



LEEDS
BECKETT
UNIVERSITY

Citation:

Zamboni, P and Malagoni, AM and Menegatti, E and Ragazzi, R and Tavoni, V and Tessari, M and Beggs, CB (2020) Central venous pressure estimation from ultrasound assessment of the jugular venous pulse. PLoS One, 15 (10). ISSN 1932-6203 DOI: <https://doi.org/10.1371/journal.pone.0240057>

Link to Leeds Beckett Repository record:

<http://eprints.leedsbeckett.ac.uk/id/eprint/7226/>

Document Version:

Article (Published Version)

Creative Commons: Attribution 4.0

The aim of the Leeds Beckett Repository is to provide open access to our research, as required by funder policies and permitted by publishers and copyright law.

The Leeds Beckett repository holds a wide range of publications, each of which has been checked for copyright and the relevant embargo period has been applied by the Research Services team.

We operate on a standard take-down policy. If you are the author or publisher of an output and you would like it removed from the repository, please [contact us](#) and we will investigate on a case-by-case basis.

Each thesis in the repository has been cleared where necessary by the author for third party copyright. If you would like a thesis to be removed from the repository or believe there is an issue with copyright, please contact us on openaccess@leedsbeckett.ac.uk and we will investigate on a case-by-case basis.

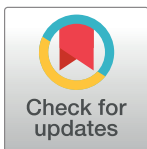
RESEARCH ARTICLE

Central venous pressure estimation from ultrasound assessment of the jugular venous pulse

Paolo Zamboni¹, Anna Maria Malagoni¹, Erica Menegatti¹, Riccardo Ragazzi²,
Valentina Tavoni¹, Mirko Tessari¹, Clive B. Beggs^{3*}

1 HUB Center Regione Emilia Romagna for Venous and Lymphatics Disorders, University Hospital of Ferrara, Ferrara, Italy, **2** Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy, **3** Institute for Sport, Physical Activity and Leisure, Leeds Beckett University, Leeds, United Kingdom

* c.beggs@leedsbeckett.ac.uk



Abstract

Objectives

Acquiring central venous pressure (CVP), an important clinical parameter, requires an invasive procedure, which poses risk to patients. The aim of the study was to develop a non-invasive methodology for determining mean-CVP from ultrasound assessment of the jugular venous pulse.

Methods

In thirty-four adult patients (age = 60 ± 12 years; 10 males), CVP was measured using a central venous catheter, with internal jugular vein (IJV) cross-sectional area (CSA) variation along the cardiac beat acquired using ultrasound. The resultant CVP and IJV-CSA signals were synchronized with electrocardiogram (ECG) signals acquired from the patients. Auto-correlation signals were derived from the IJV-CSA signals using algorithms in R (open-source statistical software). The correlation r -values for successive lag intervals were extracted and used to build a linear regression model in which mean-CVP was the response variable and the lagging autocorrelation r -values and mean IJV-CSA, were the predictor variables. The optimum model was identified using the minimum AIC value and validated using 10-fold cross-validation.

Results

While the CVP and IJV-CSA signals were poorly correlated (mean $r = -0.018$, $SD = 0.357$) due to the IJV-CSA signal lagging behind the CVP signal, their autocorrelation counterparts were highly positively correlated (mean $r = 0.725$, $SD = 0.215$). Using the lagging autocorrelation r -values as predictors, mean-CVP was predicted with reasonable accuracy ($r^2 = 0.612$), with a mean-absolute-error of 1.455 cmH_2O , which rose to 2.436 cmH_2O when cross-validation was performed.

OPEN ACCESS

Citation: Zamboni P, Malagoni AM, Menegatti E, Ragazzi R, Tavoni V, Tessari M, et al. (2020) Central venous pressure estimation from ultrasound assessment of the jugular venous pulse. *PLoS ONE* 15(10): e0240057. <https://doi.org/10.1371/journal.pone.0240057>

Editor: Xiongwen Chen, Temple University, UNITED STATES

Received: May 11, 2020

Accepted: September 17, 2020

Published: October 28, 2020

Copyright: © 2020 Zamboni et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and supporting information files.

Funding: The study was funded by the Italian Ministry of Health (ref: RF-2013-02358029). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Conclusions

Mean-CVP can be estimated non-invasively by using the lagged autocorrelation r -values of the IJV-CSA signal. This new methodology may have considerable potential as a clinical monitoring and diagnostic tool.

Introduction

The jugular venous pulse (JVP), a pivotal parameter of efficient cardiac function, reflects pressure variation in the right atrium over the cardiac cycle [1]. It is represented by changes in the cross-sectional area (CSA) of the internal jugular veins (IJVs) that can be easily monitored using high resolution B-mode sonography [2, 3]. The IJVs readily respond to changes in transmural pressure because they are thin-walled floppy vessels, with the result that the CSA of these vessels fluctuates in a cyclical motion that is influenced by both the cardiac and respiratory cycles [2]. However, despite its importance, JVP evaluation is often neglected in clinical practice [4], with central venous pressure (CVP) (i.e. the pressure in the right atrium and ventricle at the end of diastole) being the parameter most commonly evaluated. CVP is a variable indicative of cardiovascular function, having the dual role of distending the diastolic right ventricle and opposing venous return [5]. As such, CVP is a useful guide for assessing cardiac preload and vascular volume status, as well as being an indicator that can assist in better understanding the reasons for changes in cardiac output, given the interaction that exists between cardiac function and venous return [6]. Its measurement remains widely used in intensive care units and emergency centers mainly for guiding fluid administration in patients with haemodynamic instability [7]. CVP is invasively acquired, requiring the insertion of a catheter via the IJV or subclavian veins. Furthermore, the procedure has inherent drawbacks because it requires high levels of skill and carries a significant risk of complication [8]. Consequently, there is a need to develop a non-invasive methodology for accurately assessing CVP.

Significant correlations have been reported between CVP and: (i) IJV-CSA [9, 10]; (ii) the IJV/common carotid artery CSA ratio [9–11]; and (iii) the external jugular venous pulse [12]. This led us to hypothesize that it should be possible to predict CVP from the JVP [13]. Indeed, several methods have been reported for monitoring CVP non-invasively [12, 14–18], although none, with the exception of near-infrared spectroscopy (NIRS) [12], have demonstrated sufficient accuracy and precision or ease of use. Recently an ultrasonographic (US) technique for obtaining the JVP from a high-resolution B-mode sonogram sequences (US-JVP), recording the changes in IJV-CSA over the cardiac cycle (CC), has been proposed [19], which appears to have potential as an approach for estimating CVP. We therefore undertook the exploratory study presented here with the aim of testing the efficacy (proof-of-concept) of a new methodology (also presented here) for estimating CVP purely from changes in IJV-CSA acquired through US investigation. This methodology, which utilizes the autocorrelation signal of the JVP (i.e. changes in IJV-CSA over the CC) and reflects the spectral characteristics of the CVP pulse, is described in the *Theory* part of the *Methods* section below, which outlines the theory underpinning the autocorrelation technique. Importantly, the methodology is generic and can be applied to individual patients, without any prior knowledge of the CVP pulse or of the patient's anatomical features (e.g. length of neck, etc).

Methods

The study was performed prospectively by a team composed of clinicians, technicians, physicists and bio-engineers, and included a data collection phase, a post-processing phase and a data analysis phase. The study was part of a project granted by the Italian Health Ministry (Ricerca Finalizzata 2013, RF-2013-02358029) that was approved by the Ethics Committee of Ferrara, Italy (reference No.160499). The study was carried out in accordance with the ethical guidelines on good clinical practice as laid down in European Directive and the Declaration of Helsinki. The trial was registered NCT03917368 (<https://clinicaltrials.gov/ct2/show/NCT03917368>).

Data collection

The data collection phase, implemented at the University Hospital of Ferrara (Italy), included the direct invasive measurement of the CVP and the US evaluation of the JVP. Both assessments were performed at the same time.

