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Improved repeatability of the estimation of pulsatility of inferior vena cava

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Abstract

The inferior vena cava (IVC) shows variations of cross-section over time (referred to as pulsatility) induced by different stimulations, like as breathing and heartbeats. The amplitude of these pulsations is affected by the volume status of the patient and can be investigated by ultrasound (US) measurements. Thus, the caval index (CI), i.e., an index of pulsatility of IVC based on US visualization, was proposed as a non-invasive indirect measurement of the volume status. However, the methodology is not standardized, operator-dependent and affected by movements of the vein and non-uniform pulsatility. We introduced a software that processes a B-mode US video-clip to track IVC movements and estimate the CI on an entire portion of the vein. This new method is here compared to the standard approach in terms

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of repeatability of the estimated CI. Furthermore, the cardiac and respiratory contributions to IVC pulsatility are separated, avoiding the confounding effects of their asynchronous summation to provide two additional selective pulsatility indexes. We report on the variability of CI estimation over the following factors: different respiratory cycles or heart pulsations, longitudinal sections of the vein and intra/inter observer reproducibility. Our method allows to reduce the variability of CI assessment, **providing** a step toward its standardization.

Keywords: Inferior vena cava, Ultrasound, Tracking, Repeatability, Volume status

1 Introduction

2 Pulsatility of the diameter of the inferior vena cava (IVC), estimated from
3 ultrasound (US) measurements, is a non-invasive procedure, widely adopted
4 to assess the intravascular volume status both in healthy subjects and condi-
5 tions of altered volemic status in patients. **However, measurement techniques**
6 **are not standardized** (Wallace et al. (2010)), as both recordings along lon-
7 gitudinal (Barbier et al. (2004); Brennan et al. (2006); Fields et al. (2011);
8 Feissel et al. (2004); Grant et al. (1980); Kircher et al. (1990); Lyon et al.
9 (2005); Moreno et al. (2019)) or transversal sections (Blehar et al. (2009);
10 Chen et al. (2010); Moreno et al. (2019)) of the vein are used. Different rec-
11 ommendations have been proposed on where to measure the vein diameter
12 along a longitudinal section (Wallace et al. (2010); Resnick et al. (2011)).
13 However, since the pulsatility of the vessel is not uniform along its longitu-
14 dinal axis (Mesin et al. (2015, 2019b)), CI values vary considerably in the
15 literature in both healthy and pathologic conditions and, as a result, diag-
16 nostic recommendations are also non homogeneous (Zhang et al. (2014)).

17 The pulsations of the vessel during the respiratory cycle are used to mea-
18 sure the caval index (CI, Blehar et al. (2012)). However, the movements
19 of the vein relative to the transducer during the respiratory cycle give an
20 additional contribution to the variability of CI. Indeed, M-mode registra-
21 tion allows to compute the vein diameter along a fixed line at the end of
22 inspiration and expiration, but, since the IVC moves during respiration, the
23 diameters end up being taken at different points, introducing a possible bias.
24 This is particularly relevant if the vein has an irregular shape, with a vari-
25 able cross-sectional area (Lichtenstein (2005)) or if the angle between the

26 M-mode line and the vein changes considerably during its movements. In
27 addition, respiration cycles may differ between each other and change among
28 subjects (e.g., breathing can be diaphragmatic, thoracic or a combination
29 of both), inducing changes in the IVC dynamics (Kimura et al. (2011)). In
30 order to minimize movements of the vein during respiration, variations of
31 the IVC section was investigated during voluntary apnoea, thus bringing for-
32 ward the effect of cardiac activity on IVC pulsatility (Folino et al. (2017);
33 Nakamura et al. (2013)), which is otherwise poorly detectable on M-mode
34 representation. However, this technique cannot be easily applied in clinics.

35 We reported on successfully tracking IVC movements in long-axis US
36 scans while estimating its diameter in each frame, along a direction moving
37 together with the vein (Mesin et al. (2015)). This method has a lower com-
38 putational cost than other advanced image processing techniques applied to
39 US images (Yang et al. (2008); Yeung et al. (1998); Krupa et al. (2007))
40 and provides a more precise estimation of the IVC local pulsatility with re-
41 spect to standard measurements, based on a fixed M-mode line (Mesin et al.
42 (2015)). However, a possible problem is that pulsatility along a single sec-
43 tion of the IVC may be not representative of the dynamics of the whole
44 vessel. Some parts of the vein are anchored to nearby structures (e.g., the
45 diaphragm or vein inlets) and show smaller pulsatility than other portions.
46 For example, lower pulsatility was reported at the level of the diaphragm
47 compared to more caudal sites (Wallace et al. (2010)). These observations
48 were confirmed in Mesin et al. (2015) (Figure 9), showing that diameter vari-
49 ations along distinct directions (moving together with the vein) resulted in
50 considerably different pulsatility. Lack of consensus about where to measure

51 diameters (Wallace et al. (2010); Resnick et al. (2011)) and the non-uniform
52 behaviour of the vessel are likely to contribute to the non-homogeneous as-
53 sessments of IVC pulsatility in the literature (Weekes et al. (2012)). Thus,
54 we recently proposed a new algorithm that tracks the movements and com-
55 putes the diameter of different sections of a whole portion of the IVC (Mesin
56 et al. (2019b)). Here, we compare this innovative method to the standard
57 approach and report on **the repeatability of information** extracted from dif-
58 ferent measurements on the same subjects.

