

Effect of Acute Hyperoxia and Hypoxia on the Central Blood Volume in Patients with Chronic Pulmonary Diseases

Satoshi IKEDA, Yoshiyuki MIYAHARA and Tatsuji NAITO

The Second Department of Internal Medicine, Nagasaki University, School of Medicine

To investigate whether the central blood volume (CBV) reflects the pulmonary vasculature, we measured CBV before and after the inhalation of 100 % or 13 % O₂ for 15 min in patients with chronic pulmonary diseases. Using the Stewart-Hamilton technique, we measured CBV using a lung water computer, employing sodium as an indicator. Thirteen patients inhaled 100 % O₂, while 8 patients breathed 13 % O₂. Hyperoxia increased CBV significantly and the delta change in CBV (Δ CBV) correlated significantly with the change in total pulmonary resistance index (Δ TPRI; $r = -0.65$, $p < 0.02$), the change in mixed venous oxygen tension (Δ PvO₂; $r = -0.58$, $p < 0.05$) and the change in the coefficient of oxygen delivery (Δ COD; $r = 0.71$, $p < 0.02$). Hypoxic breathing caused little or no change in CBV, but Δ CBV correlated well with Δ TPRI ($r = -0.74$, $p < 0.05$) and Δ PvO₂ ($r = 0.85$, $p < 0.01$). Our results suggest that Δ CBV provides a good index of the pulmonary vascular bed, on which efficient gas-exchange occurs.

Key words: Central blood volume, hyperoxia, hypoxia, pulmonary vascular bed, pulmonary hypertension.

INTRODUCTION

The central blood volume (CBV), a concept first introduced by Stewart¹⁾ and Hamilton²⁾, is calculated by multiplying the mean circulation time of a non-diffusible indicator to the extravascular tissue, by the pulmonary blood flow. This volume strictly includes the blood in those vessels between the injection and collection points, although the majority of the volume is occupied by blood present in the heart and lung. Beckett et al.³⁾ reported that the induction of pulmonary embolism in dogs, using 0.15~0.2 mm glass beads, in a minimal dose of 0.32 gm/kg, caused a reduction in CBV, as measured by indocyanine green (ICG), to approximately 2 ml. They concluded that the CBV could, therefore, detect small changes in pulmonary blood volume. Furthermore, Noble et al.⁴⁾ described a sharp increase in CBV following the injection of dextran in dogs and the induction of pulmonary edema. Böck et al.⁵⁾ also reported a change in CBV with a change in blood body posture. These results suggest that the CBV has a good

sensitivity. We investigated in the present study whether CBV reflects the status of the pulmonary vasculature in patients with chronic pulmonary diseases, before and after acute hyperoxia or hypoxia.

SUBJECTS AND METHODS

Subjects (Table 1). We studied 21 patients who had been admitted to Nagasaki University Hospital. They consisted of 8 patients with pulmonary emphysema, 10 patients with pulmonary fibrosis and 3 patients with bronchial asthma. The diagnosis was based on medical history, physical examination, chest X-ray, chest CT, pulmonary tests, and histological examination of tissue specimens obtained by transbronchial or open lung biopsy. No patients had symptoms or signs of right-sided heart failure. Thirteen patients participated in the acute hyperoxic experiments while 8 patients were exposed to acute hypoxia. An informed consent was obtained from each patient before the study.

Methods. With the subject in the supine position, a 7-Fr. Swan-Ganz thermodilution catheter (Baxter Co. TF002H-7F) was placed percutaneously into the main pulmonary artery using the Seldinger technique. A 5-Fr. lung water catheter (Elecath HE 2900) was inserted into the femoral

Table 1 Pulmonary function tests of subjects

	mean \pm SD
Sex (male : female)	14 : 7
Age (years)	62.9 \pm 7.5
VC (l)	2.65 \pm 0.80
%VC (%)	88.3 \pm 21.3
FEV1.0 (l)	1.70 \pm 0.62
FEV1.0 % (%)	68.0 \pm 18.3
%DLco (%)	63.7 \pm 22.8
DLco/VA (ml/M/mmHg/l)	3.07 \pm 1.42
TLC (l)	4.52 \pm 1.49

%DLco, predict diffusing capacity for CO; DLco/VA, diffusing capacity for CO per alveolar volume

