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An algorithm to improve the estimation accuracy of a non-invasive method for cardiac output measurement based on prolonged expiration

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Abstract— **Cardiac output (CO) monitoring is important in the hemodynamic management of critically ill patients. In a previous study, a novel non-invasive technique for CO monitoring based on prolonged expiration was proposed. The novel method showed good agreement with thermodilution on stable mechanically ventilated patients; unstable patients were excluded.**

The aim of this study is to improve the outcome of the above mentioned method on hemodynamic unstable patients, requiring vasoactive medications, and showing marked cardiogenic oscillations on waveforms related to expired gases.

This prospective study has been carried out on three cardiac surgery patients; eighteen CO measurements were performed on each patient, and these values were compared with data obtained by thermodilution.

The designed and tested algorithm allowed to reach a good agreement between CO measured by our method and by thermodilution (e.g., the mean percentage differences were 4%, 11% and 3%). Even though further validation is necessary, the results are quite promising and the adopted solution appears to allow the suitability of the prolonged expiration method also on unstable patients.

I. Introduction

The monitoring of cardiac output (CO) plays an important role in the hemodynamic management of critically ill patients. The most widely used methods to measure CO are the pulmonary artery thermodilution, regarded as the current clinical gold standard, and the Fick method. They are both invasive and are increasingly criticized because of their unclear risk– benefit ratio [1]. In order to overcome the risks related to the invasivity, several researchers focused their attention on the development of novel non-invasive or minimally invasive techniques, such as transesophageal Doppler [2] and dye dilution [3]. These methods present the advantage related to the decreasing of invasivity, on the other hand, they are affected by two main concerns: the need of expensive devices and low performances in terms of accuracy and reproducibility, as reported in the meta-analysis of Peyton *et al.* [3].

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In two previous studies [4,5] a novel non-invasive method to measure CO value in artificially ventilated patients has been described. It allows to calculate the denominator of Fick equation providing a non-invasive CO estimation. The algorithm processes the experimental trends of CO_2 and O_2 concentrations during normal breathing and when the CO_2 elimination process is perturbed by inducing a prolonged expiration. Our study differs from other Fick-based methods regarding the solution adopted to perturb the CO_2 elimination process: other studies obtain this goal by changing minute ventilation [6] or breathing frequency [7]; we obtained this perturbation by inducing a prolonged expiration using an *ad hoc* designed pneumatic resistance.

Previous experiments were carried out on hemodynamic stable patients, and results showed CO values obtained with the proposed method (CO_K) in good agreement with values obtained by thermodilution (CO_T). Since we identified cardiogenic oscillations in the concentration of expired gases flow as a potential source of error, hemodynamic unstable patients and patients with marked oscillations of gas concentration were excluded. The cardiogenic oscillations, are related to cardiac-induced variations in relative gas flows from upper and lower zones of the lungs due to pulsatile blood flow [8]. The phenomenon of oscillations can be significant in unstable patients and causes irregularities in the waveforms of CO_2 and O_2 partial pressure [9], which are the data processed by the algorithm to estimate CO.

The aim of this work is to introduce a solution, which extends the applicability of our algorithm to patients with marked cardiogenic oscillations in the trends of CO_2 and O_2. In order to reach this goal, a mathematical processing of CO_2 and O_2 raw experimental data is implemented. The new algorithm has been assessed on three unstable patients for a total number of 54 CO measurements. These values were compared with data obtained by the clinical gold standard of thermodilution. Results obtained could be useful in order to improve also other algorithms currently under research.

II. Description of the Algorithm, Patients and Methods

Three adult patients were enrolled in this prospective comparative study after cardiac surgery. They were endotracheally intubated and ventilated by Servo-I ventilators (Maquet Gmbh & Co. KG). During the post-surgery treatment in Intensive Care Unit, CO was measured by both the non-invasive approach and by thermodilution.

The measurements based on thermodilution have been obtained by the introduction of a Swan-Ganz catheter, which

was interfaced to a monitor (Vigilance II, Edwards Lifesciences). We performed eighteen measurements for each patient using this monitor, which provides a semi-continuous calculation of CO.

The non-invasive CO measurements were carried out by using the procedure briefly described in the following.

CO can be expressed as a function of the blood volume participating in gas exchange, i.e., the pulmonary blood flow (PBF):

$$CO = \frac{PBF}{1-F} \tag{1}$$

where F is the shunting factor and can be obtained by iso-shunt diagrams [10].

