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Non-invasive Estimation of Right Atrial Pressure using Inferior Vena Cava Echography

Luca Mesin[a,*], Stefano Albani[b], Gianfranco Sinagra[b]

[a] *Mathematical Biology and Physiology, Department of Electronics and Telecommunications, Politecnico di Torino, Torino, Italy*
[b] *Postgraduate School in Cardiovascular Sciences, Cardiovascular Department, University Hospital of Trieste, Trieste, Italy*

Abstract

The pulsatility of the inferior vena cava (IVC) reflects the volume status and the central venous pressure of patients. The standard clinical indicator of IVC pulsatility is the caval index (CI), measured from ultrasound (US) recordings. However, its estimation is not standardized and prone to artefacts, mostly related to IVC movements during respiration. Thus, we used a (recently patented) semi-automated method that tracks IVC movements and averages the CI across an entire section of the vein, which provides a more stable indication of pulsatility. This algorithm was used to estimate the CI, pulsatility indicators reflecting either respiratory or cardiac stimulation and the mean diameter of IVC. These IVC indices, together with anthropometric information, were used as potential features to build an innovative model for the estimation of the right atrial pressure (RAP) recorded from 49 catheterized patients. An exhaustive search was carried out for the best

*Corresponding Author: Luca Mesin, Dipartimento di Elettronica e Telecomunicazioni, Politecnico di Torino, Corso Duca degli Abruzzi, 24 - 10129 Torino - Italy; Email, luca.mesin@polito.it; Phone, +39 011.090.4085

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among all possible models which could be obtained by using combinations of these features. The model with minimum estimation error (tested with a leave-one-out approach) was selected. This model estimated RAP with an error of about 3.6±2.6 mmHg (mean±standard deviation; whereas, the error when using only operator measured variables, without the use of the software, was about 4.0±2.5 mmHg). These promising results underline the need for further study of our RAP estimation method on a larger dataset.
Keywords: Inferior Vena Cava, Ultrasound, Right Atrial Pressure, Pulsatility, Caval Index, Regression Model

Introduction

The pulsatility of the inferior vena cava (IVC), estimated from ultrasound (US) measurements by a non-invasive procedure, reflects the intravascular volume status of critical patients (Finnerty et al. (2017))(Au and Fields (2017))(Airapetian et al. (2015))(Charbonneau et al. (2014)). It has been investigated in many applied studies, e.g., in cardiology patients with heart failure (Wattad et al. (2015)), pulmonary hypertension (Galié et al. (2016)), in critical patients (Akkaya et al. (2013)), in case of liver fibrosis or cirrhosis (Kitamura and Kobayashi (2005)), in healthy blood donors (Lyon et al. (2005)) and healthy paediatric patients (Haines et al. (2012)).

However, the classical procedure (based on subjective measurements of the operator) is not standardized (Wallace et al. (2010))(Resnick et al. (2011)) (Zhang et al. (2014)) and is affected by artefacts, like those induced by the movements of the vessel relative to the transducer during the respiratory cycle (Blehar et al. (2012)).

In recent works (Mesin et al. (2015))(Mesin et al. (2018)), a semi-automated method has been introduced to track the movements of the IVC in long-axis US scans in order to compensate for respiration artefacts. Tests in simulations indicate that the method provides a more precise estimation of the IVC local pulsatility compared to the classical measurements (Mesin et al. (2015)). Moreover, computing the vein diameters from an entire portion of the vessel (Mesin et al. (2018)) and in an orthogonal direction to the IVC midline (Pasquero et al. (2015)) allows the retrieval of overall pulsation information of the considered vein portion.

Here, the classical and semi-automated approaches are further investigated in terms of the possibility of extracting information on the central venous pressure (CVP). Patients with different cardiopathies were first investigated using US scans and then catheterized to measure the right atrial pressure (RAP, assumed approximately equal to the CVP). Different patient characteristics (anthropometric and IVC statics and dynamic behaviour, estimated either using the classical or the semi-automated approach) were used to build regression models for the RAP estimation. Those with minimum error were selected.

Materials and Methods

Automated detection of the IVC borders

The algorithm proposed in (Mesin et al. (2018)) was used to process US video-clips. In brief, the algorithm (implemented in MATLAB R2018a, The Mathworks, Natick, Massachusetts, USA) processes each frame of an US B-mode video-clip of a longitudinal view of the IVC. A continuous measurement of the diameters along a whole portion of the IVC is computed after compensating for possible IVC movements.