Subjects

From September 2016 to July 2018, fifty-eight consecutive subjects (21 males and 37 females; mean age 61 ± 3 years) were enrolled as the sample study group. Participants were selected from hospitalised adult patients at University Hospital of Ferrara (Italy) requiring a scheduled central venous catheterisation (CVC) and measurement of the CVP as part of their usual care. Inclusion criteria were: age ≥ 18 years, spontaneous breathing and capacity to give informed consent. Patients were excluded if they needed a cannulation via the internal jugular venous access in order not to interfere with the ultrasound assessment, or if they were pregnant. In addition, because high quality US images and JVP trace data were required in order to develop the diagnostic model, any subjects who yielded corrupted or technically imperfect images or signals were also excluded. All participants were approached before the CVC procedure and signed a written informed consent form.

Direct invasive measurement of the CVP

In a surgery room, after moderate sedation (midazolam 4 mg intravenous) and subcutaneous infiltration of local anaesthetics (mepivacaine 1% 20 ml), patients undertook a standardized subclavian tunnelled catheterization by infraclavicular approach, under fluoroscopic control. Following the catheterisation, patients were placed out of the surgery room lying completely supine on a bed in order to measure the CVP according to the standard [20]. The central venous catheter was connected to intravenous fluid within a pressure bag inflated up to 300 mmHg. The pressure measurement system was placed on the right or left arm at the level of the fifth rib (phlebostatic axis) and the zero reference was checked and calibrated when necessary. Three electrodes were placed on patients' chests for the simultaneous assessment of the electrocardiogram (ECG) signal. The pressure line and the ECG cables were connected to a standard analogue monitor (Philips M3046A M4, Philips Medical System, Boeblingen, Germany), which in turn was connected to a video grabber system, allowing the capture and storage of the screen images on a computer, as they were not directly accessible in their digital format. A single investigator performed all the central venous catheter measurements, which served as the 'gold standard' measurement of CVP value and waveform.

US assessment of the IJVs

Alongside the direct CVP measurement, the US assessment of the IJVs (both right and left) was performed as previously described [3, 21]. A Vivid-q ultrasound system (GE Medical Systems, Horten, Norway) equipped with a linear array probe L12-RS (7.5–11 MHz) was used. Patients were asked to maintain their neck in a fixed position on the longitudinal axis, avoiding flexion, hyperextension and rotation, which might compress the veins and influence the measurements. The probe, smeared with a copious amount of gel, was placed on the patients' neck in a transverse plane with respect to the length of the vessels, at the level of C5-C6, the so-called J2 plane [22]. The IJV-CSA was insonated trying to avoid any pressure on the vessel and a B-mode video-clip of 10–15 sec was recorded and stored. This was sufficient time to record several cardiac cycles and two or three respiratory cycles. The ECG trace was automatically recorded contextually with the IJV-CSA B-mode images. All the US evaluations were performed by a single investigator.

Post-processing

The stored US IJV video clips and the CVP images were processed off-line to obtain a numerical dataset to enable the subsequent analyses and formulation of models. First of all, images and video clips were elaborated with the software *ImageJ* [23] (e.g. Fig 1). The procedure to obtain an IJV-CSA dataset of signals over time consisted of several passages both manual and automatic. This procedure provided the IJV-CSA values in cm^2 versus sonogram acquisition time, the obtained result corresponded to the JVP trace (e.g. Fig 1) [3, 19, 21], whereas the CVP time series signal dataset was produced by digitally identifying the position of each point of the CVP trace represented on the acquired image. Subsequently the JVP and the CVP traces were synchronised using the ECG signal recorded together with the measurements. Finally, the obtained datasets were elaborated with Matlab (MathWorks, Inc.) and R software [24] to remove the frequencies of non-cardiac origin, mainly CSA variations due to activation of the thoracic pump [25]. This removed noise from the traces, therefore highlighting the contribution of the cardiac contraction to both traces [21, 26]. Finally, the post processing aimed to conform the length of the traces making the comparison easier.

Theory

While the relationship between the IJV-CSA and CVP signals is difficult to interpret in the time domain, it has been shown that in the frequency domain the two signals share similar spectral characteristics [27]. Therefore, in theory it should be possible to determine a great deal about the CVP signal purely through examination of the IJV pulse. However, factors such as respiration influence the IJV pulse and there is a phase lag between the CVP pulse and the IJV pulse, which makes it difficult to interpret the relationship between the two signals.

Autocorrelation, which assesses the degree of similarity between a given time series signal and a lagged version of itself over successive time intervals, can be used to gain insights into the spectral characteristics of signals. Through the Wiener–Khinchin theorem it can be shown that the Fourier transform (used in Fourier analysis) is closely related to the autocorrelation function of a signal [28]. As such, the autocorrelation signal can be used to assess the periodicity of any given time series signal using Eq 1.

$$f = \frac{1}{D \times dt} \quad (1)$$

Where: f is the frequency of the time series signal; D is the lag distance between successive peaks in the autocorrelogram; and dt is the sampling interval.

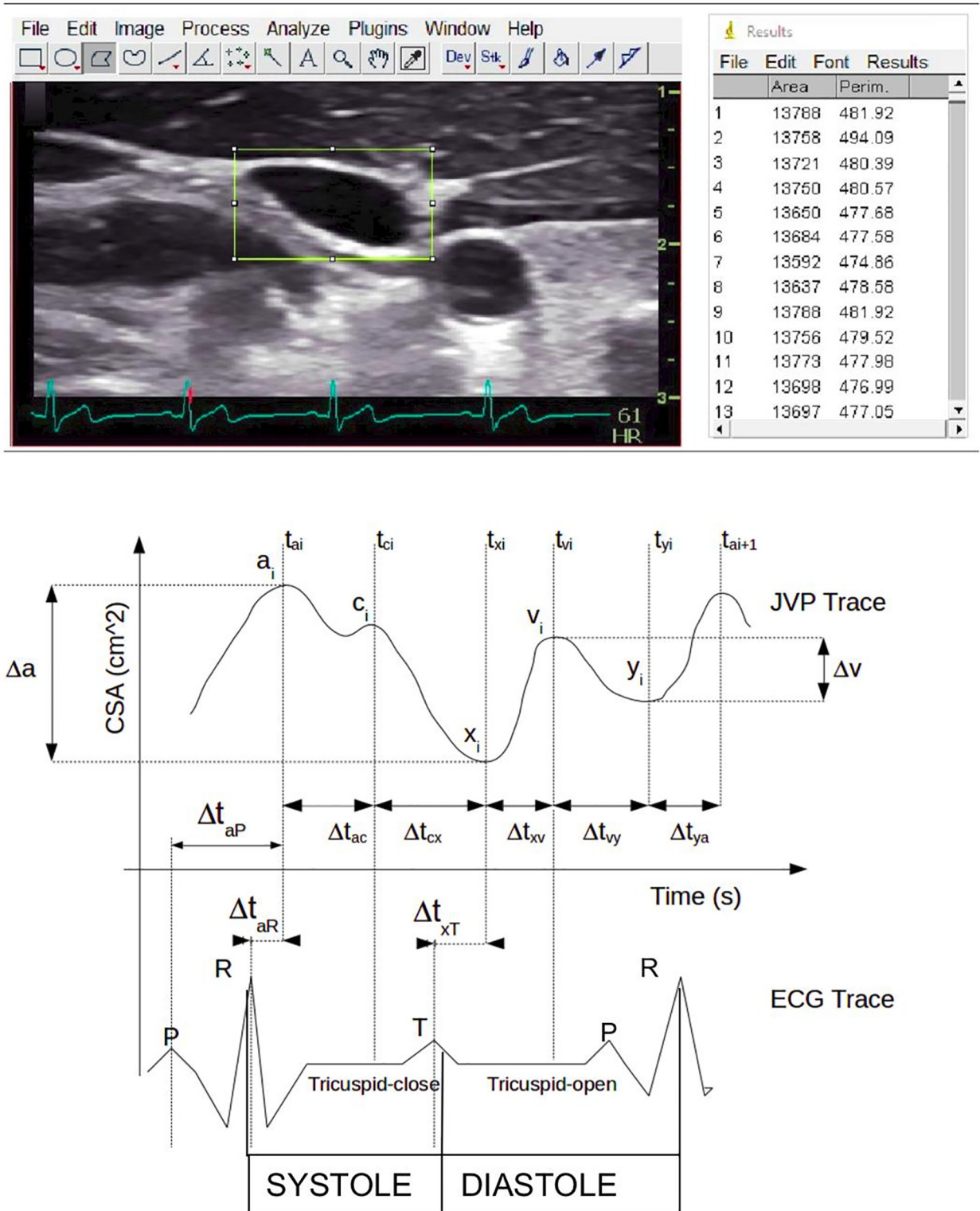


Fig 1. ImageJ custom plugin to detect area variations: The top figure shows an example of B-mode image with a rectangular Region of Interest (ROI) and synchronized ECG trace, together with a list of ROIs and collected measurements. The bottom figure shows the indicative JVP trace with a, c, v peaks and x, y troughs synchronized with the ECG trace. Systole and diastole phase as well as the corresponding opening and closure of the tricuspid valve and various time intervals (Δt) are also shown.

