New volumetric capnography-derived parameter: a potentially valuable tool for detecting hyperventilation during cardiopulmonary resuscitation in a porcine model

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Background: Volumetric capnography is increasingly being applied in cardiopulmonary resuscitation. However, during cardiopulmonary resuscitation, the abnormal ventilation state affects the monitoring effect of the most commonly used capnography-derived parameter, the partial carbon dioxide end-tidal pressure ($PetCO_2$). In this study, we evaluated the ability of a new volumetric capnography-derived parameter, the ratio between the $PetCO_2$ and the volume of carbon dioxide (CO_2) eliminated per min and per kilogram of body weight, for detecting hyperventilation during cardiopulmonary resuscitation.

Methods: We used 12 porcine models of primary ventricular fibrillation-induced cardiac arrest. Ventricular fibrillation was induced and left untreated for 4 min. Standardized chest compressions were performed throughout the experiment using mechanical cardiopulmonary resuscitation. Following 5 min of normal ventilation as a washout period, each animal underwent 4 types of ventilation. The main outcome measures were the $PetCO_2$, the ratio between the $PetCO_2$ and the volume of CO_2 eliminated per min and per kilogram of body weight with each ventilation type.

Results: Different ventilation types had a significant effect on the volumetric capnography-derived parameters. The $PetCO_2$ and ratio between the $PetCO_2$ and the volume of CO_2 eliminated per min and per kilogram of body weight values during cardiopulmonary resuscitation was significantly higher in non-hyperventilating than in hyperventilating animals. The ratio reflected hyperventilation accurately and immediately, with an area under the curve (AUC) of 0.98. The optimal cut-off point of the ratio for discriminating hyperventilation from non-hyperventilation was 6.36, with a sensitivity and specificity of 0.99 and 0.89, respectively.

Conclusions: The ratio between the $PetCO_2$ and the volume of CO_2 eliminated per min and per kilogram of body weight showed good performance in discriminating hyperventilation from non-hyperventilation and was sensitive to changes in ventilation status. This ratio may be a valuable clinical indicator for monitoring the ventilation status during cardiopulmonary resuscitation.

Keywords: Cardiac arrest; cardiopulmonary resuscitation (CPR); end-tidal CO_2 partial pressure ($PetCO_2$); hyperventilation

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Introduction

Capnography is now recommended as the standard monitoring method for advanced cardiopulmonary resuscitation (CPR) (1,2). The advantages of capnography include assessment of the correct placement of the endotracheal tube (3), evaluating the quality of chest compressions (CC) (4,5), monitoring the early return of spontaneous circulation (6), and predicting the patient prognosis (1,7,8). Additionally, capnography is recommended to monitor ventilation rates and avoid hyperventilation during CPR, according to current guidelines (7). Hyperventilation may be caused by an excessive respiratory rate (RR), high tidal volume (VT), or a combination of both. However, capnography focuses on RR monitoring, both visually and automatically (9,10).

During CPR, the purpose of ventilation is to ensure that sufficient oxygen is supplied and carbon dioxide (CO_2) is removed, thereby maintaining proper blood oxygen and CO_2 levels. Simultaneously, another important principle of ventilation is to avoid adverse effects on hemodynamics (11-13). Thus, it is not reasonable to evaluate ventilation status using RR, VT, or minute volume (MV) alone. Although arterial blood gas analysis results provide information about the ventilation status, arterial blood sampling is not routinely available and does not provide real-time results. Therefore, volumetric capnography (Vcap)-derived variables can be used to develop parameters for the real-time monitoring of ventilation status during resuscitation.

Using Vcap provides continuous and noninvasive information about the fractional concentration or partial pressure of exhaled CO_2 against the expired volume of 1 breath (14,15). One of the most commonly used Vcap-derived parameters, the end-tidal partial carbon dioxide pressure ($PetCO_2$), is affected by hyperventilation, as confirmed in animal experiments (16) and clinical observational studies (17-19). The $PetCO_2$ decreases with an increase in MV (16). Another Vcap-derived parameter, the volume of CO_2 eliminated per min ($V'CO_2$), can reflect metabolic CO_2 production, provided that ventilation and perfusion conditions remain unchanged (15). According to the results of our previous animal experiments (20), the accumulated and produced CO_2 is eliminated quickly by hyperventilation, as manifested by a rapid increase in $V'CO_2$ within 2–3 min after the change in ventilation status. The $V'CO_2$ then gradually decreases to a stable level, reflecting the true metabolic status of the body. When analyzing such experimental results, an individual's body weight should be considered. A modified parameter, the volume of CO_2 eliminated per min per kilogram of body weight ($V'CO_2$/kg), has been used for this analysis and has provided more valuable conclusions. It is theoretically feasible to use the ratio between the 2 indices to determine the ventilation status. However, this parameter's ability has not been studied in terms of its ability to detect hyperventilation to date.

