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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 (pulsatility) induced by different stimulations (e.g., breathing and heartbeats). Pulsatility is affected by patients volume status and can be investigated by ultrasound (US) measurements. An index of IVC pulsatility based on US visualization and called caval index (CI) was proposed as a non-invasive indirect measurement of the volume status. However, its estimation is not standardized, operator-dependent and affected by movements of the vein and non-uniform pulsatility. We introduced a software that processes B-mode US video-clips to track IVC movements and estimate CI on an entire portion of the vein. This method is here compared to the standard approach in terms of repeatability of the estimated CI, reporting on the variability over differ-

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ent respiratory cycles, longitudinal IVC sections and intra/inter observers. Our method allows to reduce the variability of CI assessment, making 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 con-
5 ditions of altered volemic status in patients. Specifically, the pulsations of
6 the vessel visualized by US measurements during the respiratory cycle are
7 used to estimate the caval index (CI, Blehar et al. (2012)). However, mea-
8 surement techniques are not standardized (Wallace et al. (2010)), as they
9 vary in terms of anatomical approach and sonographic technique (Finnerty
10 et al. (2017)). For example, both recordings along longitudinal (Barbier et al.
11 (2004); Brennan et al. (2006); Fields et al. (2011); Feissel et al. (2004); Grant
12 et al. (1980); Kircher et al. (1990); Lyon et al. (2005); Moreno et al. (2019);
13 Pasquero et al. (2015)) or transversal sections (Blehar et al. (2009); Chen
14 et al. (2010); Moreno et al. (2019)) of the vein are used. Different recom-
15 mendations have been proposed on where to measure the vein diameter along
16 a longitudinal section (Wallace et al. (2010); Resnick et al. (2011)). How-
17 ever, since the pulsatility of the vessel is not uniform along its longitudinal
18 axis (Mesin et al. (2015, 2019b)), CI values vary considerably in the litera-
19 ture in both healthy and pathologic conditions and, as a result, diagnostic
20 recommendations are also non homogeneous (Zhang et al. (2014)).

21 The movements of the vein relative to the transducer during the respi-
22 ratory cycle give an additional contribution to the variability of CI. Indeed,
23 M-mode registration allows to compute the vein diameter along a fixed line
24 at the end of inspiration and expiration, but, since the IVC moves during
25 respiration, the diameters end up being taken at different points, introduc-

26 ing a possible bias. This is particularly relevant if the vein has an irregular
27 shape, with a variable cross-sectional area (Lichtenstein (2005)) or if the an-
28 gle between the M-mode line and the vein changes considerably during its
29 movements. In addition, respiration cycles may differ between each other
30 and change among subjects (e.g., breathing can be diaphragmatic, thoracic
31 or a combination of both), inducing changes in the IVC dynamics (Kimura
32 et al. (2011)). In order to minimize movements of the vein during respira-
33 tion, variations of the IVC section was investigated during voluntary apnoea,
34 thus bringing forward the effect of cardiac activity on IVC pulsatility (Folino
35 et al. (2017); Nakamura et al. (2013)), which is otherwise poorly detectable
36 on M-mode representation. However, this technique cannot be easily applied
37 in clinics.

38 We reported on successfully tracking IVC movements in long-axis US
39 scans while estimating its diameter in each frame, along a direction mov-
40 ing together with the vein (Mesin et al. (2015)). This method has a lower
41 computational cost than other advanced processing techniques applied to US
42 images (Yang et al. (2008); Yeung et al. (1998); Krupa et al. (2007)) and pro-
43 vides a more precise estimation of the IVC local pulsatility with respect to
44 standard measurements, based on a fixed M-mode line (Mesin et al. (2015)).
45 However, a possible problem is that pulsatility along a single section of the
46 IVC may be not representative of the dynamics of the whole vessel. Some
47 parts of the vein are anchored to nearby structures (e.g., the diaphragm or
48 vein inlets) and show smaller pulsatility than other portions. For example,
49 lower pulsatility was reported at the level of the diaphragm compared to
50 more caudal sites (Wallace et al. (2010)). These observations were confirmed

51 in Mesin et al. (2015) (Figure 9), showing that diameter variations along
52 distinct directions (moving together with the vein) resulted in considerably
53 different pulsatility. Lack of consensus about where to measure diameters
54 (Wallace et al. (2010); Resnick et al. (2011)) and the non-uniform behaviour
55 of the vessel are likely to contribute to the non-homogeneous assessments
56 of IVC pulsatility in the literature (Weekes et al. (2012)). Thus, we re-
57 cently proposed a new algorithm that tracks the movements and computes
58 the diameter of different sections of a whole portion of the IVC (Mesin et al.
59 (2019b)). In this study, we compare this innovative method to the standard
60 approach, in terms of the repeatability (intra- and inter-operator) of infor-
61 mation extracted from different measurements on the same subjects. The
62 repeatability of IVC assessment by the standard technique was investigated
63 in a few contributions in the literature (Fields et al. (2011); Finnerty et al.
64 (2017)). The measurement of the diameter was found to be reliable, but the
65 assessment of IVC pulsatility was quite poor (Fields et al. (2011)). The sub-
66 xifoideal transabdominal long axis view in B-mode demonstrated the highest
67 inter-rater reliability (Finnerty et al. (2017)) among different anatomical ap-
68 proaches, including also the transabdominal short axis immediately inferior
69 to the inflow of the hepatic veins and the right lateral transabdominal coronal
70 long axis. Here, the possibility of tracking the IVC and examining an entire
71 portion of the vein allowed us to investigate different sources of variability in
72 the US assessment, including different respiration cycles, sections along the
73 longitudinal axis, experimental sessions and operators.

74 **Materials and Methods**

75 *Automated detection of the IVC borders*

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

81 The user is asked to indicate the location of the vein in the first frame
82 (Figure 1A). Moreover, as shown in Figure 1B, on the same frame, he chooses
83 two reference points to be tracked (to account for IVC movements and de-
84 formations) and the most proximal/distal sections (defining the portion of
85 the IVC of interest, which was between the confluence of the hepatic veins
86 into the IVC and the caudate lobe of the liver). Finally, the locations of the
87 borders of the vein along the most proximal line are indicated. The software
88 is then ready to process the video-clip. It distributes uniformly N lines in
89 the portion of IVC indicated by the user ($N=21$ in this paper) and automat-
90 ically detects the borders of the vein along these lines (as points for which an
91 abrupt change of intensity is found; Figure 1C). For each frame, the location
92 and direction of the N lines are updated depending on the movements of the
93 reference points (specifically, in general the segment joining the two reference
94 points is found slightly translated, rotated and scaled in subsequent frames;
95 the N lines are translated and rotated and their distribution is updated ac-
96 cordingly, so that in different frames they are ideally fixed on same sections
97 of the vein). In this way, the superior and inferior borders of the vein are
98 estimated in the IVC portion of interest (see Mesin et al. (2019b) for details).

