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Increased FIO₂ Influences SvO₂ Interpretation and Accuracy of Fick-based Cardiac Output Assessment in Cardiac Surgery Patients: A Prospective Randomized Study

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Abstract

Background: The study aimed to reveal how the fraction of inspired oxygen (FIO₂) affected the value of mixed venous oxygen saturation (SvO₂) and the accuracy of Fick-equation-based cardiac output (Fick-CO).

Methods: Forty-two adult patients who underwent elective cardiac surgery were enrolled and randomly divided into two groups: FIO₂ <0.7 or >0.85. Under stable general anesthesia, thermodilution-derived cardiac output (TD-CO), SvO₂, PvO₂, hemoglobin, SaO₂, PaO₂, and blood pH levels were recorded before surgical incision.

Results: Significant differences in FIO₂ values were observed between the two groups (0.56 ± 0.08 in the <70% group and 0.92 ± 0.03 in the >0.85 group; $p < 0.0001$). The increasing FIO₂ values lead to increases in SvO₂, PvO₂, and PaO₂, with little effects on cardiac output and hemoglobin levels. When comparing to TD-CO, the calculated Fick-CO in both groups had moderate Pearson correlations and similar linear regression results. Although the FIO₂ <0.7 group presented a less mean bias and a smaller limits of agreement, neither group met the percentage error criteria of <30% in Bland-Altman analysis.

Conclusions: Increased FIO₂ may influence the interpretation of SvO₂ and the exacerbation of Fick-CO estimation, which could affect clinical management.

Trial Registration: [ClinicalTrials.gov](https://clinicaltrials.gov) ID number: NCT04265924. Retrospectively registered (Date of registration: February 12, 2020).

1 Background

Optimizing stroke volume and cardiac output (CO) can improve the outcome for patients undergoing major surgeries. The standard approach to estimating CO levels involves the use of a pulmonary artery catheter in conjunction with thermodilution based on the Stewart-Hamilton equation.[1] However, the invasiveness and inherent risks of this approach[2] have led to the development of alternative methods to measure CO levels.

The calculated cardiac output based on Fick principle (Fick-CO) has been widely adopted in catheterization and pediatric cardiology, particularly for patients with congenital heart diseases.[3] The Fick principle is based on the observation that total oxygen consumption ($\dot{V}O_2$) by the body is equal to the difference between the amount of oxygen leaving and returning to the lung. Note that pulmonary oxygen consumption is negligible.[4]

A number of researchers have reported a strong correlation between thermodilution-derived CO (TD-CO) and Fick-CO,[5, 6] while others have reserved comment on this issue.[7-9] To further investigate the discrepancy, however, there has been relatively little research on the influence of the variables related to oxygen content (e.g., PaO_2 ,

SvO₂, and PvO₂) in the Fick equation. These variables could be affected by the fraction of inspired oxygen (FIO₂), manifesting as variations in Fick-CO levels. Furthermore, the value of SvO₂ is also frequently used as an indicator of tissue perfusion adequacy. If different FIO₂ leads to different SvO₂ values, the clinical management may be affected. Therefore, in this study, we sought to clarify the influence of FIO₂ levels on SvO₂ and other variables in the Fick equation in patients undergoing cardiac surgery. We then assessed the influence of each variable on the accuracy of Fick-CO measurements.

2 Methods

2.1 Study Design

This prospective randomized study was approved by the Institutional Review Board of Chang Gung Memorial Hospital in Taiwan (registration number: 104-7177B) and was retrospectively registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (ID number: NCT04265924, date of registration: February 12, 2020). At the time of conducting this study, the contemporary trend favored high intraoperative FIO₂ to prevent surgical site infection; World Health Organization guidelines published in November 2016 further advocated 80% FIO₂ for surgical patients undergoing general anesthesia with tracheal intubation.[10] Hence, we assigned our patients randomly into two groups: the higher FIO₂ group (FIO₂ >0.85)

and the lower FIO₂ group (FIO₂ <0.7). According to our past observation and the results from previous relevant studies,[11, 12] with the assumption of a 5% difference of SvO₂ between the two groups in our study, the number of subjects required was 20 in each group (power =80% and α =0.05). In case of drop-outs, the determined target sample size was 50.

2.2 Participants

Adult patients (age $\geq$ 20 years) who underwent elective cardiac surgery and provided signed informed consent were included. Any patients with an intra-cardiac shunt were excluded.

