Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Peripheral Venous Pressure as a Surrogate for Central Venous Pressure under General Anaesthesia: An Experimental Study

Hiroki Matsushita
National Cerebral and Cardiovascular Center
Takuya Nishikawa
National Cerebral and Cardiovascular Center
Yuta Nakamura
National Cerebral and Cardiovascular Center
Kazumasu Sasaki
Research Institute for Brain and Blood Vessels Akita
Kei Sato
National Cerebral and Cardiovascular Center
Hidetaka Morita
National Cerebral and Cardiovascular Center
Yuki Yoshida
National Cerebral and Cardiovascular Center
Nana Hiraki
National Cerebral and Cardiovascular Center
Masahiro Otake
National Cerebral and Cardiovascular Center
Kenta Oba
National Cerebral and Cardiovascular Center
Masafumi Fukumitsu
National Cerebral and Cardiovascular Center
Toru Kawada
National Cerebral and Cardiovascular Center
Kazunori Uemura
National Cerebral and Cardiovascular Center
Keita Saku
saku.keita@ncvc.go.jp

National Cerebral and Cardiovascular Center

Research Article

Keywords: Peripheral venous pressure, central venous pressure, estimation, vasoactive drugs, tissue pressure

Posted Date: July 6th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10029631/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: Competing interest reported. Matsushita H, Nishikawa T, Nakamura Y, Sasaki K, Sato K, Morita H, Yoshida Y, Hiraki N, Otake M, Oba K, Fukumitsu M, and Uemura K declare no competing interests. Kawada T received a consulting fee from NTT Research, Inc. Saku K received research funding from Abiomed Inc., NTT Research, Inc., Asahi Kasei ZOLL Medical Corporation, Neuroceuticals, Inc., and Zeon Medical, Inc., and honoraria from Abiomed Japan K.K. and Mallinckrodt Pharmaceuticals, Inc.

ORIGINAL ARTICLE

Peripheral Venous Pressure as a Surrogate for Central Venous Pressure under General Anaesthesia: An Experimental Study

Hiroki Matsushita,[1] Takuya Nishikawa,[2] Yuta Nakamura,[1,3] Kazumasu Sasaki,[4] Kei Sato,[1] Hidetaka Morita,[1] Yuki Yoshida,[1] Nana Hiraki,[1] Masahiro Otake,[1] Kenta Oba,[1] Masafumi Fukumitsu,[1] Toru Kawada,[1] Kazunori Uemura,[1, 5] Keita Saku[1]

[1]*Department of Cardiovascular Dynamics, National Cerebral and Cardiovascular Center Research Institute, Suita, Japan*

[2]*Department of Research Promotion and Management, National Cerebral and Cardiovascular Center, Suita, Japan*

[3]*Department of Anesthesiology, Shonan Kamakura General Hospital, Kamakura, Japan*

[4]*Akita Cerebrospinal and Cardiovascular Center, Research Institute for Brain and Blood Vessels, Akita, Japan*

[5]*NTTR-NCVC Bio Digital Twin Centre, National Cerebral and Cardiovascular Center Research Institute, Suita, Japan*

Correspondence to Keita Saku, Department of Cardiovascular Dynamics, National Cerebral and Cardiovascular Center, Suita, Japan, 6-1 Kishibe-Shimmachi, Osaka 564-8565. Tel: +81-66-170-1069; Fax: +81-66-170-1752; Email: saku.keita@ncvc.go.jp

Total word count:

4229 words

Abstract

Purpose

Peripheral venous pressure (PVP) has been proposed as a surrogate for central venous pressure (CVP). However, the PVP–CVP relationship over broad pressure ranges within the same individuals has not been systematically examined, restricting the clinical utility of continuous monitoring. This study aimed to characterise the PVP–CVP relationship across a broad pressure range, develop a PVP-based CVP estimation formula, and evaluate its accuracy under simulated clinical conditions.

Methods

This experimental study used 25 beagles under general anaesthesia. To obtain a wide pressure range, blood and fluid were infused until PVP reached approximately 30 mmHg. In 15 dogs, vasoactive agent administration, including none, norepinephrine, or trinitroglycerin, was used, and the PVP–CVP relationship was obtained during incremental pressure changes. Tissue pressure (TP) was measured. A PVP-based CVP estimation formula was derived and validated in seven dogs during sodium nitroprusside-induced vasodilation and haemorrhage.

Results

Across 0–30 mmHg, PVP and CVP demonstrated a linear relationship with strong correlation. At pressures below approximately 10 mmHg, PVP exceeded CVP, but discrepancies diminished as pressures increased and disappeared when both reached TP. Vasoactive agent administration had little effect on the PVP–CVP relationship. Estimated CVP showed lower bias and significantly smaller mean absolute error than PVP alone during both vasodilation and haemorrhage.

Conclusion

PVP exhibits a consistent, linear relationship with CVP above TP. Incorporating TP into the estimation formula in the low-pressure range enables more accurate continuous CVP estimation than PVP alone.

Keywords

54 Peripheral venous pressure, central venous pressure, estimation, vasoactive drugs, tissue
55 pressure

56

Introduction

Central venous pressure (CVP) is a crucial parameter for assessing systemic fluid status and serves as a diagnostic indicator of right heart failure in anaesthetic management of critically ill patients [1, 2]. Elevated CVP is also strongly associated with poor outcomes in patients undergoing major surgery and those treated in intensive care settings [3, 4]. Despite its clinical importance, CVP monitoring during general anaesthesia has declined due to its invasiveness and improved intravenous access techniques [5]. This highlights the need for less invasive methods to estimate CVP. Traditionally, clinicians have relied on physical examination and echocardiographic assessment as alternatives to CVP estimation [6, 7]. While useful for point-of-care evaluation, their utility is limited during surgical procedures due to low resolution, lack of continuity, and poor interrater reliability among examiners [8]. Intraoperative continuous CVP trend monitoring remains valuable in critical care, underscoring the demand for accurate, continuous, and minimally invasive CVP estimation methods.

Peripheral venous pressure (PVP) has long been of interest as a potential surrogate for CVP. Studies in various settings—including different surgeries, heart failure, and patients with left ventricular assist devices—have shown that PVP reliably approximates and tracks CVP fluctuations [9–12]. Desjardins et al. [13] reported almost identical values of PVP and CVP in patients undergoing cardiac surgery. However, other studies observed weaker agreement between PVP and CVP at lower CVP values, with PVP frequently exceeding CVP in this range [14, 15].

Clinical studies have shown that PVP and CVP generally maintain a linear relationship, although discrepancies arise at low pressures. Physiologically, several factors may influence the PVP–CVP relationship, and tissue pressure (TP)—external compression from the surrounding tissues—is considered particularly important [16]. However, no in vivo studies have assessed how TP contributes to differences between PVP and CVP across a broad range of pressures. We therefore hypothesised that evaluating the PVP–CVP relationship across a wide pressure range, while accounting for TP, would improve the accuracy of CVP estimation.

This study aimed to characterise the PVP–CVP relationship across a broad pressure range in dogs under general anaesthesia. We assessed the changes in the PVP–CVP relationship

induced by fluid infusion, and evaluated the influence of TP and vasoactive agents. We also developed a CVP estimation formula. Finally, we explored the potential applicability of the formula in the perioperative setting by evaluating the accuracy of the formula under haemodynamic fluctuations, such as drug-induced vasodilation and haemorrhage, which are conditions commonly encountered during surgery.

Methods

Animals

This study was planned and conducted in accordance with the ARRIVE 2.0 guidelines for reporting animal research. The animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research, and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 86-23, revised 1996). The protocols for this study were approved by the Institutional Animal Care and Use Committee at the National Cerebral and Cardiovascular Center, Suita, Japan, chaired by Ichiro Shiojima, on 13 March 2024 (approval no. 24003) and 12 March 2025 (approval no. 25010), covering the entire study period including protocol extensions.