99 *Subjects*

100 US data were recorded from 10 healthy volunteers (5 females, 5 males;
101 mean \pm std age 30 \pm 13 years, height 172 \pm 12 cm, weight 63 \pm 11 kg) with a
102 SonoSite M-Turbo system (SonoSite, Bothell, USA; frame rate 30 Hz, reso-
103 lution of about 0.42 mm per pixel, 256 gray levels) equipped with a convex 2-5
104 MHz probe. Two-dimensional (B-mode) longitudinal views of the IVC were
105 taken with a subxifoideal approach (as suggested by Finnerty et al. (2017)),
106 with the subject in the supine position during relaxed normal breathing.
107 The study was approved by the Ethics Committee of the University of Turin
108 and complies with the principles of the Declaration of Helsinki. All subjects
109 provided written informed consent for the collection of data and subsequent
110 analysis.

111 *Experimental set-up and protocol*

112 The experimental protocol is illustrated in Figure 2. Three operators
113 performed the US scans: one expert (PP), one in training (AR) and one be-
114 ginner (FC), with balanced arrangement of their order. An operator started
115 by taking 3 measurements of IVC diameters (as defined below) using standard
116 methodology in M-mode. Then, a 15s video-clip was recorded in B-mode,
117 allowing for at least three respiratory cycles. After the first recording, the
118 subject was asked to stand up for one minute to minimize any changes of
119 the IVC due to remaining in the supine position for a prolonged time (Folino
120 et al. (2017)). Then, the subject was asked to lie down again supine and a
121 new acquisition was taken by a second operator and, after standing up again,
122 by a third one. The whole procedure was repeated a second time, obtaining
123 six video-clips for each subject.

124 *Indexes extracted from the data*

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

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

130 The video-clips were then processed to estimate the IVC borders as detailed
131 above. Notice that the position of each point of the border is indicated by
132 time series (location along x and y directions, one value per frame). These
133 time series were low pass filtered with a 4 Hz cut-off, in order to remove high
134 frequency and quantization noises (this filter and the ones mentioned below
135 were of Butterworth type, order 4 and used in both directions to remove
136 phase distortion and delay, Mesin et al. (2019b)). Then, the borders of the
137 IVC were estimated from the confluence of the hepatic veins into IVC to 4
138 cm in distal direction (Figure 1D). Specifically, from the estimated borders,
139 the IVC midline was computed. It was then approximated by a parabolic
140 function. The location of the confluence of the hepatic veins into the IVC was
141 indicated by the user (SA, who was not an echographer) on the first frame of
142 the video-clip. This point was orthogonally projected on the IVC midline and
143 represented the starting point from which other 4 points were automatically
144 estimated, with 1 cm curvilinear distance from each other along the IVC
145 midline. Thus, 5 points were obtained, 0 to 4 cm distant from the confluence
146 of the hepatic veins into the IVC, projected on the midline of the vein.

147 Then, the sections orthogonal to the IVC midline passing from each such
148 points were considered (Mesin et al. (2019b); Pasquero et al. (2015)) and
149 the IVC diameters in these sections were computed by interpolation from
150 the estimated vein borders (see Mesin et al. (2019b) for details). These five
151 diameters are further considered in the following.

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

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

154 where D indicates the estimated diameter time series (in a specific section).
155 Local maxima and minima were computed for each respiration cycle (Figure
156 3A). Thus, an estimate of CI was obtained for each respiratory cycle and
157 for each section considered. As in the case of the manual CI estimation,
158 the CIs of 3 respiratory cycles were selected. In the cases in which more
159 than 3 cycles were present in the video-clip, the CIs closer to their mean
160 across different cycles were selected. After testing the repeatability across
161 respiration cycles, the estimated CIs were averaged. A CI accounting for the
162 overall pulsatility of the considered portion of the vein was also considered
163 (indicated as CI_{global}): it was obtained by averaging the estimates across
164 different sections.

165 Additional indexes of pulsatility were obtained after further processing
166 the diameter time series estimated by our software. The vein dynamics was
167 considered as the sum of two components, reflecting the stimulation induced
168 by respiration and heartbeat (Mesin et al. (2019a)). The two components
169 were separated as follows: the effect of respiration was computed by low
170 pass filtering the whole diameter time series with a cut-off frequency of 0.4

171 Hz. The cardiac contribution was computed by high pass filtering the whole
172 diameter time series with a cut-off frequency of 0.8 Hz. Then, the following
173 additional indexes were estimated, as shown in Figure 3.

- 174 • The respiratory caval index (RCI), applying the same formula (2) to
175 the respiration component only.
- 176 • The cardiac caval index (CCI), applying the same formula (2) to the
177 cardiac component only.

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

182 *Assessment of repeatability and discriminability*

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

- 186 • Coefficient of variation (CoV), defined as the ratio between the stan-
187 dard deviation and the mean of the estimates. It was used to test
188 variations due to different respiration cycles, sections and experimental
189 sessions (intra- and inter-operator).
- 190 • Intraclass correlation coefficient (ICC). It is defined as

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

191 where $var(S)$, $var(M)$ and $var(E)$ indicate the variability due to dif-
192 ferent subjects, measurements (i.e., experimental sessions) and residual
193 error, respectively (Bartko (1966)). It was used to test intra- and inter-
194 operator variability.

195 An index of discrimination was also employed, to test the possibility that
196 an index could be repeatable, but not able to distinguish between different
197 subjects. The Fisher ratio was used. It measures the linear discrimination
198 between two sets of values as

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

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

204 Finally, the different sources of variability were investigated by analysis of
205 variance (ANOVA). The manual CI and CI_{global} were processed with a 4-way
206 ANOVA (normality of residuals was assessed by Lilliefors test), investigating
207 the variability induced by the following factors: subject (10 individuals),
208 operator (3 levels), repetition (2 levels) and respiration cycle (3 cycles).

209 Some paired tests for significant variations among couples of variables
210 were also performed, using Wilcoxon signed rank tests. The significance
211 level was set to $p = 0.05$.

212 *Summary of investigated indexes*

213 The following indexes are considered.

- 214 1. Manual CI, which is a variable depending on the following factors: res-
215 piration cycle (3 cycles considered), subject (10 volunteers) and experi-
216 mental session (6 sections, which could be further split into 3 operators
217 repeating twice the experiment). The average across the respiration
218 cycles was also considered.
- 219 2. CI_{auto} , RCI_{auto} and CCI_{auto} , depending on the following factors: respi-
220 ration cycle (3 cycles considered) or heartbeat in the case of CCI_{auto}
221 (10 beats considered), subject, section (5 locations, measured in terms
222 of the distance from the hepatic veins) and experimental session. The
223 average across the respiration cycles/heartbeats was also considered.
- 224 3. CI_{global} , RCI_{global} and CCI_{global} , obtained by averaging the previous in-
225 dexes across the sections (obtaining a global index for the vein tract
226 under study), so that they depend on respiration cycle or heartbeat (the
227 latter in the case of CCI_{global}), subject and experimental session. The
228 average across the respiration cycles/heartbeats was also considered.