In the first frame of the clip, the user indicates the location of the vein, two reference points (which are then tracked to estimate IVC movements and deformations), the most proximal and distal lines to be considered and the location of the borders of the vein along the most proximal line. The software then uniformly distributes a number of lines between the most proximal and distal borders indicated by the user. The borders of the vein are then automatically detected along all these lines. Their location and direction are updated for each frame depending on the movements of the reference points.

The most proximal and distal lines were selected trying to include the entire vein portion that was visualized for the whole video-clip. In optimal conditions, the available tract was between the confluence of the hepatic veins into the IVC and the caudate lobe of the liver. However, for most patients, the available portion of the vein was smaller.

Once the superior and inferior borders of the vein (in the tract under investigation) have been obtained, the software computes the IVC midline. This is defined as the mean curve between the two borders. The curvilinear abscissa is then computed along the midline. Five points are then uniformly distributed along this line (i.e., with the same curvilinear distances between neighboring points), considering its extension from the 20% point to the 80% point of its length (the edges of the tract were excluded). Then, the orthogonal sections, in respect to the IVC midline, passing from each of the 5 points are considered and the pulsatility of the IVC is estimated for each of them in terms of the caval index (CI)

$$CI = \frac{\max_t (D(t)) - \min_t (D(t))}{\max_t (D(t))} \tag{1}$$

where D is the estimated diameter series over the time variable t (in a specific section) and max/min indicate local extrema. Local maxima and minima are computed for each respiration cycle. Averaging across different cycles, a stable estimation of pulsatility is computed for each section. Finally, a CI accounting for the overall pulsatility of the considered portion of the vein can be obtained by averaging the estimates across different sections (see (Mesin et al. (2018)) for details).

The following additional pulsatility indices (RCI and CCI) were also estimated. The vein dynamics were considered as resulting from two different stimulations, induced by either respiration or heartbeats, respectively. The effect of respiration was computed by low pass filtering the whole diameter time series with a cut-off frequency of 0.4 Hz. The cardiac contribution was obtained by high pass filtering the whole diameter time series with a cut-off frequency of 0.8 Hz (both filters were 4^{th} order Butterworth; they were used twice, once with time reversed, in order to remove phase distortion and delay). From the two filtered time series, applying again the definition of CI given in (1), the respiratory caval index (RCI) and the cardiac caval index (CCI) were obtained.

Experimental data

The study was approved by the Ethics Committee of the University Hospital of Trieste and complies with the principles of the Declaration of Helsinki. Informed consents were obtained from the patients participating in the study.

We prospectively enrolled 62 patients (consecutively from 1/12/2015 to 1/9/2017) undergoing echocardiographic assessment and right heart catheterization (RHC) for all clinical indications. Some of them were excluded, for the following technical problems: IVC not visible (due to either abdominal gas, excessive fat tissue, low definition of the edges of the vein) and paradoxical IVC movements (distal collapse and proximal dilatation or vice versa). Finally, 49 patients with good US scans (i.e., allowing reliable processing) could be included in the study (26 males and 23 females; mean$\pm$standard deviation - STD: age 62.2$\pm$15.2 years, weight 71.7$\pm$15.3 kg, height 168.1$\pm$9.3 cm). The selected patients had the following pathologies: 28 patients (57%) were affected by various heart disease (hypertensive, ischemic, valvular, toxic and tachy-induced cardiomyopathy), 10 patients (20.4%) had hypertrophic, dilated or restrictive cardiomyopathy and 11 patients (22.5%) showed non group 2 pulmonary hypertension. The following machines were used to record the US video-clips: VIVID E9, VIVID I and VIVID Q, by General Electric (Wauwatosa, WI USA); iU22, by Philips (Bothell, WA USA). A scan of at least 5 seconds of the IVC in the longitudinal axis was performed by B-Mode echocardiography during at rest breathing with sub-costal approach. Classical estimation of CI was obtained by measuring subjectively maximal and minimal diameters (we refer to it as the "manual" estimation).