<https://doi.org/10.1371/journal.pone.0240057.g001>

Because the autocorrelation function reflects the spectral characteristics of signals, if two time series signals such as the IJV and CVP pulses share similarities in the frequency domain, then their respective autocorrelation signals will exhibit similarities and will tend to be aligned irrespective of any lag between the two signals in the time domain. This suggests that the autocorrelation signal might be a useful tool with which to predict the characteristics of the CVP pulse using the IJV pulse.

For any given time series signal the corresponding autocorrelation signal is simply a plot of the changes in the correlation r-value as a function of delay. The autocorrelation r-value for any given lag in a time series can be computed using Eq 2.

$$r_h = \frac{\sum[(y_t - \bar{y})(y_{t+h} - \bar{y})]}{\sum[(y_t - \bar{y})^2]} \quad (2)$$

Where: r_h is the r-value for any given lag; y_t is the time series signal at lag = 0; y_{t+h} is the time series signal at lag = h; and \bar{y} is the mean of the time series signal.

From this it can be seen that the autocorrelation signal is strongly influenced by the mean of the measured signal in the time domain. Therefore, it can be hypothesized that it should be possible to estimate the mean of the CVP pulse directly from the autocorrelation signal of the IJV pulse, provided that the two share similar spectral characteristics.

Data analysis

Signal processing and statistical analysis were undertaken using in-house algorithms written in R [24]. The relationship between the IJV-CSA and CVP time series signals for the respective subjects was assessed using Pearson correlation analysis, with the time lag between the two signals computed using the ‘ccf’ cross-correlation function in R. For each patient, the autocorrelation signals were derived from the IJV-CSA and CVP time series signals using the ‘acf’ function in R. From these, the correlation r-values for successive lags of 20 time intervals from 0 to 360 (i.e. 0, 20, 40, 60, . . . 360 intervals) were extracted and used to build the CVP prediction model. Fourier analysis was also performed using the ‘fft’ function in R to produce periodograms for each patient. From these the five most dominant frequencies (with amplitudes) were extracted for each patient. A linear regression model was then produced with mean CVP as the response (dependent) variable and the extracted autocorrelation r-values for the successive lags, together with the mean IJV-CSA value, as the predictor (independent) variables. The model was then refined using an in-house algorithm, which assessed all possible combinations of the predictor variables to identify the model with the minimum Akaike information criterion (AIC). The refined linear model was then used to predict the mean CVP for the respective subjects. Finally, in order to assess the general applicability of the refined model and to test its robustness as a predictor of mean CVP, 10-fold cross-validation was performed. This gave an indication of how well the model might perform in ‘real life’ clinical situations. In addition, a *post-hoc* statistical power calculation was performed using Cohen’s f^2 with alpha = 0.05.

In order to test its clinical efficacy, the regression model was further evaluated by splitting the outcomes into three categories: (i) CVP within the normal range, 2–8 mmHg (2.72–10.88 cmH₂O) [29, 30]; (ii) CVP above the normal range; and (iii) CVP below the normal range. For each class the sensitivity score was computed, together with overall accuracy achieved by the model, which was also statistically evaluated using Cohen’s Kappa statistic for measuring agreement.

Results

The clinical US assessment of the IJVs and the invasive CVP measurement were completed in all 58 enrolled patients. The post-processing phase revealed a number of technical imperfections and/or subject related abnormalities (ECG trace or CVP images not recorded, $n = 6$; IJV-CSA edges not perfectly outlined, $n = 4$; CVP images not readable, $n = 3$; abnormal ECG, $n = 5$; abnormal IJV-CSA size, $n = 6$), which potentially could compromise model development. These traces were therefore deemed to be technically imperfect, and so the US video clips and CVP images from the 24 affected subjects were excluded from the post-processing phase in order to obtain a reliable dataset to analyse. In addition, in order to reduce the amount of data, only the right IJV US video clips were considered for this study. The right IJV was selected because this vessel is closer to the heart than the left IJV and thus is the dominant side in 80% of individuals. The clinical characteristics of the remaining 34 subjects are summarized in [Table 1](#). Video clips and images from the remaining 34 subjects (age = 60 ± 12 years; 10 males/24 females) were finally processed and analysed ([Fig 2](#)). Sample results obtained during the post-processing phase are shown in [S1 Table](#).

The results of the autocorrelation analysis are presented in [Table 2](#) and in [Fig 3](#), while the spectral analysis results are presented in [S2](#) and [S3](#) Tables. Collectively, these reveal that while the CVP and IJV-CSA time series signals were poorly correlated (mean $r = -0.018$, $SD = 0.357$), their autocorrelation counterparts were highly positively correlated (mean $r = 0.725$, $SD = 0.215$) ([Table 3](#)). The poor correlation between the time series signals was in part due to the fact that the IJV-CSA signal lagged behind the CVP signal by on average 0.241 s ($SD = 0.175$ s) ([Table 3](#)), whereas in the autocorrelation signals were generally aligned because both pulses exhibited similar spectral characteristics ([S2](#) and [S3](#) Tables). This is well illustrated in [Fig 4](#), which shows: (a) the normalized time series signals; (b) the autocorrelation signals; and (c) the combined periodogram, relating to Subject 19. From the periodogram in [Fig 4\(c\)](#) it can be seen that while both signals are dominated by a strong peak at 0.95 Hz, the CVP pulse exhibits a strong second peak at about 1.90–2.14 Hz, which is much weaker in the IJV-CSA

Table 1. Clinical characteristics of subjects.

| | |
|-----------------------------|-----------|
| Age (ys) | 60±11 |
| Male/female ratio | 10/24 |
| <i>Main diseases, n (%)</i> | |
| Neoplasia | 34 (100%) |
| Coronary artery disease | 3 (9%) |
| Thyroid diseases | 4 (12%) |
| Hypertension | 7 (21%) |
| Dyslipidaemia | 3 (9%) |
| Diabetes | 3 (9%) |
| <i>Main drugs, n (%)</i> | |
| Antihypertensives | 7 (21%) |
| Statins | 3 (9%) |
| Levothyroxine | 4 (12%) |
| Corticosteroids | 5 (15%) |
| Insulin | 2 (6%) |
| Allopurinol | 3 (9%) |
| Morphine/oxycodone | 2 (6%) |

Values are given as means \pm SD for continuous variables and numbers for categorical variables.

