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Title: Jugular vein flow calculation by synchronizing time dependent vein area and time dependent blood velocity using ECG trace

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Abstract: Current US Doppler methodology for internal jugular vein (IJV) flow rate assessment does not take into account the pulsatility nature of the IJV flow as well as its relationship with the cardiac pump. The use of just one value of cross sectional area (CSA) of the vessel could be a possible source of error.
We herein propose a technique for US IJV flow assessment that accourately account for the IJV CSA variations during the cardiac cycle. A subject is investigated with a high resolution real time B-mode video synchronized with an ECG trace. CSA variations representing the pulsatility of the IJV are overlapped to velocity curve obtained by usual spectral Doppler trace. The overlapping is point by point synchronized thanks to the common ECG pacemaker. The consequence is to experimentally measure exactly the velocity variation in relation to the change in CSA, ultimately permitting to calculate the IJV flow rate. i) The sequence of CSA variation respect to the ECG waves exactly corresponds to the jugular venous pulse (JVP) as measured in physiology. ii) the methodology permits to synchronization between velocity and CSA, which is ultimately what is currently lacking in order to precisely calculate the flow rate in the IJV by US. iii) The time averaged flow calculated with the presented technique is very close the once calculated assuming costant IJV CSA, while the time depending flow rate shows differences up to 40 for cent.
In conclusion the proposed novel methodology eliminates one source of error in the estimation of the IJV flow rate. This would be verified in further clinical studies of reproducibility.
This study was in accordance with the Ethical Standards of the Committee on Human Experimentation of the Azienda Ospedaliera Universitaria di Ferrara.

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Dear Editor,

I am writing you to kindly ask you the peer revision of this paper.

I want to thank you for your time and interest.

Sincerly,

Francesco Sisini and collaborators

Clinical applicability of the assessment of the jugular flow (rate) over the individual cardiac cycle compared with current ultrasound methodology

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Abstract

The instantaneous volumetric flow, $Q(t)$, through a blood vessel is a parameter of major interest in clinical practice. Flow in large vessels is regulated by the cardiac and respiratory activity and therefore it is not constant over time but it is normally a periodic function of the time and varies within such cycles.

Current US Doppler methodology for internal jugular vein (IJV) flow rate assessment does not take into account the pulsatility nature of the IJV flow as well as its relationship with the cardiac pump. The use of just one value of cross sectional area (CSA) of the vessel could be a possible source of error. We herein propose a technique for US IJV flow assessment that accurately account for the IJV CSA variations during the cardiac cycle. A subject is in-

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vestigated with a high resolution real time B-mode video synchronized with an ECG trace. CSA variations representing the pulsatility of the IJV are overlapped to velocity curve obtained by usual spectral Doppler trace. The overlapping is point by point synchronized thanks to the common ECG pacemaker. The consequence is to experimentally measure exactly the velocity variation in relation to the change in CSA, ultimately permitting to calculate the IJV flow rate. i) The sequence of CSA variation respect to the ECG waves exactly corresponds to the jugular venous pulse (JVP) as measured in physiology. ii) the methodology permits to synchronization between velocity and CSA, which is ultimately what is currently lacking in order to precisely calculate the flow rate in the IJV by US. iii) The time averaged flow calculated with the presented technique is very close the once calculated assuming costant IJV CSA, while the time depending flow rate shows differences up to 40 for cent. In conclusion the proposed novel methodology eliminates one source of error in the estimation of the IJV flow rate. This would be verified in further clinical studies of reproducibility. This study was in accordance with the Ethical Standards of the Committee on Human Experimentation of the Azienda Ospedaliera Universitaria di Ferrara.

