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

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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

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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 \pm 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

1 **Introduction**

2 The pulsatility of the inferior vena cava (IVC), estimated from ultra-
3 sound (US) measurements by a non-invasive procedure, reflects the intravas-
4 cular volume status of critical patients (Finnerty et al. (2017))(Au and Fields
5 (2017))(Airapetian et al. (2015))(Charbonneau et al. (2014)). It has been in-
6 vestigated in many applied studies, e.g., in cardiology patients with heart
7 failure (Wattad et al. (2015)), pulmonary hypertension (Galié et al. (2016)),
8 in critical patients (Akkaya et al. (2013)), in case of liver fibrosis or cirrho-
9 sis (Kitamura and Kobayashi (2005)), in healthy blood donors (Lyon et al.
10 (2005)) and healthy paediatric patients (Haines et al. (2012)).

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

16 In recent works (Mesin et al. (2015))(Mesin et al. (2018)), a semi-automated
17 method has been introduced to track the movements of the IVC in long-axis
18 US scans in order to compensate for respiration artefacts. Tests in simu-
19 lations indicate that the method provides a more precise estimation of the
20 IVC local pulsatility compared to the classical measurements (Mesin et al.
21 (2015)). Moreover, computing the vein diameters from an entire portion of
22 the vessel (Mesin et al. (2018)) and in an orthogonal direction to the IVC
23 midline (Pasquero et al. (2015)) allows the retrieval of overall pulsation in-
24 formation of the considered vein portion.

25 Here, the classical and semi-automated approaches are further investi-

26 gated in terms of the possibility of extracting information on the central
27 venous pressure (CVP). Patients with different cardiopathies were first in-
28 vestigated using US scans and then catheterized to measure the right atrial
29 pressure (RAP, assumed approximately equal to the CVP). Different patient
30 characteristics (anthropometric and IVC statics and dynamic behaviour, esti-
31 mated either using the classical or the semi-automated approach) were used
32 to build regression models for the RAP estimation. Those with minimum
33 error were selected.

34 **Materials and Methods**

35 *Automated detection of the IVC borders*

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

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

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

55 Once the superior and inferior borders of the vein (in the tract under
 56 investigation) have been obtained, the software computes the IVC midline.
 57 This is defined as the mean curve between the two borders. The curvilinear
 58 abscissa is then computed along the midline. Five points are then uniformly
 59 distributed along this line (i.e., with the same curvilinear distances between
 60 neighboring points), considering its extension from the 20% point to the
 61 80% point of its length (the edges of the tract were excluded). Then, the
 62 orthogonal sections, in respect to the IVC midline, passing from each of the
 63 5 points are considered and the pulsatility of the IVC is estimated for each
 64 of them in terms of the caval index (CI)

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

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

72 The following additional pulsatility indices (RCI and CCI) were also es-
 73 timated. The vein dynamics were considered as resulting from two different

74 stimulations, induced by either respiration or heartbeats, respectively. The
75 effect of respiration was computed by low pass filtering the whole diameter
76 time series with a cut-off frequency of 0.4 Hz. The cardiac contribution was
77 obtained by high pass filtering the whole diameter time series with a cut-off
78 frequency of 0.8 Hz (both filters were 4th order Butterworth; they were used
79 twice, once with time reversed, in order to remove phase distortion and de-
80 lay). From the two filtered time series, applying again the definition of CI
81 given in (1), the respiratory caval index (RCI) and the cardiac caval index
82 (CCI) were obtained.

83 *Experimental data*

84 The study was approved by the Ethics Committee of the University Hos-
85 pital of Trieste and complies with the principles of the Declaration of Helsinki.
86 Informed consents were obtained from the patients participating in the study.

