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ORIGINAL PAPER

Accuracy of right atrial pressure estimation using a multi-parameter approach derived from inferior vena cava semi-automated edge-tracking echocardiography: a pilot study in patients with cardiovascular disorders

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Abstract

The echocardiographic estimation of right atrial pressure (RAP) is based on the size and inspiratory collapse of the inferior vena cava (IVC). However, this method has proven to have limits of reliability. The aim of this study is to assess feasibility and accuracy of a new semi-automated approach to estimate RAP. Standard acquired echocardiographic images were processed with a semi-automated technique. Indexes related to the collapsibility of the vessel during inspiration (Caval Index, CI) and new indexes of pulsatility, obtained considering only the stimulation due to either respiration (Respiratory Caval Index, RCI) or heartbeats (Cardiac Caval Index, CCI) were derived. Binary Tree Models (BTM) were then developed to estimate either 3 or 5 RAP classes (BTM3 and BTM5) using indexes estimated by the semi-automated technique. These BTMs were compared with two standard estimation (SE) echocardiographic methods, indicated as A and B, distinguishing among 3 and 5 RAP classes, respectively. Direct RAP measurements obtained during a right heart catheterization (RHC) were used as reference. 62 consecutive 'all-comers' patients that had a RHC were enrolled; 13 patients were excluded for technical reasons. Therefore 49 patients were included in this study (mean age 62.2 ± 15.2 years, 75.5% pulmonary hypertension, 34.7% severe left ventricular dysfunction and 51% right ventricular dysfunction). The SE methods showed poor accuracy for RAP estimation (method A: misclassification error, ME = 51%, $R^2 = 0.22$; method B: ME = 69%, $R^2 = 0.26$). Instead, the new semi-automated methods BTM3 and BTM5 have higher accuracy (ME = 14%, $R^2 = 0.47$ and ME = 22%, $R^2 = 0.61$, respectively). In conclusion, a multi-parametric approach using IVC indexes extracted by the semi-automated approach is a promising tool for a more accurate estimation of RAP.

Keywords Right atrial pressure · Inferior vena cava · Edge-tracking · Caval Index · Cardiac Caval Index · Respiratory Caval Index

Abbreviations

BTM	Binary Tree Model
CCI	Cardiac Caval Index
CI	Caval Index
IVC	Inferior Vena Cava
IVCd	Inferior Vena Cava expiratory diameter
ME	Misclassification Error
PH	Pulmonary Hypertension
RAP	Right Atrial Pressure
RCI	Respiratory Caval Index
RHC	Right Heart Catheterization
SE	Standard Estimation
US	Ultrasound

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Background

Inspiratory collapse of the inferior vena cava (IVC) and the measurement of its diameters by ultrasound (US) assessment are validated as indirect indexes for the non-invasive estimation of right atrial pressure (RAP) [1, 2]. However, there are some critical issues about the actual reliability and reproducibility of this assessment, especially of those with intermediate RAP values [2, 3]. Guidelines give a variable measuring range of between 10 and 20 mm from the junction with the right atrium [4]. In the literature, there is lack of agreement regarding the most reliable measurement site, which is due to the difficulty in identifying key landmarks as a guide to the measurement [5]. A recent work has indicated that there is a great variability of the IVC pulsatility between different respiratory cycles and at different distances from the right atrium and that the standard methods for the evaluation of IVC show poor repeatability [5].

In one study, poor reliability was found for the echocardiographic correlation between the diameters of the IVC and the invasively estimated RAP [6]. Moreover, a study group has recently even discouraged the use of the IVC to estimate RAP due to the high inaccuracy reported in a sample of 200 patients undergoing right heart catheterization (RHC) [7]. Finally, in patients with advanced heart failure, echocardiographic methods showed only modest precision, even using complex prediction models for evaluating RAP [8].

These poor results could reflect the lack of standardization and the low reliability of IVC assessment. To partially compensate for these problems, an innovative semi-automated method has been recently introduced to track the respirophasic movements of the IVC [9] and to highlight its edges in an entire portion of the vein [10]. This method provides quantitative information on IVC pulsatility with improved reliability and repeatability with respect to standard measurements [5, 10].

This semi-automated method was recently used to extract some indexes from the IVC that, linearly combined, allowed RAP estimation with an average error of 3.6 mmHg [11] compared to RHC measures.

The aim of this study is to assess the accuracy of the estimation of RAP using two different approaches based on the semi-automated tracking technique [9, 11], compared to standard echocardiographic methods. Direct RAP measurement obtained during a RHC was used as reference.

Materials and methods

We prospectively enrolled a total of 62 consecutive patients undergoing echocardiographic assessment and RHC for all clinical indications performed by both the Cardiology Department and the Pneumology Department of the University Hospital of Trieste between 1 December 2015 and 1 September 2017. Exclusion criteria were: age < 18 years, more than 6 h between the invasive and echocardiographic assessment and liquid assumption or diuretics administration between the invasive and the ultrasonography assessments. All patients gave their informed consent for RHC in writing. The institutional ethical board approved the study and informed consent was obtained under the institutional review board policies of hospital administration.

Among the recruited patients, 13 were excluded due to technical issues (IVC not visualized by echocardiography: 6 patients; low quality of the US video clip: 4 patients; paradoxical movement of the IVC, i.e., distal collapse and proximal dilatation or vice versa: 3 patients). All patients underwent complete echocardiographic assessment within 6 h of the invasive procedure, following specific institutional protocol for all patients undergoing RHC. An ID code was assigned to each patient in line with privacy policy. The echocardiographic video clips were exported in AVI format and then sent via a cloud platform to L.M. to perform the IVC analysis.

After processing the IVC video clips, two binary tree models (BTM) based on IVC edge tracking derived parameters were considered for RAP estimation. I) BTM3 able to separate RAP in 3 classes: low (≤ 5 mmHg), intermediate (> 5; ≤ 10 mmHg) and high (> 10 mmHg), as suggested by guidelines [1, 4]. II) BTM5 able to identify 5 classes of RAP: low (< 5 mmHg), low-intermediate (≥ 5; < 10 mmHg), intermediate-high (≥ 10; < 15 mmHg), high (≥ 15; < 20 mmHg) and very high (≥ 20 mmHg), as suggested by previous authors [12].

Right heart catheterization

The invasive hemodynamic study was performed with a brachial, femoral or jugular venous approach, based on the choice of the operator. The transduction system was zeroed at the mid-thoracic level. The Swan Ganz catheter was advanced with an inflated balloon until the capillary wedge position was reached. Then the average capillary pressure was recorded. By subsequent deflation of the balloon, the pulmonary pressures (systolic, diastolic and mean) and the RAP using the proximal lumen were recorded. The classical morphology of the pressure wave had to be recognizable (two positive deflections, *a* and *v*, and two negative deflections, x and y) when evaluating the RAP and pulmonary capillary wedge pressure. Subsequently the cardiac output was measured with the thermodilution method. RAP was measured before the possible pharmacological interventions performed during the haemodynamic study.

Standard echocardiographic assessment

The echocardiographic assessment was performed within 6 h from the RHC following two different RAP evaluations detailed below, called method A and B.