59 **Materials and Methods**

60 *Automated detection of the IVC borders*

61 US video-clips were processed using the algorithm proposed in Mesin
62 et al. (2019b), which allows to obtain a continuous measurement of IVC
63 borders along an entire portion of the vessel after compensating for possible
64 movements. The algorithm was implemented in MATLAB R2018a (The
65 Mathworks, Natick, Massachusetts, USA).

66 The user is asked to indicate the location of the vein in the first frame
67 (Figure 1A). Moreover, as shown in Figure 1B, on the same frame, he chooses
68 two reference points to be tracked (to account for IVC movements and de-
69 formations) and the most proximal/distal sections (defining the portion of
70 the IVC of interest, which was between the confluence of the hepatic veins
71 into the IVC and the caudate lobe of the liver). Finally, the locations of the
72 borders of the vein along the most proximal line are indicated. The software
73 is then ready to process the video-clip. It distributes uniformly N lines in
74 the portion of IVC indicated by the user (N=21 in this paper) and automat-

75 ically detects the borders of the vein along these lines (Figure 1C). For each
76 frame, the location and direction of the N lines are updated depending on
77 the movements of the reference points. In this way, the superior and inferior
78 borders of the vein are estimated in the IVC portion of interest.

79 *Subjects*

80 US data were recorded from 10 healthy volunteers (5 females, 5 males;
81 mean \pm std age 30 \pm 13 years, height 172 \pm 12 cm, weight 63 \pm 11 kg) with a
82 SonoSite M-Turbo system (SonoSite, Bothell, USA¹; frame rate 30 Hz, reso-
83 lution of about 0.42 mm per pixel, 256 gray levels) equipped with a convex
84 2-5 MHz probe. Two-dimensional (B-mode) longitudinal views of the IVC
85 were taken with a subxifoideal approach, with the subject in the supine posi-
86 tion during relaxed normal breathing. The study was approved by the **Ethics**
87 **Committee of the University of Turin** and complies with the principles of the
88 Declaration of Helsinki. All subjects provided written informed consent for
89 the collection of data and subsequent analysis.

90 *Experimental set-up and protocol*

91 The experimental protocol is illustrated in Figure 2. Three operators
92 performed the US scans: one expert (PP), one in training (AR) and one be-
93 ginner (FC), with balanced arrangement of their order. An operator started
94 by taking 3 measurements of IVC diameters (as defined below) using stan-
95 dard methodology in M-mode. Then, a 15s video-clip was recorded, allowing
96 for at least three respiratory cycles. After the first recording, the subject was

¹M-Turbo Ultrasound System - User manual, http://www.sonosite.com/downloads/M-Turbo_UG_P07662.pdf

97 asked to stand up for one minute to minimize any changes of the IVC due to
98 remaining in the supine position for a prolonged time (Folino et al. (2017)).
99 Then, the subject was asked to lie down again supine and a new acquisition
100 was taken by a second operator and, after standing up again, by a third one.
101 The whole procedure was repeated a second time, obtaining six video-clips
102 for each subject.

103 *Indexes extracted from the data*

104 Different indexes were taken from each measurement, in order to test their
105 repeatability. Three manual measurements in M-mode were taken before
106 registering the video-clips. The operator chose three respiratory cycles. For
107 each of them, the maximum and minimum vein diameters (D_{max} and D_{min} ,
108 respectively) were indicated, and the (manual) CI was computed as

$$CI = \frac{D_{max} - D_{min}}{D_{max}} \quad (1)$$

109 The video-clips were then processed to estimate the IVC borders as detailed
110 above. Notice that the position of each point of the border is indicated by
111 time series (location along x and y directions, one value per frame). These
112 time series were low pass filtered with a 4 Hz cut-off, in order to remove high
113 frequency and quantization noises (this filter and the ones mentioned below
114 were of Butterworth type, order 4 and used in both directions to remove
115 phase distortion and delay, Mesin et al. (2019b)). Then, the borders of the
116 IVC were estimated from the confluence of the hepatic veins into IVC to 4
117 cm in distal direction (Figure 1D). Specifically, from the estimated borders,
118 the IVC midline was computed. It was then approximated by a parabolic
119 function. The location of the confluence of the hepatic veins into the IVC was

120 indicated by the user (SA, who was not an echographer) on the first frame of
 121 the video-clip. This point was orthogonally projected on the IVC midline and
 122 represented the starting point from which other 4 points were automatically
 123 estimated, with 1 cm curvilinear distance from each other along the IVC
 124 midline. Thus, 5 points were obtained, 0 to 4 cm distant from the confluence
 125 of the hepatic veins into the IVC, projected on the midline of the vein.
 126 Then, the sections orthogonal to the IVC midline passing from each such
 127 points were considered (Mesin et al. (2019b); Pasquero et al. (2015)) and
 128 the IVC diameters in these sections were computed by interpolation from
 129 the estimated vein borders (see Mesin et al. (2019b) for details). These five
 130 diameters are further considered in the following.

131 The pulsatility of the IVC in each section was described by the (auto-
 132 mated) CI, defined as

$$CI_{auto} = \frac{\max(D) - \min(D)}{\max(D)} \quad (2)$$

133 where D indicates the estimated diameter time series (in a specific section).
 134 Local maxima and minima were computed for each respiration cycle (Figure
 135 3A). Thus, an estimate of CI was obtained for each respiratory cycle and
 136 for each section considered. As in the case of the manual CI estimation,
 137 the CIs of 3 respiratory cycles were selected. In the cases in which more
 138 than 3 cycles were present in the video-clip, the CIs closer to their mean
 139 across different cycles were selected. After testing the repeatability across
 140 respiration cycles, the estimated CIs were averaged. A CI accounting for the
 141 overall pulsatility of the considered portion of the vein was also considered
 142 (indicated as CI_{global}): it was obtained by averaging the estimates across
 143 different sections.