Keywords: Internal jugular vein, Jugular venous pulse, Jugular venous flow

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Introduction

The instantaneous volumetric flow, $Q(t)$, through a blood vessel is a parameter of major interest in clinical practice. Flow in large vessels is regulated by the cardiac and respiratory activity and therefore it is not constant over time but it is normally a periodic function of the time and varies within such cycles as

$$Q(t) = w(t) \times CSA(t) \tag{1}$$

where CSA is the cross sectional area of the vessel and w is the component of the blood mean velocity perpendicular to the CSA(Hoskins, 1998; Sun et al., 1995). When $Q(t)$ is known, its time average over a period T

$$\overline{Q} = \int_0^T Q(t)dt$$

can be calculated; to the contrary, the instantaneous value $Q(t)$ cannot be obtained by its time average $\overline{Q}$. For this reason a methodology that allows to properly measure $Q(t)$ is more complete with respect one that allows just the $\overline{Q}$ assessment.

Using medical ultrasound (US) instruments it is possible to obtain informations on a number of quantities related to blood flow, especially blood velocity. (Hoskins, 1999A). Citing Hoskins again, the time averaged volumetric flow may be calculated from the integral of the instantaneous values of the measured instantaneous mean velocity($w(t)$) and instantaneous cross-sectional area ($CSA(t)$) over the cardiac cycle of period T_c(Hoskins, 1998):

$$\overline{Q} = \frac{1}{T_c} \int_0^{T_c} w(t)CSA(t)dt \tag{2}$$

The vessel diameter or area may be measured using the B-scan image and the mean velocity from the spectral trace.

In the common clinical practices, the flow is calculated as:

$$\overline{Q} = TAV \times CSA \tag{3}$$

where TAV is the time averaged velocity measured over a number N of cardiac cycles, and is given by:

$$TAV = \frac{1}{N \times T_c} \int_0^{N \times T_c} w(t)dt \tag{4}$$

which, with the assumption of a constant measure of CSA over the time, corresponds to Eq.3. However, the CSA of a vessel is subject to variation over the time during the cardiac cycle as well the instantaneous value of the velocity (see (Womersley, 1955b) for an early study), and then, the approach above is maybe not enough accurate. For such a reason, the effect of pulsatile blood artery diameter variations on blood flow estimated by Doppler ultrasound has been investigated by (Eriksen , 1992). He found that the error in the common carotid artery was in the range 0.4-3.6 for cent while the error in the femoral artery was in the range 1.5-3.8 per cent. The small error in the flow quantification, the limited range of diameter variations during the pulsation and the difficulty to obtain simultaneously both the blood velocity and the CSA variations along a time period, have probably lead researcher to not consider the pulsatile CSA variations for the arteries blood flow quantification that, despite some pioneer work (Willink and Evans, 1995) have normally neglected this effect or treated it as a statistic fluctuation(Richards et al., 2009). Recent papers by the means of particle image velocimetry (PIV), confirmed in artery the negligible error of current ultrasound clinical assessment of flow(Beulen et al., 2010; Beulen and Bijnens, 2011).

However, the considerations above do not apply for the blood flow quantification in the veins, because, differently from the arteries, veins can easily collapse with change of posture, and CSA in pulsed veins varies significantly along the cardiac cycle. Furthermore, their diameter is not representative of the area since often they have an irregular elliptical shape(Fung, 1997). The pulsatile vein with major interest in clinical practice is undoubtely the internal jugular vein (IJV), and the jugular vein pulse (JVP) is an index of paramount importance for prognosis and diagnosis of heart failure(Applefeld, 1990; Chua Chiaco et al., 2013; Drazner et al., 2001). Despite the recognized pulsatility of the IJV, clearly visible at naked eye, several recent paper assessed the IJV blood flow with a calculation based on single CSA value and TAV measurement (Zamboni et al., 2013; Doepp et al., 2004; Chambers et al., 2013; Kantarci et al., 2012). We investigated the IJV CSA variations and found that i) IJV CSA can vary more than the 30 per cent during the cardiac cycle(Sisini et al., 2015) and ii) IJV CSA is not circular but elliptic(Sisini et al., 2014). In view of this, we believe that a more accurate analysis of the IJV blood flow would take into account both the CSA variations of this vein and its elliptical shape; to neglect this evidence might comport an uncertainty whose significance has to be established. Motivated by this challenging issue, we investigated the clinical feasibility of IJV flow rate $Q(t)$ measurement, accounting of both the time dependence of the velocity $w(t)$, or even better the dependency from the individual cardiac cycle, as well as the CSA variations.