2.3 Randomization

The enrolled patients were allocated randomly with a 1:1 ration into the higher FIO₂ group (FIO₂ >0.85) or the lower FIO₂ group (FIO₂ <0.7). Randomization was performed according to a computer-generated randomization number list, from 1 to 50, which was created before commencing the study by an independent statistician not involved in data analysis. In the time order of enrollment, each patient got his corresponding number on the list; odd number represented the higher FIO₂ group (FIO₂ >0.85), while even number was the lower FIO₂ group (FIO₂ <0.7).

2.4 Interventions

The drug selection and dosage used for anesthetic induction varied basing on clinical

conditions. After intubation, FIO₂ was adjusted based on the assigned group. General anesthesia was maintained using sevoflurane (1.5%–2.5%), fentanyl (0.5–2 µg/kg according to the clinical condition), and cisatracurium (2–4 mg/30 min). All patients were mechanically ventilated at a tidal volume of 8–10 mL/kg body weight at a respiratory rate of 8–14 per minute to maintain end-tidal CO₂ concentrations of 35–45 mmHg. Throughout the study, the oximeter values were maintained at ≥98%.

2.5 Data Collection

For every patient, a pulmonary artery catheter (PAC) was inserted into the internal jugular vein, and the position of the tip was confirmed by pressure waves and transesophageal echocardiography. The PAC was connected to a Vigilance II Monitor (Edwards Lifesciences, CA, USA) or an Abbott Q2 Plus CCO/ SvO₂ Computer (Abbott Laboratories, IL, USA) to obtain continuous measurements of TD-CO levels. Blood samples drawn from the PAC were used to monitor SvO₂ and PvO₂ levels. An arterial pressure catheter was inserted into the radial artery to allow analysis of Hb, SaO₂, and PaO₂ levels. All arterial and venous gas concentrations were derived using a NOVA Critical Care Xpress Blood Gas Analyzer (Nova Biomedical, Waltham, MA, USA), which was calibrated daily according to the manufacturer's instructions, and with regular maintenance every three months to ensure accuracy. Under stable general anesthesia with assigned FIO₂ for 30 minutes, data pertaining to TD-CO and blood

analysis (Hb, SvO₂, PaO₂, and PvO₂) were recorded prior to surgical incision, when patients were anesthetized stably. Meanwhile, we also recorded body temperature and pH values of arterial blood in consideration of their influences on V'O₂ and O₂-Hb dissociation.

2.6 Fick Equation

Fick-based CO is the ratio of V'O₂ to the difference between arterial (CaO₂) and venous (CvO₂) oxygen content, as follows:

$$CO \left(\frac{L}{min} \right) = \frac{V'O_2}{CaO_2 - CvO_2}$$

$$= \frac{V'O_2(ml/min)}{1.34 * Hb \left(\frac{g}{dL} \right) * (SaO_2 - SvO_2)(\%) * 10 + 0.03 * (PaO_2 - PvO_2)(mmHg)}$$

The standard approach to obtaining CO levels is the direct Fick method; however, this is impractical in a clinical setting due to its complexity to obtain V'O₂ measurements directly. In addition, when FIO₂ exceeds 0.6, measurements of V'O₂ tend to be inaccurate.[13, 14] Thus, we adopted the indirect Fick method. The estimated V'O₂ values were obtained from the LaFarge equation[15] as below:

Male: $V'O_2(ml/min/m^2)$

$$= 138.1 - 11.49 * \log age (years) + 0.378 * HR (beats/min) * BSA(m^2)$$

Female: $V'O_2(ml/min/m^2)$

$$= 138.1 - 17.04 * \log age (years) + 0.378 * HR (beats/min) * BSA(m^2)$$

2.7 Statistical Analysis

All statistical analysis was performed using SPSS (version 22.0, SPSS Inc., Chicago, IL, USA). A paired t-test was used to determine the statistical significance of differences between two independent sets of continuous variables. The Pearson correlation coefficient and simple linear regression analysis were used to evaluate the correlation between Fick-CO and TD-CO. The degree of agreement and bias between the Fick-CO and TD-CO were evaluated using Bland–Altman analysis corrected for repeated measures.[16] Percentage errors were calculated as 1.96 times the standard deviation of the bias divided by the mean CO of the reference method (TD-CO). A percentage error of <30% was considered acceptable.[17] For all statistical analysis, $p < 0.05$ was considered statistically significant.