144 Additional indexes of pulsatility were obtained after further processing
145 the diameter time series estimated by our software. The vein dynamics was
146 considered as the sum of two components, reflecting the stimulation induced
147 by respiration and heartbeat (Mesin et al. (2019a)). The two components
148 were separated as follows: the effect of respiration was computed by low
149 pass filtering the whole diameter time series with a cut-off frequency of 0.4
150 Hz. The cardiac contribution was computed by high pass filtering the whole
151 diameter time series with a cut-off frequency of 0.8 Hz. Then, the following
152 additional indexes were estimated, as shown in **Figure 3**.

- 153 • The respiratory caval index (RCI), applying the same formula (2) to
154 the respiration component only.
- 155 • The cardiac caval index (CCI), applying the same formula (2) to the
156 cardiac component only.

157 Also for these two indexes, stimulation cycles were selected: 3 respiration
158 cycles and 10 heartbeats were included. Moreover, the subscript global
159 was added to indicate their average across different sections (RCI_{global} and
160 CCI_{global}).

161 *Assessment of repeatability and discriminability*

162 Different indicators were used to assess the repeatability of each index
163 (manual and automated CI, CCI, RCI) extracted from the 6 measurements
164 performed by the operators.

- 165 • Coefficient of variation (CoV), defined as the ratio between the stan-
166 dard deviation and the mean of the estimates. It gives an indication

167 of the agreement of an index extracted from different measurements
168 in the same conditions. It was used to test variations due to different
169 respiration cycles, different sections and different experimental sessions
170 (intra- and inter-operator).

171 • Intraclass correlation coefficient (ICC). It is defined as

$$ICC = \frac{var(S)}{var(S) + var(M) + var(E)} \quad (3)$$

172 where $var(S)$, $var(M)$ and $var(E)$ indicate the variability due to either
173 different subjects or measurements (i.e., experimental sessions) and the
174 residual error, respectively (Bartko (1966)). It was used to test intra-
175 and inter-operator variability. Notice that the ICC is equal to 1 if the
176 whole variability is due to the differences between subjects, whereas no
177 variability is due neither to the measurements nor to errors (always the
178 same value is obtained).

179 An index of discrimination was also studied, in order to avoid the possible
180 case in which an index is repeatable only because it always takes similar
181 values, even considering different subjects. The Fisher ratio was used. It
182 measures the linear discrimination between two sets of values as

$$FR = \frac{(\mu_1 - \mu_2)^2}{\sigma_1^2 + \sigma_2^2} \quad (4)$$

183 where μ_k and σ_k^2 (with $k = 1, 2$) are the mean and the variance of the k^{th} sets,
184 respectively. The sets to be compared were constituted by the 6 values of
185 a specific index extracted from the different measurements on each subject.
186 The mean of the Fisher ratios measuring the discrimination of each pair of
187 subjects was used as overall discriminability indicator.

188 Finally, analysis of variance (ANOVA) was used to investigate the differ-
189 ent sources of variability. The manual CI and CI_{global} (i.e., the automated CI
190 obtained averaging across different sections) were compared with an ANOVA
191 (normality of residuals was assessed by Lilliefors test), investigating the vari-
192 ability induced by the following factors: subject, operator, repetition and
193 respiration cycle. Some paired post-hoc tests for significant variations among
194 couples of variables were performed by either t-tests or Wilcoxon signed rank
195 tests (depending on the output of the Lilliefors normality test). The signifi-
196 cance level was set to $p = 0.05$.

197 *Summary of investigated indexes*

198 The following indexes are considered.

- 199 1. Manual CI, which is a variable depending on the following factors: res-
200 piration cycle (3 cycles considered), subject (10 volunteers) and experi-
201 mental session (6 sections, which could be further split into 3 operators
202 repeating twice the experiment). The average across the respiration
203 cycles was also considered.
- 204 2. CI_{auto} , RCI_{auto} and CCI_{auto} , depending on the following factors: respi-
205 ration cycle (3 cycles considered) or heartbeat in the case of CCI_{auto}
206 (10 beats considered), subject, section (5 locations, measured in terms
207 of the distance from the hepatic veins) and experimental session. The
208 average across the respiration cycles/heartbeats was also considered.
- 209 3. CI_{global} , RCI_{global} and CCI_{global} , obtained by averaging the previous in-
210 dexes across the sections (obtaining a global index for the vein tract
211 under study), so that they depend on respiration cycle or heartbeat (the

212 latter in the case of CCI_{global}), subject and experimental session. The
213 average across the respiration cycles/heartbeats was also considered.

214 Results

215 Figures 4-7 show different contributions to the variability of the estimates
216 of some indexes reflecting the pulsatility of IVC. For clarity, a single source
217 of variability is considered in each figure (respiration, longitudinal section,
218 experimental session and intra-/inter-operator variability, respectively) and
219 only some indexes are shown. The whole database is fully explored with the
220 statistical analysis shown in Tables 1-3.