<https://doi.org/10.1371/journal.pone.0240057.t001>

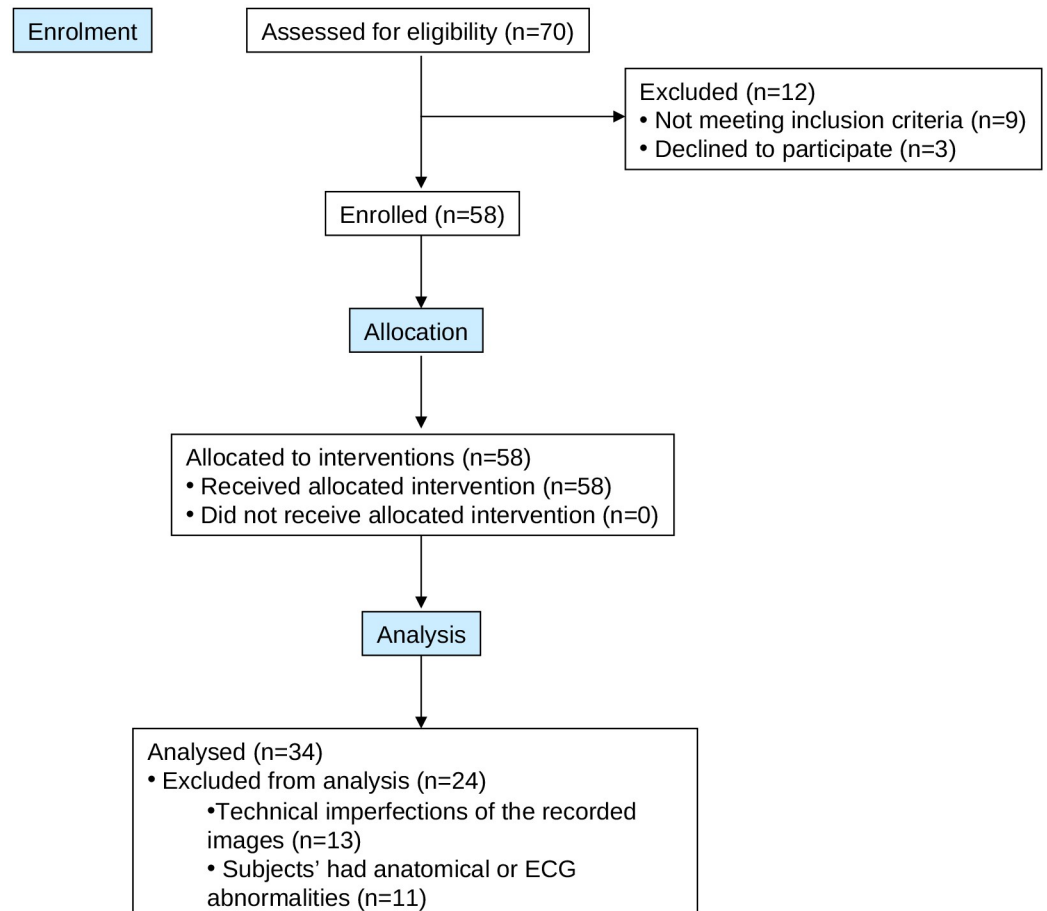


Fig 2. Flow diagram showing subject enrolment and exclusion.

<https://doi.org/10.1371/journal.pone.0240057.g002>

pulse. This difference is reflected in the respective autocorrelation signals in Fig 4(b), which reveal that although both signals have the same general periodicity (indicating the dominance of a single frequency in both signals), the CVP autocorrelation signal is more complex, indicating that it is affected to a greater extent by other additional frequencies.

The refined regression model results are presented in Table 4 and in Fig 5. This suggests that the simple algorithm shown in Eq 3 can be used to predict mean CVP with reasonable accuracy ($r^2 = 0.612$) using just the mean IJV-CSA value and selected autocorrelation r-values as predictors. Post-hoc analysis revealed Cohen's f^2 to be 1.577 with a statistical power of 0.993.

$$\begin{aligned}
 CVP_{pred} = & (2.836 \times CSA_{mean}) - (32.469 \times lag_{40}) - (22.015 \times lag_{80}) - (7.590 \times lag_{100}) - \\
 & (18.417 \times lag_{120}) - (14.016 \times lag_{140}) - (23.054 \times lag_{180}) - (11.470 \times lag_{220}) - \\
 & (5.513 \times lag_{240}) - (8.478 \times lag_{280}) - (7.059 \times lag_{320}) - 10.014
 \end{aligned} \quad (3)$$

Where: CVP_{pred} is the predicted CVP; CSA_{mean} is the mean IJV-CSA; and lag 20–340 are the r-values for the specified lags extracted from the autocorrelation signal. This linear model predicted the mean CVP for the respective subjects (Fig 4) with a mean-absolute-error (mae) of 1.455 cmH₂O, which rose to 2.436 cmH₂O when 10-fold cross-validation was performed.

Table 2. Descriptive and aggregated autocorrelation results for both the central venous pressure (CVP) and internal jugular vein cross-sectional area (IJV-CSA) signals.

| Parameter | CVP (n) | CVP (mean) | CVP (sd) | CVP (min) | CVP (max) | IJV-CSA (n) | IJV-CSA (mean) | IJV-CSA (sd) | IJV-CSA (min) | IJV-CSA (max) |
|--|---------|------------|----------|-----------|-----------|-------------|----------------|--------------|---------------|---------------|
| Mean (cmH ₂ O & cm ²) | 34 | 5.998 | 2.874 | 1.066 | 10.896 | 34 | 0.984 | 0.497 | 0.193 | 1.908 |
| sd (cmH ₂ O & cm ²) | 34 | 1.21 | 0.462 | 0.554 | 2.173 | 34 | 0.05 | 0.03 | 0.008 | 0.114 |
| Median (cmH ₂ O & cm ²) | 34 | 6.002 | 2.893 | 0.758 | 10.819 | 34 | 0.979 | 0.497 | 0.185 | 1.897 |
| Min (cmH ₂ O & cm ²) | 34 | 3.422 | 3.355 | -2.271 | 9.664 | 34 | 0.879 | 0.466 | 0.125 | 1.813 |
| Max (cmH ₂ O & cm ²) | 34 | 8.667 | 2.660 | 3.34 | 12.739 | 34 | 1.090 | 0.525 | 0.287 | 2.040 |
| lag0 (r-value) | 34 | 1.000 | 0.000 | 1.000 | 1.000 | 34 | 1.000 | 0.000 | 1.000 | 1.000 |
| lag20 (r-value) | 34 | 0.127 | 0.339 | -0.428 | 0.664 | 34 | 0.384 | 0.314 | -0.429 | 0.841 |
| lag40 (r-value) | 34 | -0.19 | 0.214 | -0.549 | 0.264 | 34 | -0.163 | 0.344 | -0.830 | 0.542 |
| lag60 (r-value) | 34 | -0.173 | 0.270 | -0.636 | 0.587 | 34 | -0.321 | 0.307 | -0.784 | 0.602 |
| lag80 (r-value) | 34 | -0.206 | 0.284 | -0.64 | 0.731 | 34 | -0.290 | 0.283 | -0.656 | 0.642 |
| lag100 (r-value) | 34 | -0.046 | 0.361 | -0.572 | 0.727 | 34 | -0.051 | 0.414 | -0.643 | 0.682 |
| lag120 (r-value) | 34 | 0.046 | 0.354 | -0.459 | 0.655 | 34 | 0.033 | 0.459 | -0.723 | 0.767 |
| lag140 (r-value) | 34 | 0.061 | 0.263 | -0.425 | 0.675 | 34 | -0.039 | 0.397 | -0.709 | 0.742 |
| lag160 (r-value) | 34 | -0.036 | 0.304 | -0.45 | 0.675 | 34 | -0.097 | 0.332 | -0.590 | 0.663 |
| lag180 (r-value) | 34 | -0.085 | 0.250 | -0.585 | 0.363 | 34 | -0.114 | 0.314 | -0.557 | 0.549 |
| lag200 (r-value) | 34 | -0.012 | 0.265 | -0.466 | 0.562 | 34 | -0.034 | 0.316 | -0.547 | 0.616 |
| lag220 (r-value) | 34 | -0.041 | 0.254 | -0.473 | 0.534 | 34 | 0.031 | 0.299 | -0.583 | 0.632 |
| lag240 (r-value) | 34 | 0.054 | 0.250 | -0.501 | 0.544 | 34 | 0.102 | 0.322 | -0.459 | 0.674 |
| lag260 (r-value) | 34 | 0.078 | 0.279 | -0.372 | 0.734 | 34 | 0.101 | 0.319 | -0.370 | 0.835 |
| lag280 (r-value) | 34 | -0.024 | 0.226 | -0.349 | 0.552 | 34 | 0.050 | 0.287 | -0.449 | 0.717 |
| lag300 (r-value) | 34 | -0.018 | 0.197 | -0.360 | 0.411 | 34 | 0.017 | 0.263 | -0.425 | 0.574 |
| lag320 (r-value) | 34 | 0.027 | 0.237 | -0.379 | 0.54 | 34 | 0.007 | 0.266 | -0.420 | 0.566 |
| lag340 (r-value) | 34 | 0.044 | 0.193 | -0.312 | 0.447 | 34 | 0.000 | 0.246 | -0.387 | 0.597 |
| lag360 (r-value) | 34 | -0.015 | 0.152 | -0.429 | 0.304 | 34 | -0.018 | 0.219 | -0.494 | 0.483 |

CVP—central venous pressure; IJV-CSA—internal jugular vein cross-sectional area; n—number of observations; mean—mean value; sd—standard deviation; min—minimum value; max—maximum value.