By reviewing previously collected data, we aimed to construct an algorithm to monitor animals' ventilation status during resuscitation. We hypothesized that $PetCO_2$ would decrease and $V'CO_2$/kg would increase after hyperventilation began, after which the $PetCO_2$/($V'CO_2$/kg) (PV ratio) would decrease significantly.

We present the following article in accordance with the ARRIVE reporting checklist (available at http://dx.doi.org/10.21037/jtd-21-50).

Methods

Data from a randomized crossover study were retrospectively analyzed. All animals had complete laboratory records, including hemodynamic and respiratory parameters. All animals received humane care following the principles of laboratory animal care formulated by the Ministry of Science and Technology of the People's Republic of China. The Ethics Committee for Animal Experiments at Peking Union Medical College Hospital approved the experimental protocol. The pigs were kept in animal houses with metal fences and concrete floors, and 2 pigs shared 1 cage with an average area of 1.5–3 m^2 per pig. The environment was well ventilated. The ambient temperature was controlled at 18–25 ℃, and the relative humidity was 30–50%. Pigs were fed with a special feed twice a day. The managers document daily observations of health, status, food, and water of the pigs. A total of 12 male domestic pigs aged 3–4 months and weighing 35.6±2.0 kg
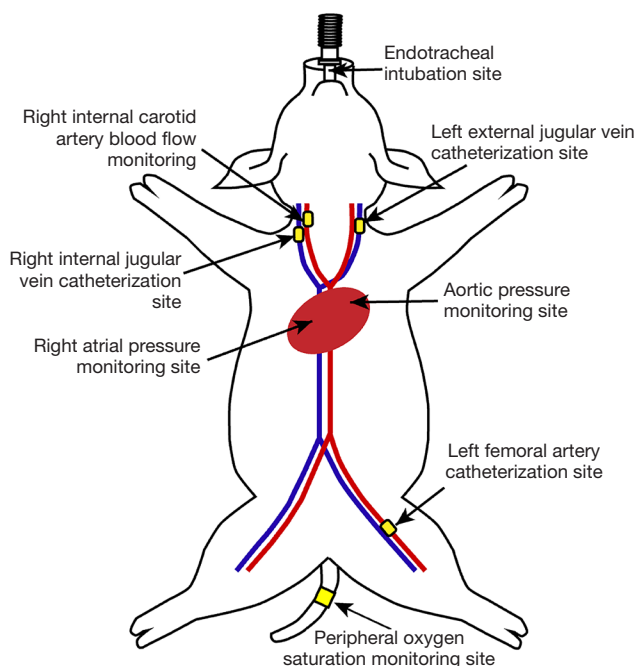
Figure 1 An electronic-tipped catheter (Mikro-Tip Transducer, Millar Instruments, Houston, TX, USA) was inserted via the left femoral artery for continuous monitoring of the aortic pressure. The left external jugular vein was surgically exposed and cannulated with an 8-French introducer sheath to monitor RAP. The RAP was maintained at 3–8 mmHg during the preparation phase. Carotid blood flow was measured using an ultrasonic flow probe (6 mm) surrounding the internal carotid artery (Transonic Systems, Ithaca, NY, USA). The right internal jugular vein was also fitted with a catheter to provide access for ventricular fibrillation induction. RAP, right atrial pressure.

were studied.

Animal preparation

Animal preparation procedures, including anesthesia, fixation, mechanical ventilation, and instrumentation methodology, were undertaken as previously described (20). The catheter position, pressure probe, and flow probe placement are shown in *Figure 1*. The animals were mechanically ventilated with a SynoVent 800 respirator in the baseline data collection stage (Mindray Biological Medical Electronic Co., Ltd., Shenzhen, Guangdong, China). The respirator was started in volume-controlled ventilation (VCV) with ventilator settings as follows: VT of 10 mL/kg; positive end-expiratory pressure (PEEP) of

4 cmH$_2$O; inspiratory to expiratory time ratio (I:E) of 1:1.5–2. The RR was titrated to maintain PetCO$_2$ of 38–42 mmHg and pulse oxygen saturation (SPO$_2$) at >95%. After the preparation period, the animals were stabilized for 15 min under the following conditions: heart rate (HR) of 80–100 beats/min, PetCO$_2$ of 38–42 mmHg, SPO$_2$ >95%, right atrial pressure (RAP) of 3–8 mmHg, and body temperature of 37.0–38.0 ℃. The animals then received a 0.6 mg/kg intravenous bolus of rocuronium bromide (NV Organon, Oss, Netherlands). To inhibit gasping, rocuronium bromide continued to be infused at a rate of 0.1–0.2 mg/kg/h during CPR.