Method A

It identifies 3 classes (low, intermediate, high) as suggested by guidelines [1, 4] (IVCd stands for inferior vena cava expiratory diameter):

- low estimated RAP (≤ 5 mmHg):
  - (a) IVCd ≤ 2.1 cm and inspiratory collapse > 50%
  - (b) IVCd ≤ 2.1 cm and inspiratory collapse < 50%
  - (c) IVCd > 2.1 cm and inspiratory collapse > 50% without secondary signs of elevated RAP[1]
- intermediate RAP (> 5 mmHg and ≤ 10 mmHg):
  - (a) IVCd ≤ 2.1 cm and inspiratory collapse < 50%
  - (a) IVCd > 2.1 cm and inspiratory collapse > 50% with secondary signs of elevated RAP
- high RAP (> 10 mmHg):
  - (a) IVCd > 2.1 cm and inspiratory collapse < 50%
  - (b) IVCd ≤ 2.1 cm and inspiratory collapse < 50%
  - (c) IVCd > 2.1 cm and inspiratory collapse > 50% but < 35% with secondary signs of elevated RAP.

Method B

It identifies 5 classes (low, low-intermediate, intermediate-high, high, very high), as suggested by previous authors [12]:

- low RAP (≤5 mmHg):
  IVCd < 1.5 cm
- low-intermediate RAP (5–10 mmHg):
  IVCd between 1.5 and 2.5 cm and inspiratory collapse > 50%
- intermediate-high RAP (10–15 mmHg):
  IVCd between 1.5 and 2.5 cm with an inspiratory collapse < 50%
- high RAP (15–20 mmHg):
  IVCd > 2.5 cm and inspiratory collapse > 50%
- very high RAP (> 20 mmHg):
  IVCd > 2.5 cm and inspiratory collapse< 50%.

IVC long axis scan was performed paying particular attention to positioning the measurement caliper as close as possible to 90° to the longitudinal axis of the vessel. Measurements were carried out between 10 and 20 mm from the outlet of the vessel into the right atrium. A 2D scan of at least 5 s of the IVC in the longitudinal axis was performed during resting breathing. From the recordings in 2D of the IVC, the maximum (expiratory) and minimum (inspiratory) diameters of the vessel were measured and CI was obtained. Right ventricular tissue Doppler and simple Doppler parameter were assessed as suggested by previous authors [13]. We did not perform Doppler of the hepatic vein because of low reliability of this parameter in our echo-lab. We estimated RAP values as recommended by guidelines, but without using the sniff manoeuvre.

We used the following US machines: VIVID E9, VIVID S6, VIVID I, VIVID Q by General Electric (Wauwatosa, WI, USA), iE33 by Philips (Bothell, WA, USA).

IVC automated analysis

A semi-automated algorithm was used to process US video clips [9, 11]. In brief, the algorithm (implemented in Matlab, the Mathworks) processes each frame of a US B-mode video clip of the IVC. In the first frame of the clip, the user indicates some parameters needed by the processing algorithm, i.e., two reference points to be tracked by the software to estimate IVC movements and the region of interest. In optimal conditions, this region was between the confluence of the hepatic veins into the IVC and the caudate lobe of the liver, but, for most patients, the available portion of vein clearly visualized in the whole video clip was smaller (see examples shown in Fig. 1).

Then, the algorithm was run to estimate the superior and inferior borders of the vein in the region of interest for all the frames. The IVC midline curve was then automatically traced as the mean curve between them. Five points were uniformly distributed along this line, considering its extension from the 20% to the 80% of its length (the edges of the tract were excluded). Then, the sections orthogonal to the IVC midline passing from each of such five points were considered and the pulsatility of the IVC

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[1] Secondary indexes of elevated RAP are considered right ventricular restrictive filling, tricuspid E wave deceleration time < 120 ms or tricuspid E/E′ > 6.

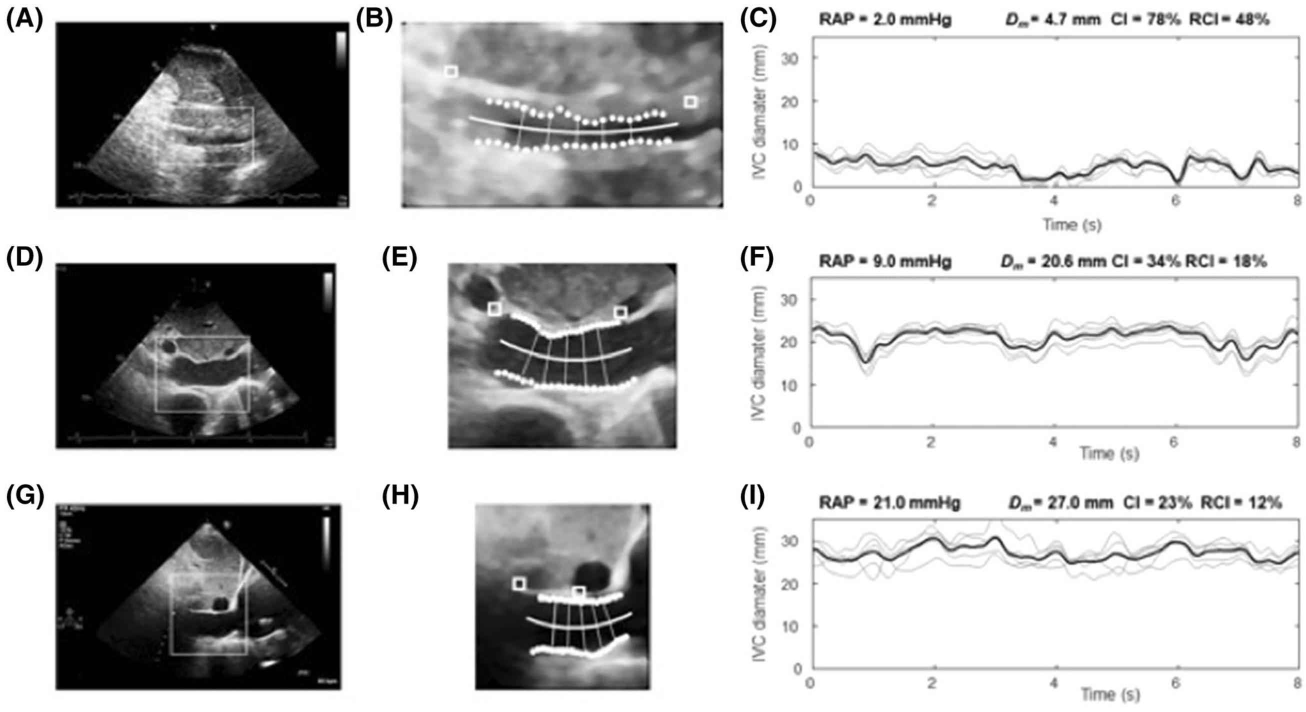


Fig. 1 Examples of US images (**A**, **D**, **G**), IVC borders, IVC midline, orthogonal diameters identification (**B**, **E**, **H**) and vessel dynamics (**C**, **F**, **I**) obtained by the semi-automated system. Three patients are shown, with a value of RAP either low (**A–C**), intermediate (**D–F**) or high (**G–I**). The estimated values of CI, RCI and mean diameter are indicated (they are the best features characterizing IVC dynamics, selected by the BTM3, shown in Fig. 4) (*CI* Caval Index, *RCI* Respiratory Caval Index, *RAP* right atrial pressure; D_m mean diameter, *IVC* inferior vena cava, *BTM* binary tree model)