87 We prospectively enrolled 62 patients (consecutively from 1/12/2015 to
88 1/9/2017) undergoing echocardiographic assessment and right heart catheter-
89 ization (RHC) for all clinical indications. Some of them were excluded, for
90 the following technical problems: IVC not visible (due to either abdominal
91 gas, excessive fat tissue, low definition of the edges of the vein) and paradox-
92 ical IVC movements (distal collapse and proximal dilatation or vice versa).
93 Finally, 49 patients with good US scans (i.e., allowing reliable processing)
94 could be included in the study (26 males and 23 females; mean±standard
95 deviation - STD: age 62.2±15.2 years, weight 71.7±15.3 kg, height 168.1±9.3
96 cm). The selected patients had the following pathologies: 28 patients (57%)
97 were affected by various heart disease (hypertensive, ischemic, valvular, toxic
98 and tachy-induced cardiomyopathy), 10 patients (20.4%) had hypertrophic,

99 dilated or restrictive cardiomyopathy and 11 patients (22.5%) showed non
100 group 2 pulmonary hypertension. The following machines were used to record
101 the US video-clips: VIVID E9, VIVID I and VIVID Q, by General Electric
102 (Wauwatosa, WI USA); iU22, by Philips (Bothell, WA USA). A scan of at
103 least 5 seconds of the IVC in the longitudinal axis was performed by B-Mode
104 echocardiography during at rest breathing with sub-costal approach. Clas-
105 sical estimation of CI was obtained by measuring subjectively maximal and
106 minimal diameters (we refer to it as the "manual" estimation).

107 *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

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

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

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

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

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

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

127 where x_r and x_m are the outputs of the multivariate regression model and
128 the measured RAP, respectively. Moreover, the standard deviation and kur-
129 tosis of the estimation error were computed. The mean value and standard

130 deviation of errors quantify the accuracy of the estimation, while the kurtosis
131 focuses on the tails of the error distribution and it measures large, spurious
132 errors.

133 To choose the optimal dimension of the model, the one with best perfor-
134 mances on the test set was selected.

135 Results

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

140 Figure 1 and Table 3 show the variables recorded from the patients used
141 to build the models for the estimation of RAP. Their relation with RAP is
142 shown. Notice that most anthropometric indices have a low correlation with
143 RAP. On the other hand, some relation is found between RAP and the fea-
144 tures extracted from the IVC. For example, the index with most correlation
145 with the RAP is IVC mean diameter (both when measured manually and
146 automatically, but with more correlation in the latter case). In addition, the
147 pulsatility indices show a good inverse correlation with RAP (again, more
148 correlation is found considering the automated estimation). Other IVC size
149 and pulsatility indices show some correlation with RAP (but were not shown
150 in Figure 1 and Table 3): for the minimum diameter, the correlations were
151 55.3 and 67.4%, for the maximum diameter 54.9 and 59.0%, for the manual
152 and semi-automated methods, respectively; for $1/(RCI + a_2)$ the correlation
153 was 57.5%, for $1/(CCI + a_3)$ it was 61.1%.

154 Figure 2 shows the best estimation models. In both cases, the low dimen-
 155 sional models provided better generalization to the test set (so that overfit-
 156 ting was found as the model included many variables). Specifically, the best
 157 model when using the manual approach uses only one feature to fit RAP:

$$RAP_{est}^{Manual} = 0.55D_m \quad (3)$$

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

$$RAP_{est}^{Manual} = 0.52 D_m + 0.0085 age \quad (4)$$

162 where age is the age of the patient measured in years (mean absolute error
 163 4.14 mmHg, STD 4.87 mmHg, kurtosis 1.89). This second model selected
 164 again the mean diameter of the IVC and added a correction term due to the
 165 age. Notice that a pulsatility index is not chosen to be included in the best
 166 models, even if Figure 1 and Table 3 show that CI_{manual} has a high inverse
 167 correlation with RAP. Indeed, the manually estimated caval index and diam-
 168 eter are quite redundant (the correlation between the measured diameter and
 169 $1/(CI_{manual} + a_0)$ is equal to 48%), so that the additional information pro-
 170 vided by the measured IVC pulsatility was not relevant enough to contribute
 171 to a reduction of the estimation error.