This study was conducted in 25 beagle dogs (22 females and 3 males; Oriental Yeast Co., Ltd., Tokyo, Japan) weighing 10.0 (9.5–10.9) kg [median (interquartile range)]. Dogs were housed under a 12:12 h light/dark cycle at 22 ± 1°C and 55 ± 15% humidity. They were confirmed to be healthy from vendor records and physical examination. Animals were acclimated to handling and laboratory conditions for 14 days prior to the study. They were fed commercial chow, with water available ad libitum. Food was withheld for at least 8 h before anaesthesia, while water was freely available. Humane endpoints were predefined, and at study completion, animals were euthanised under deep anaesthesia by intravenous administration of an overdose of pentobarbital. Animal experiments for this study were conducted between April 2024 and March 2026.

Preparation

Anaesthesia was induced with intravenous propofol administered to effect followed by endotracheal intubation. Dogs were placed in the right lateral position, and standard monitoring was performed, including end-tidal carbon dioxide ($EtCO_2$), haemoglobin oxygen saturation (SpO_2), and heart rate. Anaesthesia was maintained with 1.5% isoflurane in an oxygen-air mixture [flow rate 3 $L \cdot min^{-1}$; fraction of inspiratory oxygen (FiO_2) 0.40–0.60; SpO_2 95–99%] using a semi-closed rebreathing system. Immediately

after induction, mechanical ventilation was commenced using a ventilator (PRO-45Va; ACOMA Medical Industry Co., Tokyo, Japan) in A/C mode [volume-controlled, tidal volume (VT): 10–15 $mL \cdot kg^{-1}$; respiratory rate (fR): 16–25 $breaths \cdot min^{-1}$] to maintain eucapnia ($EtCO_2$ 35–45 mmHg). Rectal temperature was regulated at 37–38°C with a forced-air patient warmer (Circulating Thermal Water System, T-CARE; Kimuramed, Tokyo, Japan).

As shown in Figure 1A, a 4 Fr sheath was inserted into the right radial artery and connected to a pressure transducer (DX-200; Nihon Kohden, Tokyo, Japan) via fluid-filled noncompliant tubing to measure arterial pressure (AP). A pulmonary artery catheter (5 Fr) was inserted through a 10 Fr sheath via the right external jugular vein, with the tip positioned 1 cm from the wedge site near the pulmonary artery bifurcation. An infusion pump was used to infuse lactated Ringer's solution at 10 $mL \cdot kg^{-1} \cdot h^{-1}$ during the first hour, then reduced to 4 $mL \cdot kg^{-1} \cdot h^{-1}$ until the end of the study.

A biological amplifier (AB-601G, AP-641G; Nihon Kohden) amplified ECG and AP signals, which were digitised at 200 Hz using a 16-bit analog-to-digital converter [AD16-16 U (PCI)EV, Contec, Japan] and stored on a laboratory computer (LC-72 N10, Logitec, Tokyo, Japan) for offline analysis. Cefazolin (30 $mg \cdot kg^{-1}$) was administered to prevent surgical site infection. After a third to fourth intercostal thoracotomy, the pericardium was minimally incised, and an ultrasonic flow probe (model 20A594; Transonic, Ithaca, NY) was placed around the ascending aorta. The intercostal fascia and skin were sutured, and a dressing was applied over the skin to prevent air leak during ventilation.

A 22G catheter (Surflo I.V Catheter; Terumo, Japan) was inserted into the left forearm vein for continuous PVP measurement. CVP was measured through the proximal port of a pulmonary artery catheter. TP was measured using a 27G needle inserted perpendicular to the skin near the PVP catheter insertion site in the left forearm. All pressures were measured using fluid-filled pressure transducers. The transducer was placed at the level of the right atrium as a reference point for zero pressure. CO was measured continuously with a flow sensor. Transthoracic echocardiography was performed as needed. All pressure and flow values were recorded using LabChart 8 (ADinstruments, v8.1.25, Dunedin, New Zealand). Continuous measurements were averaged over 5 s.

Protocol 1

In 15 dogs, volume perturbation was performed to obtain a wide range of PVP–CVP relationship, as shown in Figure 1B. Blood was withdrawn from the arterial sheath until CVP decreased to ≤ 5 mmHg, inducing hypovolaemic shock. The withdrawn blood was then reinfused continuously at a rate of approximately 1200 $mL \cdot hr^{-1}$, followed by administration of extracellular fluid. Fluid infusion was continued until PVP exceeded 30 mmHg. During the infusion, haemodynamic parameters were recorded for each 1 mmHg increase in PVP.

To evaluate the effects of vascular conditions on the PVP–CVP relationship, the procedure was conducted under three conditions in five dogs each: no drug administration, continuous infusion of norepinephrine (NE) at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and infusion of trinitroglycerin (TNG) at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. NE or TNG was administered for 20 minutes before blood withdrawal to ensure a steady state. The dogs were randomised to three experimental conditions (no drug, NE, and TNG groups).

A previous in vitro study reported that TP influenced the PVP–CVP relationship in the low-pressure range [16]. To account for deviations in the low-pressure range (< 15 mmHg), we assumed that the difference between PVP and CVP is proportional to the difference between baseline TP and PVP, for simplicity. In this analysis, PVP and CVP represent mean pressures averaged over the predefined measurement window.

$$PVP - CVP = k \times (TP^* - PVP) \qquad (1)$$

where k is a coefficient representing the influence of extravascular tissue on PVP–CVP relationship, and TP* is the baseline TP, which was held constant during fluid infusion. Using TP* and PVP–CVP data points at low-pressure range (PVP ≤ 15 mmHg) obtained during transfusion in 15 dogs, k was calculated by nonlinear least squares fitting. Rearranging Equation (1) yielded the following equation for the estimated CVP (eCVP), which represents the estimated mean CVP:

$$eCVP = (1 + k) \times PVP - k \times TP^* \qquad (2)$$

Sensitivity Analysis

Protocol 1 was conducted with the closed chest. In contrast, under open chest condition, the influence of intrathoracic pressure is eliminated, the pericardium opens, and ventricular size is not constrained during volume perturbation, potentially altering the relationship between the right atrium and peripheral veins. To assess the effect of pericardial opening, the PVP–CVP relationship was measured in three dogs after median sternotomy in supine position.

Protocol 2

To simulate haemodynamic fluctuations under various clinical conditions, two additional protocols were performed in seven dogs that were different from those used in Protocol 1. This manuscript includes data derived in part from experiments previously reported in a study on automated anaesthesia control [17]. Of the seven dogs, datasets from four animals (#1–#4), obtained during sodium nitroprusside (SNP) infusion and blood withdrawal, were re-analysed here to investigate the PVP–CVP relationship, which was not examined in the previous publication. The remaining three dogs were studied prospectively using the same experimental protocol. eCVP was calculated using the k value and the average TP^* across the 15 dogs obtained from Protocol 1.

Protocol 2-1

CVP was estimated from PVP under haemodynamic changes induced by a vasoactive drug in 7 dogs. After surgical preparation and stabilisation for 5 min, SNP was administered continuously at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min to simulate a deep anaesthesia state. After termination of SNP infusion followed by stabilisation for 15 min (Fig. 1C), eCVP was compared with the measured CVP.

Protocol 2-2

In the same dogs used in Protocol 2-1, CVP was estimated from PVP under haemodynamic changes induced by blood withdrawal. After surgical preparation and a 5-min stabilisation period, blood was withdrawn at a rate of 2 $mL \cdot kg^{-1} \cdot min^{-1}$ for 15 min (total 30 $mL \cdot kg^{-1}$) to simulate haemorrhagic conditions. The animals were observed for

10 min following the bleeding period (Fig. 1D). Then, eCVP was calculated and compared with measured CVP.