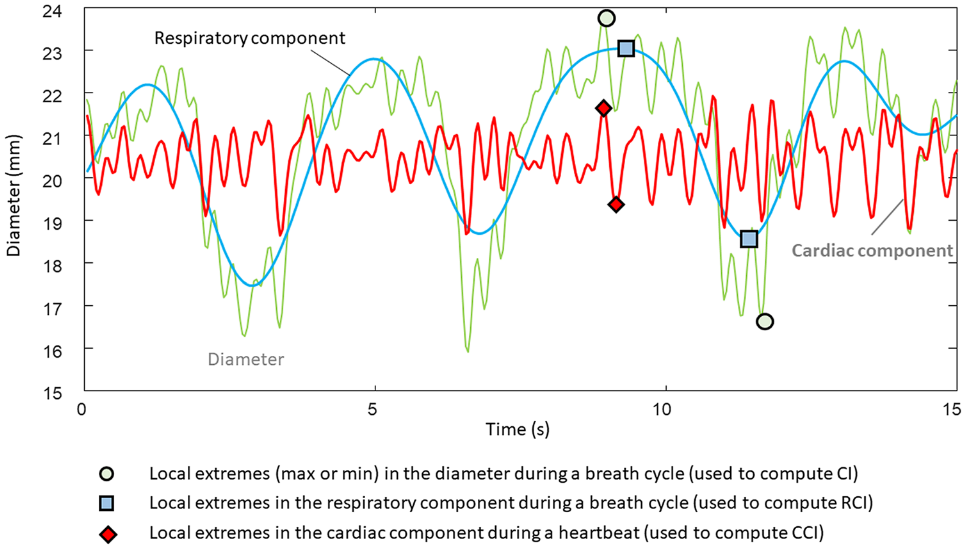


Fig. 2 Example of single diameter estimated from an US videoclip, with indication of the respiratory and cardiac components. Examples of local extremes are also shown on either a breath cycle or a heartbeat, used to compute different pulsatility indexes (*CI* Caval Index, *RCI* Respiratory Caval Index, *CCI* Cardiac Caval Index)

was estimated along them. The highest and the lowest values were computed for each respiration cycle in each of the five points. Averaging across different cycles, a stable estimation of pulsatility was computed for each section. Finally, a CI accounting for the overall pulsatility of the considered portion of the vein was obtained by averaging the estimates across different sections.

Additional indexes were also estimated. The vein dynamics were considered as the sum of two components, reflecting the stimulation induced by either the respiration or the heartbeats. These components were separated using dedicated filters (see previous study for details [11]). Using the same definition of CI, but considering either the respiration or the cardiac component, pulsatility indexes were computed and called Respiratory and Cardiac Caval Index (RCI and CCI, respectively, see Fig. 2).

Multi-class estimation models were developed based on the information provided by the outputs of the semi-automated processing discussed above (mean diameter and 3 indexes of pulsatility, i.e., CI, RCI and CCI) and some patient characteristics, i.e., height, weight, age, body surface area (BSA) and gender. Thus, 9 possible input variables were used (4 IVC indexes and 5 patient characteristics). A Matlab routine was used to fit a BTM to either our 3-class and 5-class classification problem. A BTM performs a sequential binary splitting of the data. Different models were developed considering all possible combinations of inputs and the best one was selected based on a cross-validation with 30 folds as the one guaranteeing minimal error in classifying the validation data. The maximal number of splits was imposed to be in the range of 1–6: the model with optimal dimension was selected by a further cross-validation (Figs. 4, 5) (see "Appendix" for further explanations).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or as median with interquartile range for continuous variables depending on the distribution shape. Categorical variables were expressed as counts and percentages.

Misclassification error (ME), defined as the proportion of patients classified in the wrong RAP class, was calculated for the three classes methods (Method A and BTM3) as well as the five classes ones (Method B and BTM5).

In order to compare the RAP estimations from the BTM and SE methods and methods from the literature (Table 2, panel B Online Supplement Material), similarly to Magnino et al. [7], the associations of the echocardiographic estimations with RHC values were tested using linear regression. The agreement between the measured and estimated RAP was evaluated by the Bland–Altman analysis (Table 2 panel A). However, for the BTM and SE methods, the estimated RAP (RAP_{est}) had to be defined since their output is categorical. To do so, as in Magnino et al. [7] and Tsutsui et al. [8], a numeric representative value was assigned to each of the three classes estimated by Method A and BTM3 (2.5 mmHg for low, 7.5 mmHg for intermediate and 17.5 mmHg for high)[1], and to each of the five classes estimated by Method B and BTM5 (2.5 mmHg for low, 7.5 mmHg for low-intermediate, 12.5 mmHg for intermediate-high, 17.5 mmHg for high and 22.5 mmHg for very high).

Binomial test or χ^2-test were used to check differences in methods misclassification errors between the atrial fibrillation (AF) and no-AF group. The same tests were used to compare the accuracy of methods A and B when either using or not using the software for estimating the IVC diameter. Wilcoxon rank sum test was used to compare pulsatility indexes in either all patients or in those with either low (i.e., trivial or mild) or moderate/high severity of tricuspid regurgitation.

Results

Main characteristics of the patients are shown in Table 1.

The scatter plots of the RAP and either the mean diameter or the pulsatility indexes are shown in Fig. 3. Both the semi-automated measurement of CI and the mean diameter are more related to RAP than their manual versions (semi-automated CI vs invasive RAP: $R^2 = 0.40$, $p < 0.0001$; manual CI vs invasive RAP: $R^2 = 0.19$, $p = 0.0018$ and semi-automated mean diameter vs invasive RAP: $R^2 = 0.42$, $p < 0.0001$; manual diameter vs invasive RAP: $R^2 = 0.32$, $p < 0.0001$). RCI and CCI are moderately related to RAP ($R^2 = 0.31$ for both indexes, $p = 0.0001$), however the addition of these new indexes in the BTM3 and BTM5 contribute to improve the accuracy of the models. Figures 4 and 5 show the BTM3 and the BTM5, respectively. RCI, CCI and D_m play a key role at different levels of the tree in both the BTM3 and BTM5. In the BTM3, RCI emerges as the first variable of the algorithm to consider, while in the BTM5 CCI is the first variable used for correctly classify RAP in our population. Accuracy of the automated versus SE methods is shown in Fig. 6: panel A shows the performances of the 3-class models and reveals that BTM3 has the lowest ME in classifying RAP (14%); panel B shows the accuracy of the 5-class models and BTM5 has again the lowest ME (22%).

In Table 2, the results from the BTM model (Panel A) are reported together with the main works available in the literature (Panel B, Online Supplement Material). BTM5 has the highest accuracy compared to literature data: $R^2 = 0.61$, mean bias 1.42 [− 5.70; 8.54] mmHg, 2.5 mmHg accuracy = 78%, relative accuracy = 57%.