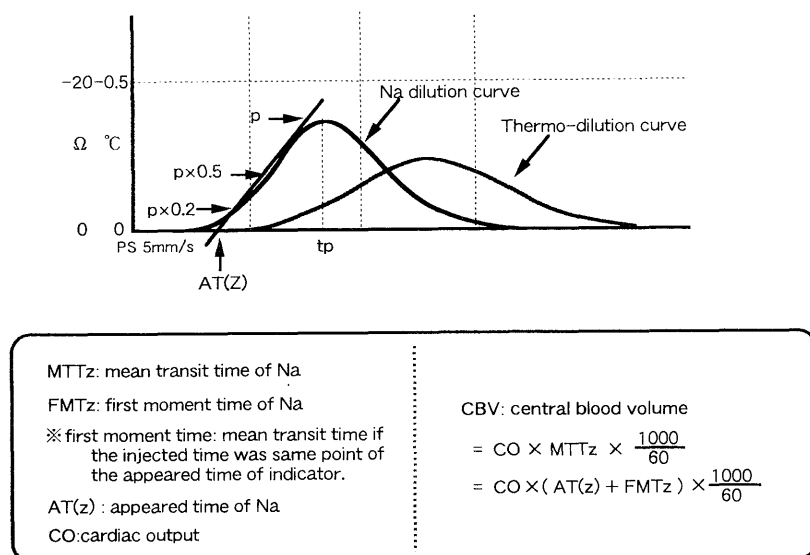


Figure 1. Calculation of CBV using the Na dilution curve.

artery and positioned at the level of the first lumbar spine in the abdominal aorta. Arterial and mixed venous blood gas samples were collected simultaneously and analyzed using a Ciba-Corning 288pH/Blood Gas Analyzer with a co-oxymeter 2500. The coefficient of oxygen delivery (COD)⁶⁾ was calculated using the following equations :

$$\text{COD} = \text{CaO}_2 / (\text{CaO}_2 - \text{CvO}_2)$$

$$\text{Where } \text{CaO}_2 = 1.34 \times \text{Hb} \times \text{SaO}_2 + 0.0031 \times \text{PaO}_2$$

$$\text{and } \text{CvO}_2 = 1.34 \times \text{Hb} \times \text{SvO}_2 + 0.0031 \times \text{PvO}_2$$

Hb, concentration of hemoglobin; SaO₂, arterial O₂ saturation; PaO₂, arterial O₂ tension; SvO₂, mixed venous O₂ saturation; PvO₂, mixed venous O₂ tension.

We also measured the cardiac output (CO) by the thermodilution technique, using a REF-1 ejection fraction/cardiac output computer (Edwards Critical Care Medicine). A sodium dilution curve was obtained, using a lung water computer (MTV-1100, Nihon Koden), by injecting 10 ml of 0 °C, 3 % NaCl into the right atrial lumen of the Swan-Ganz catheter. The central blood volume was calculated from the Na dilution curve, as illustrated in Figure 1. The total pulmonary resistance index (TPRI, resistance units, RU/m²) was calculated by dividing the mean pulmonary arterial pressure (MPAP, mmHg) by the cardiac index (CI, l/min/m²). The percent change in CBV, ΔCBV, was calculated as follows ;

$$\Delta \text{CBV} = (\text{test CBV} - \text{control CBV}) / \text{control CBV} \times 100$$

The change in other parameters was also calculated as mentioned above. Pulmonary function tests were performed with the patient in the sitting position, using the Autspirometer System 9 (Minato Medical Co.).

Protocol. After measuring pulmonary hemodynamic variables, blood gas data and CBV, the subject inhaled 100 % O₂ (13 patients) or 13 % O₂ with 87 % N₂ (8 patients) for 15 min, from a 150L Douglas bag, using a tight-fitting face mask. The test was repeated after a resting period of 15 min. No patient complained of dyspnea or palpitation or other symptoms during hypoxic and hyperoxic breathing.

Statistical analysis. The signed rank Wilcoxin test was used to examine for significant differences between control and test data. The correlation coefficient between CBV and the tested parameter was determined using the linear regression analysis. A difference was considered statistically significant when the *p* value was < 0.05. The average of triplicate measurements of CBV, CI and TPRI was used for each subject. Values are expressed as mean ± SD.

