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ORIGINAL RESEARCH

Assessment of central hemodynamic effects of phenylephrine: an animal experiment

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Abstract

Phenylephrine is an α1-adrenergic receptor agonist widely used to treat perioperative hypotension. Its other hemodynamic effects, in particular on preload and contractility, remain controversial. We, therefore, investigated the effect of continuously applied phenylephrine on central hemodynamics in eight mechanically ventilated domestic pigs. Mean arterial pressure (MAP) was increased in steps by 50%, and 100% using phenylephrine. Besides stroke volume (SV), cardiac output (CO), and MAP, mean systemic vascular resistance (SVR) and dynamic arterial elastance (Ea_{dyn}) were assessed for characterization of afterload. Changes in preload were assessed by central venous pressure (CVP), global end-diastolic volume (GEDV), mean systemic filling pressure analog (Pmsfa), pulse pressure variation (PPV), and stroke volume variation (SVV). Further, cardiac function index (CFI), global ejection fraction and dPmax were measured as markers of preload dependent contractility. MAP, SV, and CO significantly increased following both interventions, as did SVR. In contrast, Ea_{dyn} did not show significant changes. Although the volumetric preload variable GEDV increased after the first step of phenylephrine, this was not reflected by significant changes in CVP or Pmsfa. CFI and dPmax significantly increased after both steps. Phenylephrine does not only affect cardiac afterload, but also increases effective preload. In contrast to CVP and Pmsfa, this effect can be monitored by GEDV. Further, phenylephrine affects contractility.

Keywords Cardiac output · Cardiac afterload · Hemodynamics · Phenylephrine · Vascular capacitance · Vascular resistance · Transcardiopulmonary thermodilution

1 Introduction

There is increasing evidence that perioperative hemodynamic therapy has a major influence on postoperative outcome [1–3]. In particular, strategies aiming at optimizing blood flow by maximizing stroke volume (SV) using fluid loading have been advocated [1–5]. However, an excess of fluid administration is known to increase complications, predominantly due to edema formation [6, 7]. As recently published, likewise the concept of the "four D's", namely drug, dosing, duration and de-escalation, must always be discussed in terms of an adequate volume therapy [8]. In consequence, also vasopressors are routinely applied to treat perioperative hypotension and to maintain hemodynamics. The CLASSIC trial can corroborate the effect of fluid restriction and an increased vasopressor demand [9]. The use of vasopressors, on the other hand, potentially diminishes arterial blood flow, which stands against the therapeutically aims of current concepts of goal-directed therapy.

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Phenylephrine is a predominantly α1-adrenergic receptor agonist, which is widely used in this context [10, 11]. Its primary way of action is a direct increase of vascular tone. Clinically estimated as most relevant is the effect on the arterial vessels leading to an increase in blood pressure and cardiac afterload [10, 11]. In humans, this is well described for systemic and pulmonary circulation. However, the effects of phenylephrine application on cardiac output (CO) remain controversial [12–19]. CO is determined by the main factors preload or venous return, contractility, and afterload. While the effects of phenylephrine on afterload have been well described, the effects on venous return and preload are not clearly understood.

We, therefore, investigated the effect of continuously applied phenylephrine under various conditions of cardiac preload in an experimental macro-hemodynamic model, focusing on parameters of volumetric preload, venous return, fluid responsiveness, arterial load, and contractility.

2 Methods

2.1 Approval and study population

Ethical approval for this study (AZ 53/11) was provided by the Governmental Commission on the Care and Use of Animals of the city of Hamburg, Germany (Chairperson Mrs. K. Zoll, Ph.D.) on 4 August 2011 and was part of a larger animal project. Eight domestic pigs were included. The animals received care in compliance with the "Guide for the Care and Use of Laboratory Animals." The study was carried out according to the ARRIVE Guidelines [20]. All applicable international, national, and institutional guidelines for the care and use of animals were followed.