<https://doi.org/10.1371/journal.pone.0240057.t002>

With regards to clinical classification, the model correctly identified 26 out of 27 subjects (sensitivity = 96.3%) as having normal CVP; 0 out of 1 subject (sensitivity = 0.0%) as having a high CVP; and 3 out of 6 subjects (sensitivity = 50.0%) as having a low CVP. The overall classification accuracy of the model was 85.3% (Kappa = 0.472).

Discussion

The jugular venous pulse is a physiological and pivotal parameter to describe cardio-circulatory function, as well as cardiac preload. In current clinical practice, it is a parameter that over time has been abandoned due to difficulty in creating reliable measurements when physically examining patients. The corresponding invasive ‘gold standard’, CVC, and the simultaneous diffusion of echocardiography, have in fact greatly reduced its use in clinical practice. However, CVC, being an invasive technique, has the great disadvantage that it is associated with an increased risk of clinical complications [8]. Therefore, the creation of a model that allows CVP to be detected quickly, reliably and non-invasively represents an important development, one that has relevance to several clinical applications, including the management of heart failure. In particular, it may be useful when monitoring drug therapy over time, something that cannot easily be done using echocardiography or an invasive manoeuvre. Therefore, having a rapid

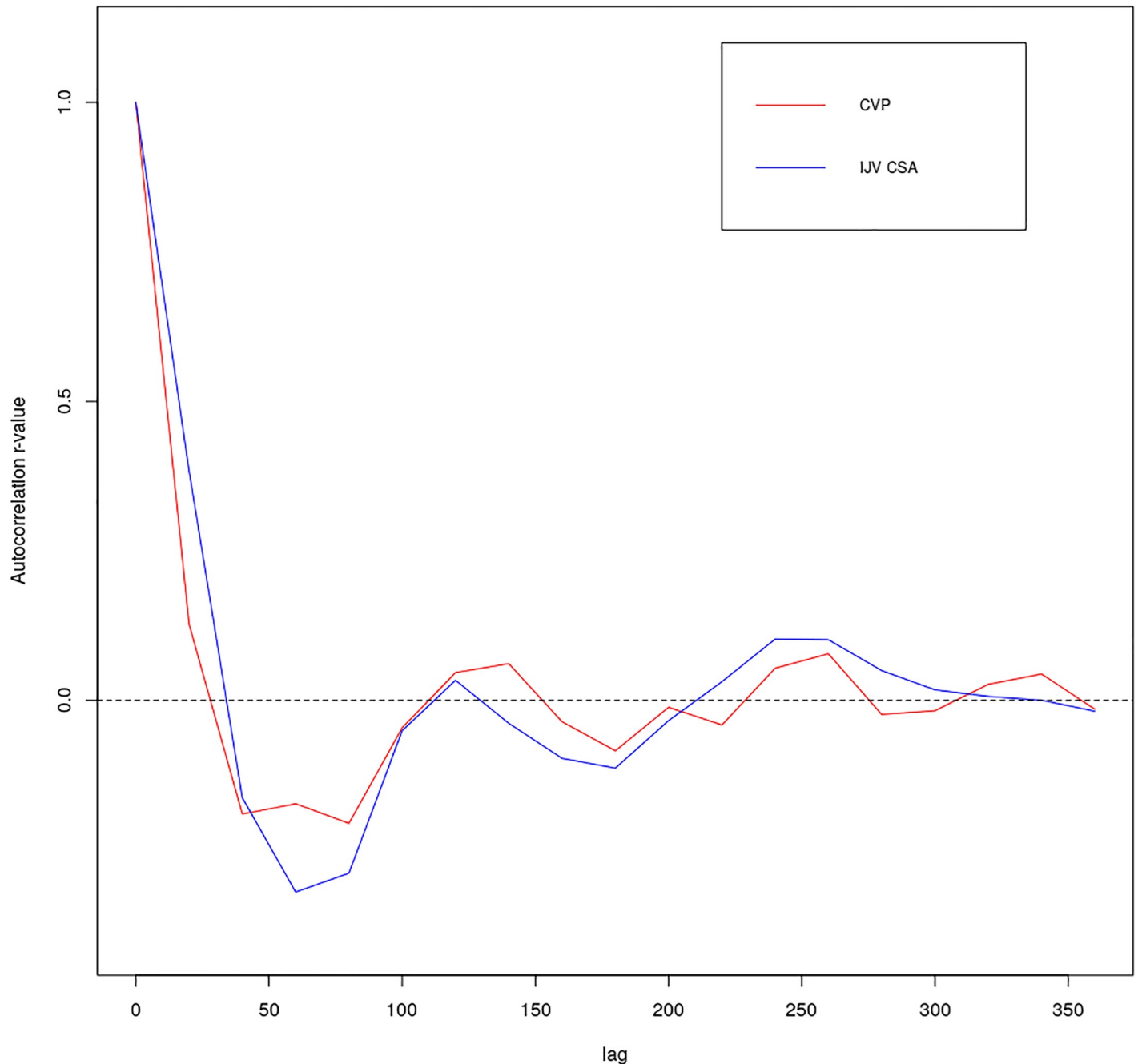


Fig 3. Mean ensemble autocorrelograms for the CVP and IJV CSA pulse signals (aggregated for all 34 subjects).

<https://doi.org/10.1371/journal.pone.0240057.g003>

ultrasonographic test, which can also be performed by the general practitioner, could be decisive in the global management of heart failure, a disease that is thought to affect approximately 1–2% in the western world, with an incidence rate approaching 5–10 per 1000 persons per year [31], and which is more prevalent amongst the elderly and more common in women [32]. In addition, the non-invasive model could also be helpful in the evaluation of suspected hypovolemia, and cerebral venous return, or even in space medicine [21].

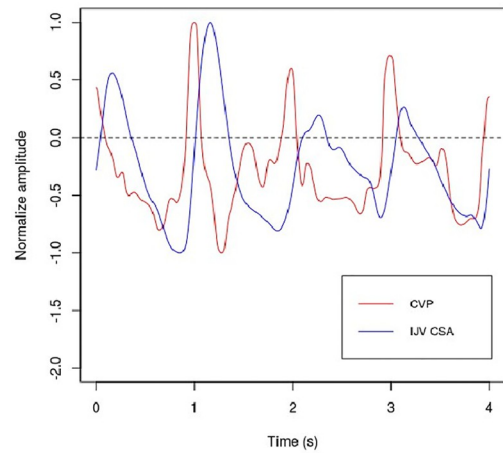
Table 3. Correlations and lag times between the central venous pressure (CVP) and internal jugular vein cross-sectional area (IJV-CSA) signals for the respective subjects.