RESULTS

1) Inhalation of 100 % O₂ (Table 2) : Acute hyperoxia reduced MPAP significantly, and increased PaO₂, PvO₂ and COD significantly. The mean CI and TPRI tended to decrease, albeit insignificantly. Inhalation of hyperoxic gas mixture increased the mean CBV significantly, compared with the control. The increase in CBV was observed in all but one patient (Fig. 2). Furthermore, the ΔCBV correlated significantly with ΔTPRI (*r* = -0.65, *p* < 0.02), ΔPvO₂ (*r* = 0.58, *p* < 0.05) and ΔCOD (*r* = 0.71, *p* < 0.02) (Figs. 3).

2) Inhalation of 13 % O₂ (Table 3) : Hypoxic breathing increased MPAP, CI and TPRI significantly and caused a

Table 2 CBV, hemodynamic variables and blood gas data before and after 100 % oxygen inhalation.

	Before	After
CBV (ml/kg)	14.0±3.5	14.9±3.6*
MPAP (mmHg)	14.8±2.7	13.4±3.8*
CI (l/min/ m ²)	4.3±1.2	4.1±0.9
MBP (mmHg)	131.0±28.5	113.5±17.7
TPRI (RU/m ²)	3.75±1.44	3.53±1.52
HR (bpm)	82.4±10.5	79.2±9.5
PaO ₂ (torr)	85.8±14.7	421.4±53.7*
PaCO ₂ (torr)	34.9±4.1	35.5±5.5
PvO ₂ (torr)	40.5±4.6	56.6±8.7*
COD	4.87±1.16	6.39±1.66*

*P < 0.05

MPAP, mean pulmonary pressure ; CI, cardiac index ; MBP, mean body pressure ; TPRI, total pulmonary resistance index, HR, heart rate; PaO₂, arterial O₂, tension ; PaCO₂, arterial CO₂ tension ; PvO₂, mixed venous O₂ tension ; COD, coefficient of oxygen delivery

Table 3 CBV, hemodynamic variables and blood gas data before and after 13 % oxygen inhalation.

	Before	After
CBV (ml/kg)	19.0±4.6	18.7±4.0
MPAP (mmHg)	15.3±4.7	19.3±5.6*
CI (l/min/ m ²)	3.5±1.0	3.8±1.0*
MBP (mmHg)	100.4±21.4	96.3±20.4
TPRI (RU/m ²)	4.80±2.23	5.44±1.98*
HR (bpm)	69.1±11.6	71.9±10.7
PaO ₂ (torr)	83.6±8.0	40.0±3.5*
PaCO ₂ (torr)	34.7±4.8	33.3±3.7
PvO ₂ (torr)	37.7±2.3	28.3±2.1*
COD	3.78±0.55	3.46±0.47

*P < 0.05

MPAP, mean pulmonary pressure ; CI, cardiac index ; MBP, mean body pressure ; TPRI, total pulmonary resistance index, HR, heart rate; PaO₂, arterial O₂, tension ; PaCO₂, arterial CO₂ tension ; PvO₂, mixed venous O₂ tension ; COD, coefficient of oxygen delivery

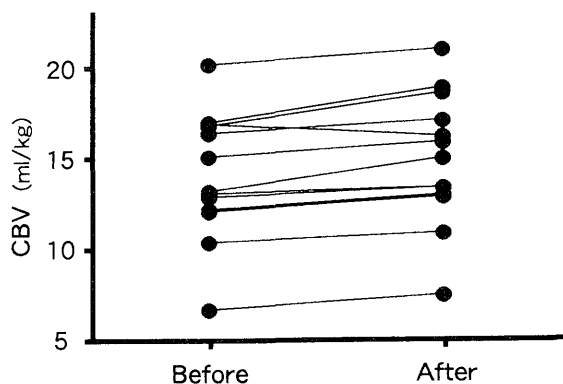


Figure 2. The change in CBV before and after administration of 100 % oxygen.

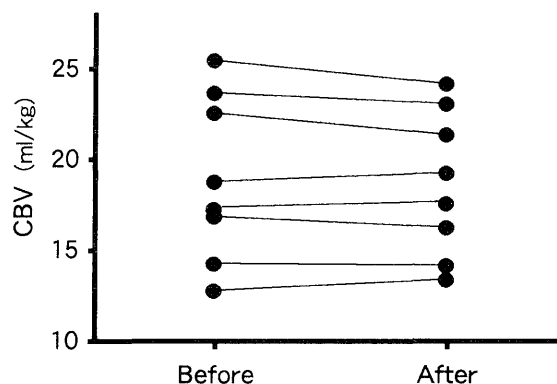


Figure 4. The change in CBV before and after inhalation of 13 % O₂.