Data Analysis

Sample size was not calculated a priori, as this analysis was exploratory and no prior data were available to estimate the expected effect size. Continuous variables are expressed as mean (standard deviation) or median [interquartile range].

Waveform data obtained in Protocol 1 were analysed. Waveform amplitude was extracted from 10 cardiac cycles gated by ECG R waves to assess pulse pressure variation. Similarity between CVP and PVP waveforms was quantified using the maximum cross-correlation coefficient (γ_{max}) obtained from the cross-correlation function over three cardiac cycles. The analyses were performed using MATLAB R2024b (The MathWorks, Natick, Massachusetts, USA), including cross-correlation analysis and derivation of the estimation formula using nonlinear least squares regression.

To assess correlation between PVP and CVP correcting for repeated measurements, the R package rmcorr in R 4.4.3 (R Foundation for Statistical Computing, Vienna, Austria) was used. This method estimates a common regression slope shared across individuals and calculates confidence intervals using a random intercept model [18]. Bland–Altman analysis was performed to assess the accuracy of eCVP compared with measured CVP. A two-sided p-value of less than 0.05 was considered statistically significant. To evaluate the accuracy of CVP estimation, the mean absolute error (MAE) of estimated CVP relative to measured CVP was calculated for both PVP and eCVP. MAE values were calculated for each animal, and paired comparisons between methods were performed using the Wilcoxon signed-rank test. A two-sided p-value <0.05 was considered statistically significant.

In Protocol 2, data from dog #6 that were affected by excessive noise were identified as outliers when their Z-scores, calculated for CVP using the mean and standard deviation, exceeded 1.5. In addition, due to a transducer malfunction during pressure measurement, data between 2712 and 2907 seconds were excluded from analysis.

Results

PVP–CVP relationship across wide pressure ranges

As shown in Figure 2A, pulsatility was observed in the CVP waveform across all pressure ranges. In contrast, the PVP waveform appeared nearly flat when PVP was below 5 mmHg, but began to resemble the CVP waveform once it exceeded 10 mmHg. The maximum cross-correlation coefficient (γ_{max}) increased from 0.46 to 0.72 as PVP rose from 5 mmHg to 10 mmHg. Between 15 mmHg and 30 mmHg, γ_{max} remained consistently high at 0.80–0.84, indicating strong waveform similarity between CVP and PVP (Fig. 2B).

In Fig. 3A, the PVP–CVP relationship obtained in 15 dogs was approximately linear over the entire venous pressure range up to 30 mmHg, with a correlation coefficient (CC) of 0.99 ($p < 0.001$). Bland–Altman analysis showed a mean bias of 0.08 mmHg between PVP and CVP, with 95% limits of agreement (LOA) ranging from −2.04 to 2.20 mmHg (Fig. 3B). PVP frequently exceeded CVP when pressure was below 10 mmHg, but the divergence between PVP and CVP decreased when pressure exceeded approximately 10 mmHg.

Figure 3C illustrates the trends in CVP, PVP, and TP during fluid infusion. Although all three pressures increased linearly with infusion, mean PVP consistently remained higher than mean CVP when pressures were below approximately 10 mmHg. The divergence between PVP and CVP gradually decreased, disappearing once PVP and CVP reached the same level as TP. In the 10–20 mmHg range, PVP and CVP were almost identical.

As shown in Fig. 3D–F, neither the presence nor the type of vasoactive agent (NE or TNG) significantly influenced the linearity of the PVP–CVP relationship, with all conditions yielding a CC of 0.99 and $p < 0.001$.

To enhance clinical applicability, data from the low-pressure range (PVP ≤ 15 mmHg) were used to estimate k by nonlinear least squares regression. The estimation yielded k = 0.19. The average TP^* of 15 dogs in Protocol 1 was 9.43 mmHg. From Equation (2), eCVP was expressed as follows:

$$PVP < TP^*: eCVP = 1.19 \times PVP - 0.19 \times TP^* \quad (3)$$

$$PVP \geq TP^{*}: eCVP = PVP \quad (4)$$

During fluid infusion under open-chest conditions in three dogs, PVP and CVP exhibited a linear relationship (Fig. 3G). PVP exceeded CVP when PVP was below 5 mmHg; the values then converged between 5 and 10 mmHg. Above 10 mmHg, however, CVP became higher, reaching a maximum difference of 7 mmHg at PVP of 20 mmHg. In two of the three dogs, tricuspid regurgitation (TR) was identified on transthoracic echocardiography when CVP exceeded approximately 10 mmHg, whereas echocardiography was not performed in the remaining dog.

Continuous CVP estimation using PVP under simulated clinical conditions

As shown in Figure 4A, which presents the time course of the mean data from seven animals with standard deviation, continuous SNP infusion markedly reduced MAP with only modest changes in CO, while both PVP and CVP declined gradually, with PVP remaining approximately 2 mmHg higher than CVP throughout.

In Protocol 2-1 (n = 7), CVP ranged from 2.8–9.7 mmHg (minimum–maximum), PVP from 3.5–9.7 mmHg, and eCVP from 2.4–9.7 mmHg (Fig. 4B, C). Bland–Altman analysis between PVP and CVP showed a mean bias of 1.76 mmHg (limits of agreement [LOA], −0.40 to 3.93), whereas analysis between eCVP and CVP revealed a smaller bias of 1.01 mmHg with narrower LOA (−0.88 to 3.08) (Fig. 4D, E). Consistent with these findings, the MAE relative to measured CVP was significantly lower for eCVP than for PVP (median paired difference −0.61 mmHg, $p < 0.05$) (Fig. 5).

In Protocol 2-2, blood withdrawal reduced both MAP and CO, while PVP remained slightly higher than CVP (Fig. 4F). CVP ranged from 1.2–9.1 mmHg, PVP from 1.4–10.1 mmHg, and eCVP from −0.1–10.1 mmHg (Fig. 4G, H). Bland–Altman analysis between PVP and CVP revealed a bias of 1.93 mmHg (LOA 0.05 to 3.81), whereas analysis between eCVP and CVP demonstrated a lower bias of 1.17 mmHg with narrower LOA (−0.67 to 3.01) (Fig. 4I, J). Similarly, the MAE was lower for eCVP than for PVP (median paired difference −0.73 mmHg, $p < 0.05$).

Discussion

In this study, we comprehensively examined the relationship between CVP and PVP under diverse haemodynamic conditions. The main findings were: (1) TP significantly influenced the PVP–CVP relationship. PVP exceeded CVP when pressures were below TP, but PVP and CVP converged when both pressures surpassed TP; (2) continuous infusion of NE or TNG had little impact on the PVP–CVP relationship; (3) eCVP, which accounts for TP-related effects on the PVP–CVP relationship, predicted CVP significantly more accurately than PVP alone during clinically relevant fluctuations including vasodilation and haemorrhage.

Impact of TP on PVP–CVP relationship

CVP remains clinically valuable in perioperative care, but direct monitoring is invasive and is not always justified during routine anaesthetic management [1–4]. In contrast, peripheral venous access is routinely available, and previous studies have shown that PVP can approximate CVP in several clinical settings [9–13]. However, prior studies have also suggested that disagreement between PVP and CVP becomes more pronounced at low pressures [14,15], indicating that the relationship may vary according to pressure range. Therefore, we investigated the PVP–CVP relationship across a broad pressure range, considering TP together with other physiological factors that might contribute to this discrepancy.

In low-pressure range, the PVP waveform was relatively flat with reduced pulse pressure and had slightly higher absolute values than the CVP waveform. With fluid infusion, pulse pressure increased, and at higher pressures, the PVP waveform closely resembled the CVP waveform (Fig. 2A). Corresponding to these changes, γ_{max}, an index of waveform similarity, rose with increasing pressure and remained high (0.80–0.84) in the 15–30 mmHg range (Fig. 2B).