2.2 Anaesthesia and surgical preparation

To prevent distress, the animals arrived 7 days before the experimental protocol started. Each animal was fasted overnight and was premedicated with an intramuscular injection of ketamine 10 mg/kg, midazolam 0.5 mg/kg, azaperone 4 mg/kg, and atropine 0.5 mg. The animals received an intravenous catheter in the ear vein (Vasofix® 0.8 mm, B. Braun, Melsungen, Germany) and were connected to an electrocardiogram and pulse oximeter. Anesthesia was maintained by continuous infusion of fentanyl (10 µg/kg/h) and inhalation of sevoflurane (end-expiratory concentration 2.5%). Animals were tracheotomized and were ventilated in a volume-controlled mode with tidal volumes of 8 mL/kg using a positive end-expiratory pressure of 5 cm H_2O (Zeus®; Drägermedical, Lübeck, Germany). The respiratory rate was adjusted to maintain an end-expiratory arterial carbon dioxide tension (pCO_2) of 35–40 mmHg. A baseline crystalloid infusion of 15 mL/kg of balanced solution (Sterofundin®, B.Braun, Melsungen, Germany) was maintained. The body temperature was kept constant using warming blankets.

For volume and drug administration and for measuring the central venous pressure (CVP), a 12 Fr. venous catheter was inserted in the internal jugular vein (Certofix® Trio S 730, 30 cm, B. Braun, Melsungen, Germany). A 5 Fr. thermistor-tipped arterial catheter (Pulsiocath 5F, Pulsion Medical Systems/Getinge, Sweden) was placed in the femoral artery and was connected to a dedicated hemodynamic monitor (PiCCO 2®, Pulsion Medical Systems/ Getinge, Sweden).

A sternotomy was performed, and two ultrasonic flow probes were placed, one probe around the ascending aorta, the other one around the pulmonary artery (Confidence PAU Flowprobe®, chronic liner, 16 mm and 20 mm, Transonic Systems Inc., Ithaca, NY, USA). Both were connected to dedicated hardware (Perivascular Flow Module®, Transonic Systems Inc., Ithaca, NY, USA). A pressure catheter was directly inserted into the pulmonary artery and fixed by a pouch suture (Millar Mikro-Tip® pressure catheters, Houston, Texas, USA). After surgery, a patch was sewn into the pericardium, the sternum was readapted using cerclage wires, and the soft tissue was closed in layers to re-establish closed chest conditions. Meticulous caution was used during surgical preparation not to breach pleural cavities on either side.

2.3 Measurements and experimental protocol

After preparation, the preload was increased by application of hydroxyethylstarch 6% (Voluven®, 130/0.4, Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany). The goal was to reach for baseline conditions in all animals a comparable level of functional preload. Fluids were therefore applied until stroke volume variation (SVV) measured by arterial pulse contour analysis reached values below 10%, reflecting a level of relative fluid unresponsiveness. After 5 min of equilibration, the baseline measurement (M0) was conducted. Then, phenylephrine was continuously applied using an automated infusion system (Perfusor®FM (MFC), B. Braun, Melsungen, Germany) with an initial dose of 5 µg/kg, and was titrated in 5 µg/kg steps, to increase the mean arterial pressure (MAP) by 50% compared to values at M0. After another 5 min of equilibration, measurement M1 was conducted. After M1, the dosage of phenylephrine was further increased until the MAP reached 100% above the value at M0. After another 5 min of equilibration, measurement M2 was conducted. After completion of the protocol, animals were euthanized by injection of 6 mL T61 (200 mg Embutramide, 50 mg Mebezonium, 5 mg Tetracaine/mL) during deep anesthesia and analgesia.

2.4 Hemodynamic data

2.4.1 Stroke volume and cardiac output

SV and CO were measured invasively by ultrasonic flow probes.

2.4.2 Parameters of preload, venous return, and fluid responsiveness

To assess preload and venous return, CVP, global end-diastolic volume (GEDV), mean systemic filling pressure analog (Pmsfa), pressure gradient of venous return (dVR), resistance to venous return (RVR), and the dynamic parameters of fluid responsiveness, pulse pressure variation (PPV) and SVV, both measured by ultrasonic flow probes, were determined. GEDV was calculated on the basis of transcardiopulmonary thermodilution, as described earlier [21]. Pmsfa is an analog of the mean systemic filling pressure (Pmsf), which can only be determined by suspended circulation. As described earlier, we, therefore, used a mathematical modelling technique to determine Pmsfa, based on MAP, CVP, and CO, which does not require suspended circulation [22, 23]. The following formula was used:

$$\mathrm{Pmsfa} = \mathrm{a(CVP)} + \mathrm{b(MAP)} + \mathrm{c(CO)(mmHg)}$$

whereas a and b are dimensionless constants (a + b = 1); typically, a = 0.96 and b = 0.04 [23] c has the dimension of resistance and is a function of the individual anthropometric data (height, weight, and age).