Multi-parameter model

The following 5 features were recorded from each patient: age, height, weight, body surface area (BSA) and sex. Moreover, further parameters were extracted from US scans using either the manual or the semi-automated approach. Specifically, via the manual approach, we measured the mean diameter and the caval index, here called CI_{manual} to distinguish it from that obtained by the semi-automated method. In this way, 7 features were considered, i.e., the general 5 features listed above plus these last 2 features. Using the semi-automated approach, we computed the mean diameter (averaging across different respiration cycles and the 5 sections) and 3 pulsatility indices, i.e., CI, RCI and CCI (thus the semi-automated approach considered 9 features, i.e., the 5 general features listed above plus these 4 features). An inverse relation was assumed between the central pressure and the caval indices. A number was also added to the denominator in order to avoid division by zero and maximize the correlation between the measured RAP and the pulsatility indices. Thus, instead of using CI_{manual}, CI, RCI, CCI as features, we used

$$\frac{1}{CI_{manual}+a_0},\ \frac{1}{CI+a_1},\ \frac{1}{RCI+a_2},\ \frac{1}{CCI+a_3}$$

respectively, where a_0=0.7, a_1=2.4, a_2=0.8, a_3=0.3.

The information contained in the features was used to estimate the RAP. The full dataset was split into training and test sets with a leave-one-out approach (Theodoridis and Koutroumbas (2008)). The training set was further split into two parts: 75% to train the models and 25% to validate them. Fifty random selections of training and validation sets were considered in order to get a robust selection of the best model.

Based on the training set, linear regression was used to map the input features into the RAP. Two different cases were considered, including only features measurable by either the manual or the semi-automated approaches. All combinations of features were considered as inputs to build different regression functions (comprehensive search): all possible choices of a single feature, all pairs, triplets, ... until using all the features. Considering maps with the same number of input features, the one providing the best generalization to the validation sets (i.e., minimum mean estimation error on the validation sets) was then selected as optimal and applied to the test data. The optimal model was almost always the same.

The performances of the regression models were evaluated by considering the mean of the absolute value of the errors on the test set

$$E = |x_r - x_m| \tag{2}$$

where x_r and x_m are the outputs of the multivariate regression model and the measured RAP, respectively. Moreover, the standard deviation and kurtosis of the estimation error were computed. The mean value and standard deviation of errors quantify the accuracy of the estimation, while the kurtosis focuses on the tails of the error distribution and it measures large, spurious errors.

To choose the optimal dimension of the model, the one with best performances on the test set was selected.

Results

Table 1 provides some general anthropometric and clinical information on the patients. Table 2 reports catheterization and echocardiographic data, as well as some information on the video processing by the semi-automated algorithm.

Figure 1 and Table 3 show the variables recorded from the patients used to build the models for the estimation of RAP. Their relation with RAP is shown. Notice that most anthropometric indices have a low correlation with RAP. On the other hand, some relation is found between RAP and the features extracted from the IVC. For example, the index with most correlation with the RAP is IVC mean diameter (both when measured manually and automatically, but with more correlation in the latter case). In addition, the pulsatility indices show a good inverse correlation with RAP (again, more correlation is found considering the automated estimation). Other IVC size and pulsatility indices show some correlation with RAP (but were not shown in Figure 1 and Table 3): for the minimum diameter, the correlations were 55.3 and 67.4%, for the maximum diameter 54.9 and 59.0%, for the manual and semi-automated methods, respectively; for $1/(RCI + a_2)$ the correlation was 57.5%, for $1/(CCI + a_3)$ it was 61.1%.

Figure 2 shows the best estimation models. In both cases, the low dimensional models provided better generalization to the test set (so that overfitting was found as the model included many variables). Specifically, the best model when using the manual approach uses only one feature to fit RAP:

$$RAP_{est}^{Manual} = 0.55 D_m \tag{3}$$

where D_m is the mean diameter measured in mm. This model suggests a direct proportionality between the central pressure and IVC diameter. The mean absolute error of this model is 4.04 mmHg (STD equal to 4.79 mmHg, kurtosis 1.94). Considering two variables, the best model is

$$RAP_{est}^{Manual} = 0.52\, D_m + 0.0085\, age \tag{4}$$

where *age* is the age of the patient measured in years (mean absolute error 4.14 mmHg, STD 4.87 mmHg, kurtosis 1.89). This second model selected again the mean diameter of the IVC and added a correction term due to the age. Notice that a pulsatility index is not chosen to be included in the best models, even if Figure 1 and Table 3 show that CI_{manual} has a high inverse correlation with RAP. Indeed, the manually estimated caval index and diameter are quite redundant (the correlation between the measured diameter and $1/(CI_{manual} + a_0)$ is equal to 48%), so that the additional information provided by the measured IVC pulsatility was not relevant enough to contribute to a reduction of the estimation error.