229 **Results**

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

236 *Variability of CI in subsequent breaths*

237 Figure 4A shows the changes in IVC diameter exhibited in a representa-
238 tive subject at rest. The tracings refer to different IVC sections (simultane-
239 ously monitored in the same video-clip), located at 0, 2 and 4 cm distal to the
240 confluence of hepatic veins into the IVC. Notice that the sections exhibit dif-
241 ferent average diameter and different amplitude of oscillatory components of
242 cardiac and respiratory origin. For example, at the confluence of the hepatic
243 vein, the algorithm estimated different respiration cycles with CIs varying
244 in the range 18%-28% and with a CoV equal to 19%. This CoV indicates
245 the variability of the CI estimations across the different respiration cycles
246 (recorded in the same video-clip, at a location fixed to the IVC). Figure 4B
247 shows the distribution of these CoVs extracted from the whole dataset. This
248 CoV, expressing the variability observed over consecutive respiratory cycles,
249 was calculated for all trials (obtaining 60 values, as we considered 10 sub-
250 jects for 6 experimental sessions) and for each IVC section. In addition, for
251 comparison, the same figure also includes the CoV of CI_{global} and CI_{manual} .
252 Notice that the median variability with respect to different respiration cycles
253 (in terms of CoV) is about 15% when considering the standard (manual)
254 method, about 5% when considering single sections (CI_{auto}) tracked by the
255 automated method (Mesin et al. (2019b)) and lower than 3% when consider-
256 ing the global CI (averaged over all IVC sections, CI_{global} ; Wilcoxon signed
257 rank test indicates that the CoV of manual and global CI are statistically
258 different).

259 *Variability of CI with longitudinal position*

260 For all the following figures, CI estimations (either manual or automated)
261 were derived as the average of the values obtained from the different respi-
262 ratory cycles.

263 Figure 5 shows the variability of CI estimation across different sections
264 along the IVC. The dependence of IVC pulsatility along the longitudinal
265 position is visible in 5A for the different subjects (CI_{auto} is shown averaged
266 over all 6 experimental sessions). Notice that there is no univocal trend in
267 CI dependence on longitudinal position. The variations of CI in different
268 positions can be relevant: e.g., in subject number 7, CI_{auto} decreases from
269 about 40% to 10%, moving caudally by 3 cm from the confluence of the
270 hepatic veins into IVC; conversely, in subject 8, CI increases from about 50%
271 to 70%, over the same distance.

272 The variability of CI_{auto} along the considered IVC tract was quantified by
273 its CoV. One estimation of CoV was obtained for each experimental session,
274 obtaining 6 values for each subject which are shown in Figure 5B. On average,
275 it is about 30%, but it is as high as about 70% in one subject (number 7 in
276 Figure 5B).

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

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

281 This evaluation was conducted separately for the different positions along
282 the IVC in order to compare automated and manual assessments. As il-
283 lustrated in Figure 6, none of the sections along the IVC exhibits a CoV

284 significantly smaller than the others. Moreover, it can be observed that i)
285 manual and automated assessments (over single sections) have similar vari-
286 ability (6A); ii) removing the respiratory component improves repeatability
287 (6B and 6D); iii) filtering out the cardiac component does not improve re-
288 peatability (6C and 6D); iv) a relevant reduction in CoV of CI_{auto} is obtained
289 by calculating the CI over the entire longitudinal portion of IVC (CI_{global}).
290 Statistically significant differences were found between CCI_{global} and manual
291 CI, CI_{global} and RCI_{global} , CCI_{global} and RCI_{global} .

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

293 Figure 7 shows a comparison between the CoV of manual CI and global
294 automated estimation (CI_{global}). Intra-operator variability was computed us-
295 ing the two repetitions of the measurement by the specific operator consid-
296 ered. Inter-operator variability was computed from the average CI obtained
297 by the operators (averaging the two repeated measurements) from each sub-
298 ject. The spread of the estimates obtained from the same subject was lower
299 for the automated method for 9 subjects out of 10 (Wilcoxon signed rank
300 test indicated that the automated method provided estimates of CI from the
301 same subject with lower standard deviations than the manual approach; the
302 CoV of manual and global CI were not statistically different, instead). Most
303 of the repeated manual measurements of each operator were quite similar
304 (mean intra-operator CoV equal to 28%), but the estimations varied a lot
305 among different operators (mean inter-operator CoV equal to 35%). The
306 automated measurements were more stable and showed similar intra- and
307 inter-operator variabilities (mean CoV equal to 24% and 18%, respectively).

308 *Repeatability assessment*

309 The figures discussed in the previous sections considered single sources
310 of variability (respiration cycle, longitudinal section, experimental session
311 and operator in Figures 4, 5, 6 and 7, respectively). Here, the statistical
312 analysis of the entire dataset is discussed. Table 1 shows the ANOVA, com-
313 paring the manual CI and CI_{global} . Notice that the total variability of CI
314 is larger when using the standard clinical approach. Moreover, as indicated
315 by the F statistics, a slightly higher percentage variability is obtained con-
316 sidering different subjects when using the automated method instead of the
317 standard one (so that a better discrimination of different subjects can be
318 obtained using the automated algorithm). On the other hand, a lower vari-
319 ability is obtained using the automated method in different experimental
320 sessions (when pooling together the factors repetition and operator, results
321 not shown) and respiration cycles (even if the variations induced by the res-
322 piration cycle are not significant). Splitting the experimental sessions into
323 the factors repetition and operator, we notice that the variations on different
324 repetitions are quite small (and not significant), whereas larger (significant)
325 differences are found considering different operators (in line with the intra-
326 and inter-operator CoV discussed above). Moreover, smaller variations over
327 different repetitions are found for the standard approach, whereas those in-
328 duced by different operators are smaller for the automated approach. Thus,
329 the automated method provided measurements that were more stable across
330 different operators, whereas, by the standard approach, the echographers ob-
331 tained twice similar values, which were however different from those of the
332 colleagues, indicating a possible bias.