| Subject ID | Correlation between the measure signals (r-value) | Correlation between the autocorrelation signals (r-value) | Incremental lag between the measure signals | Sampling interval (s) | Lag.time between the measure signals (s) |
|------------|---|---|---|-----------------------|--|
| 1 | 0.877 | 0.992 | -4.000 | 0.009 | -0.035 |
| 4 | -0.286 | 0.956 | -37.000 | 0.007 | -0.261 |
| 5 | 0.501 | 0.947 | -12.000 | 0.008 | -0.094 |
| 8 | -0.004 | 0.561 | -55.000 | 0.009 | -0.478 |
| 10 | 0.205 | 0.659 | -13.000 | 0.010 | -0.130 |
| 15 | -0.003 | 0.528 | -88.000 | 0.009 | -0.759 |
| 18 | -0.204 | 0.680 | -34.000 | 0.008 | -0.262 |
| 19 | -0.013 | 0.821 | -29.000 | 0.006 | -0.170 |
| 20 | -0.239 | 0.550 | -53.000 | 0.009 | -0.491 |
| 23 | -0.388 | 0.509 | -31.000 | 0.007 | -0.220 |
| 24 | -0.284 | 0.229 | -69.000 | 0.010 | -0.690 |
| 25 | -0.196 | 0.789 | -17.000 | 0.010 | -0.165 |
| 28 | 0.682 | 0.929 | -1.000 | 0.008 | -0.008 |
| 30 | 0.062 | 0.224 | -35.000 | 0.004 | -0.134 |
| 31 | -0.052 | 0.679 | -41.000 | 0.004 | -0.161 |
| 34 | 0.096 | 0.771 | -17.000 | 0.007 | -0.120 |
| 38 | -0.592 | 0.826 | -30.000 | 0.009 | -0.278 |
| 39 | -0.366 | 0.787 | -37.000 | 0.012 | -0.430 |
| 40 | -0.075 | 0.732 | -28.000 | 0.008 | -0.219 |
| 42 | -0.150 | 0.927 | -44.000 | 0.004 | -0.173 |
| 44 | -0.408 | 0.855 | -40.000 | 0.006 | -0.245 |
| 46 | 0.018 | 0.339 | -22.000 | 0.008 | -0.171 |
| 47 | -0.686 | 0.930 | -32.000 | 0.013 | -0.400 |
| 48 | -0.102 | 0.969 | -17.000 | 0.016 | -0.270 |
| 49 | -0.149 | 0.729 | -45.000 | 0.010 | -0.455 |
| 50 | -0.354 | 0.870 | -34.000 | 0.008 | -0.283 |
| 51 | 0.677 | 0.926 | -17.000 | 0.005 | -0.077 |
| 52 | 0.115 | 0.916 | -51.000 | 0.004 | -0.179 |
| 53 | -0.112 | 0.584 | -52.000 | 0.003 | -0.156 |
| 54 | 0.481 | 0.957 | -18.000 | 0.006 | -0.112 |
| 55 | 0.342 | 0.726 | -7.000 | 0.003 | -0.024 |
| 56 | 0.219 | 0.803 | -31.000 | 0.005 | -0.150 |
| 57 | -0.059 | 0.583 | -42.000 | 0.003 | -0.119 |
| 58 | -0.175 | 0.373 | -64.000 | 0.004 | -0.262 |
| mean | -0.018 | 0.725 | -33.735 | 0.007 | -0.241 |
| sd | 0.357 | 0.215 | 19.181 | 0.003 | 0.175 |

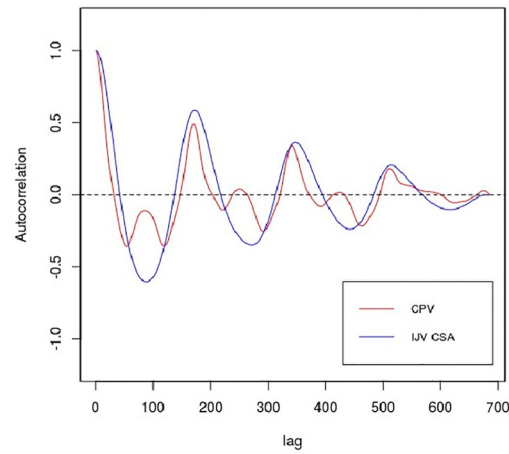
mean—mean value; sd—standard deviation.

<https://doi.org/10.1371/journal.pone.0240057.t003>

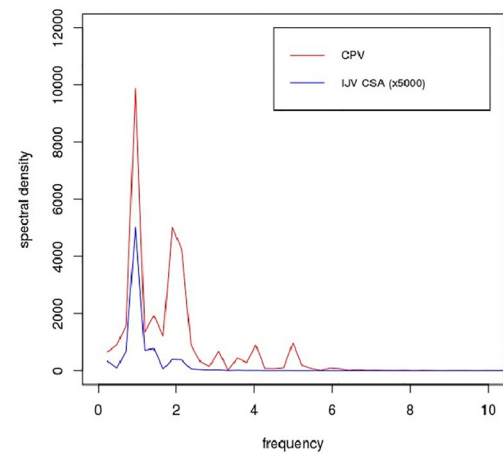
From the analysis presented above it can be seen that by utilizing the autocorrelation plot of the IJV-CSA pulse it is possible to predict mean CVP with reasonable accuracy ($r^2 > 0.6$) using a simple linear model. As such, we have been able to show that there is a clear relationship between the mean of the CVP pulse and the autocorrelation signal of the IJV pulse, as suggested by Eq 2. Having said this, we were somewhat surprised that the mean CVP could be estimated with such accuracy using just a simple linear model, given that the autocorrelation



(a)



(b)



(c)

Fig 4. (a) Normalized time series signals; (b) autocorrelation signals; and (c) periodogram of the CVP and IJV CSA pulses for Subject 19.

<https://doi.org/10.1371/journal.pone.0240057.g004>

Table 4. Refined multiple linear regression model with mean central venous pressure (CVP) as the response variable.

| Response Variable | Predictor Variables | Coefficient b (95% CI) | Significance p value | Model AIC (p value) | Model r^2 (mae) | 10-fold cross-validation r^2 (mae) |
|-------------------|---------------------|----------------------------|----------------------|---------------------|-------------------|--------------------------------------|
| CVP | Intercept | -10.014 (-19.73--0.30) | 0.044 | 161.1 (0.011) | 0.612 (1.455) | 0.498 (2.436) |
| | lag40 | -32.469 (-53.43--11.50) | 0.004 | | | |
| | Lag80 | -22.015 (-38.27--5.76) | 0.010 | | | |
| | Lag100 | -7.590 (-14.66--0.51) | 0.037 | | | |
| | Lag120 | -18.417 (-28.41--0.42) | 0.001 | | | |
| | Lag140 | -14.016 (-25.85--2.18) | 0.022 | | | |
| | Lag180 | -23.054 (-36.28--9.83) | 0.002 | | | |
| | Lag220 | -11.470 (-19.95--2.99) | 0.010 | | | |
| | Lag240 | -5.513 (-12.11--1.09) | 0.097 | | | |
| | Lag280 | -8.478 (-14.88--2.87) | 0.012 | | | |
| | Lag320 | -7.059 (-12.71--1.41) | 0.017 | | | |
| | CSA mean | 2.836 (0.93--4.74) | 0.005 | | | |

<https://doi.org/10.1371/journal.pone.0240057.t004>

signal itself is non-linear. Indeed, it was only possible to use a linear model because the CSA autocorrelation signals were dominated by a cardiac frequency of just under 1 Hz, which meant that the CSA autocorrelation signals tended to exhibit a similar periodicity, as did many of the CVP autocorrelation signals (as exemplified in Fig 4(b)). Consequently, there was a broadly linear relationship between the extracted r-values for the respective lags and the CVP mean values for the study cohort, which we were able to exploit.

While Fourier analysis is frequently used to establish the spectral characteristics of blood vessels, in practice the frequency domain results produced can be difficult to interpret. By comparison, we found the autocorrelation signals much easier to interpret because they captured the ‘combined effect’ of all the frequencies acting on the respective vessels. Thus, we were able to quickly assess the similarities and dissimilarities between the respective signals using just their autocorrelations, something, which would be more difficult to achieve using either the time domain or frequency domain plots. For example, from Fig 4(b) it can be seen that although the CVP autocorrelation signal for Subject 19 is influenced by a strong secondary frequency of approximately 2 Hz (according to the periodogram in Fig 4(c)), this does not affect the overall periodicity of the CVP autocorrelation signal, which is the same as that of the CSA autocorrelation signal—something that is difficult to determine using either the respective time domain (Fig 4(a)) or frequency domain (Fig 4(c)) plots. As such, this suggests that autocorrelation plots have considerable potential when comparing venous haemodynamic signals.

