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Transpulmonary dilution system identification for pulmonary blood volume measurements by contrast echocardiography

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Abstract— **Pulmonary blood volume (PBV) is an important parameter to assess the condition of the lungs and the transpulmonary circulation. Unfortunately, its measurement is limited by the need for central catheterization. Contrast ultrasonography allows overcoming this problem. A small bolus of ultrasound contrast agent is injected in a peripheral vein and its passage through the right ventricle and left atrium is detected non-invasively by an ultrasound transducer. The PBV is then given by the product of the mean transit time (MTT) of the contrast between the two measurement sites times the cardiac output. The MTT is estimated by specific model interpolation of the measured dilution curves. In this paper we present a new method for PBV measurements based on a system identification approach. This method identifies the parameters of the model that represents the dilution system impulse response. No subsequent model interpolation is needed. The local density random walk model is adopted to represent the transpulmonary dilution system. Volume measurements show accurate in-vitro results with a correlation coefficient higher than 0.99. The clinical feasibility is confirmed by 70 measurements in patients. Beyond an accurate quantification of pulmonary blood volume, the proposed method also permits the characterization of the transpulmonary hemodynamics, possibly adding novel diagnostic value to the measurement.**

I. Introduction

The Pulmonary Blood Volume (PBV) assessment provides valuable information on the cardiovascular and pulmonary condition [1]. Unfortunately, PBV can only be measured in operating rooms, since it requires a double central catheterization. A bolus of dye or cold saline is injected in the pulmonary artery and detected in the aorta or left ventricle. The mean transit time (MTT) of the bolus is then derived by analysis of the detected indicator dilution curve (IDC) and multiplied times the cardiac output (CO) for the PBV assessment.

The injection of an ultrasound contrast agent (UCA) bolus allows an IDC echographic measurement, resulting in a minimally invasive technique. UCAs are microbubbles (diameter from 1 to 10 μm) encapsulated in a shell of biocompatible material [2]. When invested by an ultrasonic beam, UCAs oscillate and backscatter a large part of the acoustic energy [3]. As a result, UCAs are easily detected by an ultrasound transducer. Their passage in a specific region of interest (ROI) can be detected versus time by B-mode ultrasound imaging to derive an UCA IDC.

Two IDCs can be measured in the right ventricle (RV) and left atrium (LA). The detected ICDs can be interpolated by specific models to estimate the MTT of the contrast between the RV and LA. The PBV can be directly derived as the product between MTT and CO. In [4] this approach is proposed and the Local Density Random Walk (LDRW) model adopted for the curve interpretation. This model provides the most accurate IDC interpolation and volume measurements as well as a representation of the dilution process based on fluid-dynamics laws [5]–[8]. In fact, the LDRW model is a solution of the diffusion with drift equation based on the assumption of Brownian motion of the bubbles [5]–[7]. The application of this technique permits a minimally invasive PBV assessment, which could also be performed in out patients for cardiovascular diagnostics.

In this paper we present a different method for PBV quantification. The method is still based on the injection of an UCA bolus. The transpulmonary circulation is interpreted as a linear dilution system. Therefore, the relation between the LA IDC (C_{LA}) and the RV IDC (C_{RV}) is given as $C_{\mathrm{LA}} = h * C_{\mathrm{RV}}$, where h is the impulse response of the transpulmonary dilution system. A linear system identification method is employed to estimate h. The identification of the complete transpulmonary dilution system provides more clinical information, increasing the diagnostic value of the method.

The proposed system identification method uses a Nelder-Mead Simplex method [9] to minimize the mean squared error between the real output (C_{LA}) and the estimated output ($\widehat{C}_{\mathrm{LA}} = \widehat{h} * C_{\mathrm{RV}}$) of the transpulmonary dilution system represented by the LDRW model $\widehat{h}$. To this end, the algorithm finds the optimal parameters of the model $\widehat{h}$ that lead to the least mean squares solution. No model interpolation is needed and the PBV can be directly derived from the estimated parameters for $\widehat{h}$.