$$c = \frac{0.038\,(94.17 + 0.193 \times \mathrm{age})}{4.5\,\left(0.99^{\mathrm{age}-15}\right)\,0.007184\,\left(\mathrm{height}^{0.725}\right)\,\left(\mathrm{weight}^{0.425}\right)}$$

2.4.3 Parameters of load-dependent cardiac contractility

For the determination of load-dependent cardiac contractility the cardiac function index (CFI), the global ejection fraction (GEF) and the aortic dPmx, as a parameter for pressure changes during the systolic phase, derived from the femoral pressure signal, were assessed. The following formula was used to calculate the CFI and the GEF:

$$\mathrm{CFI} = \frac{\mathrm{CO_{TD}} \times 1000}{\mathrm{GEDV}}(1/\mathrm{min})$$

$$\mathrm{GEF} = \frac{4 \times \mathrm{SV}}{\mathrm{GEDV}}(\%)$$

2.4.4 Parameters of afterload

To evaluate the intended effect of phenylephrine on the right and left ventricular afterload the MAP and the mean pulmonary arterial pressure (MPAP) were measured. MPAP was measured by a tip manometer (Millar Catheter, Millar, USA), which was surgically inserted into the pulmonary artery.

2.4.5 Parameters of arterial load assessment

To assess arterial load conditions, a two-element Windkessel model, consisting of the systemic vascular resistance (SVR) and net arterial compliance (C), was used [24].

$$\mathrm{C} = \frac{\mathrm{SV}}{\mathrm{PP}}(\mathrm{mL/mmHg})$$

$$\mathrm{SVR} = \frac{(\mathrm{MAP} - \mathrm{CVP}) \times 80}{\mathrm{CO}}(\mathrm{dyn} \times \mathrm{s/cm^5})$$

Also, functional assessment of arterial load was performed using the dynamic arterial elastance, or the ratio between PPV and flow probe-derived $\mathrm{SVV_{FP}}$, which describes the dynamic interaction between pressure and flow during a single respiratory cycle [25].

$$\mathrm{Ea_{dyn}} = \frac{\mathrm{PPV}}{\mathrm{SVV_{FP}}}$$

2.5 Data acquisition and statistical analysis

All blood pressures and flows were recorded by dedicated hardware (ADInstruments PowerLab®, ADInstruments Ltd, Oxford, United Kingdom, and Perivascular Flow Module, Transonic Systems Inc, Ithaca, NY, USA). Data analyses were performed offline by customized software (LabChart Pro, version 8, ADInstruments, Oxford, UK). Data derived by transcardiopulmonary thermodilution and arterial pulse contour analysis was recorded and stored by a dedicated monitor (PiCCO 2®, Pulsion Medical Systems, Feldkirchen, Germany). Figures were created with Microsoft Excel 2007® (Microsoft, Redmond, USA) and SPSS® for Windows® (IBM® SPSS Statistics version 22.0; Armonk, NY, USA).

Statistical analyses were conducted using SPSS® for Windows® (IBM® SPSS Statistics version 22.0; Armonk, NY, USA). All data were tested for normal distribution using the Kolmogorov–Smirnov-test. All normally distributed data are presented as mean with standard deviation, all others as median with interquartile range. In case of not normally distributed data, the Friedman repeated-measures ANOVA on ranks was used. Normally distributed data were analyzed

with a one-way analysis of variance for repeated measurements (ANOVA). Post hoc testing was performed using the Bonferroni correction. All results are given as mean and standard deviation. Significance was appraised for $p < 0.05$.

3 Results

Eight domestic pigs were studied (37.25 ± 4.4 kg). A mean cumulative dose of 150.3 ± 26.2 µg/kg phenylephrine was used per animal during the protocol.

3.1 Hemodynamic data

All hemodynamic data at the measuring points M0, M1, and M2 are listed in Table 1.

3.1.1 Mean arterial pressure and blood flow

The MAP increased significantly following both steps of phenylephrine application, as did CO. The increase in SV reached significance only after step 1 of phenylephrine application. The HR did not change significantly during the study protocol (see Table 1; Fig. 1).