The low-pressure characteristics may be explained by compression from surrounding tissues, which elevates PVP slightly above CVP and reduces pulsatility. Due to their high compliance, veins behave as “collapsible tubes” under low pressure [19], allowing

external TP to narrow or collapse the lumen, markedly reducing blood flow and pulsatility. This compression-induced narrowing may further increase vascular resistance.

In contrast, with fluid infusion, intravascular pressure increased, and PVP, CVP, and TP converged at around 10 mmHg, after which PVP and CVP tracked closely. Venous dilation at higher pressures markedly lowers resistance along the right atrium–peripheral venous pathway, as described by the Hagen–Poiseuille equation, likely contributing to the strong agreement between PVP and CVP. The converged pressures exceeded the typical TP range of 5–10 mmHg [20]. Baseline TP was approximately 9.5 mmHg and increased with volume perturbation, consistent with prior reports of infusion-induced tissue oedema [21]. These findings highlight that TP changes dynamically with fluid administration and influences the PVP–CVP relationship.

Importantly, these results were obtained by evaluating a wide pressure range within the same individuals, an approach not previously reported. However, the relationship between TP and venous pressure is not uniform, likely contributing to the interindividual differences in PVP–CVP relationship observed in the low-pressure range (Fig. 3A and B). Species-specific factors may also play an important role, underscoring the need for human studies to clarify the effects of TP before clinical application.

Effect of vasoactive drugs on PVP–CVP relationship

We examined the effects of continuous administration of vasoactive drugs on PVP–CVP relationship. The relationship changed very little during continuous infusion of either a vasoconstrictor or vasodilator. Vasoactive agents are known to act on both arterial and venous vessels. NE typically increases venous return and venous resistance by enhancing cardiac contractility and increasing stressed blood volume via venoconstriction [22], whereas TNG decreases venous return and resistance by lowering vascular resistance and venous tone [23]. According to Ohm's law, pressure gradient is equal to resistance multiplied by blood flow, suggesting that these agents should alter the PVP–CVP gradient. However, as shown in Fig. 3E and F, neither drug altered the linearity of the PVP–CVP relationship.

This stability probably reflects the dominant influence of TP and the high compliance of the venous system. Additionally, since PVP was measured in a peripheral vein close to

the central venous system, drug-induced changes in venous compliance may have had minimal impact on the PVP–CVP relationship. It should be noted that the present findings pertain to the effects of continuous drug infusion. The influence of bolus administration or acute haemodynamic changes immediately after drug initiation remains unclear and warrants further study.

Continuous and accurate CVP estimation using PVP in clinical setting

Our findings suggest that eCVP provides continuous estimation of CVP in clinical settings by measuring PVP and applying the equation derived from the PVP–CVP relationship in Protocol 1. As shown in Fig. 4A and F, PVP was consistently approximately 2 mmHg higher than CVP in both Protocols 2-1 and 2-2. Desjardins et al. [13] reported that PVP and CVP were nearly identical during cardiac surgery, whereas Amar et al. [10] recommended subtracting 2 mmHg from PVP to estimate CVP with high precision. These differences may reflect the distinct CVP–PVP gradients observed in low- ($< \sim$10 mmHg) versus high- ($\geq \sim$10 mmHg) pressure ranges, as illustrated in Figure 3C.

In Protocol 2, during both SNP infusion and blood withdrawal, eCVP showed a significantly lower MAE relative to measured CVP than PVP alone. These findings support the clinical utility of the proposed estimation equation, which accounts for the TP-related discrepancy between PVP and CVP under the low-pressure conditions characteristic of general anaesthesia. The CVP estimation equation derived from PVP enables minimally invasive, continuous CVP monitoring, suitable not only for outpatient care, but also intraoperative management, and ICU settings. Studies indicate that intraoperative PVP monitoring is minimally influenced by factors such as site and type of surgery, position of peripheral vein cannulation, and needle size [24], supporting the broad application of PVP-based CVP estimation to diverse surgical procedures.

Although all primary experiments were performed under closed-chest conditions, sensitivity analysis under open-chest conditions showed that CVP exceeded PVP in the high-pressure range (Fig. 3G). In two dogs, echocardiography confirmed TR when CVP rose above 10 mmHg. TR is known to increase CVP, and, as shown in Figure 6B, prominent v waves appeared in the CVP waveform in dogs with TR, while synchronous v-like waves were also observed in the PVP waveform. This suggests that marked v-like

391 waves in PVP may indicate TR and could lead to CVP underestimation if unrecognised.
392 Previous reports have also described cases in which PVP over-estimated CVP [11, 12],
393 discrepancies that may reflect not only measurement error but also valvular pathology.

394 To our knowledge, this is the first study to report a CVP estimation equation that
395 incorporates physiological insights into the PVP–CVP discrepancy, specifically
396 accounting for the influence of TP. Since the non-linearity of TP and its influence on the
397 PVP–CVP gradient may differ between species, further clinical studies are needed to
398 evaluate the applicability of this estimation method across diverse patient populations and
399 surgical settings.

400

401 **Limitations**

402 This study has several limitations. First, the small sample size may limit the
403 generalisability of the findings. Anatomical differences between species, such as venous
404 valve distribution and limb proportions, could influence the applicability of the PVP–
405 CVP relationship to humans. Haemodilution from fluid infusion may reduce vascular
406 resistance, whereas higher haemoglobin levels may increase resistance due to blood
407 viscosity, potentially impacting the PVP–CVP relationship. In this study, observations
408 were limited to PVP ≥ 3 mmHg. At lower pressures, more pronounced venous collapse
409 may occur, and the difference between PVP and CVP may be more variable. Additionally,
410 the PVP estimation formula was developed using data below 15 mmHg. As shown in
411 Figure 3G, at very high pressures, such as PVP ≥ 25 mmHg, CVP may surpass PVP due
412 to valve regurgitation, which could contribute to discrepancies. Sensitivity analysis
413 revealed that TR significantly influenced the PVP–CVP relationship, although
414 echocardiographic data from all animals were not available for analysis.

415 Second, PVP monitoring was performed using 22G cannulation at a fixed forearm
416 position. PVP may be higher in lower extremities due to abdominal organ drainage. To
417 date, few studies have directly compared peripheral venous pressure between upper and
418 lower extremities, highlighting the need for further investigation.

419 Third, in estimating eCVP in Protocol 1, the influence of the difference between TP and
420 PVP on the PVP–CVP relationship may not be linear. Moreover, TP can also be affected
421 by fluid conditions or mechanical compression. Although the average baseline TP

obtained from Protocol 1 was used in Protocol 2, TP may differ in humans and in dogs. Additionally, this study was conducted under general anaesthesia and does not reflect conditions with rapid changes in vascular tone, such as during sympathetic activation in the awake state or in response to pain. Intraoperative factors, such as rapid blood loss leading to excessive drops in CVP and sudden onset of TR due to surgical manipulation, may also compromise the accuracy of the estimation.

Conclusion

In a dog model, PVP exhibits a consistent, linear relationship with CVP in the pressure range above TP, regardless of the use of vasoactive agents. However, under low pressure conditions, PVP tends to be higher than CVP, likely due to the influence of TP. Taking the above factors into account in deriving an equation to estimate CVP from measured PVP provides a simple, minimally invasive approach for continuous CVP monitoring, even during haemodynamic instability. Clinical validation in humans, including assessment of TP, is essential to move toward practical clinical application.