Experimental protocol

Clinical research has reported that rescue personnel's ventilation frequency may be up to 30 breaths/min during out-of-hospital cardiac arrest (CA) rescue (10). This result prompted us to investigate 3 levels of RR (10, 20, and 30 breaths/min). Simultaneously, we also wanted to compare the effect of hyperventilation caused by high VT on the target parameters. Since a high VT may cause lung injury, and as exceeding double the normal VT is not common clinically, we studied only 2 VT levels (10 and 20 mL/kg). Therefore, this study investigated the following 4 ventilation types: normal ventilation (NV), RR at 10 breaths/min, VT at 10 mL/kg; double RR hyperventilation (DRRH), RR at 20 breaths/min, VT at 10 mL/kg, double VT hyperventilation (DVTH), RR at 10 breaths/min, VT at 20 mL/kg; triple RR hyperventilation (TRRH), RR at 30 breaths/min, and VT at 10 mL/kg. According to the ventilation type used, the 12 pigs were divided into 4 groups (n=3 per group).

Each animal underwent 2 successive sessions of the original experiment. In this retrospective analysis, we only included data from the first session for analysis. The experimental timeline of the first session and grouping is shown in *Figure 2*. In the first session of the experiment, no vasoactive drugs, including epinephrine or electric defibrillation, were used. Methods of CA induction and experimental processes were used as described previously (20). Briefly, ventricular fibrillation (VF) was induced after recording the baseline parameters. The animals were then disconnected from the ventilator support, and drug infusion was halted. After 4 min of untreated VF, CCs were started with an impedance threshold device (ITD) with a frequency of 120 compressions/min at a depth of 25% of the anteroposterior chest diameter, using special
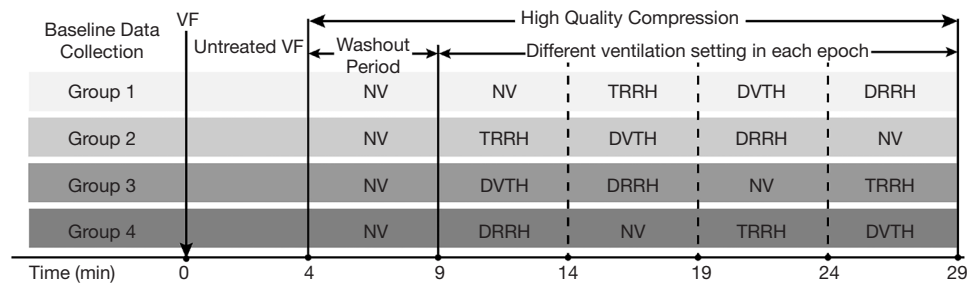
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Figure 2 Experimental timeline. RR, respiratory rate; VT, tidal volume; VF, ventricular fibrillation; NV, normal ventilation (RR: 10 breaths/min and VT: 10 mL/kg); DRRH, double RR hyperventilation (RR: 20 breaths/min and VT: 10 mL/kg); DVTH, double VT hyperventilation (RR: 10 breaths/min and VT: 20 mL/kg); TRRH, triple RR hyperventilation (RR: 30 breaths/min and VT: 10 mL/kg).

animal mechanical CPR equipment (WISH-SL-FS-A, Wuhan, Hubei, China). The same compression was applied throughout the experimental process without interruption. Ventilation was synchronized with the mechanical CC. The percentage of time being compressed was 40% of the entire compression cycle, and the percentage of time being held was 20%. The VCV was selected with ventilator settings as follows: trigger was disabled, a fraction of inspiratory oxygen of 100%, PEEP of 0 cmH$_2$O, I:E of 1:1.5–2, and either VT or RR, depending on the group allocation. To achieve stable CO$_2$ excretion, a 5 min washout period was set to avoid interference of CO$_2$ retention during CA. Following the 5 min standard CPR with NV, each animal underwent 4 ventilation trials of 5 min, based on a randomized crossover design. The order of ventilation types was counterbalanced and randomized using the closed envelope method. The animals were euthanized when the experiment had been completed.

Measurements

A T8 Mindray monitor (Mindray Biological Medical Electronic Co., Ltd., Shenzhen, Guangdong, China) was used to monitor the following parameters continuously: HR, electrocardiogram, RAP, central aortic pressure (AoP), and SPO$_2$. Coronary perfusion pressure (CPP) was calculated as the difference between the AoP and RAP during the CPR decompression phase. Continuous acquisition of graphical on-screen hemodynamic data, including AoP, RAP, CPP, and carotid blood flow, was performed using a multichannel physiological recorder (BIOPAC MP150, BIOPAC Systems, Inc., Goleta, CA, USA). The RR, VT, and MV were recorded continuously using the respiratory background storage system.