The aim of this research is to show a simple US technique for assessment of flow in pulsatile IJV available to commercial US scanner and to compare it with the current Doppler methodology.

Materials and Methods

Subjects scanning and protocol

One voluntary subject underwent US scan of the neck by using Vivid-q ultrasound system (GE Medical Systems ultrasound, Horten, Norway) equipped with a linear probe (L12-RS). We set the frame rate at 30 Hz in order to have the adequate time resolution to capture the CSA variation of the vein along the cardiac cycle. In addition, such US system allows to acquire the ECG signal by setting three electrodes on the subject chest. The assessment of the jugular CSA needs to was performed using a B-mode scan in the transverse plane of the right IJV at c5/c6 level producing a video clip. Such region corresponds to the segment close to the junction of the IJV with the subclavian vein. We recorded first a sonogram sequence video clip and immediately after a velocity spectral-Doppler trace whose was frozen producing a screen shot. Both for at least four cardiac cycles. The Doppler trace was automatically overlapped by a line highlighting the blood mean velocity (see Fig. 2) recorded in the sample volume , which has been opened in order to cover almost the entire vessel CSA. A minimum distance from the vein wall would prevent the low frequency noise due to the wall movement. The subject was asked to not breathing during the few seconds of acquisition in order to not have CSA variation due to the respiratory activity.(Doepp et al., 2003)

This study was conducted in accordance with the Ethical Standards of the Committee on Human Experimentation of the Azienda Ospedaliera Universitaria di Ferrara. All the volunteers signed an informed consent form.

Cross sectional area, velocity and ECG datasets acquisition

The CSA and the ECG datasets have been obtained by digital processing the acquired transversal video (see Fig. 1). The CSA is produced as described in (Sisini et al., 2015) while the ECG dataset acquisition details are described in Appendix A.

The common commercial US systems do not allow to export the Doppler dataset, for this reason, in this work, the mean velocity dataset is obtained by digitally processing the image shot of the Doppler trace. The detailed procedure is described in Appendix B.

Cross sectional area and blood velocity phasing

The R wave, presents in both the ECG datasets, is a common physiological clock shared by the longitudinal and transversal acquisition and it has been already used as event markers to phase the velocity and CSA traces(Eriksen , 1992). We define t_{TR} the time corresponding to a given R wave in the EGC obtained by processing the transversal video clip (in this case the firs R wave) and t_{LR} the time corresponding to a given R wave in the EGC dataset obtained by the spectral Doppler image shot (the firs R wave again). The two acquisition have been acquired once few seconds after the other assuming that no relevant physiological variation occur in the subject. The influence of the respiration over the IJV CSA has been neglected because we asked the subject to do not breath during the scanning. With such underlying assumption the following relation can be assumed valid:

$$ECG_{videoclip}(t) = ECG_{imageshot}(t + d) \tag{5}$$

and allow to calculated d as:

$$d = t_{LR} - t_{TR} \tag{6}$$

Once d is calculated the $CSA(t)$ and velocity $w(t)$ datasets can be put in phase allowing to calculate the instantaneous flow rate $Q(t)$. The procedure to phase such datasets, described in Appendix C, results in w_k and CSA_k datasets.