3 Results

Fifty patients were enrolled between December 2015 and June 2016. Eight of them were excluded due to an intra-cardiac shunt newly found by trans-esophageal echocardiography during the surgeries (Figure 1). A total of 42 patients underwent final analysis. Patient characteristics are listed in Table 1. Each of the groups ($\text{FIO}_2 > 0.85$ and $\text{FIO}_2 < 0.7$) included 21 patients. Fick-CO and TD-CO levels were recorded prior to incision. The TD-CO values in the two groups were similar (Table 1). During the study period, none of the patients needed inotropes.

Table 1. Patient Characteristics

		Higher-FIO ₂ Group (FIO ₂ >0.85, n=21)	Lower-FIO ₂ Group (FIO ₂ <0.7, n=21)
Preoperative Data	Age (years)	60 ±13	63 ±13
	Gender (M/F)	12/9	16/5
	Ejection Fraction (%)	65 ±13	56 ±17
	Pulmonary Hypertension: Moderate/Severe	3/0	4/1
	Ventilatory Impairment in Pulmonary Function Test: Moderate/Severe	4/1	6/1
	HTN	10	10
	DM	8	11
	CVA history	2	3
	ESRD	2	2
Operation	CABG	9	11
	Valve	10	10
	Aortic Root	2	0
TD-CO		3.6 ±1.5	3.6 ±
<p>NOTE: Data are expressed as mean ± standard deviation or number. The preoperative ejection fraction values were statistically nonsignificant different between the two groups (p =0.324).</p> <p>Abbreviation: FIO₂, fraction of inspired oxygen; HTN, hypertension; DM, diabetes mellitus; CVA, cerebrovascular accident; ESRD, end stage renal disease; CABG, coronary artery bypass grafting; TD-CO, cardiac output measured through thermodilution.</p>			

3.1 Effects of FIO₂ on SvO₂, PaO₂, and PvO₂

Significant differences in FIO₂ values were observed between the two groups (0.92 ±0.03 in the >0.85 group and 0.56 ±0.08 in the <0.7 group; p <0.0001); however, no significant differences in V'O₂, body temperature, pH, or Hb values were observed (Table 2). SvO₂, PaO₂, and PvO₂ values were significantly higher in the FIO₂ >0.85

group, and the difference between PaO₂ and PvO₂ was statistically pronounced (Table 2; $p = 0.009$, $p < 0.0001$, $p = 0.007$, and $p < 0.0001$, respectively).

Table 2. Results of Each Variables and Statistical Significance (p value) between 2 Groups

Parameter	Higher -FIO ₂ Group (FIO ₂ > 0.85, n=21)	Lower -FIO ₂ Group (FIO ₂ < 0.7, n=21)	P value
FIO ₂	0.92 ± 0.03	0.56 ± 0.08	<0.0001
BT	36.1 ± 0.6	36.2 ± 0.5	0.974
pH	7.4 ± 0.0	7.4 ± 0.0	0.151
V'O ₂	156.0 ± 13.6	158.8 ± 10.2	0.456
Hb	12.3 ± 1.5	11.6 ± 1.1	0.113
SvO ₂	85.1 ± 5.6	79.9 ± 6.4	0.009
PaO ₂	402.9 ± 71.8	236.4 ± 102.9	<0.0001
PvO ₂	53.0 ± 7.1	47.3 ± 5.1	0.007
PaO ₂ -PvO ₂	349.0 ± 73.0	189.0 ± 100.4	<0.0001
NOTE: Data are expressed as mean ± standard deviation. Abbreviation: FIO ₂ , fraction of inspired oxygen; BT, body temperature (°C); V'O ₂ , oxygen consumption (ml/min/m ²); Hb, hemoglobin (g/dL); SvO ₂ , mixed venous oxygen saturation (%); PaO ₂ , partial pressure of arterial oxygen (mmHg); PvO ₂ , mixed venous oxygen tension (mmHg).			