The choice for a least-squares deconvolution algorithm is due to the small signal-to-noise ratio (SNR) of UCA dilution curves [10]. Other least mean squares deconvolution methods, such as the Wiener filter proposed in [11] or the singular value decomposition proposed in [12] have been considered. However, these non-parametric methods require the model interpolation of the estimated impulse response, and the PBV estimate depends on the quality of the estimated impulse response. The employment of a (parametric) model based approach does not require subsequent model fitting as the parameters for the PBV assessment are directly estimated by the system identification method. Moreover, the proposed parametric approach results in reduced sensitivity to noise and lack of high frequency components in the frequency spectrum of the input IDC, which might not excite the

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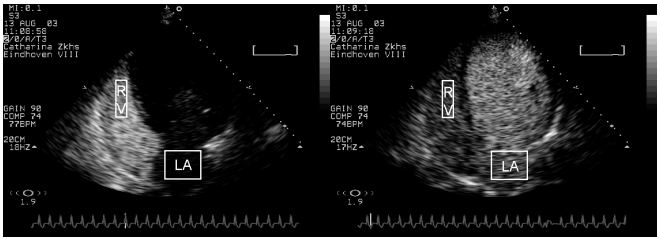

Fig. 1. Transthoracic echocardiographic four-chamber view. Two ROIs are placed on the RV and LA for the IDC measurements. The opacification of the right and left side (after the transpulmonary passage of the UCA bolus) of the heart can be noticed on the left and right image, respectively.

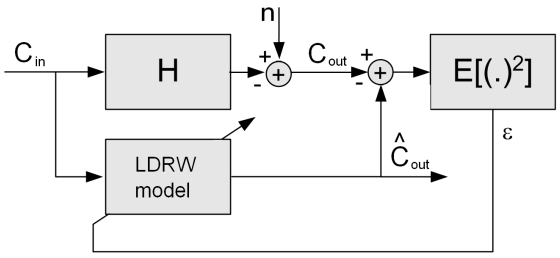

Fig. 2. Scheme of the implemented system identification algorithm.

higher frequencies of the dilution impulse response [13]. Another advantage of this method over non-parametric methods consist of the limited number of model parameters to be estimated, which lowers the computational complexity.

For a direct application of indicator dilution theory, a linear relationship between UCA concentration and detected acoustic intensity is necessary. The adopted setting of the ultrasound scanner is power modulation mode with low Mechanical Index (MI) to limit the bubble disruption. The use of specific contrast detection modes [14], such as power modulation, allows reducing UCA concentrations while increasing the image signal-to-noise ratio (SNR). Since the relationship between contrast concentration and acoustic intensity is linear for low concentrations and MI [4], [15], the employment of a power modulation mode at low MI permits a direct application of indicator dilution theory.

Noise in the IDC is mainly introduced by the measurement system and is due to flow and pressure variations in the ventricles [16]. Specific low-pass filters are designed to suppress the measurement noise in the input (C_{RV}) and output (C_{LA}) IDC [17]. As both curves are filtered by the same filter, the impulse response is not affected.

The volume measurements are validated in-vitro with excellent results. The correlation coefficient between the estimated and the real volumes is larger than 0.99. The clinical feasibility of the method is tested by 70 measurements in patients with promising results. All the measurements were recorded at the Department of Cardiology of the Catharina hospital in Eindhoven (The Netherlands).

II. Methodology

A. Indicator dilution curve measurement

The proposed technique for contrast echocardiographic quantifications is based on the measurement of several IDCs in the central circulation after an peripheral injection of an UCA bolus. In this study we use a bolus of 0.05 mL of SonoVue® contrast agent (Bracco s.p.a., Milan). The dose, which is determined on the basis of a previous calibration study [4], ensures the contrast concentration to be bounded in a low range (< 2.5 mL/L) such that the relationship between contrast concentration and acoustic intensity is linear. This linear relationship is required by the following linear system identification method.

The adopted ultrasound scanner is a Sonos 5500 (Philips Medical Systems) and the acoustic intensity is measured by software Q-Lab® (Philips Medical systems). The scanner is set in power modulation mode at 1.9 MHz and low MI equal to 0.1. The power modulation mode increases the SNR for low UCA concentrations while the low MI reduces the bubble disruption. IDCs are measured by a transthoracic ultrasound transducer (S3 probe, Philips Medical Systems) as the average acoustic intensity in two ROIs placed on the RV and LA. As shown in Fig. (1), an echocardiographic four chamber view is adopted for this measurement.

B. Dilution system identification

Once the input (RV IDC) and output (LA IDC) signals of the dilution system are known, the system can be identified by means of a deconvolution technique that estimates the dilution impulse response. Due to the low SNR of measured IDCs, the employment of a least squares deconvolution technique is an appropriate solution [18].