3.1.2 Parameters of preload and fluid responsiveness

Following the application of phenylephrine, a significant increase in the volumetric preload parameter GEDV could be recognized. This is illustrated Fig. 2. Neither the CVP nor Pmsfa increased significantly after phenylephrine application (see Fig. 3), the pressure gradient to venous return (Pmsfa–CVP) was significantly increased. The SVV, indicating fluid responsiveness, did not change significantly throughout the study protocol, which accounted for both measurement techniques, arterial pulse contour analysis, and ultrasonic flow probe. In contrast, PPV showed a significant decrease compared to baseline under high dosages of phenylephrine (M0: 10.8% ± 3.4% vs. M2: 6.5% ± 2.9%; $p < 0.05$). For all parameters see Table 1.

3.1.3 Parameters of load-dependent cardiac contractility

The CFI (M0: 7.1 (1/min) ± 1.1 (1/min) vs. M1: 8.5 (1/min) ± 1.1 (1/min) vs. M2: 9.7 (1/min) ± 1.6 (1/min); all $p < 0.05$), and dPmx (M0: 627.5 mmHg/s ± 285.2 mmHg/s vs. M1: 1104.8 mmHg/s ± 534.6 mmHg/s vs. M2: 1607.3 mmHg/s ± 757.7 mmHg/s; all $p < 0.05$) significantly increased following both steps of phenylephrine application. The GEF significantly increased between M0 and M1, but not between the measuring points M1 and M2 [M0: 33.3 (%) ± 5.7 (%) vs. M1: 38.5 (%) ± 3.5 (%)* vs. M2: 39.2 (%) ± 4 (%) (see Table 1)].

Table 1 Changes of hemodynamic parameters during the treatment interval

Parameter	Baseline M0	MAP > 50% M1	MAP > 100% M2
CO (L/min)	1.9 ± 0.5	2.5 ± 0.5*	2.9 ± 0.6*+
SV (mL)	22.3 ± 4.2	27.7 ± 3.4*	28.2 ± 2.4*
CVP (cm H_2O)	8.1 ± 3.6	8.8 ± 4.5	8.9 ± 5.6
GEDV (mL)	362 ± 51	405 ± 72*	415 ± 58*
PPV (%)	10.8 ± 3.4	7 ± 2.3	6.5 ± 2.9
SVV_{FP} (%)	11 ± 2.4	10.7 ± 5.3	9.3 ± 1.7
PPV_{PC}	8.2 ± 1.4	6.1 ± 2.5	6.3 ± 1.2*
SVV_{PC}	7.2 ± 1.3	6.6 ± 1.6	6.9 ± 1.5
Pmfsa (mmHg)	9.1 ± 2	10.4 ± 1.4	11.1 ± 1.6
dVR (mmHg)	2.5 ± 0.2	3.6 ± 0.2*	4.7 ± 0.2*+
RVR	1.43 ± 0.26	1.51 ± 0.14	1.75 ± 0.23*
CFI (1/min)	7.1 ± 1.1	8.5 ± 1.1*	9.7 ± 1.6*+
GEF (%)	33.3 ± 5.7	38.5 ± 3.5*	39.2 ± 4*
dPmx (mmHg/s)	628 ± 285	1105 ± 535*	1607 ± 758*+
MAP (mmHg)	62 ± 7	87 ± 5*	112 ± 4*+
MPAP (mmHg)	31.3 ± 3.9	33.8 ± 3.4	34.3 ± 4*
HR (bpm)	86 ± 11	91 ± 9*	101 ± 12*
SVR (dyn × s/cm^5)	1187 ± 397	1577 ± 450*	1875 ± 505*+
Ea_{dyn}	1.06 ± 0.53	0.67 ± 0.22	0.68 ± 0.3
R (mmHg/L/min)	35.8 ± 7.2	36.9 ± 3.8	42.6 ± 6.4*
C (mL/mmHg)	0.79 ± 0.18	0.61 ± 0.12*	0.48 ± 0.08*+