SE methods A and B show poor accuracy in RAP estimation (ME = 51%, $R^2 = 0.22$ and ME = 69%, $R^2 = 0.26$, respectively), whereas the BTM3 and BTM5 have higher accuracy (ME = 14%, $R^2 = 0.47$ and ME = 22%, $R^2 = 0.61$, respectively) in correctly classifying RAP.

Additional analyses showed that there is no statistical difference using the mean IVC diameter (derived from the software) instead of the single IVC diameter measured manually from the B-mode video clips (Online Table 1) when applying method A or B to assess RAP. Further analysis suggests, in our cohort, no difference of the performance of the BTMs in patients with and without atrial fibrillation (Online Table 2) and no relationships between tricuspid regurgitation and CCI and RCI indexes (Online Table 3).

Online Table 4 provides data on the reclassification of patients with pulmonary hypertension (PH), using the BTM. Indeed using standard assessment of the RAP

Table 1 Main characteristics of the patients

	All patients n 49 SD/median/IQR
Baseline variables	
Age (years)	62 ± 15
Sex (males)	26 (53%)
Body Mass Index (kg/m^2)	25.2 ± 4.3
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%)
Ischemic heart disease[a]	4 (8.2%)
Valvular heart disease	3 (6.1%)
Hypertensive heart disease[a]	3 (6.1%)
Idiopathic dilated cardiomyopathy	5 (10.2%)
Hypertrophic cardiomyopathy	3 (6.1%)
Restrictive cardiomyopathy	3 (6.1%)
Toxic (ethanol, chemotherapy) heart disease[a]	4 (8.2%)
Combined heart disease (hypertensive, ischemic, valvular, tachy-induced, toxic)	17 (24.7%)
Idiopathic and connective tissue related pulmonary hypertension	7 (14.3%)
All group pulmonary hypertension	37 (75.5%)
NYHA functional class 1	2 (4%)
NYHA functional class 2	15 (30.6%)
NYHA functional class 3	28 (57.1%)
NYHA functional class 4	4 (8.3%)
Brain natriuretic peptide (pg/ml)	681 (331–1415)
Heart failure with preserved ejection fraction	14—mean EF: 64 ± 6.7%
Heart failure with mildly reduced ejection fraction	1—mean EF: 48 ± 0%
Heart failure with moderately reduced ejection fraction	3—mean EF: 36 ± 0.6%
Heart failure with severely reduced ejection fraction	17—mean EF: 25 ± 5.2%
Echocardiographic data	
Systolic blood pressure	120 (100–126)
Diastolic blood pressure	70 (60–80)
Heart rate	73 (63–83)
LV ejection fraction (%)	48.2 ± 19.7
LV end diastolic volume indexed (ml/m^2)	63.6 ± 43.9
LV end systolic volume indexed (ml/m^2)	39.5 ± 37.9
Severe LV systolic dysfunction (EF < 35%)	17 (34.7%)
Tricuspid annular plane systolic excursion (mm)	17 ± 4.7
RV fractional area change (%)	35.6 ± 12.8
End diastolic RV area (Cm^2)	25.0 ± 9.8
End systolic RV area (Cm^2)	16.9 ± 8.9
RV systolic dysfunction (TAPSE < 18 mm, RVFAC < 35%)	25 (51.0%)
Septal E/E′	18.3 ± 11.6
Transmitral E wave deceleration time (ms)	170.2 ± 60.9
Transmitral E/A ratio	1.79 ± 1.24

Table 1 (continued)

	All patients n 49 SD/median/IQR
Tricuspid E/E’	5.6 ± 2.9
Tricuspid E/A ratio	1.2 ± 0.4
End-systolic LA volume index (ml/m^2)	58.5 ± 27.5
End Systolic RA area (cm^2)	25.8 ± 9.3
Expiratory IVC diameter (mm)	20.4 ± 5.5
Inspiratory IVC diameter (mm)	14.0 ± 6.5
IVC collapsibility index	0.35 ± 0.2
Estimated right atrial pressure (mmHg)	12.5 ± 7.4
Estimated pulmonary artery systolic pressure (mmHg)	53.0 ± 19.1
RV outflow tract acceleration time (ms)	78.9 ± 27.7
Trivial or mild tricuspid regurgitation	33 (67.3%)
Moderate or severe tricuspid regurgitation	16 (32.7%)**
Right heart catheterization data	
Systolic blood pressure	122 (103–138)
Diastolic blood pressure	68 (60–78)
Heart rate	72 (65–86)
ΔEcho-Cath Time (min)	213 ± 122
Cardiac index (thermodilution—l/min/m^2)	2.64 ± 0.69
Normal cardiac index (≥ 2.6 l/min/m^2)	21—(42.9%)
Borderline cardiac index (2.2–2.5 l/min/m^2)	9—(18.4%)
Mildly to moderate cardiac index reduction (1.5–2.1 l/min/m^2)	12—(24.5%)
Severe cardiac index reduction (1.4 ≤ l/min/m^2)	7—(14.3%)
Pulmonary vascular resistance (Wood Unit)	3.9 ± 3.6
Pulmonary capillary wedge pressure (mmHg)	17.6 ± 7.3
Systolic pulmonary artery pressure (mmHg)	52.4 ± 19.45
Diastolic pulmonary artery pressure (mmHg)	22.4 ± 9.7
Mean pulmonary artery pressure (mmHg)	33.4 ± 11.6
Right atrial pressure (mmHg)	10 ± 5.6

SD standard deviation, *IQR* interquartile range, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *HCM* hypertrophic cardiomyopathy, *DCM* idiopathic dilated cardiomyopathy, *RCM* restrictive cardiomyopathy, *NYHA* New York Heart Association, *IVC* inferior vena cava, *RV* right ventricle, *LV* left ventricle, *RA* right atrium, *FAC* fractional area change

[a] With left ventricular dysfunction

[b] Only 2 patients had severe tricuspid regurgitation

with method A, 39% ($R^2 = 0.81$, p value < 0.0001) of the patients were classified in another PH class, compared with only 14% and 17% ($R^2 = 0.95$, p value < 0.0001 both), using BTM3 and BTM5, respectively. More specifically, 3 patients with no pulmonary hypertension, according to 2015 ESC guidelines [14], were classified to low pulmonary hypertension using RAP measured by standard echocardiography whereas with the semi-automated methods only 1 false positive was observed. In all three methods, only one false negative was observed. Online Table 5 provides the main patients’ characteristics according to invasive RAP. Patients with higher values of RAP presented higher values of pulmonary and wedge pressure (respectively 40 ± 11 mmHg, $p < 0.0001$ and 16 ± 5 mmHg, $p = 0.017$).

Discussion

The main findings of our study are as follows.