This experiment mainly studied 2 Vcap-derived parameters, namely, PetCO$_2$ and V'CO$_2$/kg. The measurements of PetCO$_2$ and V'CO$_2$ were obtained directly from a Vcap connector (NICO; Respironics Inc., Wallingford, CT, USA). V'CO$_2$/kg was calculated by dividing V'CO$_2$ by the animal's body weight in the data processing stage after the experiment. The PV ratio was calculated by dividing PetCO$_2$ by V'CO$_2$/kg. The accuracy of the V'CO$_2$ calculation was affected by the oscillation of the gas in the ventilation tube during CPR. We resolved this problem using an ITD since its design principle allows the exhaled gas to be discharged in the compression phase and prevents the gas from entering the decompression phase (17). The reasons for this are explained in detail elsewhere (20).

All of the parameters mentioned above were measured at 30 s intervals, and the mean values were used in the analysis.

Statistical analysis

All statistical analyses were performed using the statistical software SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Normally distributed data were expressed as mean ± standard deviation (SD), and repeated-measures analysis of variance (RM-ANOVA) was used for comparisons. Non-normally distributed variables were expressed as medians (upper quartile, lower quartile), and the Friedman test was used for comparison. A generalized linear mixed model was used to test the changes in hemodynamic and ventilatory parameters between ventilation types. A pairwise comparison with Bonferroni adjustment was performed for *post-hoc* analysis. Receiver operating characteristic (ROC) curves with area under the curve (AUC) analyses were used to assess the ability of the PV ratio to discriminate between
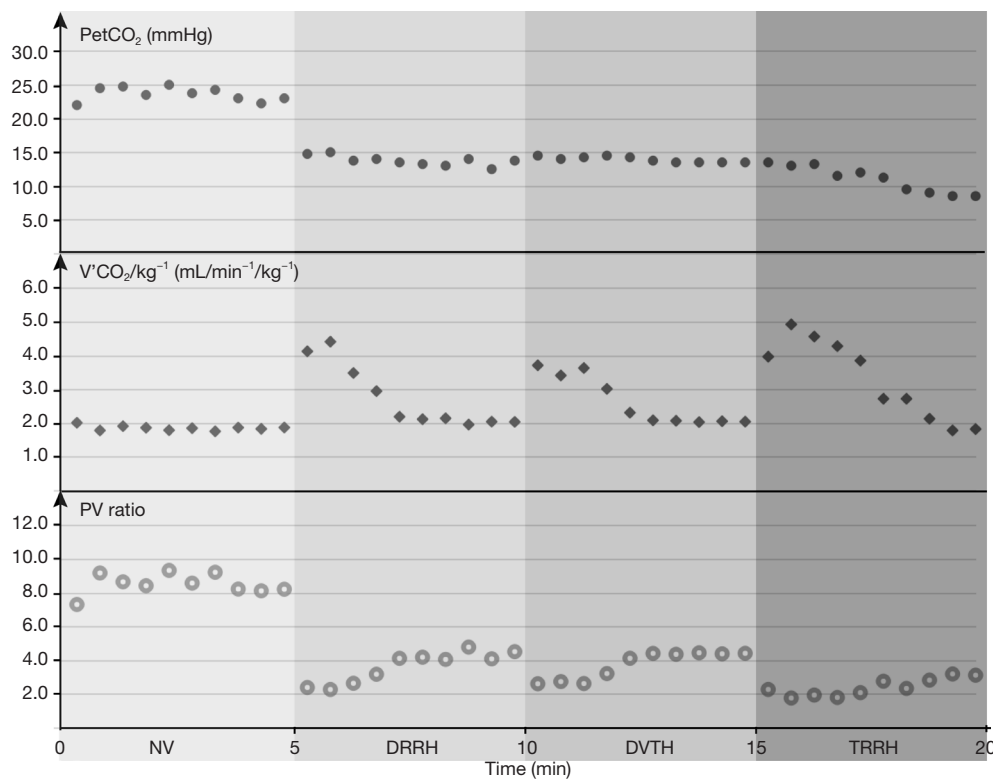
Figure 3 $PetCO_2$, $V'CO_2$/kg, and PV ratio for each ventilation type during CPR. PV ratio, the ratio between $PetCO_2$ and $V'CO_2$/kg. $PetCO_2$, partial end-tidal carbon dioxide pressure; $V'CO_2$/kg, the volume of carbon dioxide eliminated per min and per kilogram of body weight; RR, respiratory rate; VT, tidal volume; VF, ventricular fibrillation; NV, normal ventilation (RR: 10 breaths/min and VT: 10 mL/kg); DRRH, double RR hyperventilation (RR: 20 breaths/min and VT: 10 mL/kg); DVTH, double VT hyperventilation (RR: 10 breaths/min and VT: 20 mL/kg); TRRH, triple RR hyperventilation (RR: 30 breaths/min and VT: 10 mL/kg).

hyperventilation and non-hyperventilation conditions and between 2-fold (DRRH, DVTH) and 3-fold normal MV (TRRH). Statistical significance was considered when two-tailed P values <0.05.