333 Tables 2 and 3 show respectively the ICC and the Fisher ratio of the caval
334 indexes computed either by the standard or the automated method (manual
335 CI, CI_{global} , CCI_{global} and RCI_{global}). Intra-operator values were computed
336 considering only the estimates obtained by each operator, separately; inter-
337 operator values were obtained by grouping together the estimates of the
338 same operator. Notice that the most experienced operator obtained quite
339 high values of ICC and Fisher ratio, considering both the standard method
340 and the indexes extracted from the video-clips that he recorded. The CIs
341 measured with the standard method had a correlation with those estimated
342 by our software using the corresponding video-clips (i.e., those registered after
343 the M-mode assessment) which was found to be related to the experience:
344 FC, AR and PP (i.e., the operators in order of increased experience) showed a
345 correlation coefficient of 36.2%, 58.1% and 70.8%, respectively (the definition
346 of correlation coefficient is

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

347 where $x[n]$, $y[n]$ are the series to be compared and \bar{x} , \bar{y} are their means).
348 Notice that the estimates of CI obtained by the automated method are more
349 consistent across different operators (inter-operator ICC about 70%, whereas
350 it is about 61% for the standard estimation). High values of ICC were ob-
351 tained also for the estimation of CCI, lower values for RCI (in line with
352 Figure 6). Notice also that the video-clips acquired by the most experienced
353 operator allowed to get more repeatable estimates of the automated indexes
354 (this indicates the importance of acquiring good video-clips to get repeatable
355 results also from the automated processing). The results on ICC are in line

356 with those shown by the Fisher ratio (Table 3): indeed, a larger repeatability
357 of the estimation of pulsatility of each subject allows to better discriminate
358 between different subjects.

359 **Discussion**

360 *Summary*

361 Repeatability of standard CI estimations was assessed in a group of
362 healthy subjects, the results indicating rather poor values in terms of both
363 intra- (mean CoV=28%, ICC in the range 49-82%) and inter-operator vari-
364 ability (mean CoV=41%, ICC=61.5%). These results are in line with the
365 previous studies in the literature (Fields et al. (2011); Finnerty et al. (2017)).
366 For example, Fields et al. (2011) reported a high inter-rater reliability of IVC
367 diameter estimation, but a lower repeatability of pulsatility assessment, with
368 ICC very similar to ours.

369 Here, we propose the use of a semi-automated algorithm, analysing 15s
370 lasting B-mode video-clips of the IVC acquired with the subxifoideal ap-
371 proach in long axis (which demonstrated the highest inter-rater reliability,
372 Finnerty et al. (2017)). We found

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

378 Since the choice of the insonation point and the breath cycle is arbitrary,
379 these factors can induce a variability between different measurements. In the

380 present work, we attempted to limit these sources of variability mediating
381 estimations obtained from different breath cycles and on a 4 cm portion of
382 the IVC in long axis. Due to this averaging, in addition to the tracking of
383 the vein movements (with reliability already proven in Mesin et al. (2015)),
384 the algorithm offers a more objective and reliable measurement of the CI
385 (here called global CI), reducing the overall variability (intra- and inter-
386 operator mean CoV equal to 24% and 18%, respectively; ICC=70.4%). The
387 inter-rater reliability of the estimation of the CI is higher than that found
388 using the standard approach. It is also higher than the one reported in
389 the literature (Fields et al. (2011); Finnerty et al. (2017)), even if healthy
390 eu-volemic subjects were considered (in the literature, improvement in inter-
391 rater reliability was found when assessing hyper- and hypo-volemic patients
392 Fields et al. (2011); Finnerty et al. (2017)). In addition, the identification
393 of the respiratory and the cardiac oscillatory components may provide new
394 insights and possibilities for the analysis of IVC dynamics, with repeatability
395 performances close to those of the standard CI and global CI, respectively.

396 *Discussion of different sources of variability*

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

401 The repeatability of the estimation of the IVC pulsatility has been inves-
402 tigated in few studies (Fields et al. (2011); Finnerty et al. (2017)). It is a very
403 important information, as low repeatability hampers clinical usefulness. For
404 the problem at hand, it reflects an uncertainty that limits the discrimination

405 of the volume status of different patients and the reliability in the follow up.
406 In this paper, we report low repeatability of classical CI assessment, investi-
407 gate relevant sources of variability and propose a method that improves the
408 measurement. Specifically, the following sources of variability were explored.

- 409 • The variation of the depth and modality of respiration induces different
410 IVC pulsatility for each breath cycle. Notice that controlling the res-
411 piration cycle (e.g., by a spirometer, even if only the respiration depth,
412 not the modality, could be controlled) could possibly reduce this source
413 of variability. Indeed, in the case of mechanically ventilated patients,
414 the respiration cycles are regular and the dynamics of the IVC diame-
415 ter was found to be useful to detect fluid responsiveness (Feissel et al.
416 (2004)). To overcome the variability induced in spontaneous breathing,
417 the analysis of cardiac pulsatility has been proposed: pulsatility was
418 measured during a short apnoea, thus caused by the heartbeats only
419 (Folino et al. (2017); Nakamura et al. (2013)).
- 420 • Variations of the pulsatility in different sections of the vein. These
421 variations were noticed both in longitudinal (Mesin et al. (2015, 2019b))
422 and transversal scans (Blehar et al. (2012)).
- 423 • Variations introduced by the operator. In different measurements, the
424 investigated 2D section can be slightly different. Furthermore, the US
425 probe handled by the operator must follow the movements of the pa-
426 tient during respiration: the ability to follow the movement without
427 affecting the measurement depends on the level of experience of the
428 operator.

429 In addition, there are variations of the investigated IVC section, due to move-
430 ments of the vein during an M-mode measurement (as the M-mode registra-
431 tion fixes the considered section in space). Consider that both translation
432 and rotation of the vein with respect to the studied direction are expected
433 to occur in general. The former induces an error in the estimated diameter
434 dependent on the shape of the vein, while rotation affects the estimated di-
435 ameter even if the vein is a perfect cylinder. The problem is reflected by an
436 error in the estimation of pulsatility, which depends on the range of move-
437 ments and anatomy of the vein (Mesin et al. (2015)). In this paper, such
438 a problem affected only manual estimations. The automated IVC tracking
439 (introduced in Mesin et al. (2015, 2019b)) allows to remove this source of
440 uncertainty.

441 The other three sources of variation mentioned above were investigated
442 in this study, considering both the standard manual measurements and the
443 automated estimations provided by the algorithm proposed in Mesin et al.
444 (2019b), which estimates the IVC sections in a whole portion of the vein.
445 Figures 4-7 show repeatability in terms of CoV, so that the variation is
446 measured as the standard deviation of the estimates normalized with respect
447 to their mean.

- 448 • The CI (as a measurement of IVC pulsatility) in different respiration
449 cycles had median variation which was about the 15% and 5% or 3%
450 of the mean value, for the manual and the automated methods respec-
451 tively, either considering a single section or averaging across a portion
452 of the vein (Figure 4). A large variability among different subjects was
453 observed, with the largest variations being about the 90% and the 30%,

454 for the manual and the global automated method (averaging across sec-
455 tions), respectively. The repeatability is much larger for the automated
456 method than considering the clinical standard. For the following dis-
457 cussion, this variability was removed considering the average CI among
458 respiration cycles (for both the manual and the automated method).