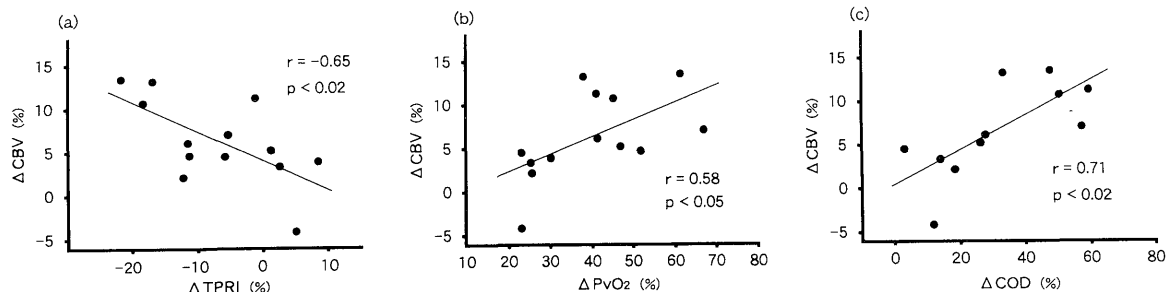


Figure 3. The relationship between ΔCBV and ΔTPRI (a), ΔPvO₂ (b), and ΔCOD (c) during breathing of 100 % O₂.

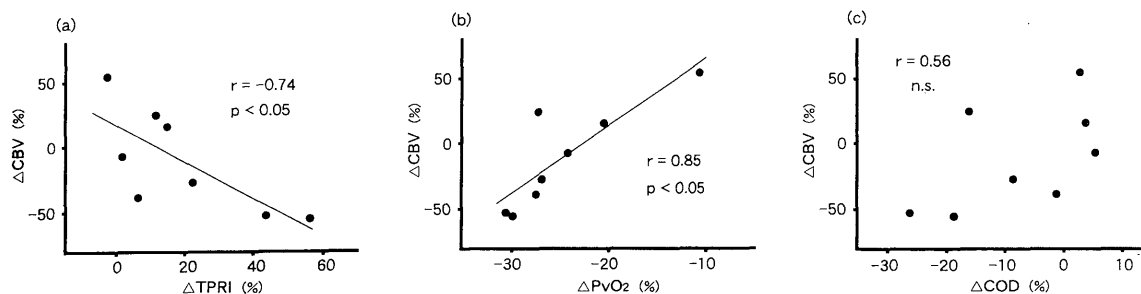


Figure 5. The relationship between Δ CBV and Δ TPRI (a), Δ PvO₂ (b), and Δ COD (c) during inhalation of 13% O₂

fall in PaO₂ and PvO₂. The CBV tended to decrease, albeit insignificantly, although it increased in 3 patients (Fig. 4). The Δ CBV increased with decreases in Δ TPRI ($r = -0.74$, $p < 0.05$), while it correlated positively with Δ PvO₂ ($r = 0.85$, $p < 0.01$) (Figs. 5a and 5b). In contrast, there was no relationship between Δ CBV and Δ COD (Fig. 5c). There was also no relationship between the control CBV level and other parameters, such as pulmonary function tests, blood gases and hemodynamic variables.

DISCUSSION

Sodium was used as the non-diffusible indicator in the present study for the following reasons, (a) the simple operation of the lung water computer (MTV-1100), (b) a satisfactory reproducibility of measurements⁷, (c) accuracy of measurements, compared with those made using other indicators. Noble et al.⁴ reported that the volume of sodium leaking to the extravascular tissue was less than that of ICG, and that CBV measured with Na (CBVNa) correlated well with CBV measured using ICG (CBVICG) although the level of CBVNa was slightly higher than that of CBVICG.