As reported in our previous studies [4, 5], PBF can be obtained by applying the Fick principle to CO_2:

$$PBF = \frac{\dot{V}_{CO2}}{S\left(P_V CO_2 - P_a CO_2\right)} \tag{2}$$

being V_{CO2} the CO_2 volume produced by the patient in unit of time, S the CO_2 solubility in blood (assumed equal to 4.7 $mL \cdot L^{-1} \cdot mmHg^{-1}$), P_aCO_2 and P_vCO_2 the partial pressure of CO_2 in the arterial and venous blood, respectively.

In order to non-invasively estimate CO, we focused our attention on the estimation of the denominator of (2), by improving an algorithm developed by Kim *et al.* [11].

The estimation of PBF (2) is based on the analysis of gases. The analysis is carried out, during a normal breathing and a prolonged expiration, by a metabolic monitor (Quark RMR, Cosmed srl), that was previously characterized [12, 13]. The prolonged expiration was induced by using a two-branch element with an *ad hoc* designed pneumatic resistance, as described in detail in [4].

As schematically reported in the left side of Fig. 1, the monitor provides the values of CO_2 and O_2 partial pressure in the expired gas by sampling the gas from the breathing circuit; these values are considered equal to the alveolar ones (P_ACO_2 and P_AO_2). The algorithm, developed in LabVIEW® environment (National Instruments Corporation), processes the data in three consecutive steps:

1) it performs a quadratic regression between P_ACO_2 and P_AO_2, contained in the gases during the prolonged expiration, than calculates the slope, *s*, of the parabola. To calculate the best fitting parabola, we used only the points where the P_ACO_2 value is higher than 60% of its maximum value, in order to not consider gases coming from the dead space;

2) the values of *s* is used to calculate the instantaneous exchange ratio, *R*, by the following equation:

$$R = \frac{s - F_I O_2 \cdot s - F_I CO_2}{1 - F_I O_2 \cdot s - F_I CO_2} \tag{3}$$

where F_IO_2 and F_ICO_2 are the inspiratory fractions of O_2 and CO_2, respectively;

3) it performs the linear regression between R and P_ACO_2; afterwards, starting from the fitting line, it calculates P_vCO_2 (considered equal to the P_ACO_2 value at which R=0.32 for the Haldane effect) and P_aCO_2 (considered equal to the P_ACO_2 value, at which R=RQ, where RQ is the mean value of R calculated during a normal breathing).

It emerges that the experimental trends of P_ACO_2 and P_AO_2, as a function of time, play a crucial role in the reliability of CO estimation because their values are used in the first step of the algorithm in order to obtain *s*. The algorithm was not able to measure CO in hemodynamically unstable patients, requiring vasoactive medications, because they presented marked oscillations in P_ACO_2 and P_AO_2 trends, as also reported in [5].

In order to overcome this concern, we introduce a further step to the algorithm (right side of fig. 1), which consists of an exponential fitting of the trend in time of $FeCO_2$ and FeO_2. The curves used to fit the experimental data are:

$$y = A \cdot \exp\left(-B \cdot t\right) + C \tag{4}$$

being A, B and C three empirically calculated constants, y represents the concentration [%] of O_2 or CO_2.

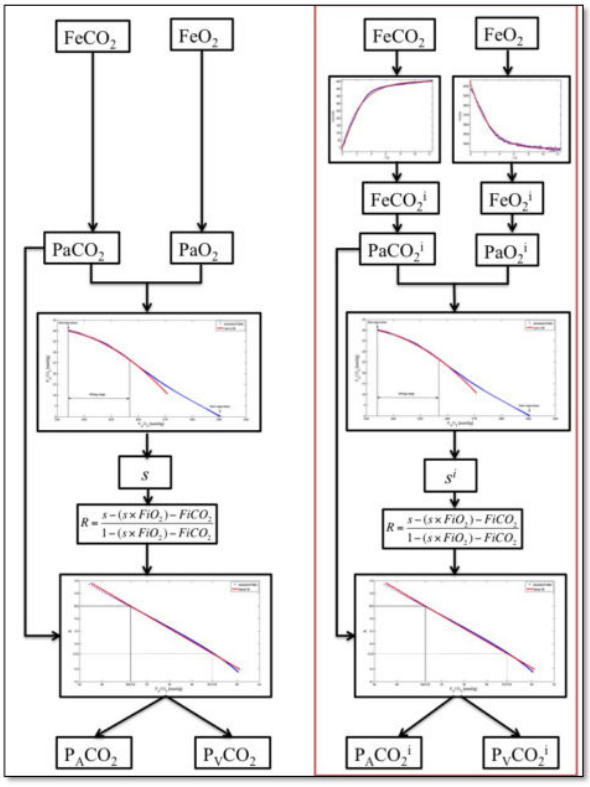

Figure 1. Left side: schematic of the algorithm used to estimate CO in [4,5]; right side: algorithm used in this work.