459 • A large variation of CI was observed when considering different sec-
460 tions along the IVC (Figure 5), confirming that the vein pulsations
461 vary a lot, depending on anatomical properties of the vein and of the
462 surrounding tissues (e.g., the presence of anchoring sites). The sections
463 were studied using the automated method, which tracked their motion.
464 The average CoV was about 40%, with great variations among sub-
465 jects (the one showing the largest differences among sections showed a
466 CoV of about 70%). No section can be considered better than others
467 in terms of repeatability of the estimations: the best one varies among
468 the subjects and also considering different measurements on the same
469 subject. Moreover, a large variability of CI was observed among sub-
470 jects, without a clear trend of pulsatility when going in proximal or
471 distal direction along the considered longitudinal section of the IVC
472 (extending 4 cm distal from the confluence of the hepatic veins). The
473 great variability of IVC pulsatility along the cranio-caudal direction
474 can lead to misinterpretation of the overall dynamics of the IVC.

475 • Considering the measurements of different echographers, we observed
476 a large variability, both among experimental sections (Figure 6) and
477 intra-/inter-operators (Figure 7). The operators had different expe-

478 rience: more than 20 years (PP), 2 years (AR) and less than 1 year
479 (FC). Their procedures in taking the manual measurements were quite
480 different.

481 – PP tried to select a direction orthogonal to the IVC midline (Pas-
482 quero et al. (2015)). On average, the measuring site was 2.4 cm
483 from the confluence of the hepatic veins, i.e., close to the centre
484 of the considered portion of IVC.

485 – AR took the measurement quite close to the diaphragm, on aver-
486 age 1.7 cm from the confluence of the hepatic veins (25% of times,
487 the measuring site was at a distance from the confluence of the
488 hepatic veins lower than 1 cm). This procedure helped him in
489 getting stable measurements in different experiments, as there are
490 anatomical references which could be easily found. However, in
491 that region, the vein pulsatility is affected by anchoring tissues
492 and the blood flow from the hepatic vein, so that the accuracy of
493 the measurement could be questionable.

494 – FC showed a lower experience than the colleagues, as her measure-
495 ments required longer time and efforts. On average, the measuring
496 site was 2.7 cm from the confluence of the hepatic veins and the
497 distribution of chosen sites was the most dispersed among the col-
498 leagues (std of about 1.4 cm, whereas it was 0.94 and 1.15 for PP
499 and AR, respectively).

500 The ANOVA allows to interpret the different sources of uncertainty in CI
501 estimation and to assess the intra- and inter-operator variability. Our re-

502 sults suggest that the operators had a different consistent bias when taking
503 measurements following the standard procedure. Indeed, their intra-operator
504 estimates were quite consistent (mean CoV=28%), but differed from those
505 of their colleagues (inter-operator CoV=35%). This possibly reflects the dif-
506 ferent preferred measurement sites of the operators (so that the longitudinal
507 section is similar for the repeated measurements, but different among the
508 three operators). The automated approach, when compared to the stan-
509 dard one, provided smaller variability (mainly inter-operator), suggesting
510 that it could contribute to standardizing CI measurements (intra-operator
511 and inter-operator mean CoV equal to 24% and 18%, respectively). Fur-
512 thermore, the average ICC and Fisher ratio were higher in the CI estimated
513 by the automated method, suggesting that the new approach may allow to
514 better discriminate different subjects. Finally, comparing the standard and
515 automated CI estimations, a direct correlation emerged with operators' expe-
516 rience (the lowest and highest correlation for the least and most experienced
517 echographer, respectively). Hence, the automated method could also be a
518 reference for teaching to novices how to make a manual measurement.

519 A real time rendering of the identified IVC borders could be a useful feed-
520 back to guide the acquisition of a B-mode video-clip. Notice also that the
521 most experienced operator (who made measurements highly correlated to
522 those of the automated method) selected the M-mode line along the direc-
523 tion mostly orthogonal to the IVC midline: our results further support this
524 choice, already suggested in Pasquero et al. (2015).

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

526 As the automated method provides not only local estimates, but time
527 series, more information can be extracted by post-processing. Specifically,
528 the respiratory and cardiac oscillatory components were separated and addi-
529 tional indexes (RCI and CCI) were computed. Figure 6 shows that RCI has a
530 larger variability than CCI. It is reasonable that the variability is lower when
531 considering an index reflecting the cardiac instead of the breath stimulation.
532 Indeed the effect of the heartbeats is about constant, whereas the respiration
533 cycles can be more variable, so that their effect on different measurements
534 can be important. Moreover, the number of heartbeats is much larger than
535 that of respiration cycles found in the same video-clip, so that more estima-
536 tions can be averaged when computing CCI than RCI.

537 Notice that the CoV of the RCI is larger than that of the automated esti-
538 mation of the CI (CI_{global}), even if the latter is affected by the asynchronous
539 super-position of the heartbeats over the respiration cycles, which introduces
540 a variation in the estimations. However, even if the variability of the estima-
541 tions of CI is a bit larger than that of the RCI, the mean value is much lower
542 for the latter than the first, so that its CoV is larger. A similar interpreta-
543 tion can be given concerning the results of CCI: the estimates are very stable
544 (with a much lower variability than that of CI), but their absolute values are
545 very small. However, CCI is the index providing the largest ICC (Table 2)
546 and Fisher ratio (Table 3), indicating that it has high repeatability and can
547 better discriminate different subjects. Further work is needed to understand
548 how the information provided by these two indexes correlate with the state
549 of the patient (this work investigates only the repeatability of their estima-

550 tions). For example, we expect that irregular cardiac rhythm may cancel or
551 largely affect the cardiac component, so that the relative weight of the two
552 components could be of help in discriminating some patients.

553 *General comments*

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

562 In order to improve the reliability and repeatability of the estimations,
563 a possible solution is averaging more measurements. Different CIs measured
564 on more respiration cycles can be averaged. In this way, an index is obtained
565 accounting for different vein dynamics, induced by different breath stimula-
566 tions. Moreover, averaging allows to reduce estimation errors due to small
567 mistakes in measuring on still images the maximal and minimal diameters
568 (also affected by the asynchronous summation of heartbeats and respiration
569 cycles). Furthermore, an average of information from different sections could
570 further improve the estimation of IVC pulsatility, at the expense of spending
571 time repeating more M-mode investigations along different sections.

572 Our method allows to estimate and average information from different
573 respiration cycles and sections automatically, processing a single US video-
574 clip. This provides a fast and robust overall estimation of the pulsatility in

575 an entire portion of the vein. Here, we show that the averaged estimation
576 provided by our semi-automated method is also more repeatable than the
577 manual assessment.