Although in this initial proof-of-concept study we succeeded in producing an algorithm that can approximately predict mean CVP from the IJV-CSA pulse, we are aware that despite achieving an overall accuracy of 85%, the Kappa statistic was only 0.472, indicating just

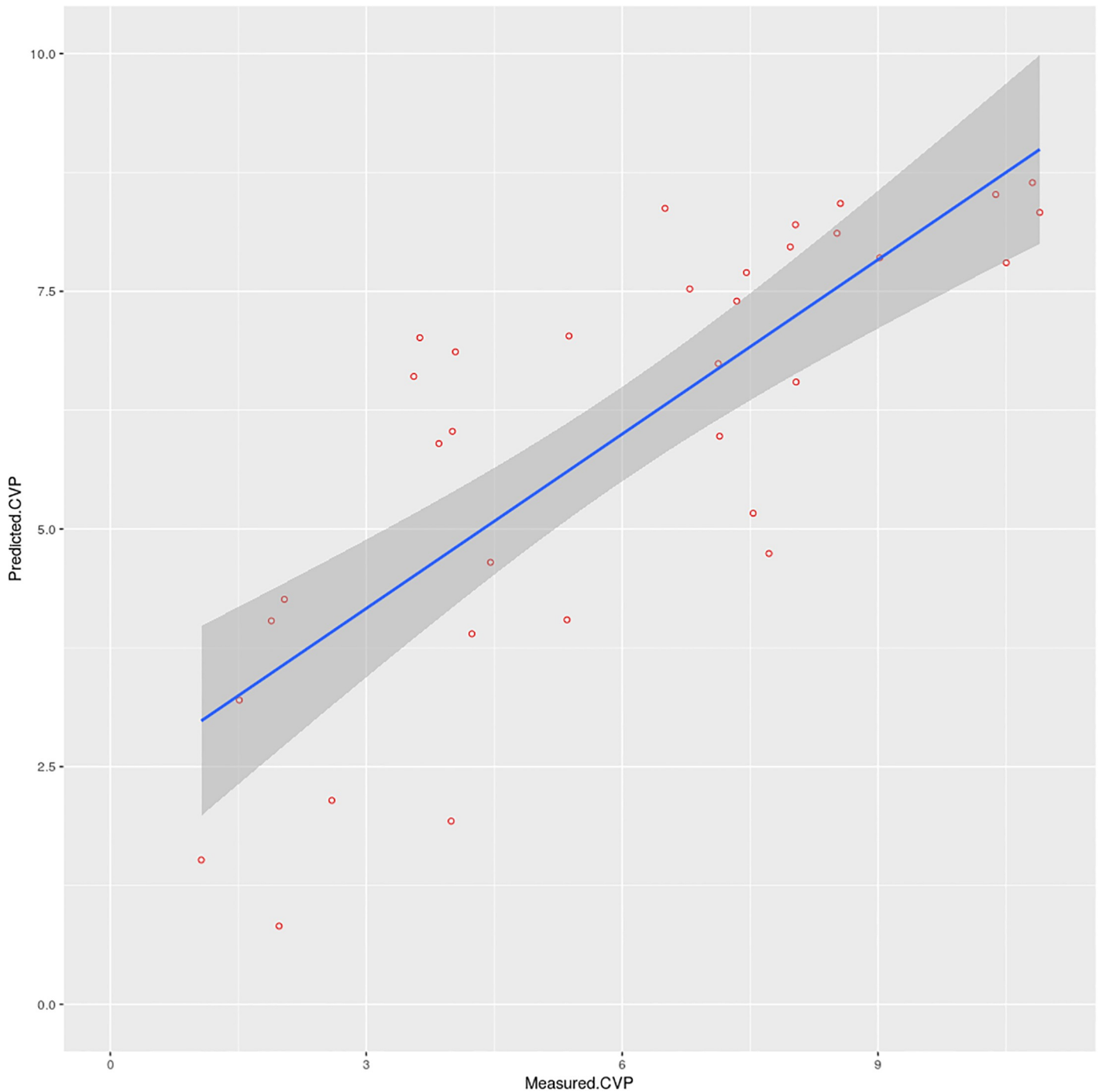


Fig 5. Regression scatter plot showing predicted and measured mean CVP values for the 34 subjects (units are in cmH_2O).

<https://doi.org/10.1371/journal.pone.0240057.g005>

moderately good performance when clinically classifying patients. However, this was achieved using a simple linear model and a relatively small cohort, and it is anticipated that it should be possible in future studies to improve the predictive accuracy of the model by utilising a sophisticated machine learning strategy, such as a random forest [33]. Notwithstanding this, our results are promising when compare with those achieved using existing methodologies. For

example, CVP has traditionally been assessed through visual inspection of changes in volume of the right IJV, when the upper body is inclined, using the sternal angle as the reference point. However, the IJV is often obscured by the overlying neck tissues making clear visual identification difficult, particularly for the less experienced examiner [34]. Consequently, the accuracy of the visual inspection technique has been shown to be little better than about 50–60% [35, 36]. It should also be noted that substantial variations can occur in observed CVP due to errors in transducer placement when taking invasive catheter measurements [37]. In the light of this, the methodology presented here appears to have merit and potentially could be extremely helpful particularly in emergency situations due to the speed with which vital information can be obtained non-invasively using a simple ultrasound investigation that can be easily performed at the patients' bedside. Moreover, by utilising the model as a classification tool split into three categories (normal, high and low CVP), it is possible to facilitate its applicability to clinical practice.

One major limitation of our study is that the model was only tested on individuals with no signs or symptoms of: chronic or acute heart failure; arrhythmias; or relevant stenosis/insufficiency of the cardiac valves. Thus, we recommend that in future studies the applicability of the model to patients with concurrent heart diseases be studied as these might influence the behaviour of the algorithms used in the model. Also, because the model was produced using a relatively small study cohort, we recommend that further studies be undertaken using a larger cohort to confirm our findings and establish the sensitivity of the model. In addition, we are conscious that in this study we only used data from the right IJV and it may be that utilising both IJVs might produce superior results. However, none of our patients was affected by tricuspid regurgitation or pulmonary hypertension. It is therefore recommended that future work should explore both JVPs and their relationship with CVP in more challenging clinical conditions. Finally, future studies should evaluate the US-JVP methodology against alternative strategies such as NIRS.

In conclusion, we have been able to show that the autocorrelation signals of the respective CVP and IJV-CSA pulses exhibit marked similarities, and that the lagging r -values of the autocorrelation of the IJV-CSA pulse can be used to estimate mean CVP with reasonable accuracy. This novel approach appears to have considerable clinical potential, because it allows CVP to be measured non-invasively using ultrasonic assessment of the JVP. As such, the technique may have potential as a clinical monitoring and diagnostic tool.

Supporting information

S1 Raw data.

(XLS)

S1 Table. Mean and standard deviations of the internal jugular vein cross-sectional area (IJV-CSA) and central venous pressure (CVP) signals for each of the respective subjects.

(DOC)

S2 Table. Top five spectral frequencies, together with amplitudes, for the central venous pressure (CVP) signals from the respective subjects.

(DOC)

S3 Table. Top five spectral frequencies, together with amplitudes, for the internal jugular vein cross-sectional area (IJV-CSA) signals from the respective subjects.

(DOC)

S1 Checklist. TREND statement checklist.

(PDF)

S1 Protocol.

(DOCX)

S2 Protocol.

(DOCX)

Author Contributions**Conceptualization:** Paolo Zamboni, Anna Maria Malagoni.**Data curation:** Anna Maria Malagoni.**Formal analysis:** Paolo Zamboni, Anna Maria Malagoni, Erica Menegatti, Riccardo Ragazzi, Valentina Tavoni, Mirko Tessari, Clive B. Beggs.**Funding acquisition:** Paolo Zamboni.**Investigation:** Anna Maria Malagoni, Erica Menegatti, Riccardo Ragazzi, Valentina Tavoni, Mirko Tessari.**Methodology:** Paolo Zamboni, Anna Maria Malagoni, Clive B. Beggs.**Software:** Clive B. Beggs.**Writing – original draft:** Paolo Zamboni, Anna Maria Malagoni, Clive B. Beggs.**Writing – review & editing:** Paolo Zamboni, Anna Maria Malagoni, Erica Menegatti, Riccardo Ragazzi, Valentina Tavoni, Mirko Tessari, Clive B. Beggs.**References**