221 *Variability of CI in subsequent breaths*

222 Figure 4A shows the changes in IVC diameter exhibited in a representa-
223 tive subject at rest. The tracings refer to different IVC sections, located at
224 0, 2 and 4 cm distal to the confluence of hepatic veins into the IVC. Notice
225 that the sections exhibit different average diameter and different amplitude
226 of oscillatory components of cardiac and respiratory origin. For example, at
227 the confluence of the hepatic vein, the algorithm estimated different respi-
228 ration cycles with CIs varying in the range 18%-28% and with a CoV equal
229 to 19% (indicating the variability of the CI estimations across different res-
230 piration cycles). Figure 4B shows the CoV of the estimations of the CIs
231 assessed on single respiratory cycles, extracted from the whole dataset. This
232 CoV, expressing the variability observed over consecutive respiratory cycles,
233 was calculated for all trials (obtaining 60 values of CI_{auto}^2) and for each IVC

²60 values of CoV are obtained as we considered 10 subjects for 6 experimental sessions.

234 section. In addition, for comparison, the same figure also includes the CoV
235 of CI_{global} and CI_{manual} . Notice that the median variability with respect to
236 different respiration cycles (in terms of CoV) is about 15% when considering
237 the standard (manual) method, about 5% when considering single sections
238 tracked by the automated method Mesin et al. (2015) (CI_{auto}) and lower than
239 3% when considering the global CI (averaged over all IVC sections, CI_{global} ;
240 Wilcoxon signed rank test indicated that the CoV of manual and global CI
241 were statistically different).

242 *Variability of CI with longitudinal position*

243 All the following figures show indexes obtained by averaging estimations
244 on different respiration cycles.

245 Figure 5 shows the variability of CI estimation across different sections
246 along the IVC. The dependence of IVC pulsatility along the longitudinal po-
247 sition is visible in 5A for the different subjects (CI_{auto} is shown averaged over
248 all 6 experimental sessions). Notice that there is no location showing larger
249 or lower pulsatility, being the patterns very different among the subjects.
250 The dependence of CI on position can be relevant: e.g., in subject number
251 7, CI_{auto} decreases from about 40% to 10%, moving caudally by 3 cm from
252 the confluence of the hepatic veins into IVC; conversely, in subject 8, CI
253 increases from about 50% to 70%, over the same distance.

254 The variability of CI_{auto} along the considered IVC tract was quantified by
255 its CoV. One estimation of CoV was obtained for each experimental session,
256 obtaining 6 values for each subject which are shown in Figure 5B. On average,
257 it is as high as 30% (which means that the range of variation is larger than

258 the mean value³).

259 *Variability of CI, RCI and CCI over the different experimental sessions*

260 For the different indexes (now including also RCI and CCI), the CoV
261 was computed over the 6 experimental sessions, thus providing a measure of
262 repeatability of the assessment for each subject.

263 This evaluation was conducted separately for the different positions along
264 the IVC in order to compare automated and manual assessments. As illus-
265 trated in Figure 6, none of the sections along the IVC exhibits a CoV signif-
266 icantly smaller than the others. Moreover, it can be observed that i) manual
267 and automated (over single **section**) assessments have similar variability (6A);
268 ii) removing the respiratory component improves repeatability (6B and 6D);
269 iii) filtering out the cardiac component does not improve repeatability (6C
270 and 6D); iv) a relevant reduction in CoV of CI_{auto} is obtained by calculating
271 the CI over the entire longitudinal portion of IVC (CI_{global}). **Statistically**
272 significant differences were found between the manual CI and CCI_{global} and
273 between CI_{global} and RCI_{global} .

274 *Intra- and inter-operator variability of CI assessment*

275 Figure 7 shows a comparison between the CoV of manual CI and global
276 automated estimation (CI_{global}). **Intra-operator variability was computed us-**
277 **ing the two repetitions of the measurement** by the specific operator consid-
278 ered. Inter-operator variability was computed from the average CI obtained

³Assume a Gaussian distribution of the estimates of CI along the sections: the range is about 4 times the standard deviation of the estimates. Thus, if CoV is 30%, the range is about 120% of the mean.

279 by the operators (averaging the two repeated measurements) from each sub-
280 ject. The spread of the estimates obtained from the same subject was lower
281 for the automated method for 9 subjects out of 10 (a statistically signifi-
282 cant difference is indicated by the Wilcoxon signed rank test applied to the
283 standard deviations of the estimates obtained using either the manual or
284 the automated CIs; the CoV of manual and global CI were not statistically
285 different, instead). Most of the repeated manual measurements of each op-
286 erator were quite similar (mean intra-operator CoV equal to 28%), but the
287 estimations varied a lot among different operators (mean inter-operator CoV
288 equal to 35%). The automated measurements were more stable and showed
289 similar intra- and inter-operator variabilities (mean CoV equal to 24 and
290 18%, respectively).

291 *Statistical analysis*

292 The statistical analysis of our data is shown in Tables 1-3. Table 1 shows
293 the ANOVA, comparing the manual CI and CI_{global} . Notice that the total
294 variability of CI is larger when using the standard clinical approach. More-
295 over, as indicated by the F statistics, a slightly higher percentage variability
296 is obtained considering different subjects when using the automated method
297 instead of the standard one (so that a better discrimination of different sub-
298 jects can be obtained using the automated algorithm). On the other hand, a
299 lower variability is obtained using the automated method in different exper-
300 imental sessions (when pooling together the factors repetition and operator,
301 results not shown) and respiration cycles (even if the variations induced by
302 the respiration cycle are not significant). Splitting the experimental sessions
303 into the factors repetition and operator, we notice that the variations on

304 different repetitions were quite small (and not significant), whereas larger
305 (significant) differences were found considering different operators (in line
306 with the inter- and intra-operator CoV discussed above). Moreover, smaller
307 variations over different repetitions were found for the standard approach,
308 whereas those induced by different operators were smaller for the automated
309 approach. Thus, the automated approach provides measurements that are
310 more stable across different operators, whereas, by the standard approach,
311 the echographers obtained twice similar values, which were however different
312 from those of the colleagues, indicating a possible bias.