Ethical statement

The Ethics Committee for Animal Experiments at the Peking Union Medical College Hospital approved the experimental protocol (XHDW-2019-023). All animals received humane care in accordance with the "principles of laboratory animal care" formulated by the Ministry of Science and Technology of the People's Republic of China.

Results

Data from 12 pigs were analyzed, and each pig underwent 4 types of ventilation; thus, a total of 48 data epochs were

used for analysis.

A single animal from each group was randomly selected to evaluate the change in Vcap-derived parameters during the 4 ventilation types, as shown in *Figure 3*. After changing the ventilation type, $PetCO_2$ decreased rapidly and then quickly reached a stable state; $V'CO_2$/kg first increased and then decreased, gradually reaching a stable state within 2–3 min. The PV ratio decreased rapidly at the beginning of the switch to hyperventilation and then gradually recovered to a stable state after 1–2 min.

The generalized linear mixed model revealed that the 4 different ventilation types had no significant effect on hemodynamic indices, but a significant effect was noted on Vcap-derived parameters (P<0.001). The $PetCO_2$, $V'CO_2$/kg, and the PV ratio during each ventilation type are displayed in *Figure 4*. The average values of the hemodynamic variables and Vcap-derived parameters are listed in *Table 1*. When comparing the 4 ventilation
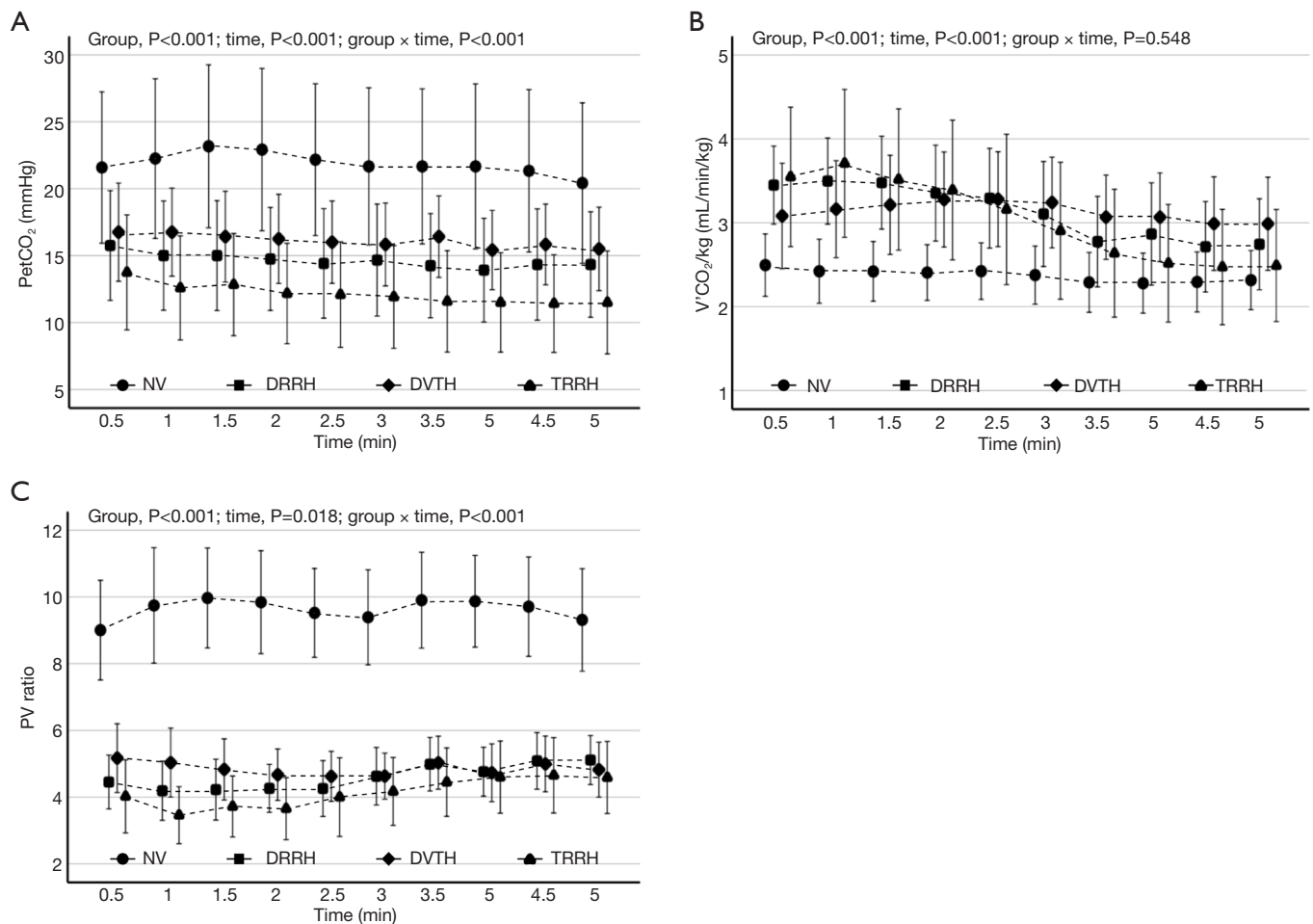
Figure 4 $PetCO_2$, $V'CO_2/kg$, and PV ratio during each ventilation type. (A) $PetCO_2$ during each ventilation type. (B) $V'CO_2/kg$ during each ventilation type. (C) PV ratio during each ventilation type. RR, respiratory rate; VT, tidal volume; $PetCO_2$, the partial pressure of end-tidal carbon dioxide; $V'CO_2/kg$, the volume of carbon dioxide eliminated per min and per kilogram of body weight; PV ratio, the ratio of $PetCO_2$/ ($V'CO_2/kg$); NV, normal ventilation (RR: 10 breaths/min and VT: 10 mL/kg); DRRH, double RR hyperventilation (RR: 20 breaths/min and VT: 10 mL/kg); DVTH, double VT hyperventilation (RR: 10 breaths/min and VT: 20 mL/kg); TRRH, triple RR hyperventilation (RR: 30 breaths/min and VT: 10 mL/kg).