The values of P_ACO_2 and P_AO_2 provided by the fitting ($P_ACO_2^i$ and $P_AO_2^i$) were used to perform the three steps of the above described algorithm. This solution allows to remove the oscillations in the trends of P_ACO_2 and P_AO_2 and gives the chance to estimate CO on unstable patients, as reported in Section III.

The manoeuvre of prolonged expiration was executed 18 times for each patient. In order to allow the recovery of the steady conditions by the patient, we waited for about 2 minutes between consecutive manoeuvres.

In summary, we performed eighteen measurements with thermodilution each of one followed by a non-invasive measurement. This protocol was repeated for all three patients.

III. Results and Discussion

In this research, the algorithm described in the previous section is applied to estimate CO on three mechanically ventilated patients requiring high doses of vasoactive medications (>5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of dopamine or dobutamine). CO has been measured eighteen times by our method (CO_K) and by thermodilution (CO_T), for all patients. In each trial, P_ACO_2 and P_AO_2 in the gases sampled during prolonged expiration showed marked oscillations. By way of example the experimental trends of P_ACO_2 and P_AO_2 obtained during a prolonged expiration are reported in figure 2.A and 2.B. They start with an initial period of about 7 s where CO_2 and O_2 values remain almost constant. During this period, gas which does not participate to alveolar gas exchange is sampled, being contained in the volume between the upper respiratory airway and the lungs. After this period, P_ACO_2 shows an increasing trend, on the other hand P_AO_2 shows a decreasing trend. Moreover, the waveforms show marked cardiogenic oscillations.

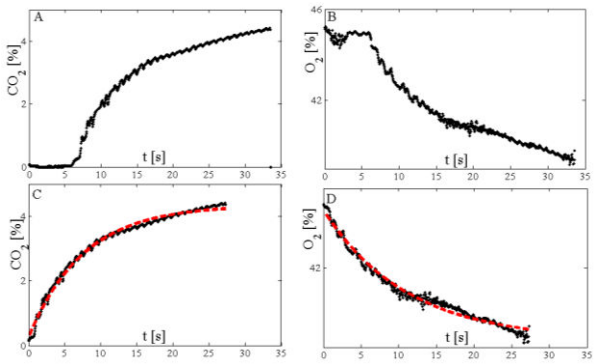

Figure 2. Experimental trends of P_ACO_2 and P_AO_2 during the entire prolonged expiration (A and B); experimental data without dead space and best fitting curves (4) are also reported (C and D).

In order to obtain reliable measurements of CO, the exponential fitting (4) was carried out on the P_ACO_2 and P_AO_2 trends, as reported in Fig. 2C and 2D; the first part of the trends, where P_ACO_2 and P_AO_2 remain constant, was not considered. The experimental results agrees with the fitting curves (4), as shown in Fig. 2C and 2D; this is confirmed by the high correlation coefficients between the experimental values and the best fitting curves for both P_ACO_2 and P_AO_2 (r^2>0.96 for all 54 trials).

Data obtained by the exponential fittings are used to perform the other three steps of the algorithm.

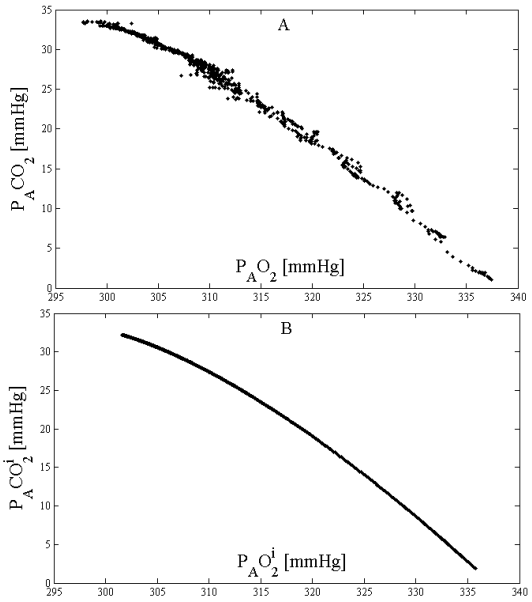

Figure 3. A) Experimental trend of P_ACO_2 vs P_AO_2; B) trend of data obtained by means of the exponential fittings ($P_ACO_2^i$ vs $P_AO_2^i$).