3.2 Effects of FIO₂ on the Accuracy of Fick-CO

As indicated by the Pearson correlation coefficient (PCC) values in Table 3, both of the groups had a moderate correlation to TD-CO, as follows: FIO₂ > 0.85 group (PCC = 0.475; $p < 0.05$) and FIO₂ < 0.7 group (PCC = 0.490; $p < 0.05$). As shown in Fig. 2, both of the groups presented a similar linear regression result between Fick-CO and TD-CO, as follows: FIO₂ > 0.85 group ($r^2 = 0.225$) and FIO₂ < 0.7 group ($r^2 = 0.24$). Nevertheless, as shown in Fig. 3, Bland-Altman analysis revealed a greater discrepancy between Fick-

CO measurements and TD-CO values in the FIO₂ >0.85 group than in the FIO₂ <0.7, as follows: FIO₂ >0.85 group (mean bias = 1.17; limit of agreement = -1.81~4.15; and percentage error = 82.00%) and FIO₂ <0.7 group (mean bias = 0.89; limit of agreement = -0.78~2.56; and percentage error = 46.02%). Neither group met the percentage error criterion of <30%.

Table 3. Results and Statistics between Fick-CO and TD-CO

	Higher-FIO ₂ Group (FIO ₂ >0.85, n=21)		Lower-FIO ₂ Group (FIO ₂ <0.7, n=21)	
	Fick-CO	TD-CO	Fick-CO	TD-CO
Mean ±SD	4.8 ±1.4	3.6 ±1.5	4.5 ±1.0	3.6 ±0.6
Pearson Correlation (p value)	0.475 (0.03)		0.490 (0.024)	
NOTE: Data are expressed as mean ± standard deviation. Abbreviation: Fick-CO, cardiac output calculated by Fick method; TD-CO, cardiac output measured through thermodilution; FIO ₂ , fraction of inspired oxygen.				

4 Discussion

Our results reveal that increasing FIO₂ values leads to increases in SvO₂, PvO₂, and PaO₂ as well as a more pronounced difference between partial arterial and venous oxygen pressure (PaO₂-PvO₂), with little or no effect on cardiac output and hemoglobin levels. The increase in these values was shown to increase the effects of bias and the percentage error of Fick-CO when using TD-CO as the reference standard. These results indicate the non-negligible influence of FIO₂ on the clinical interpretation of SvO₂ and Fick-CO values.

4.1 Increased FiO₂ vs. SvO₂

Mixed venous oxygen saturation reflects the balance between oxygen consumption and delivery, clinically used as a surrogate for tissue perfusion adequacy. This indicator is sensitive to cardiopulmonary instability. A pronounced decrease in SvO₂ has been associated with severe impairments in cardiopulmonary circulation,[18] whereas a low and therapy-unresponsive SvO₂ value is predictive of poor outcomes.[19, 20] Thus, many guidelines suggest using SvO₂ to guide therapy, and a number of researchers suggest maintaining SvO₂ (or central venous saturation, ScvO₂) above 70% to reduce morbidity and mortality.[21-23] Improvements in SvO₂ values often indicate the suitability and timeliness of treatments.

Nonetheless, many situations can lead to an increase in SvO₂ levels, such as hyperdynamic sepsis,[24] intracardiac shunts,[25] liver failure,[26] excessive inotropic administration,[27] and increased carboxyhemoglobin levels.[26, 28] Our findings indicate that an increase in FIO₂ leads to elevated SvO₂ levels, which is consistent with previous studies.[11, 12, 29, 30] Perry *et al.* reported that each 100 mmHg increase in PaO₂ led to a 4.9% increase in SvO₂, despite a constant CO.[30] The possible explanation is that hyperoxia may reduce V'O₂[31] through mechanisms such as a decrease in myocardial oxygen consumption[32] or a reduction in the metabolism of cells and tissues.[33, 34] Besides, hyperoxia has been shown to increase arteriolar

constriction,[35, 36] reducing functional capillary density and nutritive organ blood flow, leading to a subsequent decrease in peripheral oxygen delivery, which can contribute to a reduction in $V'O_2$. A reduction in $V'O_2$ would tend to increase residual oxygen levels and PvO_2 . Even if there were no changes in oxygen delivery, Perry *et al.* proved that during hyperoxia, there could be an increase in SvO_2 levels due to an increase in tissue oxygen tension (via the Fickian diffusion of excess dissolved oxygen), resulting in elevated PvO_2 values.[30] A modest increase in PvO_2 could lead to a significant increase in SvO_2 due to the sigmoid shape of the oxygen-Hb dissociation curve.[12] Ultimately, the affected value of SvO_2 caused by increased FIO_2 could conceal a situation involving insufficient oxygen delivery, thereby hindering therapy. Therefore, whenever SvO_2 is used as an indicator to evaluate tissue perfusion or the adequacy of measures aimed at resuscitating critically ill patients,[21-23, 37] it is necessary to take FIO_2 values into account as well as their effect on SvO_2 .