The analysis of the IDC noise spectrum shows that the main noise components are introduced by the measurement system and, therefore, do not enter the dilution system. In fact, the main noise components in the spectrum lie at the heart-beat fundamental frequency and its harmonics [17]. This can be explained by the cyclic variations of blood velocity and pressure in the measurement sites [4]. Velocity variations produce artifacts in the adopted power modulation detection mode because they are interpreted as nonlinearities of the medium. Also pressure variations in the cardiac chambers affect the acoustic intensity measurement because they influence the backscatter coefficient of the diluted UCA according to the Rayleigh-Plesset equation [16].

This noise characterization allows us to design specific pre-filters to suppress the measurement noise before the deconvolution is applied. In order to avoid phase distortion, a Finite Impulse Response (FIR) low-pass filter is implemented. The cut-off frequency is fixed at 0.5 Hz for a sampling frequency of 20 Hz (maximal frame rate in our measurements in patients). The transition band is 0.2 Hz.

The proposed system identification method exploits the a priori knowledge on the dilution system and performs a parametric estimation of the dilution-system impulse response based on the LDRW model. The identification problem reduces to the estimation of few parameters rather than the

estimation of the entire frequency spectrum of the dilution-system transfer function, which is performed for instance by the Wiener method in [10]. The general scheme is presented in Fig. 2, where the block *LDRW model* represents the parametric model of the dilution system. The symbols C_{in}, C_{out}, n, and ϵ in Fig. 2 indicate respectively the RV IDC, the LA IDC, the noise introduced by the dilution system, and the squared error between the real and the estimated output IDC. The blocks H, and $E[(.)^2]$ represent the real dilution system and the squared error calculation. The Nelder-Mead Simplex method is adopted for the minimization of the squared error between the real and estimated output IDC. The initial values of the model parameters before minimization are determined on the basis of the average values in patients. The algorithm is implemented in Matlab® (The MathWorks).

C. Pulmonary blood volume measurement

The impulse response of the transpulmonary dilution system between the RV and LA can be represented by the LDRW model as

$$C(t) = \frac{m}{Q} e^{\lambda} \sqrt{\frac{\lambda}{2\pi\mu t}} e^{-\frac{\lambda}{2}\left(\frac{t}{\mu}+\frac{\mu}{t}\right)}, \qquad (1)$$

where m is the injected dose of contrast, Q is the flow, μ is the MTT that the contrast takes to cover the distance between injection and detection sites after an impulse injection, and λ is a parameter related to the diffusion constant of the dilution system [4]–[8], [15]. Once the parameters Q and μ are determined, the volume V between the two detection sites is given as

$$V = Q \cdot \mu. \qquad (2)$$

The parameters m/Q, μ, and λ of the LDRW model are directly estimated according to the scheme in Fig. 2. The value m/Q equals the integral of the model [5]–[7]. Since the absolute relationship between contrast concentration and acoustic intensity is subject dependant due to unequal attenuating tissues, the flow Q, which corresponds to the CO, cannot be determined by (1) and it is measured by echo-Doppler time integration in the aorta. Fig. 3 shows an in-vivo application of the proposed method. The LA IDC is estimated as the convolution between the pre-filtered RV IDC and the estimated transpulmonary impulse response.

Modelling the system impulse response by the LDRW model also provides a description of the hemodynamics of the transpulmonary circulation. In particular, the parameter λ equals half of the *Peclet* number. The Peclet number is a parameter related to the diffusion constant of the system and it is used to quantify the ratio between convection and diffusion in a dilution process [8]. An increase of λ can be interpreted as a small contribution of diffusion with respect to convection, and it corresponds to an increase of the symmetry of the transpulmonary impulse response. In contrast, for small λ diffusion plays a major role and the resulting impulse response is very skew [15]. Impulse response modelling can therefore open new clinical possibilities to characterize the hemodynamics of the transpulmonary circulation and, perhaps, relate it with pathologic conditions for clinical diagnostics.

III. Results

The volume measurements are tested in-vitro by the set-up described in [4]. The results are then compared to those

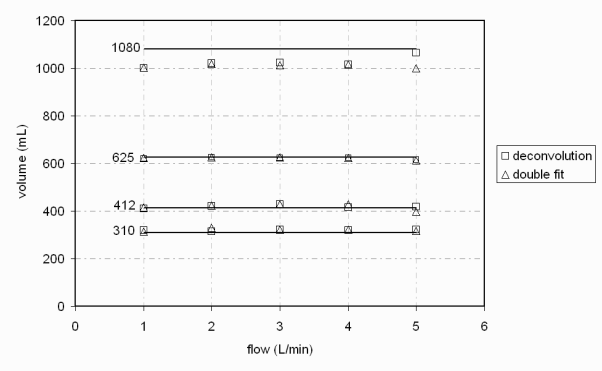

Fig. 4. In-vitro volume measurements for 4 different volumes and 5 different flows by the deconvolution and double fit methods.

