterial elastance (Ea) according to compliance (1/C) variation (panel A) and peripheral vascular resistance (cPVR) variation (panel B) using linear regression analysis.

cardiac cycle using a cable displaying the cycle on the echocardiography screen.

Conclusion: Etomidate induced hypotension is associated with a decrease in arterial elastance mainly due to change in arterial compliance rather than in arterial resistance.

Authors contribution

EL and MOF designed the study.

OAA, ABA, AH, AC, CB, PH, SB and EL collected the data and carried out analyses.

OAA, PGG and EL drafted the manuscript.

Acquisition data: OAA, ABA, EL, AC, EB, AB, PH, CB

All the authors approved the manuscript.

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None

Ethical statement

The study protocol was approved by the local independent ethics committee (reference 2015-A00765-44) on 26 November 2015. The present report was drafted in line with the STROBE statement for cohort studies. The study complied with the Declaration of Helsinki on ethical principles for medical research involving human subjects. All patients provided written, informed consent prior inclusion to the study.

Disclosure of interest

The authors declare they have no conflict of interests.

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