313 Tables 2 and 3 show respectively the ICC and the Fisher ratio of the caval
314 indexes computed either by the standard or the automated method (manual
315 CI, CI_{global} , CCI_{global} and RCI_{global}). Intra-operator values were computed
316 considering only the estimates obtained by each operator, separately; inter-
317 operator values were obtained by grouping together the estimates of the same
318 operator. Notice that the most experienced operator obtained quite high val-
319 ues of ICC and Fisher ratio, considering both the standard method and the
320 indexes extracted from the video-clips that he recorded. The CIs measured
321 with the standard method had a correlation with those estimated by our
322 software using the corresponding video-clips (i.e., those registered after the
323 M-mode assessment) which was found to be related to the experience: FC,
324 AR and PP (i.e., the operators in order of increased experience) showed a

325 correlation coefficient of 36.2%, 58.1% and 70.8%, respectively⁴. The second
 326 operator in order of experience (AR) had a personal technique to measure
 327 the CI in M-mode (further commented in the Discussion section) which al-
 328 lowed him to get similar values in repeated measurements by the standard
 329 approach, so that his ICC and Fisher ratio are quite high. Notice that the es-
 330 timates of CI obtained by the automated method are more consistent across
 331 different operators (inter-operator ICC about 70%, whereas it is about 61%
 332 for the standard estimation). High values of ICC were obtained also for the
 333 estimation of CCI, lower values for RCI (in line with Figure 6). Notice also
 334 that the video-clips acquired by the most experienced operator allowed to
 335 get more repeatable estimates of the automated indexes (this indicates the
 336 importance of acquiring good video-clips to get repeatable results also from
 337 the automated processing). The results on intraclass correlation are in line
 338 with those shown by the Fisher ratio: indeed, a larger repeatability of the
 339 estimation of the pulsatility of each subject allows to better discriminate
 340 between different subjects.

⁴The following definition of correlation coefficient is used:

$$C = \frac{\sum_n (x[n] - \bar{x})(y[n] - \bar{y})}{\sqrt{\sum_n (x[n] - \bar{x})^2 \sum_m (y[m] - \bar{y})^2}} \quad (5)$$

where $x[n]$, $y[n]$ are the series to be compared and \bar{x} , \bar{y} are their means.

341 **Discussion**

342 *Summary*

343 For the first time, repeatability of standard CI estimations was assessed in
344 a group of healthy subjects, the results indicating rather poor values in terms
345 of both intra- (mean CoV=28%, ICC in the range 49-82%) and inter-operator
346 variability (mean CoV=41%, ICC=61.5%).

347 With the help of a semi-automated algorithm analysing 15s lasting video-
348 clips of the IVC in long axis, it was possible to show

- 349 1. high variability of the CI over the respiratory pattern (CoV about 5%,
350 whereas it is about 15% for the standard approach),
- 351 2. high variability of the CI depending on the longitudinal site of assess-
352 ment (median of CoV ranging among 10 and 70% for different subjects,
353 after averaging across respiration cycles).

354 By 1) averaging over consecutive breathing cycles, 2) tracking IVC longi-
355 tudinal movements and 3) averaging over multiple longitudinal sites, the
356 algorithm offers a more objective and reliable measurement of the CI (here
357 called global CI), reducing the overall variability (intra- and inter-operator
358 mean CoV equal to 24% and 18%, respectively; ICC=70.4%). In addition,
359 the identification of the respiratory and the cardiac oscillatory components
360 may provide new insights and possibilities for the analysis of IVC dynamics,
361 with repeatability performances close to those of the standard CI and global
362 CI, respectively.

363 *Discussion of different sources of variability*

364 The pulsatility of the IVC by the CI estimation is widely used to assess the
365 volemic status in different clinical conditions. However, the measurements
366 are not standardized and the recommendations given in the literature are
367 not univocal (Zhang et al. (2014)).

368 To the best of our knowledge, the repeatability of the estimation of the
369 IVC pulsatility has never been assessed previously. However, it would be a
370 very important information, as it could provide an indication of the limits
371 of the method to discriminate the volume status of different patients or in
372 the follow up. In this paper, we explored different sources of variability that
373 may affect the assessment of IVC pulsatility.

- 374 • Variation of the depth and modality of respiration, which induce dif-
375 ferent IVC pulsatility for each breath cycle. Notice that controlling
376 the respiration cycle (e.g., by a spirometer, even if only the respiration
377 depth, not the modality, could be controlled) could possibly reduce this
378 source of variability. Indeed, in the case of mechanically ventilated pa-
379 tients, the respiration cycles are regular and the dynamics of the IVC
380 diameter was found to be useful to detect fluid responsiveness (Feissel
381 et al. (2004)). As an alternative, measuring the pulsatility during a
382 short apnoea, thus caused by the heartbeats only (Folino et al. (2017);
383 Nakamura et al. (2013)), could help to standardize the measurement.
- 384 • Variations of the pulsatility in different sections of the vein. These
385 variations were noticed both in longitudinal (Mesin et al. (2015, 2019b))
386 and transversal scans (Blehar et al. (2012)).

387 • Variations introduced by the operator. In different measurements, the
388 investigated 2D section can be slightly different. Furthermore, the US
389 probe handled by the operator must follow the movements of the pa-
390 tient during respiration: the ability to follow the movement without
391 affecting the measurement depends on the level of experience of the
392 operator.