The best model when using the semi-automated approach uses the 2 features which are most correlated with RAP, reflecting the size of the vein and its pulsatility:

$$RAP_{est} = \frac{4.13}{CI + a_1} + 0.52\, D_m \tag{5}$$

It has a mean absolute error of 3.64 mmHg on the test set (STD equal to 4.48 mmHg, kurtosis equal to 2.09). The best models using either 1 or 3 features are given by the following expressions

$$RAP_{est} = 0.60\, D_m \tag{6}$$

$$RAP_{est} = \frac{3.98}{CI + a_1} + 0.52\, D_m + 0.0008\, age \tag{7}$$

and have a mean estimation error of 3.78 and 3.71 mmHg, with STD of the error equal to 4.53 and 4.55 and kurtosis of 2.02 and 2.03, respectively. Notice that these 3 models are built upon the same predictors. The mean diameter is the main feature (it is also the index with the highest correlation with RAP among the considered features, as shown in Figure 1). CI is used to fit the data better, by adding a slight modification to the model with a single feature (indeed, the coefficient multiplying the diameter is reduced when comparing the models with either 1 or 2 predictors and the additional term $1/(CI+a_1)$, directly correlated with RAP, is multiplied by a positive coefficient). Finally, the best model using three features, in addition to the previous information on IVC size and pulsatility, includes age (with a positive contribution, i.e., a larger RAP is obtained for older patients, as also indicated by the positive correlation shown in Figure 1. Notice, when comparing this model with the one with two indices, that the contribution of IVC diameter is unaltered and only the coefficient multiplying the pulsatility term is varied, i.e., slightly decreased to add the contribution of age).

The Bland-Altman plots shown in Figure 2 (considering the best manual and semi-automated models) indicate that the range of estimation error is between ±10 mmHg, but for more than 65% of tests the estimation error was lower than 5 mmHg. For both models, there is a bias, as the errors are mainly positive and negative for low and large values of RAP, respectively, indicating an average underestimation of the variations of RAP among different patients. However, this bias is lower for the model based on semi-automated estimation of features (slope of interpolation line equal to 0.75 and 0.53 for the manual and semi-automated models, respectively).

Discussion

Estimating RAP from US scans is a difficult inverse problem. Some relation between size and pulsatility of IVC and the pressure in the right atrium has been suggested in the literature and collected into guidelines (Lang et al. (2015))(Rudski et al. (2010)). However, the lack of standardization of the procedure meant some doubts have arisen on the reliability of the estimates (Magnino et al. (2017)). Recent developments have allowed more accurate and repeatable estimation of the dynamics of the IVC, due to the tracking of the vein (Mesin et al. (2015)) and to the average of information from an entire tract of the vessel (Mesin et al. (2018)) provided by an innovative semi-automated algorithm.

This work shows that, in line with (Magnino et al. (2017)), IVC pulsatility investigated with the classical procedure does not provide stable information on RAP. However, the information extracted by the innovative algorithm can be profitably used to get an estimation of RAP that showed an average error of about 3.6 mmHg.

A limitation of our study is that the method was tested on a small database, as processing was successful only for 49 out of 62 patients. Future developments will include the engineering of the software in a US system, so that the original data could be directly processed and a real time rendering could guide the operators in order to acquire video-clips for which the processing is feasible.

Some properties of the patients were not available, but they could affect the estimation of the RAP. For example, IVC pulsatility also depends on the volume status of the subject (which could be in part investigated by bioimpedance analysis), compliance of the vein and interaction with surrounding tissues. Some information could also possibly be extracted from short axis scans of the vein (Folino et al. (2017)).

Thus, there is room to improve the estimation model, by extending the dataset, updating the processing algorithm (by integrating it with the acquisition of the US scan) and including more information on the patients. However, the preliminary results are promising and indicate that the semi-automated processing (including IVC movement tracking and the investigation of an entire portion of the vessel) is useful for better characterization of IVC pulsatility and its relation with RAP.