The trends obtained by implementing the exponential fitting ($P_ACO_2^i$ *vs* $P_AO_2^i$) show a more regular trend (P_ACO_2 *vs* P_AO_2) than raw data; a comparison between these two trends is reported in Fig. 3A and 3B. This solution allows to estimate CO also in the three patients with marked cardiogenic oscillations.

The differences (ΔCO) between CO values estimated by our approach (CO_K) and the value obtained by thermodilution (CO_T) are calculated for all 54 measures (Fig. 4A). Also the Bland Altman plot is reported (Fig. 4B).

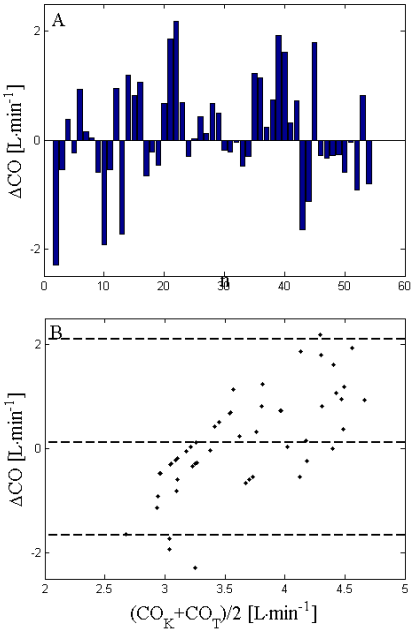

Figure 4. A) Differences (ΔCO) between CO_K and CO_T in all 54 measures; B) Bland Altman plot: ΔCO values are reported on the y axis, the mean between CO_K and CO_T are reported on the x axis. The mean ΔCO and the limit of agreement are reported with dashed lines.

The good agreement between CO_K and CO_T is confirmed by the low value of their mean difference considering all the

measurements (i.e., 0.11 L·min^{-1}), and by the low value of the differences considering the single trials: about the 80% of the percentage differences are lower than 30%, that is the value recommended by Peyton *et al.* [4]. With the aim to spotlight the improvement of CO estimation accuracy obtained by introducing the exponential fitting, we performed the CO calculation by the algorithm reported in [4,5] which did not use the exponential fitting. On these unstable patients, results show that only the 40% of the percentage differences are lower than 30% (*vs* the abovementioned 80% obtained using the exponential fittings).

Table I reports the mean values of CO_K and CO_T, the absolute value of their differences, $|\Delta CO|$, and the percentage differences, $\Delta CO_{\%}$, considering the three patients. Also the uncertainty has been calculated by using a Student reference distribution and a level of confidence of 95 %, as recommended in [14].

TABLE I. MEAN VALUES AND UNCERTAINTIES OF CO_K AND CO_T FOR THE THREE PATIENTS. THEIR DIFFERENCES ARE ALSO REPORTED.

	$CO_K \pm \delta CO_K$ [L·min^{-1}]	$CO_T \pm \delta CO_T$ [L·min^{-1}]	$\lvert \Delta CO \rvert$ [L·min^{-1}]	$\Delta CO_{\%}$ [%]
P_1	3.9±0.5	4.1±0.1	0.2	4%
P_2	3.6±0.3	3.2±0.05	0.4	11%
P_3	3.6±0.5	3.5±0.04	0.1	3%

A further encouraging result emerges from the analysis of the mean percentage differences between CO_K and CO_T: their values are low for all three patients (i.e., 4%, 3%, and 11%). This negligible difference between CO_K and CO_T on unstable patients is the main finding of the present work, showing values in line with the results reported by Peyton *et al.* [3].

Moreover, the difference with our technique is lower than the difference reported by Killick and Parkin [15]: they report a bias of -0.60 L·min^{-1} *vs* our result of 0.11 L·min^{-1}.

IV. CONCLUSION

In this work a solution to improve the outcome of a previously described [4,5] non-invasive method to monitor CO is presented. In particular, we introduce a further step in the algorithm allowing to monitor CO also in patients, requiring high doses of vasoactive medications and showing marked cardiogenic oscillations in P_ACO_2 and P_AO_2 trends. In this prospective study we enrolled three patients and carried out 54 measurements (18 for each patient) with our non-invasive approach (CO_K). These values were compared with results obtained by thermodilution (CO_T). The good agreement between CO_K and CO_T and other advantages of our method (e.g., the non-invasivity of the method, the measurements can be carried out at short interval of time) encourage to carry out further investigation.

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