393 In addition, there are variations of the investigated IVC section, due to move-
394 ments of the vein during an M-mode measurement (as the M-mode registra-
395 tion fixes the considered section in space). Consider that both translation
396 and rotation of the vein with respect to the studied direction are expected
397 to occur in general. The former induces an error in the estimated diameter
398 dependent on the shape of the vein, while rotation affects the estimated di-
399 ameter even if the vein is a perfect cylinder. The problem is reflected by an
400 error in the estimation of pulsatility, which depends on the range of move-
401 ments and anatomy of the vein (Mesin et al. (2015)). In this paper, such
402 a problem affected only manual estimations. The automated IVC tracking
403 (introduced in Mesin et al. (2015, 2019b)) allows to remove this source of
404 uncertainty.

405 The other three sources of variation mentioned above were investigated
406 in this study, considering both the standard manual measurements and the
407 automated estimations provided by the algorithm proposed in Mesin et al.
408 (2019b), which estimates the IVC sections in a whole portion of the vein.
409 Figures 4-7 show repeatability in terms of CoV, so that the variation is
410 measured as the standard deviation of the estimates normalized with respect
411 to their mean.

- 412 • The CI (as a measurement of IVC pulsatility) in different respiration
413 cycles had median variation which was about the 15%, 5% and 3% of
414 the mean value, for the manual and the automated methods respec-
415 tively, either considering a single section or averaging across a portion
416 of the vein (Figure 4). A large variability among different subjects was
417 observed, with the largest variations being about the 90% and the 30%,
418 for the manual and the global automated method (averaging across sec-
419 tions), respectively. The repeatability is much larger for the automated
420 method than considering the clinical standard. For the following dis-
421 cussion, this variability was removed considering the average CI among
422 respiration cycles (for both the manual and the automated method).

- 423 • A large variation of CI was observed when considering different sec-
424 tions along the IVC (Figure 5), confirming that the vein pulsations
425 vary a lot, depending on anatomical properties of the vein and of the
426 surrounding tissues (e.g., the presence of anchoring sites). The sections
427 were studied using the automated method, which tracked their motion.
428 The average CoV was about 40%, with great variations among sub-
429 jects (the one showing the largest differences among sections showed a
430 CoV of about 70%). No section can be considered better than others
431 in terms of repeatability of the estimations: the best one varies among
432 the subjects and also considering different measurements on the same
433 subject. Moreover, a large variability of CI was observed among sub-
434 jects, without a clear trend of pulsatility when going in proximal or
435 distal direction along the considered longitudinal section of the IVC
436 (extending 4 cm distal from the confluence of the hepatic veins). The

437 great variability of IVC pulsatility along the cranio-caudal direction
438 can lead to misinterpretation of the overall dynamics of the IVC.

439 • Considering the measurements of different echographers, we observed
440 a large variability, both among experimental sections (Figure 6) and
441 intra-/inter-operators (Figure 7). The operators had different expe-
442 rience: more than 20 years (PP), 2 years (AR) and less than 1 year
443 (FC). Their procedures in taking the manual measurements were quite
444 different.

445 – PP tried to select a direction orthogonal to the IVC midline (Pas-
446 quero et al. (2015)). In the average, the measuring site was 2.4 cm
447 from the confluence of the hepatic veins, i.e., close to the centre
448 of the considered portion of IVC.

449 – AR took the measurement quite close to the diaphragm, in the
450 average 1.7 cm from the confluence of the hepatic veins (25% of
451 times, the measuring site was at a distance from the confluence
452 of the hepatic veins lower than 1 cm). This procedure helped him
453 in getting stable measurements in different experiments, as there
454 are anatomical references which could be easily found. However,
455 in that region, the vein pulsatility is affected by anchoring tissues
456 and the blood flow from the hepatic vein, so that the accuracy of
457 the measurement could be questionable.

458 – FC showed a lower experience than the colleagues, as her mea-
459 surements required longer time and efforts. In the average, the
460 measuring site was 2.7 cm from the confluence of the hepatic veins

461 and the distribution of chosen sites was the most dispersed among
462 the colleagues (std of about 1.4 cm, whereas it was 0.94 and 1.15
463 for PP and AR, respectively).

464 The ANOVA allows to interpret the different sources of uncertainty in CI
465 estimation and to assess the intra- and inter-operator variability. Our re-
466 sults suggest that the operators had a different consistent bias when taking
467 measurements following the standard procedure. Indeed, their intra-operator
468 estimates were quite consistent (mean CoV=28%), but differed from those
469 of their colleagues (inter-operator CoV=35%). This possibly reflects the dif-
470 ferent preferred measurement sites of the operators (so that the longitudinal
471 section is similar for the repeated measurements, but different among the
472 three operators). The automated approach, when compared to the standard
473 one, provided smaller inter-operator variability, suggesting that it could con-
474 tribute to standardizing CI measurements (intra-operator and inter-operator
475 mean CoV equal to 24 and 18%, respectively). Furthermore, the average
476 ICC and Fisher ratio were higher in the CI estimated by the automated
477 method, suggesting that the new approach may allow to better discrimi-
478 nate different subjects. Finally, comparing the standard and automated CI
479 estimations, a direct correlation emerged with operators' experience (the low-
480 est and highest correlation for the least and most experienced echographer,
481 respectively). Hence, the automated method could also be a reference for
482 teaching to novices how to make a manual measurement.

483 A real time rendering of the identified IVC borders could be a useful feed-
484 back to guide the acquisition of a B-mode video-clip. Notice also that the
485 most experienced operator (who made measurements highly correlated to

486 those of the automated method) selected the M-mode line along the direc-
487 tion mostly orthogonal to the IVC midline: our results further support this
488 choice, already suggested in Pasquero et al. (2015).