1. Based on new indexes, such as CCI and RCI combined in a multi-parameter approach with CI and mean IVC diameter, BTM5 (with 5 output classes) shows high accuracy (ME = 22%, $R^2 = 0.61$) in predicting the correct level of RAP (split into five values: low, low-intermediate, intermediate-high, high, and very high). The method outperforms previously reported results [7, 8].
2. Compared to various SE methods of RAP assessment currently used (in our paper referred to as methods A

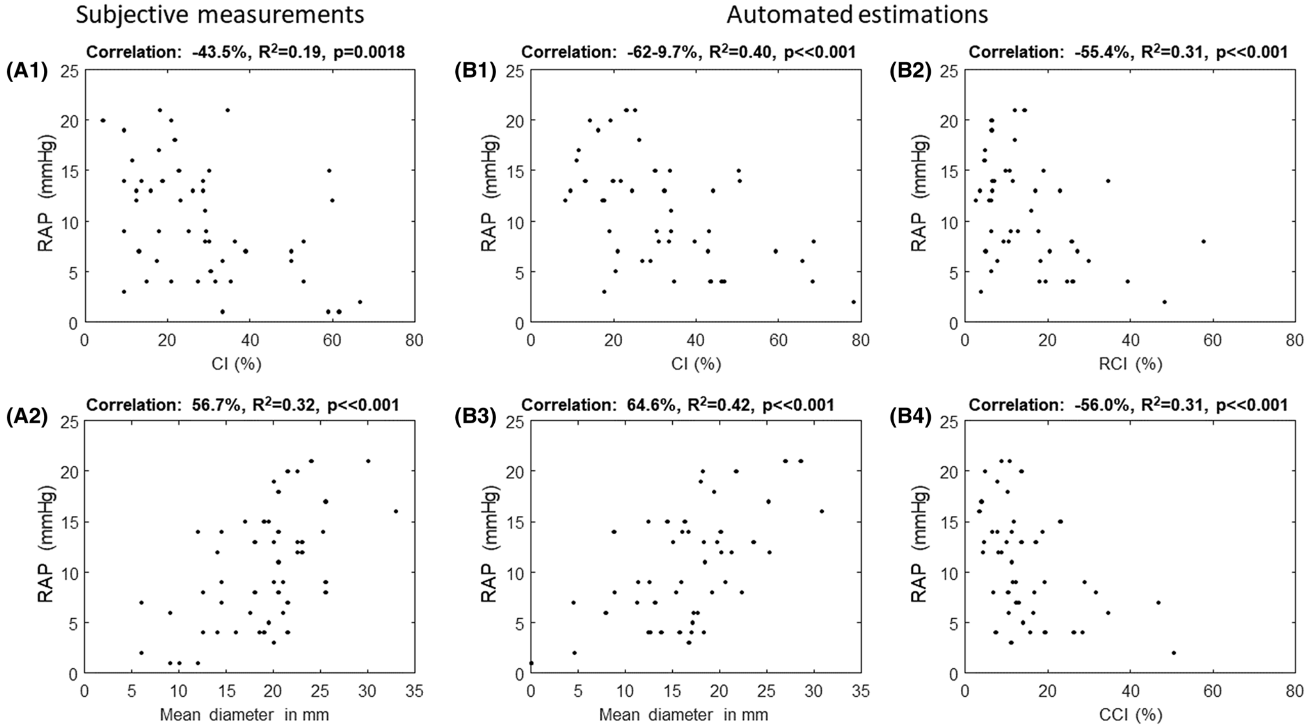


Fig. 3 Scatter plot and correlation between RAP and different parameters reflecting IVC static and dynamic properties, estimated with either a manual (A1 and A2) or a semi-automated approach (B1–B4) (*CI* Caval Index, *RCI* Respiratory Caval Index, *CCI* Cardiac Caval Index, *RAP* right atrial pressure)

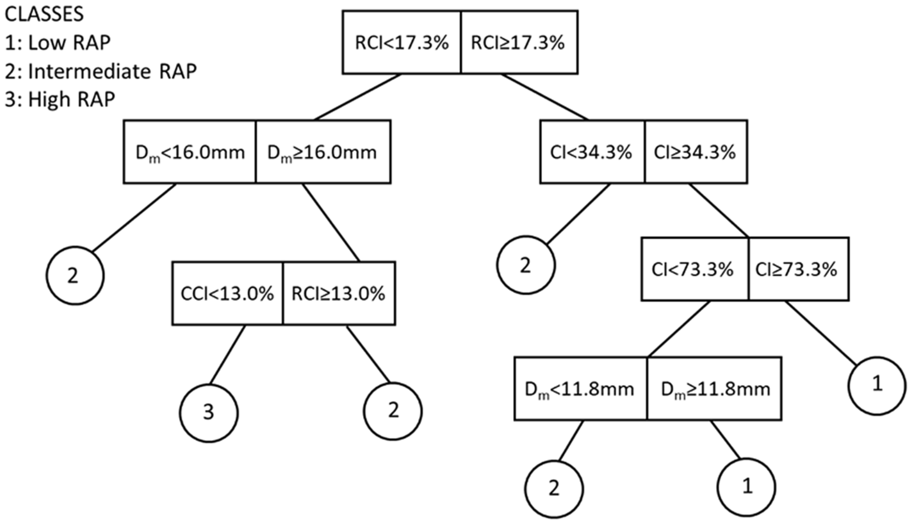


Fig. 4 Best binary tree model (BTM) to discriminate RAP in 3 classes (BTM3) in our population (*CI* Caval Index, D_m mean IVC diameter, *RCI* Respiratory Caval Index, *CCI* Cardiac Caval Index)

and B), both BTM3 and BTM5 are superior (Figs. 3, 4).

(3) RAP estimation from the mean IVC diameters using various methods of SE has low accuracy in predicting the correct class of RAP, similar to using single IVC diameter.

Interestingly, and in contrast to most of the available data in the literature [3], the parameters included in the BTM3 and BTM5 reflect both static and dynamic behaviour of the IVC: mean IVC diameter, CI, CCI and RCI. Literature data on this topic come to heterogeneous conclusions: some authors found that CI is not a reliable

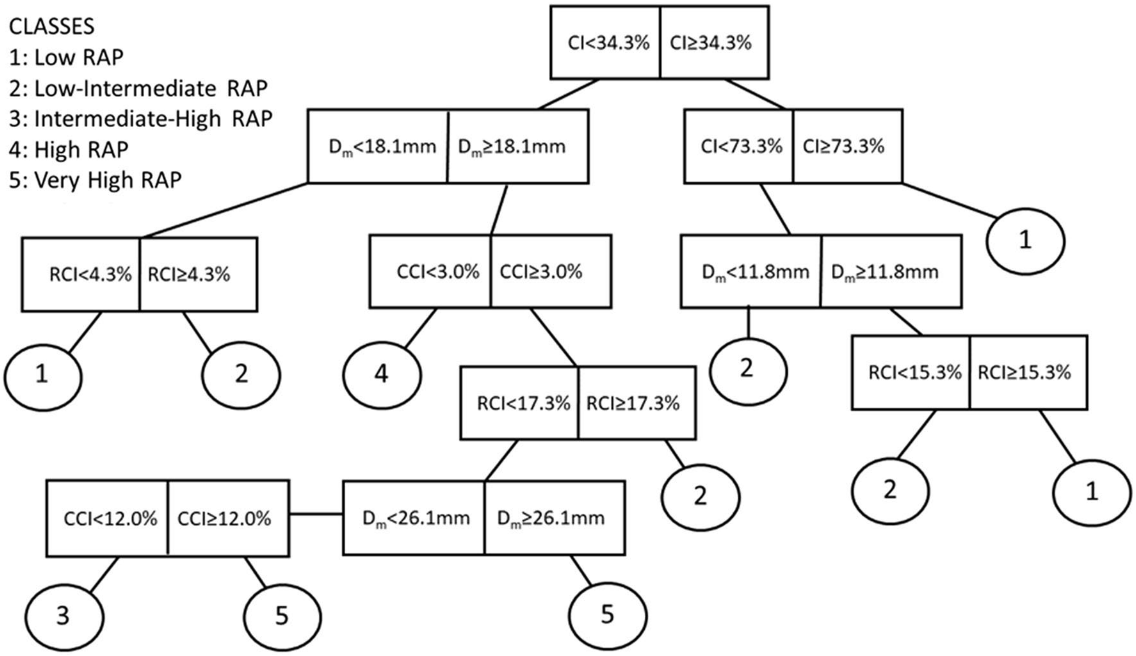


Fig. 5 Best binary tree model (BTM) to discriminate RAP in 5 classes (BTM5) in our population (*CI* Caval Index, D_m mean IVC diameter, *RCI* Respiratory Caval Index)