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

$$RAP_{est} = \frac{4.13}{CI + a_1} + 0.52 D_m \quad (5)$$

175 It has a mean absolute error of 3.64 mmHg on the test set (STD equal to
 176 4.48 mmHg, kurtosis equal to 2.09). The best models using either 1 or 3
 177 features are given by the following expressions

$$RAP_{est} = 0.60 D_m \quad (6)$$

178

$$RAP_{est} = \frac{3.98}{CI + a_1} + 0.52 D_m + 0.0008 age \quad (7)$$

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

195 The Bland-Altman plots shown in Figure 2 (considering the best manual
 196 and semi-automated models) indicate that the range of estimation error is
 197 between ± 10 mmHg, but for more than 65% of tests the estimation error was

198 lower than 5 mmHg. For both models, there is a bias, as the errors are mainly
199 positive and negative for low and large values of RAP, respectively, indicat-
200 ing an average underestimation of the variations of RAP among different
201 patients. However, this bias is lower for the model based on semi-automated
202 estimation of features (slope of interpolation line equal to 0.75 and 0.53 for
203 the manual and semi-automated models, respectively).

204 **Discussion**

205 Estimating RAP from US scans is a difficult inverse problem. Some rela-
206 tion between size and pulsatility of IVC and the pressure in the right atrium
207 has been suggested in the literature and collected into guidelines (Lang et al.
208 (2015))(Rudski et al. (2010)). However, the lack of standardization of the
209 procedure meant some doubts have arisen on the reliability of the estimates
210 (Magnino et al. (2017)). Recent developments have allowed more accurate
211 and repeatable estimation of the dynamics of the IVC, due to the tracking
212 of the vein (Mesin et al. (2015)) and to the average of information from an
213 entire tract of the vessel (Mesin et al. (2018)) provided by an innovative
214 semi-automated algorithm.

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

220 A limitation of our study is that the method was tested on a small
221 database, as processing was successful only for 49 out of 62 patients. Future

222 developments will include the engineering of the software in a US system,
223 so that the original data could be directly processed and a real time render-
224 ing could guide the operators in order to acquire video-clips for which the
225 processing is feasible.

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

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

239 An instrument implementing the algorithm described in this paper was re-
240 cently patented by the Politecnico di Torino and Università di Torino (patent
241 number 102017000006088).

242 **Conclusions**

243 A new promising technique has been introduced for the estimation of
244 RAP. Higher accuracy is obtained when using a semi-automated method for
245 the tracking and assessment of IVC pulsatility in an entire portion of the

246 vessel, than by considering manual subjective measurements (in the latter
247 case, IVC pulsatility did not improve accuracy of RAP estimation).

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

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330 **Figure Captions**

331 **Figure 1:** Different variables versus right atrial pressure (RAP), with indi-
332 cation of the correlation.

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

General Data	Mean \pm STD
Systolic Blood Pressure (mmHg)	115.9 \pm 21.1
Diastolic Blood Pressure (mmHg)	71.3 \pm 9.8
Heart Rate (bpm)	75.4 \pm 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
Δ Echo-Cath Time (min)	213 \pm 122
Mean Pulmonary Artery Pressure (mmHg)	33.4 \pm 11.6
Right Atrial Pressure (mmHg)	10 \pm 5.6
Echocardiographic data	Mean \pm STD
LV Ejection Fraction (%)	48.2 \pm 19.7
Tricuspid Annular Plane Systolic Excursion (mm)	17 \pm 4.7
RV FAC (%)	35.6 \pm 12.8
Tricuspid E/E	5.6 \pm 2.9
Tricuspid E/A ratio	1.2 \pm 0.4
Expiratory IVC diameter (mm)	20.4 \pm 5.5
Inspiratory IVC diameter (mm)	14.0 \pm 6.5
IVC Collapsibility Index	0.35 \pm 0.2
Measured Right Atrial Pressure (mmHg)	12.5 \pm 7.4
Pulmonary Artery Systolic Pressure (mmHg)	53.0 \pm 19.1
Video Processing	Mean \pm STD
Length of processed IVC tract (cm)	44.5 \pm 12.3
Duration of US video clips (s)	9.3 \pm 4.6
Identified respiration cycles	2.5 \pm 1.3
Identified heartbeats	13.8 \pm 7.5

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

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