types' analyzed parameters, the RM-ANOVA of $PetCO_2$ and PV ratio revealed significant group effects, time effects, and group-time interactions. The RM-ANOVA of $V'CO_2/kg$ revealed significant time and group effects. All hemodynamic parameters decreased over time, regardless of ventilation type. A significant decrease in $PetCO_2$ and PV ratio was found in the DRRH, DVTH, and TRRH groups in comparison with the NV group. The $PetCO_2$ and PV ratios showed no significant differences between the DRRH and DVTH groups. Although the value of $V'CO_2/kg$ was the highest in the NV group, no significant difference was found among the other 3 groups.

The performance of the PV ratio for detecting hyperventilation during CRP is shown in *Figure 5*. For discriminating hyperventilation from non-hyperventilation, the AUC for the PV ratio was 0.98 [95% confidence interval (CI): 0.97 to 0.99, P<0.001]. As determined by the Youden index, the optimal cut-off point of the PV ratio for discriminating hyperventilation from non-hyperventilation was 6.36, with a sensitivity of 0.99, specificity of 0.89, a positive likelihood ratio of 9.00, and a negative likelihood ratio of 0.01. However, for discriminating 2-fold (DRRH, DVTH) from 3-fold normal MV (TRRH), the AUC was 0.68 (95% CI: 0.61 to 0.74, P<0.001).

Table 1 Key hemodynamic variables and Vcap-derived parameters for the 4 ventilation types during cardiopulmonary resuscitation

Parameter	NV	DRRH	DVTH	TRRH	P
PetCO$_2$ (mmHg)	21.88±9.01[bcd]	14.64±6.12[a]	16.12±6.87[ad]	12.13±5.88[ac]	0.001
V'CO$_2$/kg (mL/min/kg)	2.37±0.54[bcd]	3.13±0.90[a]	3.14±0.86[a]	3.03±1.29[a]	0.001
P/V ratio	9.62±2.27[bcd]	4.60±1.28[a]	4.85±1.31[ad]	4.13±1.62[ac]	0.001
AoP (mmHg)	37.72±10.92	39.81±9.99[a]	39.60±11.96[ad]	37.27±12.43[ac]	0.329
RAP (mmHg)	31.31±8.13	30.95±7.46	31.63±9.05	31.32±8.47	0.981
CPP (mmHg)	5.5 (–0.31 to 12.85)	7.56 (–0.55 to 12.11)	6.99 (–0.57 to 13.12)	7.03 (0.71–14.59)	0.062
CBF (mL/min)	31.14 (19.37–51.23)	27.70 (19.07–51.44)	28.06 (16.36–58.13)	28.78 (18.58–49.23)	0.055