index to estimate RAP [15, 16], others found only weak association with IVC diameters [15, 17–19], and some others came to the opposite conclusion [16, 20, 21]. Our data show some correlation between RAP and the IVC diameter: indeed, it is the IVC parameter with the highest correlation with RAP. However, when following guidelines to estimate RAP using the expiratory diameter, poor results were obtained (in line with those also reported in the literature [8]). It has to be noted that the majority of patients studied by RHC, and then enrolled in non-invasive hemodynamic correlation studies, showed advanced cardiac diseases [2, 15, 19, 20]. Therefore, we speculate that the prolonged duration of high loading conditions might be one of the leading factors responsible for the IVC size in this cohort of patients, and this might influence the reliability of the IVC expiratory diameter. Conversely, we obtained a much better estimation of RAP when pulsatility indexes were included in our prediction models (either BTM3 or BTM5, Figs. 3, 4) in addition to a measurement of IVC mean diameter. In particular, our models to estimate the RAP included four indexes reflecting the static and dynamic behaviour of IVC, i.e., mean diameter and derived collapsibility indexes (CCI, RCI and CI), excluding other anthropometric descriptors (like patient's age, gender, weight, BSA, etc.). Interestingly, this is in contrast with other studies in which, using SE IVC assessment, there was a strong relationship between BSA and IVC diameter [22], suggesting that the features used in our methods included all information needed to predict RAP, even excluding patients anthropometric values.

The accuracy achieved in predicting non-invasively RAP is probably related to the use of new highly sensitive indexes (CCI and RCI). It must be noted that all IVC indexes considered in this paper were assessed only during resting respiration, to avoid motion artefacts as much as possible. An alternative could be measuring the IVC response to specific manoeuvres. The sniff manoeuvre has been described in experimental work by Simonson et al. [18], in which the authors directly measured the inspiratory pressure using a sonospirometer and found that the inspiratory pressure required to totally collapse the IVC (i.e., diameter reduction of more than 85%) was close to RAP. Subsequently, Brennan et al. found the highest accuracy of the IVC sniff diameter, with sensibility of 91% and specificity of 94%, to identify high values of RAP if the IVC diameter was > 12 mm [2] during the sniff manoeuvre (this result was acquired by guidelines [1]). The rationale of sniff is to correctly assess the collapsibility value in patients with chest breathing. This procedure could overestimate the value of RAP due to an underestimation of collapsibility [2, 18], as in the case of athletes [23] who usually have dilated IVC with lower values of CI compared to normal subjects, but normal values of RAP. However, in clinical practice, the sniff manoeuvre may be a source of reduced reliability of RAP estimation for many reasons. The degree of deep inspiration during the sniff manoeuvre is variable due to the age, manner of breathing, BMI and clinical conditions of the patients [3,