An instrument implementing the algorithm described in this paper was recently patented by the Politecnico di Torino and Universitá di Torino (patent number 102017000006088).

Conclusions

A new promising technique has been introduced for the estimation of RAP. Higher accuracy is obtained when using a semi-automated method for the tracking and assessment of IVC pulsatility in an entire portion of the vessel, than by considering manual subjective measurements (in the latter case, IVC pulsatility did not improve accuracy of RAP estimation).

The non-invasive assessment of RAP could have an active role in the management of patients. The new tool which has been proposed, if validated in further studies, could have an important role in a variety of clinical settings.

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Figure Captions

Figure 1: Different variables versus right atrial pressure (RAP), with indication of the correlation.

Figure 2: Performances of the best models for the estimation of RAP when using indices estimated with the standard (manual) or semi-automated approach. Bland-Altman plots show the difference between estimated and correct RAP versus their mean.

General Data	**Mean ± STD**
Systolic Blood Pressure (mmHg)	115.9±21.1
Diastolic Blood Pressure (mmHg)	71.3 ± 9.8
Heart Rate (bpm)	75.4 ± 15.5
Smokers	6 (12.2%)
Essential Hypertension	31 (63.3%)
Dyslipidemia	10 (20.4%)
Diabetes	14 (28.6%)
Atrial Fibrillation	14 (28.6%)
COPD	4 (8.2%)
CKD	14 (28.6%)
Cardiomyopathy (HCM, DCM, RCM)	10 (20.4%)
Non Group 2 Pulmonary Hypertension	11 (22.5%)
MHD	28 (57.1%)

Table 1: Main features of the population (COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; HCM: Hypertrophic Cardiomyopathy; DCM: Idiopathic Dilated Cardiomyopathy; RCM: Restrictive Cardiomyopathy; MHD: Multifactorial Heart Disease, i.e., hypertensive, ischemic, valvular, tachy-induced, toxic).

Right heart catheterization data	**Mean $\pm$ STD**
ΔEcho-Cath Time (min)	213 ± 122
Mean Pulmonary Artery Pressure (mmHg)	33.4 ± 11.6
Right Atrial Pressure (mmHg)	10 ± 5.6
Echocardiographic data	**Mean $\pm$ STD**
LV Ejection Fraction (%)	48.2 ± 19.7
Tricuspid Annular Plane Systolic Excursion (mm)	17 ± 4.7
RV FAC (%)	35.6 ± 12.8
Tricuspid E/E	5.6 ± 2.9
Tricuspid E/A ratio	1.2 ± 0.4
Expiratory IVC diameter (mm)	20.4 ± 5.5
Inspiratory IVC diameter (mm)	14.0 ± 6.5
IVC Collapsibility Index	0.35 ± 0.2
Measured Right Atrial Pressure (mmHg)	12.5 ± 7.4
Pulmonary Artery Systolic Pressure (mmHg)	53.0 ± 19.1
Video Processing	**Mean $\pm$ STD**
Length of processed IVC tract (cm)	44.5 ± 12.3
Duration of US video clips (s)	9.3 ± 4.6
Identified respiration cycles	2.5 ± 1.3
Identified heartbeats	13.8 ± 7.5

Table 2: Echocardiographic and catheterization data (LV: Left Ventricle; RV: Right Ventricle; FAC: Fractional Area Change; IVC: Inferior Vena Cava).

Variable	**Mean ± STD**	**CC with RAP**
Age (years)	62.2±15.2	15.9%
Height (cm)	168.1±9.3	5.8%
Weight (kg)	71.8±15.3	14.9%
BSA (m^2)	1.81±0.22	12.8%
Sex	23 females/26 males	4.2%
IVC mean diameter (manual estimation)	18.6±5.7 mm	56.7%
IVC mean diameter (semi-automated estimation)	15.9±6.9 mm	64.6%
CI (manual estimation)	28.7±16.0 %	-43.5%
CI (semi-automated estimation)	36.7±23.2 %	-62.9%
RCI	20.7±23.6 %	-55.4%
CCI	20.5±22.9 %	-56.0%

Table 3: Variables used as features for the estimation models and their correlation coefficients (CC) with RAP (BSA: Body Surface Area; IVC: Inferior Vena Cava; CI: Caval Index; RCI: Respiratory Caval Index; CCI Cardiac Caval Index).