Flow rate and time averaged flow calculation

The instantaneous flow rate and the time averaged flow rate has been calculated following three different approaches. The first approach i) is based on the CSA and velocity phasing technique herein presented: the flow rate is given by:

$$Q_k = w_k \times CSA_k \tag{7}$$

while the time averaged flow is given by the average of the right term of Eq. (7) over a cardiac cycle

$$\overline{Q} = 1/n \sum_{i=1}^{i=n} Q_k \tag{8}$$

where n is the number of sonograms in for cardiac cycle given by $n = \frac{T_c}{FR}$. ii) The second approach accounts for the time varying velocity but neglects the CSA variation, the flow rate is given by:

$$Q_k = w_k \times \overline{CSA} \tag{9}$$

and its time averaged flow is calculated as:

$$\overline{Q} = 1/n \sum_{i=1}^{i=n} Q_i \tag{10}$$

with $\overline{CSA} = 1/m \times \sum_{i=1}^{m} Q_i$. iii) Finally, the third approach is the most common in clinical practice (see Eq. (3)) and consists in multiply the TAV value for a single value for the CSA registered along the cardiac cycle. Here we test such approach on three possible CSA value:

$$\begin{aligned} \overline{Q}_{Mean} &= TAV \times \overline{CSA} \\ \overline{Q}_{Max} &= TAV \times CSA_{Max} \\ \overline{Q}_{Min} &= TAV \times CSA_{Min} \end{aligned} \tag{11}$$

where TAV is defined in Eq. (B.4) and CSA_{Max} and CSA_{Min} are the maximum and minimum CSA value assumed by the IJV during the cardiac cycle.

Results

Cross sectional area, velocity and ECG datasets acquisition

The CSA_i dataset is plotted together the ECG_i in Fig.3 The IJV CSA oscillates between 0.15 and 0.36 cm^2 , the mean CSA is around 0.25 cm^2 . The a, c and v waves are well visible in the CSA time diagram, as well the P, Q, R, S and T waves in the ECG. The CSA time diagram actually corresponds with the well known JVP diagram(Sisini et al., 2015; Sahani et al., 2015). The relationship between the ECG and CSA time diagram (JVP waves) is the following: the R wave is just after the a wave and before the c wave. The T wave happens just at the end of the x descent while the P wave is after the v wave and before the a wave.

The w_k dataset is plotted in Fig. 4 together the EGC . The velocity track shows two waves followed by an evident descent. From the P wave to the S,

the velocity is minimum and this corresponds to the descent described, then the velocity rise to its maximum (the first wave) in correspondence to the T wave. The velocity decrease to rise again (second wave) in correspondence between the T and the P wave. The flow/time diagram follows grossly the velocity/time diagram, it is composed by two evident waves having with the ECG the same relationship described for the velocity diagram. That results are in agreement with our mathematical model of describing blood velocity and flow in the IJV under a pressure gradient governed by the JVP (under review).

Cross sectional area and blood velocity pulse phasing

The w_i and CSA_i datasets are plotted together in Fig. 5. The velocity trace follows roughly the CSA trace time-derivative, it is crescent when the CSA is descent and vice versa; more over, the velocity is null where the CSA has its maximum. In different words, the velocity has its first wave in correspondence to the x descent of the JVP, its second wave in correspondence of the y descent.

Flow rate calculation

Instantaneous flow rate, calculated using Eq. (7) is plotted in Fig. 6 ($Q(t)$). It presents two waves and two descents like the instantaneous velocity; the flow values range from 5.3 to 16.8 cm^3/s during the cardiac cycle, while its time average over a cardiac cycle is 10.7 cm^3/s. For the examined case, flow and velocity are substantial in phase. Instantaneous flow rate, calculated using Eq. (9) is plotted in Fig. 6 ($Q'(t)$) it ranges from 4.2 to 22.3 cm^3/s while its time average is about 10.8 cm^3/s. Despite the negligible

difference between the two obtained time averaged flow, the instantaneous flow rates obtained by Eq. (9) is different to which obtained by Eq. (7) up to 40 for cent. Finally, time averaged flow calculated by Eq. (11) results 11.2, 16.3 and 6.6 cm^3/s for the mean, maximum and minimum IJV CSA respectively. While the Q_{Mean} value is very close to the value obtained using Eq. (8), Q_{Max} and Q_{Min} differ for more the 50 for cent.