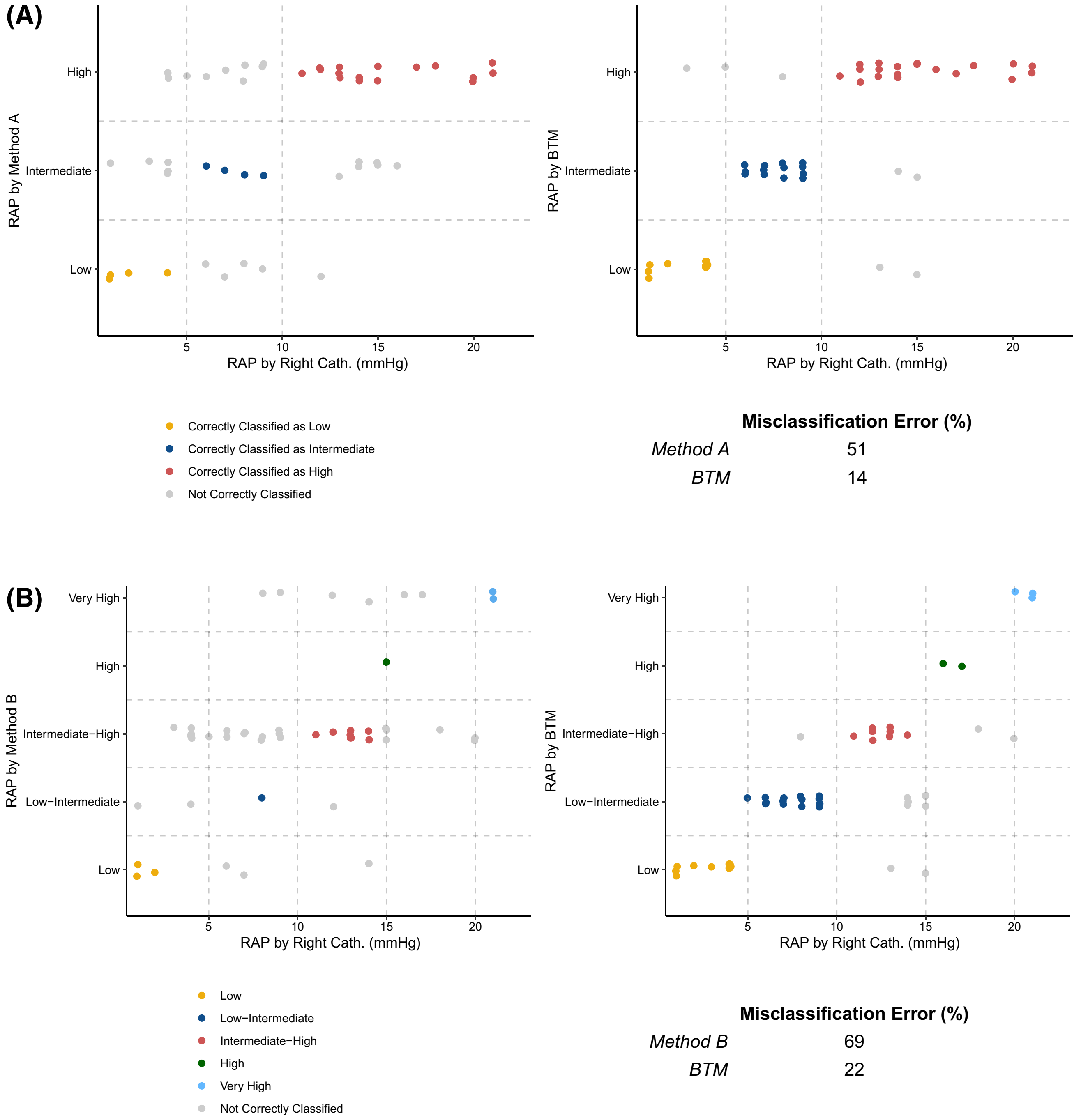


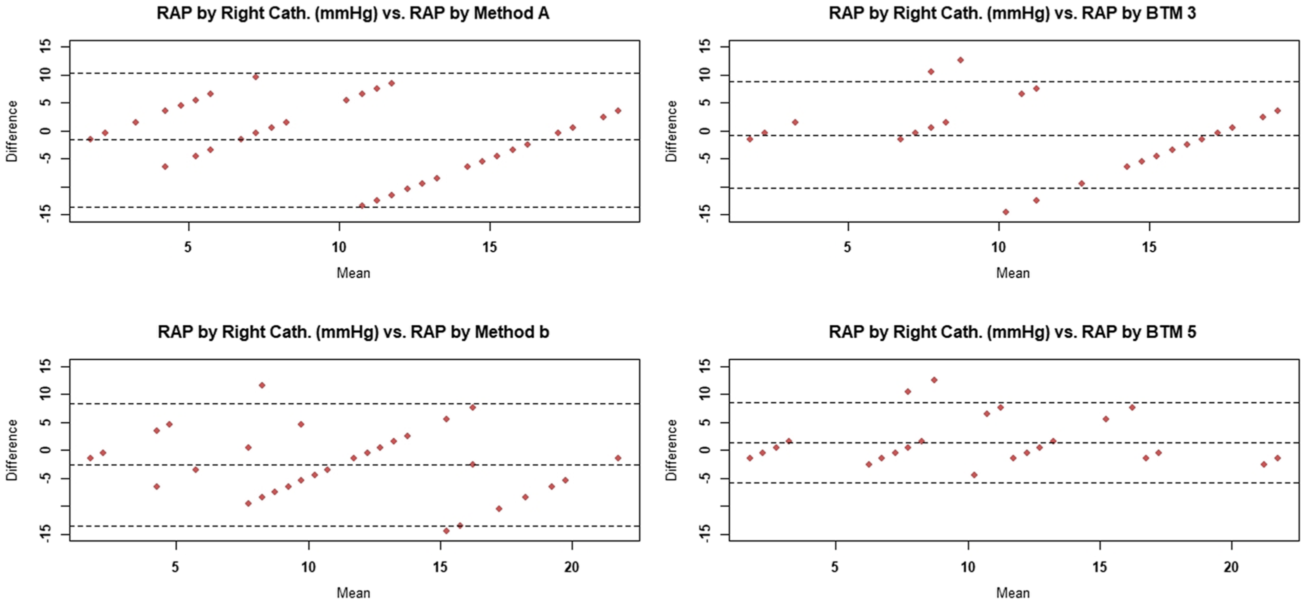
Fig. 6 **A** Compares the accuracy of BTM3 to SE method A in estimating RAP. **B** Compares the accuracy of BTM5 to SE method B in estimating RAP (*RAP* right atrial pressure, *SE* standard estimation model, *MCD* mean IVC diameter model, *BTM* binary tree model)

24]. Moreover, the rapid movement of the patients' abdomen could enhance the well-known physiological IVC movement, causing sample errors such as foreshortening of the vein [25]. Furthermore, the accuracy of this manoeuvre was weaker when intermediate and low RAP values were identified [1, 2]. Finally, a recent study using 3D echocardiography of the IVC to estimate RAP in cardiogenic shocked patients underlines the low reliability of the sniff manoeuvre, even when using an advanced imaging technique [26, 27].

The feasibility of our semi-automated tracking system (i.e., the number of processed video clips from the total) is 79%, which is in line with data reported by Magnino et al. [7] and was not related to the use of the software (drop-out patients' IVC was not correctly evaluated, neither by 2D

Table 2 Panel A compares the accuracy of RAP estimation between the automated methods and the SE methods A and B

Model	R^2	P value	Mean bias (mmHg) [limits of agreement]	2.5 mmHg accuracy	Relative accuracy
3 classes methods					
Method A	0.22	< 0.01	− 1.64 [− 13.65; 10.36]	14 (29%)	15 (31%)
BTM 3 classes	0.47	< 0.01	− 0.72 [− 10.18; 8.73]	30 (61%)	26 (53%)
5 classes methods					
Method B	0.26	< 0.01	− 2.56 [− 13.45; 8.33]	18 (37%)	16 (33%)
BTM 5 classes	0.61	< 0.01	1.42 [− 5.70; 8.54]	38 (78%)	28 (57%)



The mean bias and the limits of agreement are represented by dashed lines (top), Bland–Altman analysis between the measured and estimated RAP with all the methods is provided (bottom)

manual measurements, nor by semi-automated tracking). Future developments of the software could allow its real-time application, improving the quality of the processed data (source video clip, instead of exported data) and providing support to the operator to record data feasible for processing [10, 11]. This could help increase the feasibility of our processing algorithm.

Future perspectives

RAP is an essential parameter to guide medical therapy in many different clinical settings and especially in patients with heart failure. If BTM accuracy would be optimized with a larger sample size, it will provide an important tool for therapy decision making and potential risk stratification in patients with heart failure, as recently pointed out by Pellicori et al. in an elegant work in which congestion was assessed with an US based multi-parameter approach [28]. Our technique could be of interest even in the field of PH, in which evidences suggest that RAP is a reliable prognostic parameter [29]; indeed, in our cohort of patients, the semi-automated system helps to better classify PH severity compared to standard echocardiographic assessment (Online Table 4).

Study limitations

This validation study has some limitations.

1. Video clips were recorded with different echocardiographic machines, exported in AVI format and then sent to L.M. for processing. The analysis is semi-automated and time consuming. This limitation could certainly be overcome via improvements in the technology of this promising technique, also by integrating the software in US machines or in analysis workstations and making it fully automated. If real-time processing and rendering were available, the acquisition of high quality video clips would also be supported.
2. In this study, we included patients with advanced cardiac disease: 51% of them were affected by right ventricular

dysfunction and increased IVC diameters were found even in patients with low values of RAP, because of the enrolment criteria, probably related to chronic volume overload conditions. Furthermore, normal controls were not included in the present study. This limitation is shared with the majority of the studies in this field and is mainly related to ethical concerns in proposing invasive measurements in healthy people. To overcome this limitation, future studies could assess patients requiring electrophysiology procedures in which it would be possible to measure RAP invasively. For all these reasons, selection bias could not be excluded and our models (BTM3 and BTM5) should be considered fit to our cohort of patients with cardiovascular disorders.

3. The time elapsed between the RHC and the echocardiographic evaluation could have lowered the accuracy of RAP estimation. However, most of the studies available in literature are not simultaneous [2, 7].
4. The presence of few outlier patients in terms of extreme values of RAP is another limitation of this study that has to be acknowledged.
5. We did not perform any measurement using the short axis approach, therefore we cannot exclude that our measurements are affected by IVC displacement during respiratory cycle [24]. Further studies should be performed using also the short axis approach to evaluate the potential accuracy improvement provided by a 2 plane evaluation of the IVC.