1. Garg N, Garg N. Jugular venous pulse: an appraisal. *Journal, Indian Academy of Clinical Medicine*. 2000; 1(3):261–9.
2. Applefeld MM. The jugular venous pressure and pulse contour. In: Walker HK, Hall WD, Hurst JW, editors. *Clinical methods: The history, physical, and laboratory examinations*. Boston: Butterworth; 1990.
3. Sisini F, Tessari M, Menegatti E, Vannini ME, Gianesini S, Tavoni V, et al. Clinical applicability of assessment of jugular flow over the individual cardiac cycle compared with current ultrasound methodology. *Ultrasound in medicine & biology*. 2016; 42(8):1750–63.
4. Chiacio JM, Parikh NI, Fergusson DJ. The jugular venous pressure revisited. *Cleveland Clinic journal of medicine*. 2013; 80(10):638–44. <https://doi.org/10.3949/ccjm.80a.13039> PMID: 24085809
5. Sondergaard S, Parkin G, Aneman A. Central venous pressure: soon an outcome-associated matter. *Curr Opin Anaesthesiol*. 2016; 29(2):179–85. <https://doi.org/10.1097/ACO.0000000000000305> PMID: 26825283.
6. Magder S. Central venous pressure: A useful but not so simple measurement. *Crit Care Med*. 2006; 34(8):2224–7. <https://doi.org/10.1097/01.CCM.0000227646.98423.98> PMID: 16763509.
7. Roger C, Muller L, Riou B, Molinari N, Louart B, Kerbrat H, et al. Comparison of different techniques of central venous pressure measurement in mechanically ventilated critically ill patients. *BJA: British Journal of Anaesthesia*. 2017; 118(2):223–31. <https://doi.org/10.1093/bja/aew386> PMID: 28100526
8. Gilbert M. Central venous pressure and pulmonary artery pressure monitoring. *Anaesthesia & Intensive Care Medicine*. 2018; 19(4):189–93.
9. Bano S, Qadeer A, Akhtar A. Measurement of Internal Jugular Vein and Common Carotid Artery Diameter Ratio by Ultrasound to Estimate Central Venous Pressure. *Cureus*. 2018; 10(3).
10. Hossein-Nejad H, Mohammadinejad P, Ahmadi F. Internal jugular vein/common carotid artery cross-sectional area ratio and central venous pressure. *Journal of Clinical Ultrasound*. 2016; 44(5):312–8. PMID: 27028522

11. Bailey JK, McCall J, Smith S, Kagan RJ. Correlation of internal jugular vein/common carotid artery ratio to central venous pressure: a pilot study in pediatric burn patients. *Journal of Burn Care & Research*. 2012; 33(1):89–92.
12. Sathish N, Singh NG, Nagaraja PS, Sarala BM, Prabhushankar CG, Dhananjaya M, et al. Comparison between noninvasive measurement of central venous pressure using near infrared spectroscopy with an invasive central venous pressure monitoring in cardiac surgical Intensive Care Unit. *Annals of Cardiac Anaesthesia*. 2016; 19(3):405. <https://doi.org/10.4103/0971-9784.185520> PMID: 27397443
13. Amelard R, Hughson RL, Greaves DK, Pfisterer KJ, Leung J, Clausi DA, et al. Non-contact hemodynamic imaging reveals the jugular venous pulse waveform. *Scientific reports*. 2017; 7:40150. <https://doi.org/10.1038/srep40150> PMID: 28065933
14. Uthoff H, Siegemund M, Aschwanden M, Hunziker L, Fabbro T, Baumann U, et al. Prospective comparison of noninvasive, bedside ultrasound methods for assessing central venous pressure. *Ultraschall in der Medizin-European Journal of Ultrasound*. 2012; 33(07):E256–E62.
15. Ward KR, Tiba MH, Barbee RW, Ivatury RR, Arrowood JA, Spiess BD, et al. A new noninvasive method to determine central venous pressure. *Resuscitation*. 2006; 70(2):238–46. <https://doi.org/10.1016/j.resuscitation.2005.12.013> PMID: 16820258
16. Keller AS, Melamed R, Malinchoc M, John R, Tierney DM, Gajic O. Diagnostic accuracy of a simple ultrasound measurement to estimate central venous pressure in spontaneously breathing, critically ill patients. *Journal of Hospital Medicine*. 2009; 4(6):350–5. <https://doi.org/10.1002/jhm.503> PMID: 19670356
17. Deol GR, Collett N, Ashby A, Schmidt GA. Ultrasound accurately reflects the jugular venous examination but underestimates central venous pressure. *Chest*. 2011; 139(1):95–100. <https://doi.org/10.1378/chest.10-1301> PMID: 20798190
18. Lipton B. Estimation of central venous pressure by ultrasound of the internal jugular vein. *The American journal of emergency medicine*. 2000; 18(4):432–4. <https://doi.org/10.1053/ajem.2000.7335> PMID: 10919533
19. Sisini F, Tessari M, Gadda G, Di Domenico G, Taibi A, Menegatti E, et al. An ultrasonographic technique to assess the jugular venous pulse: a proof of concept. *Ultrasound in medicine & biology*. 2015; 41(5):1334–41.
20. Ansari BM, Zochios V, Falter F, Klein AA. Physiological controversies and methods used to determine fluid responsiveness: a qualitative systematic review. *Anaesthesia*. 2016; 71(1):94–105. <https://doi.org/10.1111/anae.13246> PMID: 26459299
21. Zamboni P, Sisini F, Menegatti E, Taibi A, Gadda G, Tavoni V, et al. Ultrasound monitoring of jugular venous pulse during space missions: proof of concept. *Ultrasound in medicine & biology*. 2018; 44(3):726–33.
22. Nicolaidis AN, Morovic S, Menegatti E, Viselner G, Zamboni P. Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound. Recommendations for a protocol. *Functional neurology*. 2011; 26(4):229. PMID: 22364944
23. Rueden CT, Schindelin J, Hiner MC, DeZonia BE, Walter AE, Arena ET, et al. ImageJ2: ImageJ for the next generation of scientific image data. *BMC bioinformatics*. 2017; 18(1):529. <https://doi.org/10.1186/s12859-017-1934-z> PMID: 29187165
24. Team-R-Core. R: A language and environment for statistical computing. 2013.
25. Zamboni P, Menegatti E, Pomidori L, Morovic S, Taibi A, Malagoni AM, et al. Does thoracic pump influence the cerebral venous return? *J Appl Physiol* (1985). 2012; 112(5):904–10. <https://doi.org/10.1152/jappphysiol.00712.2011> PMID: 22174396.
26. Tavoni V. Technical note for post processing of jugular venous pulse, central venous pressure and velocity trace. *Veins and Lymphatics*. 2020; 9(1).
27. Beggs CB, Malagoni AM, Menegatti E, Tavoni V, Giovanardi L, Ragazzi R, et al. Spectral signals of the jugular venous pulse as diagnostic biomarkers related to the central venous pressure. *Diagnostics* (submitted to). 2020.
28. Chatfield C. *The analysis of time series: an introduction*. Fourth ed. London: Chapman and Hall; 1989. 94–5 p.
29. Marino PL. *The ICU Book*. 4th ed: Wolters Kluwer Health; 2014. 157–9 p.
30. Killu K, Sarani B. *Fundamental Critical Care Support*. 6th ed: Society of Critical Care Medicine; 2017. 93–114 p.
31. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007; 93(9):1137–46. <https://doi.org/10.1136/hrt.2003.025270> PMID: 17699180

32. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *Jama*. 2003; 289(2):194–202. <https://doi.org/10.1001/jama.289.2.194> PMID: 12517230
33. Breiman L. Random forests. *Machine learning*. 2001; 45(1):5–32.
34. Conn RD, O'Keefe JH. Simplified evaluation of the jugular venous pressure: significance of inspiratory collapse of jugular veins. *Missouri medicine*. 2012; 109(2):150. PMID: 22675798
35. Brennan JM, Blair JE, Goonewardena S, Ronan A, Shah D, Vasaiwala S, et al. A comparison by medicine residents of physical examination versus hand-carried ultrasound for estimation of right atrial pressure. *The American journal of cardiology*. 2007; 99(11):1614–6. <https://doi.org/10.1016/j.amjcard.2007.01.037> PMID: 17531592
36. Demeria DD, MacDougall A, Spurek M, Reid J, Laframboise K, Taylor-Gjevre RM, et al. Comparison of clinical measurement of jugular venous pressure versus measured central venous pressure. *Chest*. 2004; 126(4):747S.
37. Figg KK, Nemergut EC. Error in central venous pressure measurement. *Anesthesia & Analgesia*. 2009; 108(4):1209–11.