Discussion

In this study has been proposed a simple ultrasound technique to calculate the IJV flow rate accounting of both velocity and cross sectional are variations during the cardiac cycle. This t is a step forward to the elimination of the sources of error affecting the IJV flow quantification. The technique takes advantage of the ECG trace that is available in the commercial US scanner, if the ECG trace would be available to be exported in a standard format like DICOM it would results in a simplification of the technique itself.

We have conceived and developed such technique autonomously and we are not aware of previously paper reporting the same technique, however we know that the idea to use the ECG as event marker is not new(Eriksen , 1992) and is possible that other researchers have developed the same technique. The presented technique is based on B-mode and Doppler scanning that are normally performed in clinical settings without the need of contrast medium. The Off line analysis required can be performed using a electronic spread sheet. The digital processing of the CSA video clip can be performed by the algorithm described in(Sisini et al., 2015) or can be also manually performed(Sisini et al., 2015). This technique can be reproduced in different

laboratory in order to confirm our results.

In this study we calculated the instantaneous blood flow in the IJV of a subject. The phase relationship between the instantaneous blood flow in the IJV and the ECG trace has been obtained and described, this is a step forward in the knowledge of the IJV haemodynamic in physiological condition. We have shown that the IJV CSA pulsation actually affects the instantaneous blood flow on a healthy subject. The extension of this study to a larger sample will be useful to estimate the clinical importance of this finding. Moreover we have shown that also the time averaged blood flow is affected by such pulsation and therefore when neglected the IJV pulsation has to be listed in the sources of blood flow estimation errors.

As "collateral effect" of this study, the relationship between the ultrasonic JVP technique and he ECG trace has been here obtained and it results to be the same reported in physiology(Applefeld, 1990), this is motivating in the use of the US methodology to produce the JVP.

There are two technical limitations in order to reproduce our results. The first is to set the frame-rate of the US equipment at an adequate resolution close to that described in the methods. The latter is to check the synchronism of the ECG trace with the B-mode real-time. Both are necessary condition to permit the verification of the proposed technique.

The presented technique allows to put in phase the cross sectional area and the velocity instant value obtained at different time. These parameter change in time because of the cardiac activity but can be also influenced by the respiratory cycle(Zamboni et al., 2012). In this research we did not account of the haemodynamic variation due to the respiration, for that we asked the

subject to not breath during the examination. It could be of interest to extend the results here reported investigating the flow rate also during the respiratory activity.

Acknowledgements

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Appendix A. CSA dataset acquisition

The CSA dataset is produced by digital processing the transversal video clip as described in (Sisini et al., 2015). The procedure is however herein briefly described. An operator manually traces a ROI of the IJV contour on the first sonogram of the video clip and then a semi-automatic procedure detects the change in shape of the given ROI throughout the whole video clip. The procedure provides the CSA value of the IJV vs the sonogram acquisition time, i.e. the $CSA(t)$ function. The same procedure can also be operated manually.

The ECG trace is overlapped to each B mode sonogram in the video clip and is represented as a leading cursor tracing the ECG line. The position of the cursor on the sonogram represents the ECG at the time the sonogram has been acquired. Consequently, the ECG dataset has been created by identifying, for each sonogram in the clip, the ECG cursor position coordinate (x,y), expressed in pixel, on the screen by using an in home developed computer procedure. Each sonogram of the clip is used to produce two values, one is

the IJV CSA_i the other is the ECG_i , where i is image number (i.e. the cardinal position of the processed sonogram in the clip); such number is then transformed in the temporal coordinate by dividing it by the frame rate (FR) of the clip:

$$t_i = i/FR \tag{A.1}$$

Appendix B. Velocity dataset acquisition

The mean velocity ($w(t)$) is represented as a line overlapping the spectral Doppler trace (Fig. 2).The line is composed of m pixels. An in home developed procedure identifies the pixel belonging the line by their RGB tern. The coordinates x_k and y_k of each pixel have been automatically recorded by the procedure, where k is an index going from 1 to m. The function $w(t)$ has been obtained from the x_k and y_k values by using the following procedure:

$$t_k = \frac{x_k}{PS} \tag{B.1}$$

$$w_k = \frac{y_k}{PW} \times 100 \tag{B.2}$$

where k is the index for the pixels, PS is the distance in pixels between two time division (separated by 1 s) of the time axes while PW is the distance in pixel between the 0 and 100 cm/s division, measured along the y axis. Combining the two expression in Eq. (B.1) results

$$w(t_k) \equiv w_k = \frac{y_k}{PW} \times 100 \tag{B.3}$$

Following Eq. (4), the above formulation can be used to calculate the TAV as:

$$TAV = 1/m \times \sum_{k=1}^{m} w_k \tag{B.4}$$

.

The algorithm has been used to scan the ECG curve that is plotted at the bottom of the velocity trace. Two datasets, w_k and ECG_k, have been obtained.

Appendix C. Datasets phasing

The datasets CSA_i and w_k is put in phase by finding the couple of indexes i_R and k_R corresponding to the instant time t_{TR} and t_{LR} respectively, so that

$$i_R = k_R + d/FR \tag{C.1}$$

However the frame rate FR of the transversal acquisition is normally different from $1/PS$ representing the pixel rate (see Eq. B.1), for this reason Eq. (C.1) does not hold for $k+1$ and $i+1$. For this reason, the w_k dataset has been fitted with a Fourier series $f(t)$ up to the 12-th order. New velocity dataset has been then calculated as:

$$w_k = f(t_k) \tag{C.2}$$

by using the same time sampling (t_k) used for CSA_k. The Fourier coefficients have been calculated using the weighted sum squared residual (WSSR) method built in Gnuplot software.

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Figure Captions

Fig.1 Ultrasound sonogram representing the transversal section of the internal jugular vein (IJV). The selected sonogram is part of a video clip sonogram sequence. The ECG trace is also shown.

Fig.2. Doppler trace of the internal jugular vein blood velocity. The red blood cells velocity spectrum is presented in grey-scale. The cyan line superimposed the velocity spectrum represents the averaged RBG velocity i.e. the averaged blood velocity. The ECG trace is also shown.

Fig. 3. Jugular venous pulse obtained by measuring the cross sectional area (CSA) of the internal jugular vein (IJV) along several cardiac cycles. The ECG trace is also shown.

Fig. 4. Internal jugular vein (IJV) blood velocity and ECG trace. The two curves are are obtained by sampling the IJV blood velocity Doppler trace and the relative ECG.

Fig. 5. Jugular venous pulse (JVP), ECG and averaged blood velocity w(t) are presented on the same time line along a cardiac cycle.

Fig. 6. Blood velocity w(t) and flow rate Q(t) are plotted along a cardiac cycle. The mean value of the flow rate over a cardiac cycle is also represented. The Q'(t) curve represents the flow rate calculate neglecting the variation in time of the vein cross sectional area.