489 *RCI and CCI: new indexes estimated by the automated method*

490 As the automated method provides not only local estimates, but time
491 series, more information can be extracted by post-processing. Specifically,
492 the heartbeat and respiratory contributions were separated and additional
493 indexes (CCI and RCI) were computed. Figure 6 shows that RCI has a
494 larger variability than CCI. It is reasonable that the variability is lower when
495 considering an index reflecting the cardiac instead of the breath stimulation.
496 Indeed the effect of the heartbeats is about constant, whereas the respiration
497 cycles can be more variable, so that their effect on different measurements
498 can be important. Moreover, the number of heartbeats is much larger than
499 that of respiration cycles found on the same video-clip, so that more estima-
500 tions can be averaged when computing CCI than RCI.

501 Notice that the CoV of the RCI is larger than that of the automated esti-
502 mation of the CI (CI_{global}), even if the latter is affected by the asynchronous
503 super-position of the heartbeats over the respiration cycles, which introduces
504 a variation in the estimations. However, even if the variability of the esti-
505 mations of CI is a bit larger than that of the RCI, the mean value is much
506 lower for the latter than the first, so that its CoV is larger. A similar inter-
507 pretation can be given concerning the results of CCI: the estimates are very
508 stable (with a much lower variability than that of CI), but their absolute
509 values are very small. However, CCI is the index providing the largest intr-
510 aclass correlation (Table 2) and Fisher ratio (Table 3), indicating that it has

511 high repeatability and can better discriminate different subjects. Further
512 work is needed to understand how the information provided by these two
513 indexes correlate with the state of the patient (this work investigates only
514 the repeatability of their estimations). For example, we expect that irregular
515 cardiac rhythm may cancel or largely affect the cardiac component, so that
516 the relative weight of the two components could be of help in discriminating
517 some patients.

518 *General comments*

519 The consequence of the large variability of the standard measurement
520 is that clinical CI estimations should be considered with caution (Magnino
521 et al. (2017)). Indeed, problems are expected when the index is used to
522 discriminate between patients with different pathologies: for example, only
523 differences among subjects in the order of 20-30% can be assessed with some
524 confidence. Moreover, it is difficult to monitor a patient in the follow up,
525 as only large variations can be assessed. Finally, clinicians using different
526 approaches in selecting the M-mode line could get different diagnoses.

527 In order to improve the reliability and repeatability of the estimations,
528 a possible solution is averaging more measurements. Different CIs measured
529 on more respiration cycles can be averaged. In this way, an index is obtained
530 accounting for different vein dynamics, induced by different breath stimula-
531 tions. Moreover, averaging allows to reduce estimation errors due to small
532 mistakes in measuring on still images the maximal and minimal diameters
533 (which are also affected by the oscillations induced by the heartbeats, which
534 are asynchronously superimposed to those induced by respiration). Further-
535 more, an average of information from different sections could further improve

536 the estimation of IVC pulsatility, at the expense of spending time repeating
537 more M-mode investigations along different sections.

538 Our method allows to average information from different respiration cy-
539 cles and sections, processing a single US video-clip. This provides a fast and
540 robust overall estimation of the pulsatility in an entire portion of the vein.
541 Here, we show that the averaged estimation provided by our semi-automated
542 method is also more repeatable than the manual assessment. Our results
543 could be considered preliminary, due to the low number of investigated sub-
544 jects (i.e., 10). However, other indications of the reliability of the informa-
545 tion extracted by our automated algorithm are available. For example, the
546 pulsatility of IVC extracted by our algorithm has been recently used to esti-
547 mate the right atrial pressure, with performances largely superior than those
548 that could be obtained from the manual estimations (Mesin et al. (2019a)).
549 Moreover, works are in progress on the applications on patients, where our
550 algorithm allows to get better discrimination of patients affected by either
551 hypo- or hyper-volaemia.

552 Using an automated method reduces the problems due to subjective in-
553 terpretations. However, the procedure is still dependent on the quality of the
554 video recorded by the operator, so that the experience of the echographer is
555 still important. In future, the real time rendering of the output of the pro-
556 cessing algorithm could provide a feedback to help the operator to acquire
557 a video-clip of good quality. Even considering this limitation of our work
558 (in which the processing was executed off-line), our algorithm allowed to get
559 CI estimations closer to those obtained by the most experienced operator,
560 also when applied to video-clips recorded by a low experience echographer.

561 Thus, we propose this innovative algorithm as a step towards standardizing
562 measurements of IVC pulsatility.

563 An instrument applying the algorithm described in this paper was patented
564 by Politecnico di Torino and Università di Torino (patent number 102017000006088).

565 **Conclusions**

566 Different sources of variability affect the estimation of IVC pulsatility
567 from US measurements, e.g., the respiration cycles and the selected section
568 of the vein. Our semi-automated algorithm allows to track vein movements
569 and deformations along the long axis, to compute the diameter of different
570 sections orthogonal to the vein and to provide an estimation of pulsatility
571 which is averaged across respiration cycles and sections. The pulsatility
572 estimations of this software were found to be more repeatable than those
573 obtained by the standard approach. This method can provide an important
574 contribution in the standardization of the assessment of IVC pulsatility, with
575 important outcomes expected in the estimation of the central venous pressure
576 and volemic status of patients.