578 Our results could be considered preliminary, due to the low number of
579 investigated subjects (i.e., 10). However, other indications of the reliability
580 of the information extracted by our automated algorithm are available. For
581 example, the pulsatility of IVC extracted by our algorithm has been recently
582 used to estimate the right atrial pressure, with performances largely superior
583 than those that could be obtained from the manual estimations (Mesin et al.
584 (2019a)). Moreover, works are in progress on the applications on patients,
585 where our algorithm allows to get better discrimination of patients affected
586 by either hypo- or hyper-volaemia.

587 Using an automated method reduces the problems due to subjective in-
588 terpretations. However, the procedure is still dependent on the quality of the
589 video recorded by the operator, so that the experience of the echographer is
590 still important. In future, the real time rendering of the output of the pro-
591 cessing algorithm could provide a feedback to help the operator to acquire
592 a video-clip of good quality. Even considering this limitation of our work
593 (in which the processing was executed off-line), our algorithm allowed to get
594 CI estimations closer to those obtained by the most experienced operator,
595 also when applied to video-clips recorded by a low experience echographer.
596 Thus, we propose this innovative algorithm as a step towards standardizing
597 measurements of IVC pulsatility.

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

600 **Conclusions**

601 Different sources of variability affect the estimation of IVC pulsatility
602 from US measurements, e.g., the respiration cycles and the selected section
603 of the vein. Our semi-automated algorithm allows to track vein movements
604 and deformations in long axis, to compute the diameter of different sections
605 orthogonal to the vein and to provide an estimation of pulsatility which is
606 averaged across respiration cycles and sections. The pulsatility estimations
607 of this software were found to be more repeatable than those obtained by
608 the standard approach. This method can provide a contribution in the stan-
609 dardization of the assessment of IVC pulsatility, with important outcomes
610 expected in the estimation of the central venous pressure and volemic status
611 of patients.

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

704 **Figure 1:** A) Selection of a rectangle including the IVC portion of interest in
705 the first frame of the video-clip. B) Reference points (squares), leftmost
706 and rightmost sections of interest (continuous lines) and points close
707 to the vessel edges along the leftmost section (indicated by X). C)
708 The algorithm computes 21 lines uniformly distributed between the
709 extreme sections indicated in B) and estimates the profile of the vein
710 along them (the estimated border points are indicated with circles). D)
711 From the estimated border of the vessel, the midline is computed and
712 interpolated with a parabola (dash-dot line); five equidistant points are
713 selected on this parabola, starting from the confluence of the hepatic
714 vein in the IVC and new lines perpendicular to it are considered as
715 sections along which to compute the vein diameters (border points
716 indicated with diamonds).

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

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

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

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

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

742 **Figure 6:** Coefficient of variation (CoV) for each index (manual CI and au-
743 tomated estimation of CI, CCI and RCI) computed across different
744 experimental sessions (median, quartiles and range; outliers shown in-
745 dividually). A), B) and C): CoV of the indexes (CI, CCI and RCI,
746 respectively) extracted at different distances from the confluence of the
747 hepatic vein into the IVC and, to the right, the CoV of manual and
748 global estimations (averaging the CI across sections). D) Comparison
749 of CoV of the manual and global CI.

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

751 dex (CI) values. Intra- and inter-operator variabilities are considered
752 (showing the distribution of 10 values, one for each subject, in terms
753 of median, quartiles and range, plus an outlier shown individually).
754 The manual CI estimations are the mean of three CI measurements in
755 M-mode (reflecting the choice of 3 respiration cycles). The automated
756 CI estimations are given by the mean of all CI measurements obtained
757 from each video-clip (CI_{global} , obtained averaging across 3 respiration
758 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						

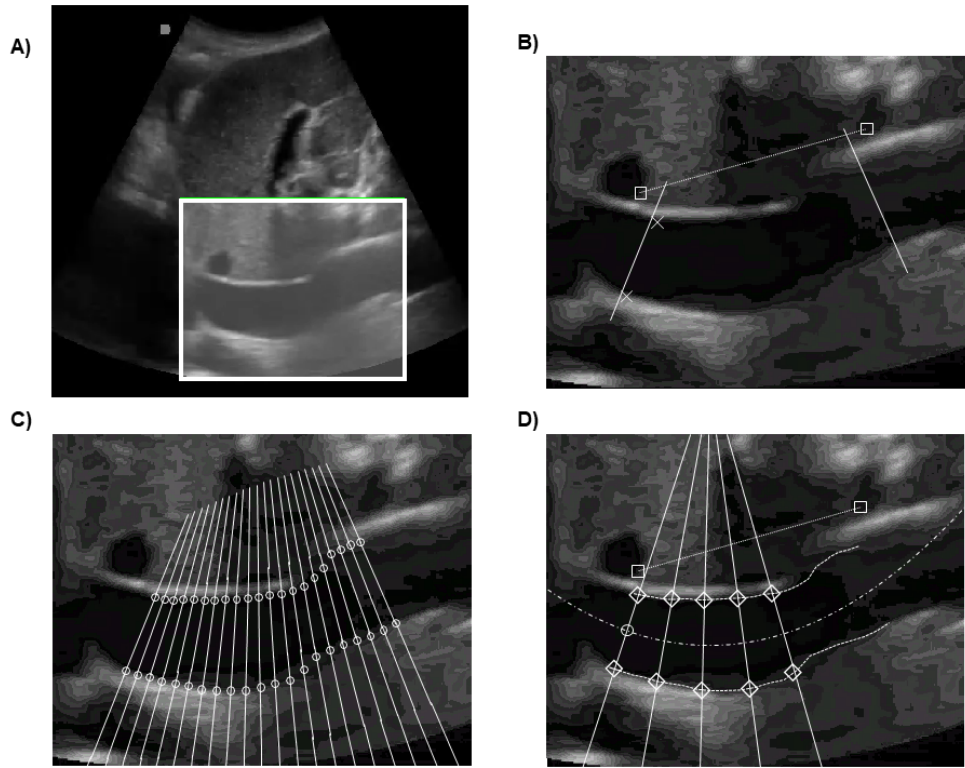


Figure 1: A) Selection of a rectangle including the IVC portion of interest in the first frame of the video-clip. B) Reference points (squares), leftmost and rightmost sections of interest (continuous lines) and points close to the vessel edges along the leftmost section (indicated by X). C) The algorithm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