Tables

Figure1

Click here to download Figure: Fig_1.eps

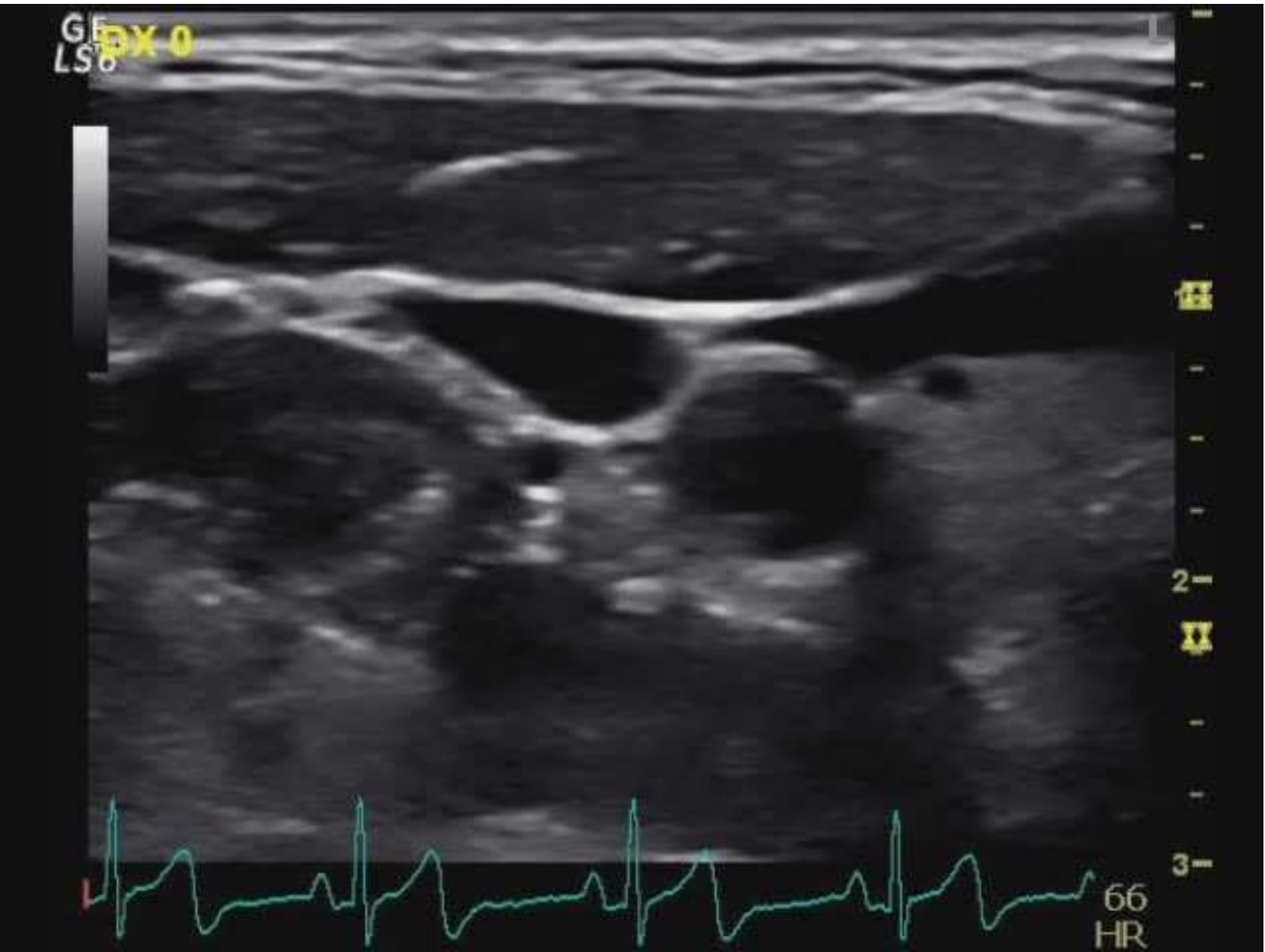

Figure2

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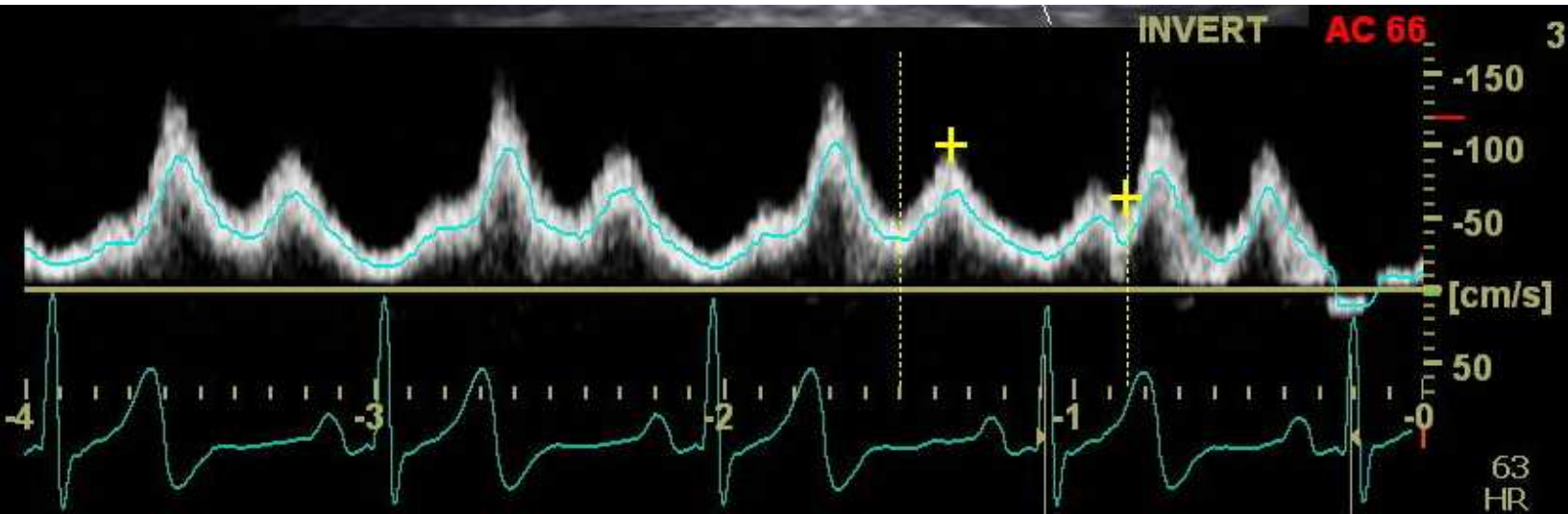