SV stroke volume, *CO* cardiac output, *CVP* central venous pressure, *GEDV* global end-diastolic volume, *PPV* pulse pressure variation, SVV_{FP} flow-probe derived stroke volume variation, PPV_{PC} pulse pressure variation measured by arterial pulse contour analysis, SVV_{PC} stroke volume variation measured by arterial pulse contour analysis, *Pmfsa* mean systemic filling pressure analogue, *dVR* pressure gradient of venous return, *RVR* resistance to venous return, *CFI* cardiac function index, *GEF* global ejection fraction, *MAP* mean arterial pressure, *MPAP* mean pulmonary artery pressure, *HR* heart rate, *SVR* systemic vascular resistance, Ea_{dyn} dynamic arterial elastance, *R* resistance, *C* compliance

Most data are presented as mean and standard deviation; GEDV as not normally distributed data is presented as median with interquartile range

Points of measurements are: M0 = baseline, M1 = MAP increase > 50%, M2 = MAP increase > 100%

*Significantly different to baseline measurement ($p < 0.05$)

+Significantly different to previous point of measurement ($p < 0.05$)

3.1.4 Parameters of cardiac afterload

The SVR increased significantly from M0 (1187 dynes s/cm^5 ± 397 dynes s/cm^5) to M1 (1577 dynes s/cm^5 ± 450 dynes s/cm^5), and to M2 (1875 dynes s/cm^5 ± 505 dynes s/cm^5). Also the MPAP increased significantly from M0 (31.3 mmHg ± 3.9 mmHg) to M2 (34.3 mmHg ± 4 mmHg).

Although there was a trend for the Ea_{dyn} to decrease following phenylephrine application, this change did not reach significance (see Table 1).

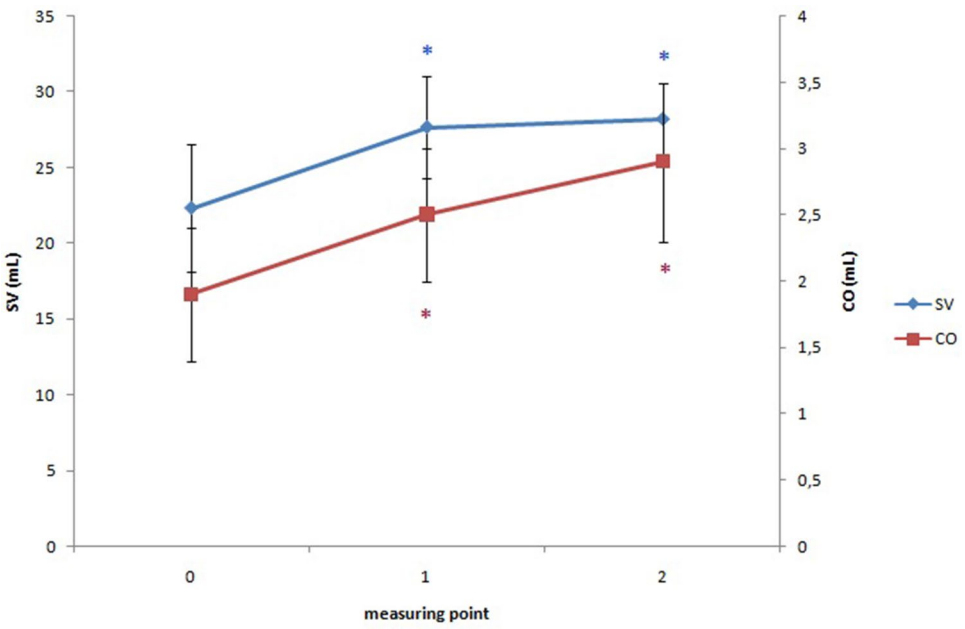

Fig. 1 Changes of stroke volume (SV, blue line) and cardiac output (CO, red line) during the treatment interval. Results are given as mean and standard deviation. Points of measurements are: 0 = baseline, 1 = MAP increase > 50%, 2 = MAP increase > 100%. *Significantly different to baseline measurement ($p < 0.05$)