Statements and Declarations

Funding: This study was partly supported by Grants-in-Aid for Scientific Research (JSPS KAKENHI 24K12155, 24K11283, 24K23449, 24K23422, 24K00885, 25K12304, 25K22628), the Intramural Research Fund for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center (24-B-7), a research grant from JST (JPMJPF2018), a research grant from Neuroceuticals, Inc., and a research grant from NTT Research, Inc. These funders had no role in the study design, conduct of the study, data analysis, manuscript preparation, or decision to submit the article for publication.

Competing interests: Matsushita H, Nishikawa T, Nakamura Y, Sasaki K, Sato K, Morita H, Yoshida Y, Hiraki N, Otake M, Oba K, Fukumitsu M, and Uemura K declare no competing interests. Kawada T received a consulting fee from NTT Research, Inc. Saku K received research funding from Abiomed Inc., NTT Research, Inc., Asahi Kasei ZOLL Medical Corporation, Neuroceuticals, Inc., and Zeon Medical, Inc., and honoraria from Abiomed Japan K.K. and Mallinckrodt Pharmaceuticals, Inc.

Ethics approval: The study protocols were approved by the Institutional Animal Care and Use Committee at the National Cerebral and Cardiovascular Center, Suita, Japan, chaired by Ichiro Shiojima, on 13 March 2024 (approval no. 24003) and 12 March 2025 (approval no. 25010), covering the entire study period including protocol extensions.

Consent to participate: Not applicable.

Consent to publish: Not applicable.

Data availability: The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Acknowledgements: The authors thank the staff at the Department of Cardiovascular Dynamics, National Cerebral and Cardiovascular Center, for technical assistance. The authors also thank Ms Teresa Nakatani for English language editing.

Authors' contributions: Matsushita H contributed to conceptualization, methodology, investigation, formal analysis, data curation, visualization, and writing – original draft. Nishikawa T and Nakamura Y contributed to conceptualization, methodology,

467 investigation, formal analysis, data curation, and writing – review and editing. Sasaki K,
468 Sato K, Morita H, Yoshida Y, Hiraki N, Otake M, Oba K, and Fukumitsu M contributed
469 to methodology, investigation, and writing – review and editing. Kawada T contributed
470 to conceptualization, methodology, supervision, and writing – review and editing.
471 Uemura K contributed to formal analysis, validation, supervision, and writing – review
472 and editing. Saku K contributed to conceptualization, methodology, supervision, project
473 administration, funding acquisition, and writing – review and editing. All authors read
474 and approved the final manuscript.

475 **Previous presentation:** Preliminary data from this study were presented in part at the
476 30th Annual Meeting of the Japanese Society of Cardiovascular Anaesthesiologists.

477

478 **List of abbreviations**

479 AP, arterial pressure
480 CC, correlation coefficient
481 CO, cardiac output
482 CVP, central venous pressure
483 eCVP, estimated central venous pressure
484 ECG, electrocardiogram
485 $EtCO_2$, end-tidal carbon dioxide
486 FiO_2, fraction of inspired oxygen
487 NE, norepinephrine
488 PVP, peripheral venous pressure
489 SNP, sodium nitroprusside
490 SpO_2, peripheral oxygen saturation
491 TNG, trinitroglycerin
492 TP, tissue pressure
493 TR, tricuspid regurgitation
494 γ_{max}, maximum cross-correlation coefficient

References

1. Joseph A, Petit M, Vignon P, Viecaillard-Baron A. Fluid responsiveness and venous congestion: unraveling the nuances of fluid status. Crit Care 2024; 28(1):140.
2. Zhang H, Lian H, Zhang Q, Zhao H, Wang X. Can central venous pressure help identify acute right ventricular dysfunction in mechanically ventilated critically ill patients? Ann Intensive Care 2024; 14(1):114.
3. Zhao Y, Zhang H, Wang X, Liu D. Impact of central venous pressure during the first 24 h and its time-course on the lactate levels and clinical outcomes of patients who underwent coronary artery bypass grafting. Front Cardiovasc Med 2023; 10:1298638.
4. Chen CY, Zhou Y, Wang P, Qi EY, Gu WJ. Elevated central venous pressure is associated with increased mortality and acute kidney injury in critically ill patients: a meta-analysis. Crit Care 2020; 24(1):80.
5. Rubin DS, Apfelbaum JL, Tung A. Trends in central venous catheter insertions by anesthesia providers: an analysis of the Medicare Physician Supplier Procedure Summary From 2007 to 2016. Anesth Analg 2020; 130(4):1026-1034. doi: 10.1213/ANE.0000000000004530.
6. McGee SR. Physical examination of venous pressure: a critical review. Am Heart J 1998; 136(1):10-18.
7. Ciozda W, Kedan I, Kehl DW, Zimmer R, Khandwalla R, Kimchi A. The efficacy of sonographic measurement of inferior vena cava diameter as an estimate of central venous pressure. Cardiovasc Ultrasound 2016; 14(1):33.
8. Rollas K, Kılıçaslan B, Erden A, Kılıçaslan I, Ortaç Ersoy E, Akıncı SB. The interrater reliability of inferior vena cava ultrasonography performed by intensive care fellows. J Crit Intensive Car. 2021; 12(2):32-36.
9. Kim SH, Park SY, Cui J, Lee JH, Cho SH, Chae WS, Jin HC, Hwang KH. Peripheral venous pressure as an alternative to central venous pressure in patients undergoing laparoscopic colorectal surgery. Br J Anaesth 2011; 106(3):305-311.

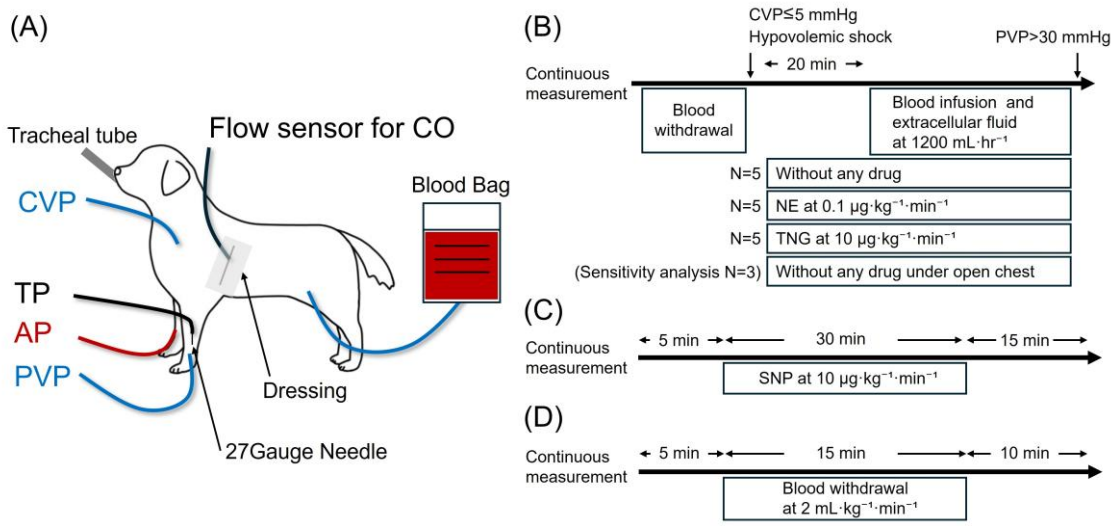
10. Amar D, Melendez JA, Zhang H, Dobres C, Leung DH, Padilla RE. Correlation of peripheral venous pressure and central venous pressure in surgical patients. J Cardiothorac Vasc Anesth 2001; 15(1):40-43.
11. Vlismas PP, Wiesenfeld E, Oh KT, Murthy S, Vukelic S, Saeed O, Patel S, Shin JJ, Jorde UP, Sims DB. Relation of peripheral venous pressure to central venous pressure in patients with heart failure, heart transplant, and left ventricular assist device. Am J Cardiol 2021; 138:80-84.
12. Tan W, Small A, Gallotti R, Moore J, Aboulhosn J. Peripheral venous pressure accurately predicts central venous pressure in the adult Fontan circulation. Int J Cardiol. 2021; 326:77-80.
13. Desjardins R, Denault AY, Bélisle S, Carrier M, Babin D, Lévesque S, Martineau R. Can peripheral venous pressure be interchangeable with central venous pressure in patients undergoing cardiac surgery? Intensive Care Med 2004; 30(4):627-632.
14. Kumar D, Ahmed SM, Ali S, Ray U, Varshney A, Doley K. Correlation between central venous pressure and peripheral venous pressure with passive leg raise in patients on mechanical ventilation. Indian J Crit Care Med 2015; 19(11):648-654. doi: 10.4103/0972-5229.169338.
15. Cave G, Harvey M. The difference between peripheral venous pressure and central venous pressure (CVP) decreases with increasing CVP. Eur J Anaesthesiol 2008; 25(12):1037-40.
16. Harvey MG, Cave G. Influence of tissue pressure on central venous pressure/peripheral venous pressure correlation: An experimental report. World J Emerg Med 2011; 2(2):93-8.
17. Matsushita H, Nishikawa T, Uemura K, Sasaki K, Nakamura Y, Sato K, Morita H, Ohba K, Kawada T, Kataoka Y, Alexander J Jr, Saku K. Automated Hemodynamic Management System for the Prevention of Hypotension and Cardiac Output Reduction During General Anesthesia: Preclinical Experimental Validation. J Anesth 2026. In press.
18. Bakdash JZ, Marusich LR. Repeated measures correlation. Front Psychol. 2017; 8:456.