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663 siveness in critically ill patients: Systematic review and meta-analysis.
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665 **Figure Captions**

666 **Figure 1:** A) Selection of a rectangle including the IVC portion of interest in
667 the first frame of the video-clip. B) Reference points (squares), leftmost
668 and rightmost sections of interest (continuous lines) and points close
669 to the vessel edges along the leftmost section (indicated by X). C)
670 The algorithm computes 21 lines uniformly distributed between the
671 extreme sections indicated in B) and estimates the profile of the vein
672 along them (the estimated border points are indicated with circles). D)
673 From the estimated border of the vessel, the midline is computed and
674 interpolated with a parabola (dash-dot line); five equidistant points are
675 selected on this parabola, starting from the confluence of the hepatic
676 vein in the IVC and new lines perpendicular to it are considered as
677 sections along which to compute the vein diameters (border points
678 indicated with diamonds).

679 **Figure 2:** Experimental protocol. Each operator acquired three manual
680 measurements (in M-mode) and then the video (in B-mode). The same
681 procedure was followed twice for each of the three operators.

682 **Figure 3:** A) Caval index (CI) estimated on the whole signal. The local
683 maxima and minima of the respiratory component are found; then a
684 window of 1 s duration centred on each of these points is explored
685 to find the maxima or minima on the whole signal (indicated with
686 circles). B) Respiratory caval index (RCI), computed on the breath
687 component. This component is isolated with a low pass filter; then,
688 maxima and minima (indicated with circles) are automatically found

689 and used for RCI calculation. C) Cardiac caval index (CCI) computed
690 on the heartbeat component. The component is isolated with a high
691 pass filter; then, its local maxima and minima (indicated with circles)
692 are computed and used for CCI estimation.

693 **Figure 4:** A) Time course of IVC diameter at three different sections si-
694 multaneously monitored in a representative subject. B) Distribution
695 of CoV of CI_{auto} , obtained considering the 6 measurements from all 10
696 subjects, separately for the five sections and compared with manual CI
697 and CI_{global} .

698 **Figure 5:** Variation of the Caval Index (CI) when estimated by the au-
699 tomated method at different longitudinal positions, expressed as the
700 distance from the confluence of the hepatic veins. A) Each trace cor-
701 responds to one subject (average of all sessions). B) Median, quartiles
702 and range (outliers shown individually) of the coefficient of variation
703 (CoV) of the CI across the 5 sections along the vein, for each subject.

704 **Figure 6:** Coefficient of variation (CoV) for each index (manual CI and au-
705 tomated estimation of CI, CCI and RCI) computed across different
706 experimental sessions (median, quartiles and range; outliers shown in-
707 dividually). A), B) and C): CoV of the indexes (CI, CCI and RCI,
708 respectively) extracted at different distances from the confluence of the
709 hepatic vein into the IVC and, to the right, the CoV of manual and
710 global estimations (averaging the CI across sections). D) Comparison
711 of CoV of the manual and global CI.

712 **Figure 7:** Comparison between CoV of manual and automated Caval In-

713 dex (CI) values. Intra- and inter-operator variabilities are considered
714 (showing the distribution of 10 values, one for each subject, in terms
715 of median, quartiles and range, plus an outlier shown individually).
716 The manual CI estimations are the mean of three CI measurements in
717 M-mode (reflecting the choice of 3 respiration cycles). The automated
718 CI estimations are given by the mean of all CI measurements obtained
719 from each video-clip (CI_{global} , obtained averaging across 3 respiration
720 cycles and 5 longitudinal sections).

Table 1: ANOVA table considering the CI obtained using either the standard approach (manual CI) or the automated one (CI_{global}); DOF - degrees of freedom, RC - respiration cycle.

Source	DOF	Sum of squares		Mean squares		F		p-value	
		<i>manual</i>	<i>global</i>	<i>manual</i>	<i>global</i>	<i>manual</i>	<i>global</i>	<i>manual</i>	<i>global</i>
Subject	9	4.03	2.30	0.45	0.25	29.01	30.01	$\approx 10^{-29}$	$\approx 10^{-29}$
Repetition	1	$6 \cdot 10^{-4}$	0.026	$6 \cdot 10^{-4}$	0.026	0.03	3.03	0.84	0.083
Operator	2	1.05	0.111	0.53	0.055	34.22	6.49	$\approx 10^{-13}$	0.002
RC	2	0.02	$3.5 \cdot 10^{-4}$	0.01	$1.7 \cdot 10^{-4}$	0.67	0.02	0.51	0.98
Error	165	2.54	1.40	0.015	0.008				
Total	179	7.66	3.84						

Table 2: Intraclass correlation coefficient (ICC), considering intra- and inter-operators estimates of different caval indexes (manual and automated CI, CCI and RCI, obtained averaging across different sections). Different operators are shown in order of increasing experience (FC less than 1 year, AR 2 years, PP more than 20 years of experience).

	ICC			
<i>Operator</i>	<i>CI standard</i>	<i>CI_{global}</i>	<i>CCI_{global}</i>	<i>RCI_{global}</i>
FC	48.9%	45.3%	61.2%	6.9%
AR	81.7%	46.8%	72.8%	41.0%
PP	77.6%	78.6%	89.5%	70.7%
Inter-operator	61.5%	70.4%	87.5%	49.9%

Table 3: Fisher ratio of estimates of different caval indexes (manual and automated CI, CCI and RCI, obtained averaging across different sections), considering intra- and inter-operator values.

	Fisher ratio			
<i>Operator</i>	<i>CI standard</i>	<i>CI_{global}</i>	<i>CCI_{global}</i>	<i>RCI_{global}</i>
FC	3.20	2.24	2.54	1.43
AR	31.52	2.11	48.83	3.02
PP	9.11	7.34	25.92	9.73
Inter-operator	2.06	8.21	23.52	2.56