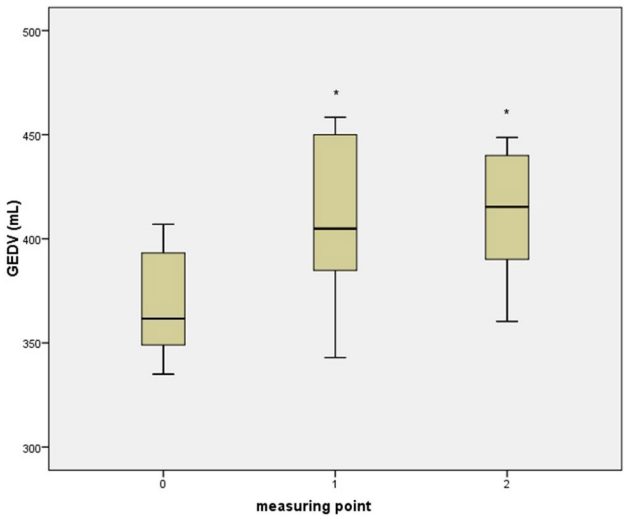

Fig. 2 Course of global end-diastolic volume during the treatment interval as box plot diagram. Results are given as median with interquartile range. Points of measurements are: 0 = baseline, 1 = MAP increase > 50%, 2 = MAP increase > 100%

4 Discussion

Our results demonstrate that the preload-enhancing effects of phenylephrine are most prominent in lower dosages. This effect is reflected by changes in GEDV. Furthermore, our data support evidence that with higher dosages phenylephrine influences contractility.

With the significant changes of the MAP and the MPAP during the study protocol, we could prove the well-known effect of phenylephrine on cardiac afterload [26, 27]. This effect is also most likely mirrored by the increase of the systemic vascular resistance and the decrease of the arterial compliance between the measuring points M0 and M2. Recently, Monge Garcia and Cecconi described the effects of phenylephrine on arterial load by Ea_{dyn} [28–30]. The Ea_{dyn} is calculated by the ratio of PPV and SVV. SVV is primarily determined by the effects of mechanical ventilation on cardiac function, whereas PPV is also influenced by the elastic properties of the arterial system. Monge Garcia and colleagues showed in 18 rabbits that continuous infusion of phenylephrine leads to an acute increase in cardiac afterload with a significant decrease of Ea_{dyn} [29]. In the present data, we also observed a small decrease of Ea_{dyn} with escalating phenylephrine dosing, although this did not reach statistical significance.

The effect of phenylephrine on the venous vasculature in individuals under anesthesia has been discussed controversially [13, 17, 31]. Cannesson et al. described in an animal model that the continuous application of phenylephrine caused—besides an increase of MAP of around 20%—also a significant increase in CVP [17]. They demonstrated that this was associated with an increase of central venous blood flow, which suggested an increase of venous return to the heart. Further, Kalmar et al. just recently showed in 17 patients immediately after induction of anesthesia that single dose application of phenylephrine increases venous return, reflected by an increase in CVP and Pmfsa with a concomitant increase in stroke volume in preload dependent patients [32]. Cannesson described the same mechanism, in particular in subjects with high values of SVV, i.e. in patients being fluid responsive [17]. Our data further support