19. Griffiths DJ. Steady fluid flow through veins and collapsible tubes. Med Biol Eng 1971; 9(6):597-602. doi: 10.1007/BF02474639.
20. Staudt JM, Smeulders MJ, van der Horst CM. Normal compartment pressures of the lower leg in children. J Bone Joint Surg Br 2008; 90(2):215-219.

21. Voldby AW, Brandstrup B. Fluid therapy in the perioperative setting-a clinical review. J Intensive Care 2016; 4:27.
22. Maas JJ, Pinsky MR, de Wilde RB, de Jonge E, Jansen JR. Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. Crit Care Med 2013; 41(1):143-150.
23. Mason DT, Braunwald E. The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm. Circulation 1965; 32(5):755-766.
24. Tugrul M, Camci E, Pembeci K, Al-Darsani A, Telci L. Relationship between peripheral and central venous pressures in different patient positions, catheter sizes, and insertion sites. J Cardiothorac Vasc Anesth 2004; 18(4):446-450.

Figures

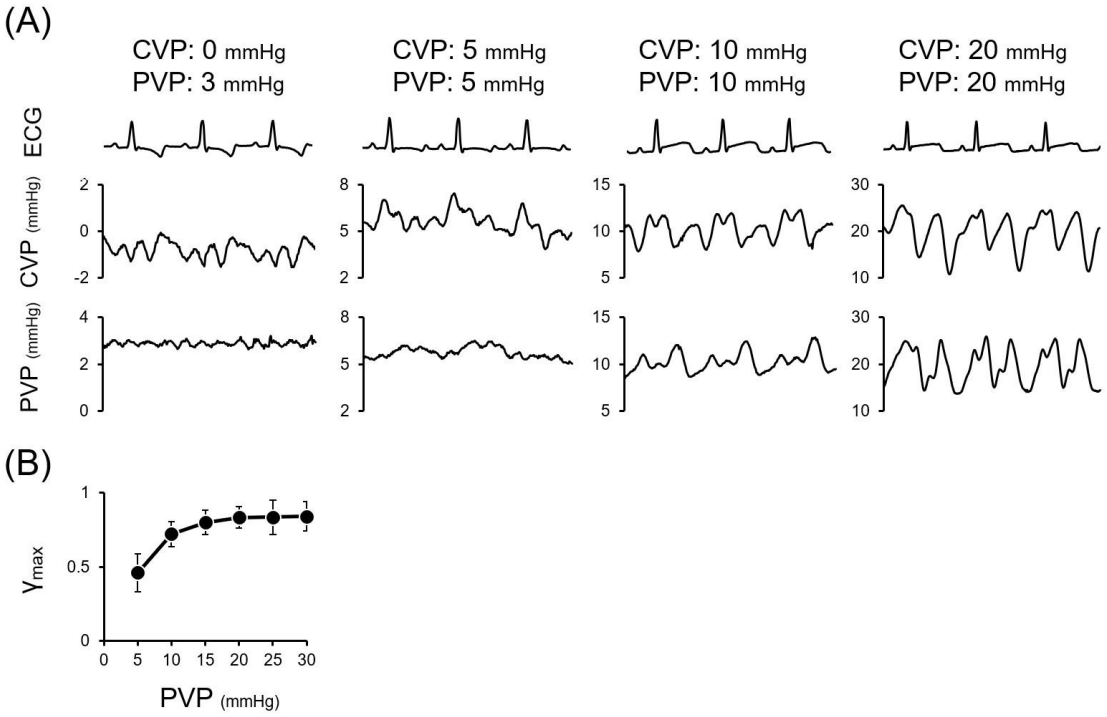
Fig. 1



Animal preparation and experimental protocols.

(A) AP was measured via a radial arterial catheter. After limited thoracotomy and minimal pericardial incision, an ultrasonic flow probe was placed around the ascending aorta to measure CO. The thoracic incision was closed, and a 22G catheter was placed in the left forearm vein for continuous PVP measurement. CVP was measured through the proximal port of a pulmonary artery catheter. A 27G needle was inserted near the PVP catheter site for TP measurement. (B) In 15 dogs, blood was withdrawn until CVP ≤ 5 mmHg. Then blood was reinfused (~1200 mL·hr^{-1}) followed by infusion of extracellular fluid until PVP > 30 mmHg. Haemodynamics were recorded at each 1 mmHg rise in PVP under three conditions (n = 5 each): without any drug, NE administration (0.1 μg·kg^{-1}·min^{-1}), and TNG administration (10 μg·kg^{-1}·min^{-1}). (C) In 7 dogs, after stabilisation for 5 min, SNP (10 μg·kg^{-1}·min^{-1}) was infused for 30 min, followed by recovery for 15 min. (D) In 7 dogs, after 5-min stabilisation, blood was withdrawn at 2 mL·kg^{-1}·min^{-1} for 15 min (30 mL·kg^{-1} in total) to simulate haemorrhage, followed by 10-min recovery. AP, arterial pressure; CO, cardiac output; PVP, peripheral venous pressure; CVP, central venous pressure; TP, tissue pressure; NE, norepinephrine; TNG, trinitroglycerin; SNP, sodium nitroprusside.

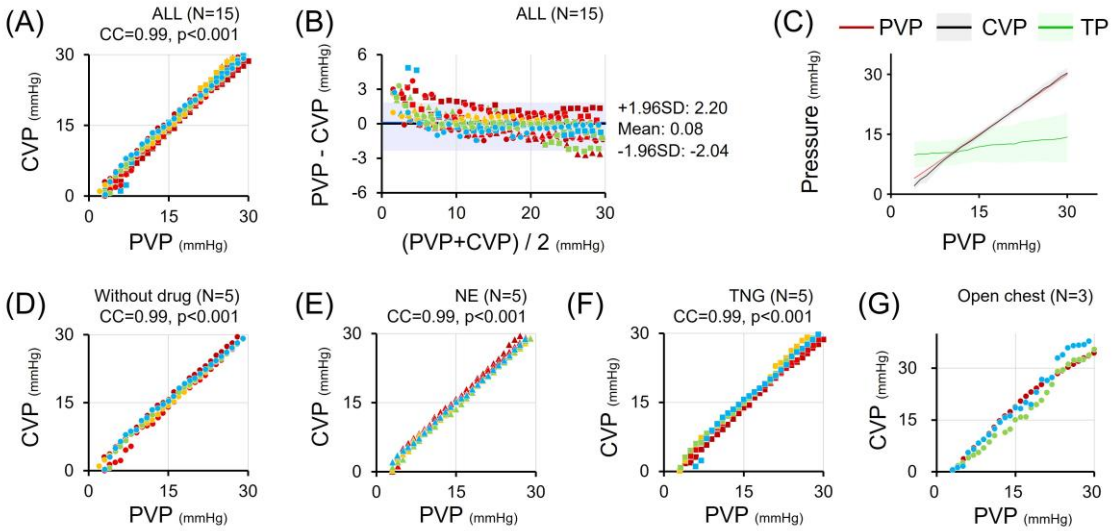
Fig. 2



Waveform analysis of CVP and PVP with fluid infusion.