We need to extend our technique to a larger and heterogeneous sample including a wide rate of normal individuals, to create a more reliable and consistent model considering also the impact of the sniff test and the effect of tricuspid regurgitation.

The lack of use of the sniff manoeuvre was established in line with protocol. This choice could be a weakness of our study with overestimation of RAP in most patients due to lower collapsibility obtained without the sniff (which could be overcome in the future by including this manoeuvre and processing the IVC response with our software).

Conclusions

Our multi-parameters prediction models, based on semi-automated edge-to-edge tracking of the IVC in resting respiration, could be accurate and effective tools to improve RAP estimation. They were found to be promising techniques, capable to estimate RAP with good accuracy in our small cohort of patients affected by heart failure and pulmonary hypertension.

Parameters most closely associated to RAP are the CI, mean IVC diameter and the new derived collapsibility indexes CCI and RCI. Conversely, measurements performed using the mean IVC diameter have the same (weak) accuracy as SE measurements using the single IVC diameter. This pilot study sets a new stage for further investigations aimed at identifying the best method for non-invasive assessment of RAP.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest. The authors have full control of all primary data and they agree to allow the journal to review their data if requested.

Appendix

The parameters were selected automatically by the routine implementing the training of the binary tree models (BTM). Specifically, all possible input features were considered. Given the input set of a specific BTM to be trained, the development of the BTM requires choosing the specific features for each binary separation (thus, which feature and in which order), selecting the threshold value for each splitting and how many divisions to consider. The BTM was implemented in MATLAB R2019a (The Mathworks, Natick, Massachusetts, USA), using the Gini's diversity index as splitting criterion. The best categorical predictor split was chosen from all possible combinations of choices. The models were cross-validated considering 30 folds. The one providing the best generalization to the validation sets (i.e., minimum number of misclassified observations in the validation sets) was then selected.

References

1. Rudski LG, Lai WW, Afilalo J et al (2010) Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 23:685–713
2. Brennan JM, Blair JE, Goonewardena S et al (2007) Reappraisal of the use of inferior vena cava for estimating right atrial pressure. J Am Soc Echocardiogr 20:857–861
3. Beigel R, Cercek B, Luo H, Siegel RJ (2013) Noninvasive evaluation of right atrial pressure. J Am Soc Echocardiogr 26:1033–1042
4. Lang RM, Badano LP, Mor-Avi V et al (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Hear J Cardiovasc Imaging 16:233–271
5. Mesin L, Giovinazzo T, D'Alessandro S et al (2019) Improved repeatability of the estimation of pulsatility of inferior vena cava. Ultrasound Med Biol 45(10):2830–2843

6. Fisher MR, Forfia PR, Chamera E et al (2009) Accuracy of doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 179:615–621
7. Magnino C, Omedè P, Avenatti E et al (2017) Inaccuracy of right atrial pressure estimates through inferior vena cava indices. Am J Cardiol 120:1667–1673
8. Tsutsui RS, Borowski A, Tang WHW et al (2014) Precision of echocardiographic estimates of right atrial pressure in patients with acute decompensated heart failure. J Am Soc Echocardiogr 27:1072–1078.e2
9. Mesin L, Pasquero P, Albani S et al (2015) Semi-automated tracking and continuous monitoring of inferior vena cava diameter in simulated and experimental ultrasound imaging. Ultrasound Med Biol 41:845–857
10. Mesin L, Pasquero P, Roatta S (2019) Tracking and monitoring pulsatility of a portion of inferior vena cava from ultrasound imaging in long axis. Ultrasound Med Biol 45:1338–1343
11. Mesin L, Albani S, Sinagra G (2019) Non-invasive estimation of right atrial pressure using inferior vena cava echography. Ultrasound Med Biol 45(5):1331–1337
12. Otto C (2004) Textbook of Clinical Echocardiography, 5th edn. W.B. Saunders, Philadelphia
13. Milan A, Magnino C, Veglio F (2010) Echocardiographic indexes for the non-invasive evaluation of pulmonary hemodynamics. J Am Soc Echocardiogr 23:225–239
14. Galiè N, Humbert M, Vachiery J-L et al (2016) 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 37:67–119
15. Mintz GS, Kotler MN, Parry WR et al (1981) Reat-time inferior vena caval ultrasonography: normal and abnormal findings and its use in assessing right-heart function. Circulation 64:1018–1025
16. Nakao S, Come PC, McKay RG, Ransil BJ (1987) Effects of positional changes on inferior vena caval size and dynamics and correlations with right-sided cardiac pressure. Am J Cardiol 59:125–132
17. Jue J, Chung W, Schiller NB (1992) Does inferior vena cava size predict right atrial pressures in patients receiving mechanical ventilation? J Am Soc Echocardiogr 5:613–619
18. Simonson JS, Schiller NB (1988) Sonospirometry: a new method for noninvasive estimation of mean right atrial pressure based on two-dimensional echographic measurements of the inferior vena cava during measured inspiration. J Am Coll Cardiol 11:557–564
19. Moreno FL, Hagan AD, Holmen JR et al (1984) Evaluation of size and dynamics of the inferior vena cava as an index of right-sided cardiac function. Am J Cardiol 53:579–585
20. Kircher BJ, Himelman RB, Schiller NB (1990) Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. Am J Cardiol 66:493–496
21. Ommen SR, Nishimura RA, Hurrell DG, Klarich KW (2000) Assessment of right atrial pressure with 2-dimensional and doppler echocardiography: a simultaneous catheterization and echocardiographic study. Mayo Clin Proc 75:24–29
22. Taniguchi T, Ohtani T, Nakatani S et al (2015) Impact of body size on inferior vena cava parameters for estimating right atrial pressure: a need for standardization? J Am Soc Echocardiogr 28:1420–1427
23. Goldhammer E, Mesnick N, Abinader EG, Sagiv M (1999) Dilated inferior vena cava: a common echocardiographic finding in highly trained elite athletes. J Am Soc Echocardiogr 12:988–993
24. Kimura BJ, Dalugdugan R, Gilcrease GW et al (2011) The effect of breathing manner on inferior vena caval diameter. Eur J Echocardiogr 12:120–123
25. Blehar DJ, Resop D, Chin B et al (2012) Inferior vena cava displacement during respirophasic ultrasound imaging. Crit Ultrasound J 4:18
26. Seo Y, Iida N, Yamamoto M (2017) Estimation of central venous pressure using the ratio of short to long diameter from cross-sectional images of the inferior vena cava. J Am Soc Echocardiogr 30:461–467
27. Huguet R, Fard D, d'Humieres T et al (2018) Three-dimensional inferior vena cava for assessing central venous pressure in patients with cardiogenic shock. J Am Soc Echocardiogr 31:1034–1043
28. Pellicori P, Shah P, Cuthbert J et al (2019) Prevalence, pattern and clinical relevance of ultrasound indices of congestion in outpatients with heart failure. Eur J Heart Fail 21(7):904–916
29. Lee W-TN, Ling Y, Sheares KK et al (2012) Predicting survival in pulmonary arterial hypertension in the UK. Eur Respir J 40:604–611

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