[a], P<0.05 compared to NV; [b], P<0.05 compared to DRRH; [c], P<0.05 compared to DVTH; [d], P<0.05 compared to TRRH. Values are shown as mean ± standard deviation or medians and interquartile ranges. PetCO$_2$, partial end-tidal carbon dioxide pressure; V'CO$_2$/kg, volume of carbon dioxide eliminated per minute and per kg of body weight; PV ratio, ratio of PetCO$_2$/(V'CO$_2$/kg); RR, respiratory rate; VT, tidal volume; VF, ventricular fibrillation; NV, normal ventilation (RR: 10 breaths/min and VT: 10 mL/kg); DRRH, double RR hyperventilation (RR: 20 breaths/min and VT: 10 mL/kg); DVTH, double VT hyperventilation (RR: 10 breaths/min and VT: 20 mL/kg); TRRH, triple RR hyperventilation (RR: 30 breaths/min and VT: 10 mL/kg). AoP, central aortic pressure; RAP, right atrial pressure; CPP, coronary perfusion pressure; CBF, carotid blood flow.
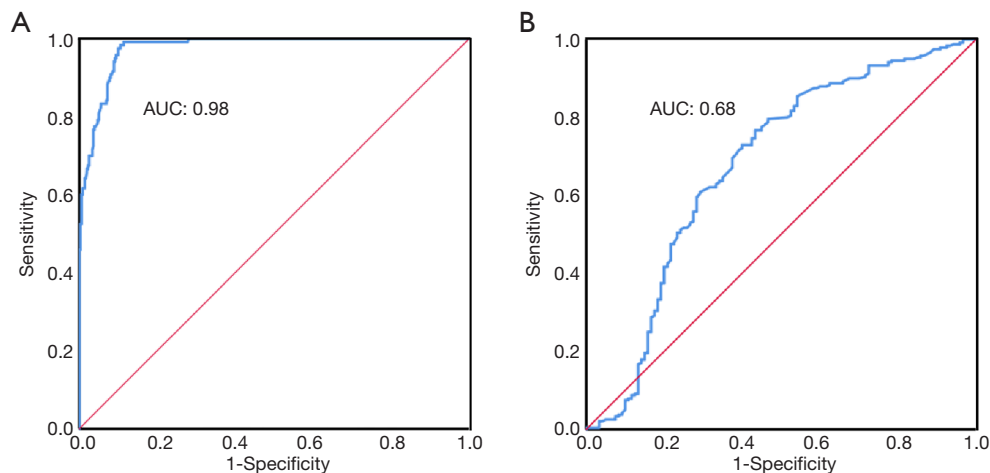

Figure 5 The performance of the PV ratio for detecting hyperventilation during CRP. (A) ROC curves evaluating the ability of the PV ratio to discriminate between hyperventilation and non-hyperventilation. AUC of panel A: 0.98 (95% CI: 0.97 to 0.99). (B) ROC curves evaluating the PV ratio ability to discriminate between 2-fold normal minute volume from 3-fold normal minute volume. AUC of panel B: 0.68 (95% CI: 0.61 to 0.74). PetCO$_2$, the partial pressure of end-tidal carbon dioxide; V'CO$_2$/kg, the volume of carbon dioxide eliminated per min and per kilogram of body weight; PV ratio, the ratio of PetCO$_2$/(V'CO$_2$/kg); ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

Discussion

We found a significant decrease in the PV ratio when porcine CPR models were hyperventilated. Moreover, the PV ratio decrease was significantly faster than that of the other 2 Vcap-derived parameters. A significant decrease in the PV ratio was observed when the RR increased. In hyperventilation caused by simply increasing VT (DVTH), the PV ratio also decreased significantly compared with NV. Regarding the ability to detect hyperventilation from non-hyperventilation, the PV ratio showed excellent performance, with an AUC of 0.98. This parameter's optimal cut-off point was 6.36, providing evidence that lower values during CPR are highly likely to indicate

hyperventilation. However, the AUC for the PV ratio was only 0.68 for discriminating 2-fold (DRRH, DVTH) from 3-fold normal MV (TRRH).

These findings indicate that the PV ratio is a useful parameter for monitoring the ventilation status in real-time and noninvasively during CPR. The 2015 American Heart Association (AHA) CPR guidelines emphasize avoiding excessive ventilation to achieve high-quality CPR (21). Although the guidelines recommend that the provider should deliver 10 breaths per min when ventilating via an advanced airway, hyperventilation during advanced life support remains common among uncertified or inexperienced CPR providers (22). An inappropriately high RR (>25 breaths/min) is commonly observed during CPR (11,23). For this reason, capnography is important as a continuous monitoring method to avoid hyperventilation. By analyzing previous animal experimental data, we found that a simple calculation using Vcap-derived parameters may determine the relationship between gas supply and CO_2 removal. This value facilitates making changes to the mode of ventilation monitoring during resuscitation from monitoring RR or MV to evaluate the correspondence between the MV and CO_2 production.

The $PetCO_2$ is determined by CO_2 production, pulmonary blood flow, and alveolar ventilation (24). In our experiment, a unified CA animal model was used, and the same quality CC was provided to ensure relative stability of CO_2 production and pulmonary blood flow during CPR. A 2- or 3-fold MV was then set by adjusting the RR or VT separately to evaluate the effect of different levels of hyperventilation on $PetCO_2$. Similar to other experiments, we found that with the increase in MV, $PetCO_2$ decreased gradually, and its monitoring value for the quality of CC and prognosis decreased. The $PetCO_2$ decreased to a stable level within 1–2 min after switching to hyperventilation modes.