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

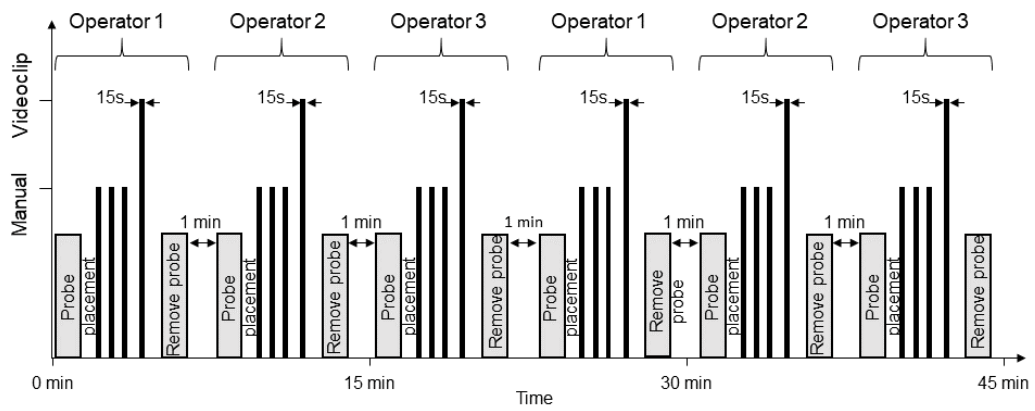


Figure 2: Experimental protocol. Each operator acquired three manual measurements (in M-mode) and then the video (in B-mode). The same procedure was followed twice for each of the three operators.

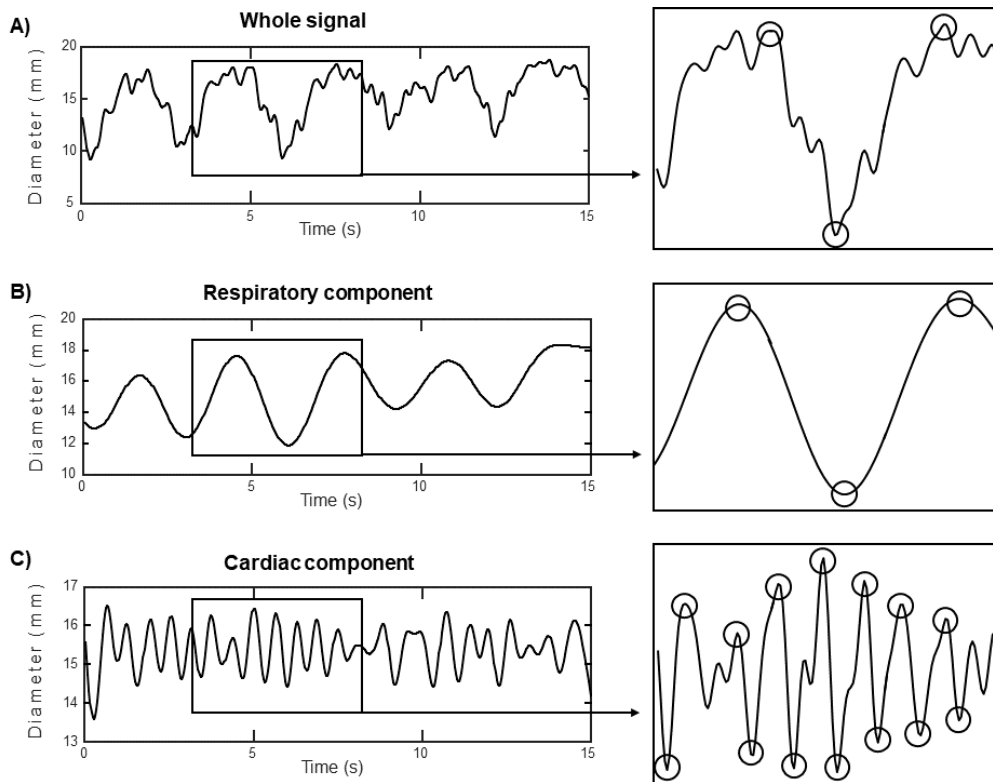


Figure 3: A) Caval index (CI) estimated on the whole signal. The local maxima and minima of the respiratory component are found; then a window of 1 s duration centred on each of these points is explored to find the maxima or minima on the whole signal (indicated with circles). B) Respiratory caval index (RCI), computed on the breath component. This component is isolated with a low pass filter; then, maxima and minima (indicated with circles) are automatically found and used for RCI calculation. C) Cardiac caval index (CCI) computed on the heartbeat component. The component is isolated with a high pass filter; then, its local maxima and minima (indicated with circles) are computed and used for CCI estimation.

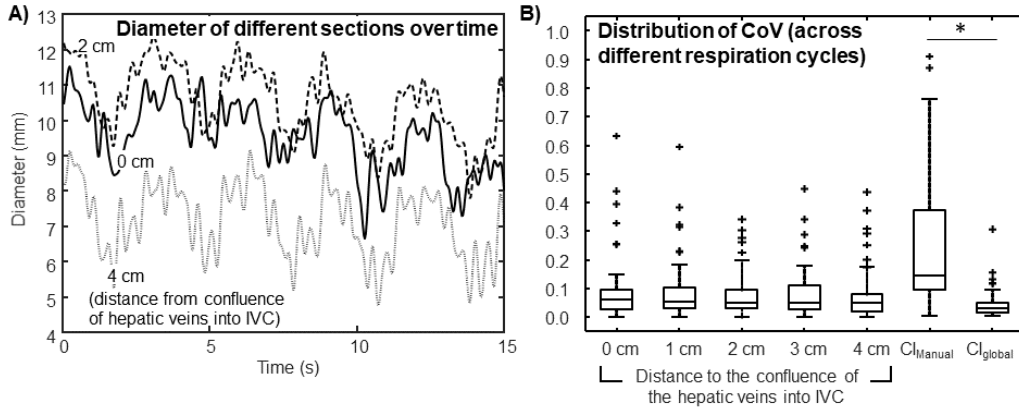


Figure 4: A) Time course of IVC diameter at three different sections simultaneously monitored in a representative subject. B) Distribution of CoV of CI_{auto} , obtained considering the 6 measurements from all 10 subjects, separately for the five sections and compared with manual CI and CI_{global} .

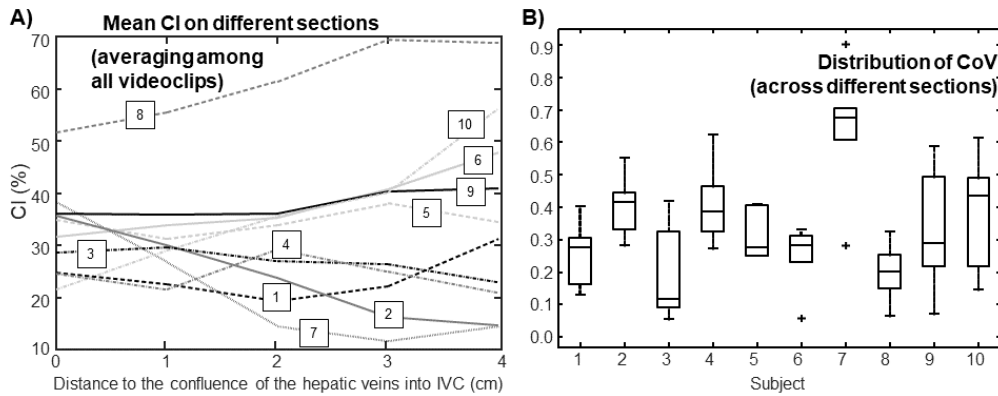


Figure 5: Variation of the Caval Index (CI) when estimated by the automated method at different longitudinal positions, expressed as the distance from the confluence of the hepatic veins. A) Each trace corresponds to one subject (average of all sessions). B) Median, quartiles and range (outliers shown individually) of the coefficient of variation (CoV) of the CI across the 5 sections along the vein, for each subject.