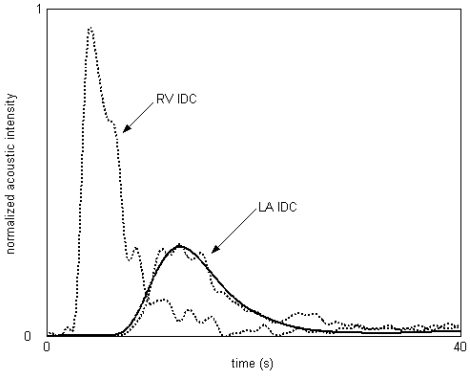

Fig. 3. Example of RV and LA IDC measured in a patient (dotted lines). The continuous curve represents the estimated LA IDC (correlation coefficient equal to 0.97).

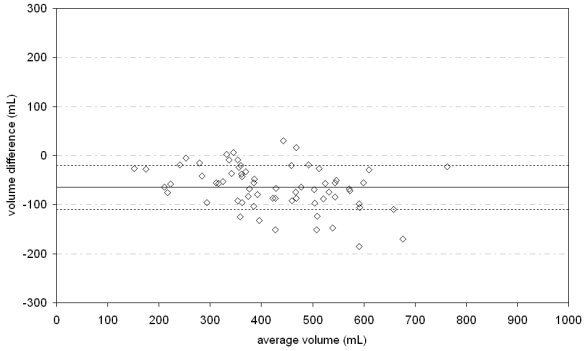

Fig. 5. Bland-Altman plot comparing the PBV estimates by the deconvolution and double fit methods in 70 measurements in patients.

obtained by the double LDRW model IDC fit proposed in [4]. UCA dilution curves are measure before and after a capillary network whose volume is varied between 310 mL and 1080 mL. The flow is generated by a calibrated centrifugal pump (Medtronic 550 bio-console) and measured by the electromagnetic flowmeter embedded in the pump. Flows ranging from 1 to 5 L/min are generated with steps of 1 L/min. The results are presented in Fig. 4.

The determination coefficients with the real volumes are 0.9986 and 0.9995, and the average standard deviations are 1.73% and 1.28% for the double IDC fit and the deconvolution method, respectively. The largest volume is slightly underestimated. However, this underestimation is less evident when the deconvolution method is used. Nevertheless, it is important to notice that volumes larger than 900 mL have never been measured in patients.

The clinical feasibility of the method is tested in patients. A set of 70 measurements is performed and the two methods compared. The IDCs are measured by a Sonos 5500 scanner equipped with transthoracic S3 probe after the injection of a 0.05 mL bolus of SonoVue® in an arm vein. The results are shown in the Bland-Altman plot in Fig. 5 [19]. The mean difference between the volume estimates by the deconvolution and the double LDRW model fit methods is -64 mL with a standard deviation of 45 mL. The volume overestimation by the double fit method with respect to the deconvolution method might be due to UCA recirculation issues. Due to recirculation, UCA concentration rises mask the IDC tail and influence the LDRW fit. This problem is not present when the deconvolution method is used. Moreover, a complete system identification brings additional information on the hemodynamics of the transpulmonary circulation, which is not available when only the MTT is measured.

IV. Discussion and conclusions

A novel method for the assessment of PBV by means of contrast echocardiography is proposed. A small bolus of contrast is injected in a peripheral vein and subsequently detected in the RV and LA. Two IDCs are then derived and processed for the estimation of the dilution system between the measurement sites and, therefore, to characterize the transpulmonary circulation.

The results are accurate and very promising. The PBV quantification is also possible without a complete system identification method (only the contrast MTT is necessary). However, a dilution system identification and modelling provides more insight on the transpulmonary hemodynamics, possibly resulting in increased diagnostic value. Clinical studies based on the proposed method could relate the model parameters to different pathologies.

In the present study, CO is measured by ultrasound echo-Doppler time integration. However, with the employment of transesophageal probes, which can be placed almost in touch with the LA, inter-subject variations of the acoustic attenuation are limited and an absolute relationship between acoustic intensity and contrast concentration could be established. As a result, we might be able to assess the CO by applying the Stewart-Hamilton equation to the RV IDC, before the contrast loss in the lungs [15].

In general, a more extensive validation remains necessary and PBV in patients should be compared with gold standard techniques such as transpulmonary dye- or thermo-dilution measurements.

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