1) Inhalation of 100% O₂. The beneficial effect of oxygen therapy has already been demonstrated in patients with chronic pulmonary diseases and pulmonary hypertension (PH)^{8,9}. Not only this effect has been proved in long term use of oxygen, but also after a short term administration. In this regard, Ashutosh et al.¹⁰ suggested that the effect of acute hyperoxia was one of the important prognostic factors during treatment of patients with chronic pulmonary diseases. Holt et al.¹¹ reported that inhalation of O₂ caused a significant decrease in pulmonary arterial pressure and pulmonary vascular resistance, together with a small fall in the cardiac index, as tested in 13 patients with pulmonary emphysema. The investigators concluded that oxygen reduces pulmonary vasoconstriction. Wilson and Dempsey¹² demonstrated that acute hyperoxia decreased

the pulmonary arterial pressure in part due to a fall in the cardiac output and a decrease in pulmonary vascular resistance. Our results of a significant decrease in MPAP and the small reduction in CI and TPRI confirm these early findings. Furthermore, Hunt et al.¹³ demonstrated in 17 COPD patients that the administration of 100% O₂ increased the ratio of dead-space to tidal volume (VD/VT), causing a redistribution of pulmonary blood flow from the well ventilated areas to the poorly ventilated areas, as a result of a reduced hypoxic pulmonary vasoconstriction. Uchida et al.¹⁴ also demonstrated a redistribution of the pulmonary blood flow during the inhalation of 90% oxygen, as measured by the Krypton-81 m perfusion images. Our results demonstrated a significant increase in CBV in response to hyperoxia, and that Δ CBV correlated well with Δ TPRI, Δ PvO₂ and Δ COD. These results suggest that a change in CBV due to hyperoxia reflects an increased pulmonary vascular bed due to a redistribution of blood flow.

2) Inhalation of 13% O₂. In 1946, von Euler et al.¹⁵ were the first group of researchers to demonstrate the development of hypoxic pulmonary vasoconstriction and pulmonary hypertension during exposure of cats to 10% O₂. Several studies have also examined the vasoconstrictive effect of acute hypoxia on the pulmonary vasculature in humans^{8,10,16-22}. In general, the results of these studies indicate that acute hypoxia increases pulmonary arterial pressure. While Weitzemblem et al.²² reported a similar increase in pulmonary resistance, they also reported a large inter-individual variability.

On the other hand, exposure to hypoxia induces other cardiovascular changes. For example, Doyle et al.²¹ described a slight increase in CO in both normal adults and patients with cardiopulmonary diseases following the administration of 10% O₂. Furthermore, Naeije et al.¹⁷ reported that hypoxic breathing increased CO in normal subjects due to a lack of change in O₂ transport. It is of interest that patients with severe PH respond to acute hypoxia by increasing CO without modifying the

pulmonary vascular resistance while patients with a less severe PH develop a more severe vasoconstriction and increased vascular resistance without changing CO^{10} . In contrast, Motley et al.¹⁶ described a decrease in CO in four normal subjects and one patient with aortic valve regurgitation following inhalation of 10% O_2 . Thus, there is a discrepancy regarding the effect of acute hypoxia on CO. In present study, hypoxia increased MPAP, CO and pulmonary vascular resistance. However, hypoxia did not increase these parameters in all patients. Furthermore, the mean change in CBV was a decrease in its value, albeit insignificantly, although three patients did not develop a decrease in CBV while breathing 13% O_2 . A lack of a clear-cut effect of hypoxia on CBV was also reported by Fretts et al.¹⁶ and Doyle et al.²¹. We believe that the variability of Δ CBV in our study was due to (a) inter-individual differences in the extent of pulmonary vascular constriction²², (b) differences in the extent of pulmonary vascular involvement within the lung²³, (c) the recruitment of new lung regions caused by increased CO.

Our results indicated the presence of a significant correlation between Δ CBV and Δ TPRI and Δ Pv O_2 . Furthermore, changes in Pv O_2 correlated with changes in the volume of oxygen delivery. On the other hand, Pv O_2 reflected the level of PO_2 at the end of tissue capillaries²⁰. We assumed that Δ CBV represented an increase or decrease in the pulmonary vascular bed, on which efficient gas-exchange occurred. Furthermore, we believe that the lack of a correlation with Δ COD was probably due to a lack of effect of acute hypoxia on COD²⁰.

The control level of CBV did not relate with pulmonary function tests and pulmonary circulation. This is probably due to a large variability among subjects, age and their disease state.

CONCLUSIONS

We measured the central blood volume using the Stewart-Hamilton dilution technique and sodium as an indicator, while 100% or 13% O_2 was inhaled by patients with chronic pulmonary diseases. The Δ CBV correlated well with Δ TPRI and Δ Pv O_2 . Our results suggest that Δ CBV is a good index of the pulmonary vascular bed, on which efficient gas-exchange occurs.

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