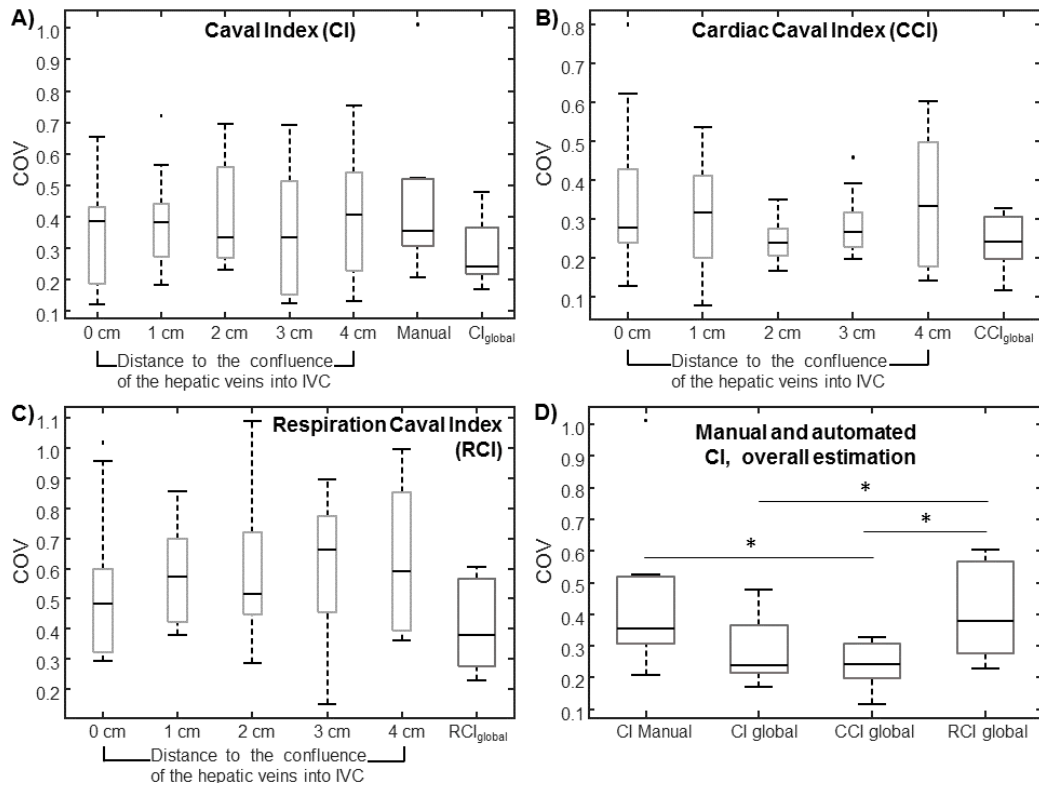


Figure 6: Coefficient of variation (CoV) for each index (manual CI and automated estimation of CI, CCI and RCI) computed across different experimental sessions (median, quartiles and range; outliers shown individually). A), B) and C): CoV of the indexes (CI, CCI and RCI, respectively) extracted at different distances from the confluence of the hepatic vein into the IVC and, to the right, the CoV of manual and global estimations (averaging the CI across sections). D) Comparison of CoV of the manual and global CI.

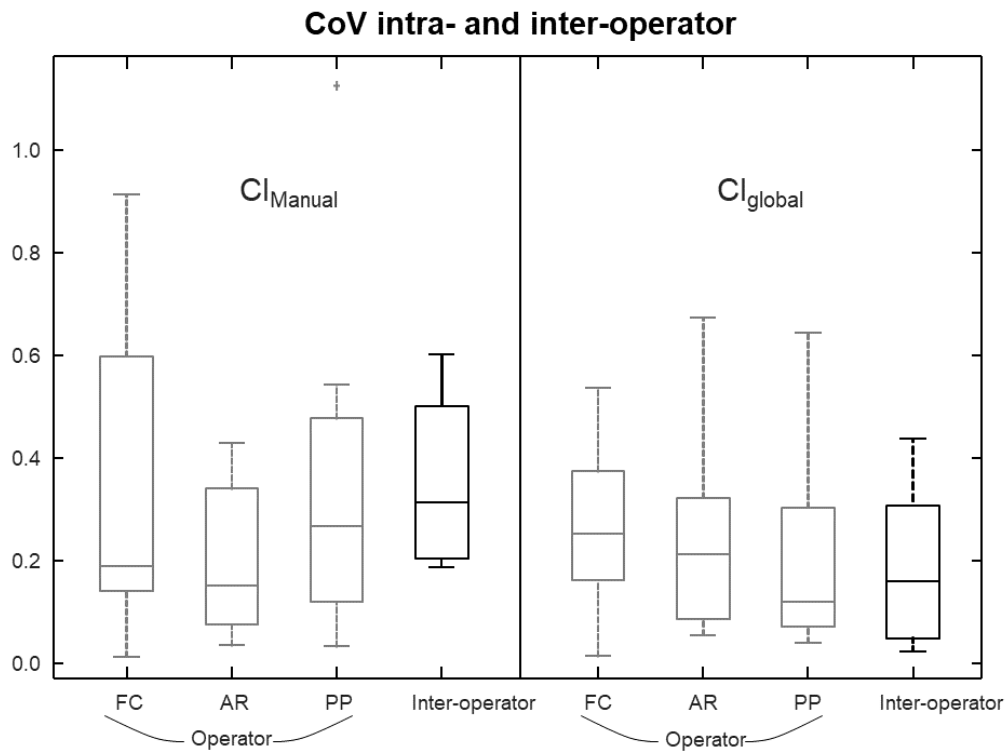


Figure 7: Comparison between CoV of manual and automated Caval Index (CI) values. Intra- and inter-operator variabilities are considered (showing the distribution of 10 values, one for each subject, in terms of median, quartiles and range, plus an outlier shown individually). The manual CI estimations are the mean of three CI measurements in M-mode (reflecting the choice of 3 respiration cycles). The automated CI estimations are given by the mean of all CI measurements obtained from each video-clip (CI_{global} , obtained averaging across 3 respiration cycles and 5 longitudinal sections).