(A) Representative time traces show pulsatility in the CVP waveform across all pressure ranges. In contrast, the PVP waveform appeared nearly flat when PVP was below 5 mmHg but began to resemble the CVP waveform when the pressure exceeded 10 mmHg. (B) Group data analysis showed increase of γ_{max} from 0.46 to 0.72 as PVP rose from 5 mmHg to 10 mmHg. Between 15 mmHg and 30 mmHg, γ_{max} remained consistently high at 0.80–0.84, indicating strong waveform similarity between CVP and PVP. CVP, central venous pressure; PVP, peripheral venous pressure; γ_{max}, maximum cross-correlation coefficient.

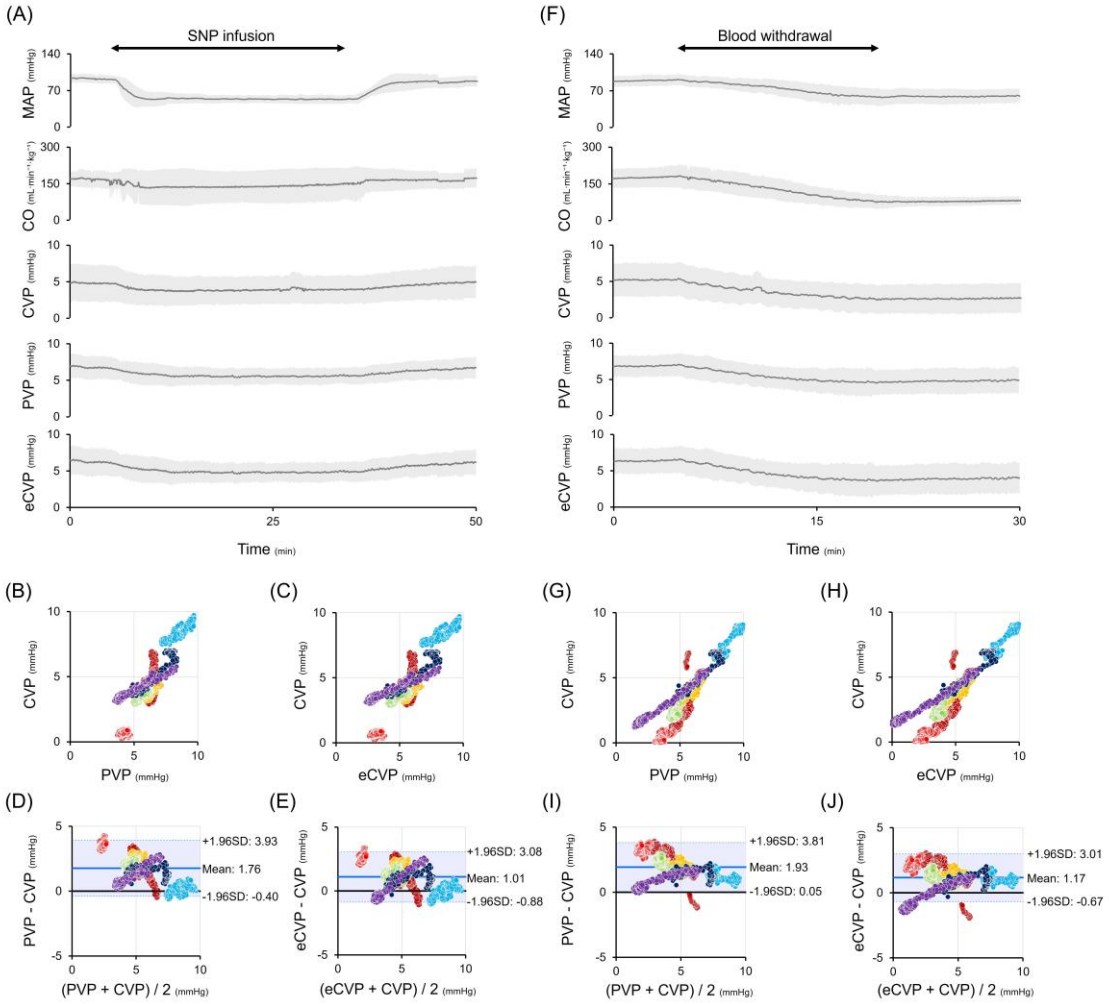
Fig. 3



PVP–CVP relationship during fluid infusion with and without vasoactive drugs.

(A) In 15 dogs, the PVP–CVP relationship was approximately linear up to 30 mmHg (CC = 0.99, $p < 0.001$). (B) Bland–Altman analysis showed a mean bias of 0.08 mmHg with 95% LOA from –2.04 to 2.20 mmHg. Divergence between PVP and CVP decreased once pressure exceeded ~10 mmHg, but PVP often exceeded CVP below 10 mmHg. (C) During fluid infusion, all pressures increased gradually. PVP remained higher than CVP below ~10 mmHg, but the difference diminished as both reached TP. Between 10–20 mmHg, PVP and CVP were nearly identical. (D–F) Infusion of vasoactive agents (NE, TNG) did not affect the linearity of the PVP–CVP relationship (all CC = 0.99, $p < 0.001$). (G) In three open-chest dogs, a general linear trend was observed: PVP was higher than CVP at below 5 mmHg, the two pressures converged between 5–10 mmHg, and CVP surpassed PVP above 10 mmHg, with a maximum difference of 7 mmHg at PVP 20 mmHg. Symbols of different colours denote data from different dogs. PVP, peripheral venous pressure; CVP, central venous pressure; TP, tissue pressure; LOA, limits of agreement; NE, norepinephrine; TNG, trinitroglycerin; CC, correlation coefficient.