The other indicator, $V'CO_2/kg$, first showed an increasing trend and then decreased to a stable state, which took approximately 2–3 min. It was previously found that $V'CO_2/kg$ showed no significant difference between NV and hyperventilation caused by increased RR after reaching a stable state and that it could be used as a more stable indicator to determine the quality of CC during hyperventilation. At the same time, $V'CO_2/kg$ performed better than $PetCO_2$ in predicting survival. According to the change in the trend of $V'CO_2/kg$ provided by our experimental animal data, once hyperventilation occurs, the parameter will suddenly increase to become

"normal gradually", and it loses the ability to identify hyperventilation after 3 min. Therefore, for this indicator, in the actual clinical CPR scenario, the change in trend in the process of CPR is more valuable than the observation value at a given point. In our study, $PetCO_2$ decreased, and $V'CO_2/kg$ increased immediately after hyperventilation. This makes the PV ratio a sensitive index for detecting ventilation changes rapidly. The results showed that the PV ratio decreased rapidly and significantly, then gradually and slightly increased, and finally stabilized at a lower level after approximately 2 min. Based on the advantages of the PV ratio mentioned above, it may be another valuable index for detecting hyperventilation during CPR.

Another meaningful property of the PV ratio is that it reflects the essence of ventilation, meaning whether the volume of gas provided matches the volume required for CO_2 removal. According to the current guidelines, we standardized the ventilation settings for animals, ignoring individual differences. In real-world CPR, the ventilation needs of patients with CA are often complex and difficult to assess. In patients with lung diseases, such as acute respiratory distress syndrome, the dead space is enlarged, leading to decreased effective alveolar ventilation. Under these circumstances, if ventilation support is still implemented according to the guidelines, there is a risk of insufficient ventilation. Therefore, monitoring ventilation quality during CPR should not be limited to monitoring the RR or MV, but instead should be based on the volume supplied to meet the demand for CO_2 removal. The PV ratio, a new Vcap-derived parameter, can be obtained through simple calculations and shows a good ability to detect hyperventilation and changes immediately after hyperventilation in an animal model. Our results were based on animal experiments, and the values of the optimal cut-off point and reference ranges in the results are not suitable for clinical applications. However, this parameter points to the possibility of future noninvasive, real-time, and continuous monitoring of ventilation status in clinical CPR.

It should be noted that the definition of NV during CPR in our experiment was not accurate. The amount of gas provided by the ventilator should match the reduced pulmonary blood flow during resuscitation. The NV parameters set in the experiment may have resulted in the overventilation of the animals. Although we standardized the animal CA model as much as possible, the heterogeneity between individuals made it difficult to set a unified "NV parameter". It is difficult to monitor pulmonary blood flow in real-time. Blood gas analysis may provide some

information, but it is usually delayed. Therefore, in the selection of NV parameters, our protocol is not perfect.

While the PV ratio may be a valuable parameter, we still face challenges in applying it to real-world resuscitation. Accurate monitoring of RR and Vcap-derived parameters relies on high-quality capnogram recordings. In future real-world clinical resuscitation scenarios, the PV ratio application will depend on the improvement of monitoring technology and equipment.

Limitations

This study had several limitations. First, this was a retrospective analysis of previously performed experiments; thus, the experimental design was not based on this study's purpose. Second, we used healthy animals, which may not represent the conditions leading to CA, since in clinical resuscitation, most patients with CA have underlying pathologies. Third, a clean capnogram was difficult to obtain during CPR because of numerous issues (device malfunction, leakage/occlusion of ventilation circuit, and ongoing CC effort) (9,25). The accuracy of our results may be related to the analysis of data from an animal model. To avoid the interference of gas oscillation in the ventilation tube caused by CC with CO_2 measurement, ITDs were also used to improve the accuracy of the V'CO_2 measurement. However, ITDs are not commonly used in clinical practice, following the current guidelines. Fourth, the results of this animal study may not be suitable for generalization to human patients. Nevertheless, the results show that the PV ratio may have potential applicability in clinical practice.

Conclusions

In this study, experimental porcine models of primary VF-related CA were used to show that the PV ratio was significantly lower during hyperventilation than under NV conditions. Additionally, this indicator changed rapidly in response to hyperventilation, reduced immediately after hyperventilation onset, and then slightly increased and stabilized at a low level after approximately 2 min. The PV ratio showed good performance in discriminating hyperventilation from non-hyperventilation (AUC =0.98).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Ethics Committee for Animal Experiments at the Peking Union Medical College Hospital approved the experimental protocol (XHDW-2019-023). All animals received humane care in accordance with the "principles of laboratory animal care" formulated by the Ministry of Science and Technology of the People's Republic of China.

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