4.2 Increased FIO_2 vs. Fick-CO

An increase in FIO_2 can affect a number of variables in the Fick-CO equation (SvO_2 , PvO_2 , PaO_2 , and $PaO_2 - PvO_2$), which could influence the accuracy of Fick-CO calculations. In this study, all of these values were significantly higher in the $FIO_2 > 0.85$ group than in the $FIO_2 < 0.7$ group. Omitting the difference between PaO_2 and PvO_2 in the denominator of the fraction, as in a number of previous studies,[5, 6, 38] would lead

to an even greater error in Fick-CO estimation, particularly in cases of hyperoxia.

In a similar study on swine, Perry *et al.* evaluated the accuracy of Fick-CO assessments with an increase in FIO₂, [30] while their conclusions contradict our findings. Further analysis of their data revealed that the SvO₂ values were much lower in swine ($58.2 \pm 7.27\%$ under FIO₂ = 0.6, and $61.0 \pm 6.7\%$ under FIO₂ = 0.8) than in the humans in the current study ($79.9 \pm 6.4\%$ under FIO₂ = 0.56, and $85.1 \pm 5.6\%$ under FIO₂ = 0.92). The disparity leads to the different results obtained in the two studies.

One possible reason for the impact of FIO₂ on the Fick-CO estimation is measurement error. Previous studies have reported that a 10% increase in SvO₂ would result in an observed erroneous 32.8% increase in Fick-CO estimates, which would become increasingly prominent with a decrease in the difference between arterial oxygen content and venous oxygen content (CaO₂-CvO₂). [39] This underlines the importance of accounting for the value of FIO₂ in any research based on Fick-CO. In short, any discussion pertaining to the clinical utility of Fick-CO must take the effects of FIO₂ into consideration.

4.3 Limitations

In this prospective study, we used the LaFarge equation to estimate V'O₂ instead of obtaining measurements directly, which was the primary limitation of this study. Note that we opted for this approach due to the fact that V'O₂ measurements are prone to

inaccuracy when $\text{FIO}_2 > 0.6$. [13, 14] Further study will be required to determine the means by which changes in $\text{V}'\text{O}_2$ alter Fick-CO estimates under elevated FIO_2 levels.

5 Conclusions

An increase in FIO_2 leads to increases in SvO_2 , PvO_2 , and PaO_2 . The hyperoxia-influencing value of SvO_2 may conceal insufficient oxygen delivery, which could affect clinical management. Increases in SvO_2 , PvO_2 , and PaO_2 could also exacerbate errors in Fick-CO estimates. Thus, the influence of FIO_2 should be considered in any study based on Fick-CO.

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Figure Legends

Figure 1. Study Flow Chart

Figure 2. Simple Linear Regression between Fick-CO and TD-CO. The continuous line indicates the regression line, and the striped lines are the 95% confidence interval. Each dot represents a patient.

Figure 3. Bland-Altman Analysis for Fick-CO and TD-CO Measurements. The continuous line indicates the mean bias, the striped lines are the 95% limit of agreement, and the dotted line is the value of 0. Each dot represents a patient.

Disclosures and Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the Chang Gung Medical Foundation Institutional Review Board in Taiwan (registration number: 104-7177B) and with the 1964 Helsinki declaration. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Availability of data and materials

The data used and analyzed in this study are not publicly available, but are available from the corresponding author if there is a reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SYL contributed to the study design, data collection, interpretation of the results, manuscript preparation, tables and figures preparation. FCC contributed to the study design, data collection, and interpretation of the results. JRL analyzed and interpreted the patient data. AHC contributed to the study design, data collection, and interpretation of the results. YFT contributed to the study design and interpretation of the results. CCL contributed to the study design and interpretation of the results. YCL contributed to the interpretation of the results and manuscript preparation. CYC contributed to the study design, data analysis, interpretation of the results, and manuscript preparation. All authors read and approved the final manuscript.

Figures

Figure 1

Study Flow Chart

Figure 2

Simple Linear Regression between Fick-CO and TD-CO. The continuous line indicates the regression line, and the striped lines are the 95% confidence interval. Each dot represents a patient.

Figure 3

Bland-Altman Analysis for Fick-CO and TD-CO Measurements. The continuous line indicates the mean bias, the striped lines are the 95% limit of agreement, and the dotted line is the value of 0. Each dot represents a patient.