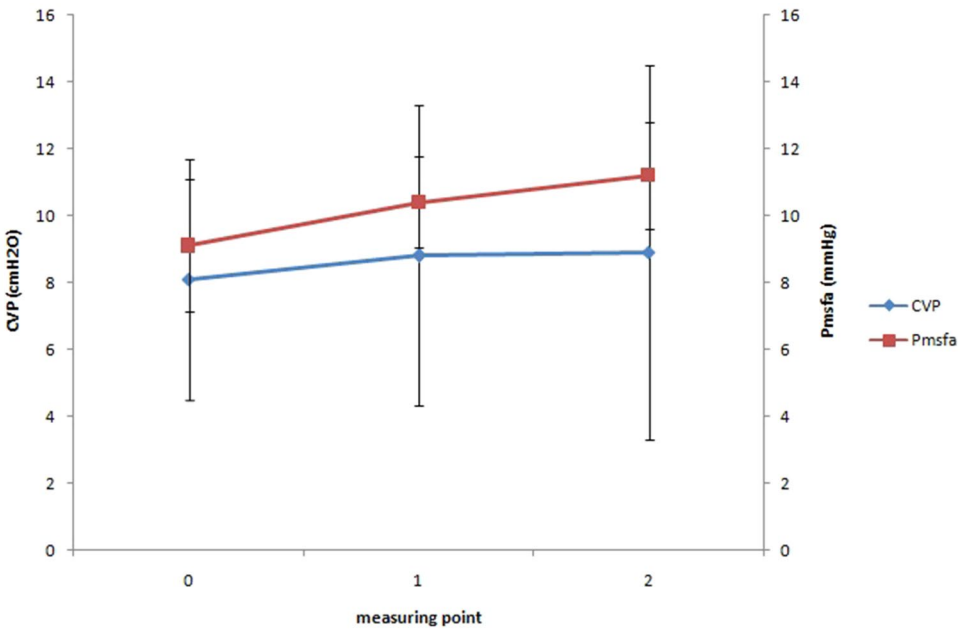

Fig. 3 Changes of central venous pressure (CVP, blue line) and mean systemic filling pressure analogue (Pmsfa, red line) during the treatment interval. Results are given as mean and standard deviation. Points of measurements are: 0 = baseline, 1 = MAP increase > 50%, 2 = MAP increase > 100%

this phenomenon, since we observed a comparable preload effect of phenylephrine in our investigation, but only within the lower range of concentration.

Interestingly, this effect was reflected by the volumetric parameter GEDV, but not by the pressure-based parameters CVP and Pmfsa. This finding means that although GEDV reflects a "virtual volume," it adequately allows assessing the venous effects induced by phenylephrine affecting the blood volume, which is then available for the heart to generate stroke volume. This "effective preload-recruitment" is also mirrored by the functional variables CFI and dPmax, which both have shown to allow quantifying changes in mainly preload-dependent contractility [33, 34]. However, conflicting with these earlier investigations, we could not identify this preload-enhancing effect with the pressure-based parameters CVP or Pmsfa. This observation is interesting since we would expect even much stronger and more uniform signals in controlled experimental conditions compared to a clinical investigation. However, in our study the application of phenylephrine was not performed as a bolus, but with a syringe pump, so changes in dosing were applied much slower. If these different types of application also had an effect on the results, although unlikely, cannot be finally ruled out. Also, mathematical coupling of CO and GEDV cannot be ruled out completely, although this "coupling effect" was described as small in earlier clinical investigations [35, 36]. Volumetric data from a second reference method, as from echocardiography would have been useful and should be investigated in future studies.

A new finding is that with higher dosages of phenylephrine, a further increase in preload volume could not be observed, neither by GEDV nor by CVP, Pmfsa, SVV, or PPV. However, we further detected an increase in CO, CFI, and dPmax which therefore cannot be explained by further preload recruitment. Already in 1989, Curiel found evidence for a weak positive inotropic effect of α_1-receptor agonists in healthy volunteers [37]. In 1984 Brückner et al. demonstrated a positive inotropic effect of phenylephrine in an isolated heart model under current ß-blockade [38]. Our data now corroborate the positive inotropic effects of phenylephrine in particular in higher dosages.

An interesting phenomenon is that SVV and PPV measured by the ultrasonic aortic revealed to all three measuring points higher values compared to pulse contour analysis. However, this is in accordance to earlier experimental findings showing a systematic overestimation of SVV and PPV by arterial pulse contour analysis under the effect of vasopressors [39]. However, since the primary aim for baseline conditions in this experiment was to establish inter-individual comparability regarding the level of preload, we do not consider this systematic difference between methods as a limitation.

Some methodological weaknesses of the present study need to be discussed. First, a relatively small animal study will always only serve as a model for human physiology, and results cannot be directly transferred into clinical practice. Further, additional information—in particular on load independent contractility derived from pressure volume loops with the use of a conductance catheter—would have further strengthened the presented data.

In conclusion, these results show that a continuous infusion of phenylephrine, especially in the lower dose range, leads to an increase of MAP due to a combined increase of arterial and venous tone, and to a recruitment of effective

preload volume. These data strengthen the approach to use phenylephrine in clinical practice to endogenously recruit preload. Higher doses of phenylephrine seem to increase load-independent contractility.

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Author contributions KHW: study concept and design, acquisition, analysis and interpretation of data, draft of the manuscript, statistical analysis. MFG, SAN: acquisition, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. CRB, MAP, MIMG: interpretation of data, critical revision of the manuscript for important intellectual content. HOP: statistical analysis, interpretation of data, critical revision of the manuscript for important intellectual content. CJCT, DAR: study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content, study supervision.

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Compliance with ethical standards

Conflict of interest DAR provided scientific advice for Pulsion/Getinge. MIMG is consultant for Edwards Lifesciences. All other authors declare no conflicts of interest.

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