Fig. 4

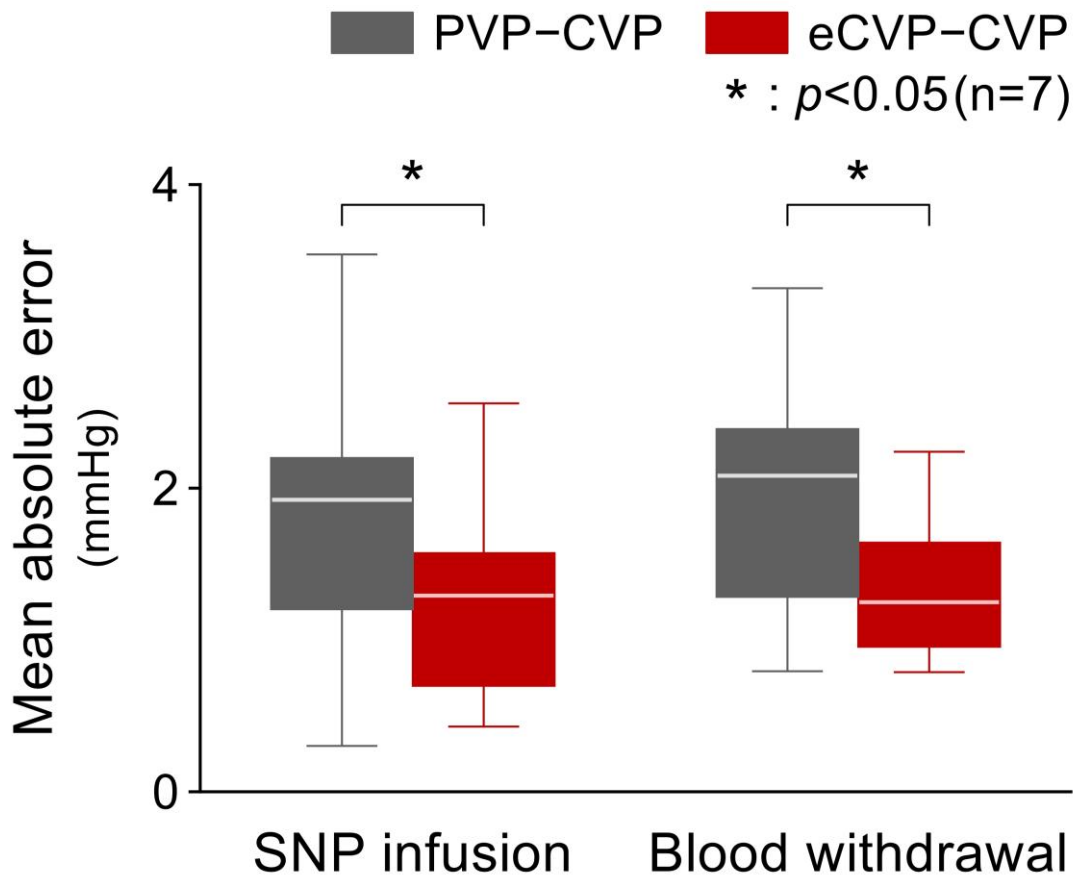


Time courses of parameters during haemodynamic fluctuations induced by SNP infusion or blood withdrawal.

(A) The solid line indicates the mean value, and the shaded area indicates the mean value ± standard deviation. During simulated hypotension induced by continuous SNP infusion, PVP was initially approximately 2 mmHg higher than CVP, and the difference remained stable throughout infusion. (B) PVP ranged from 3.5 to 9.7 mmHg and CVP from 2.8 to 9.7 mmHg, with both pressures fluctuating in parallel. (C) eCVP calculated from PVP showed a strong linear correlation with measured CVP. (D) Bland–Altman analysis between PVP and CVP showed a mean bias of 1.76 mmHg, with 95% LOA from –0.40 to 3.93 mmHg. (E) Bland–Altman analysis between eCVP and CVP demonstrated a mean bias of 1.01 mmHg and LOA from –0.88 to 3.08 mmHg. (F) During simulated haemorrhagic conditions, PVP remained slightly higher than CVP. (G) PVP ranged from 1.4 to 10.1 mmHg, and CVP from 1.2 to 9.1 mmHg. (H) A strong linear relationship was also observed between eCVP and measured CVP. (I) Bland–Altman analysis between PVP and CVP showed a mean bias of 1.93 mmHg, with LOA from 0.05 to 3.81 mmHg. (J) Bland–Altman analysis between eCVP and CVP revealed a

645 mean bias of 1.17 mmHg, with LOA from –0.67 to 3.01 mmHg. MAP, mean arterial pressure; CO,
646 cardiac output; CVP, central venous pressure; PVP, peripheral venous pressure; eCVP, estimated
647 central venous pressure; SNP, sodium nitroprusside; LOA, limits of agreement.
648
649

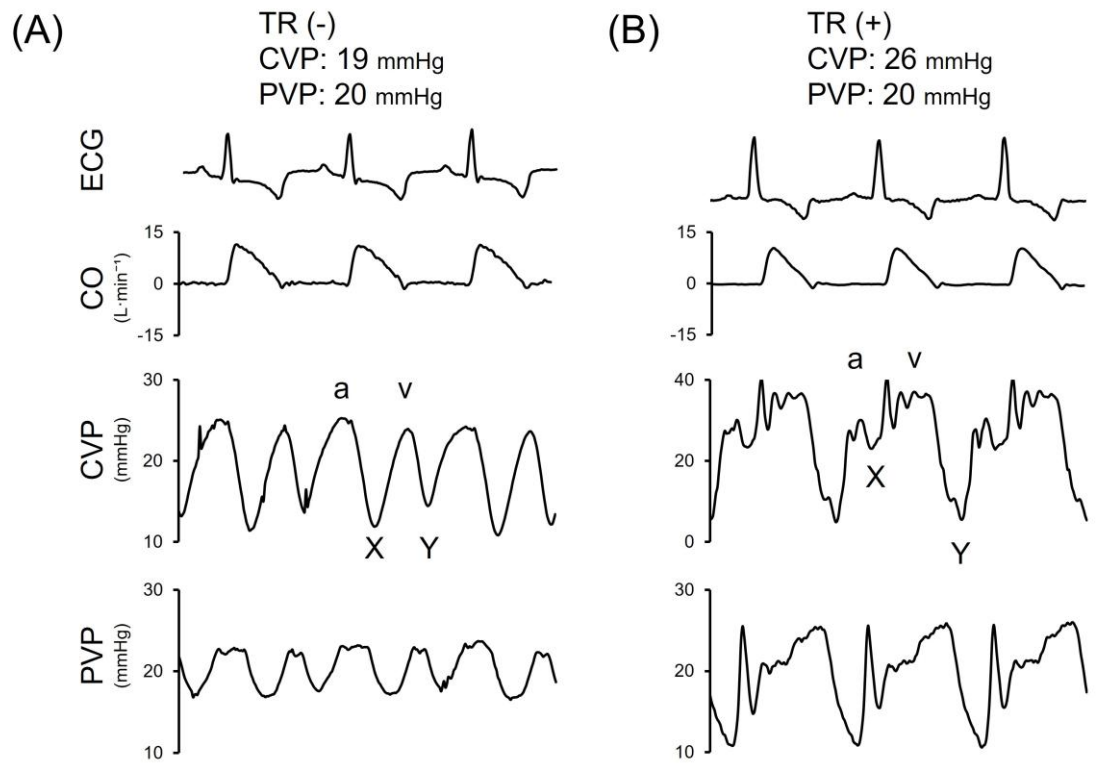
Fig. 5



Comparison of mean absolute error for predicting CVP between PVP and eCVP in Protocol 2.

Boxplots show the MAE relative to measured CVP for PVP and eCVP during SNP infusion (Protocol 2-1) and blood withdrawal (Protocol 2-2) (n = 7). In both protocols, the MAE was significantly lower for eCVP than for PVP (SNP infusion: median paired difference, −0.61 mmHg, $p < 0.05$; Blood withdrawal: median paired difference, −0.73 mmHg, $p < 0.05$). Boxes indicate the interquartile range, centre lines indicate the median, and whiskers indicate the minimum and maximum values. CVP, central venous pressure; PVP, peripheral venous pressure; eCVP, estimated central venous pressure; SNP, sodium nitroprusside; MAE, mean absolute error.

Fig. 6



Representative waveforms recorded under closed-chest and open-chest conditions.

(A) Representative traces obtained under the closed-chest condition, in a dog without tricuspid regurgitation (TR−).

(B) Representative traces obtained under the open-chest condition, in a dog with tricuspid regurgitation on echocardiography (TR+). Although the mean PVP remained similar to that in panel A, the mean CVP was higher and the CVP waveform showed prominent v waves, resulting in a discrepancy between CVP and PVP. ECG, electrocardiogram; CO, cardiac output; CVP, central venous pressure; PVP, peripheral venous pressure; TR, tricuspid regurgitation.