Figure5

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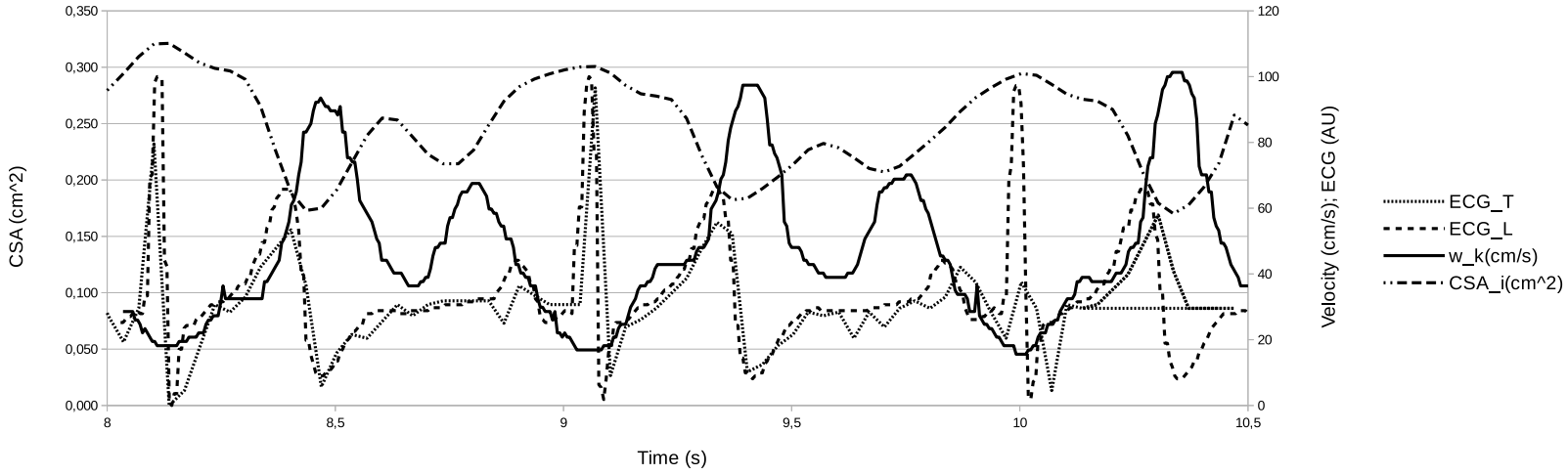

Figure6

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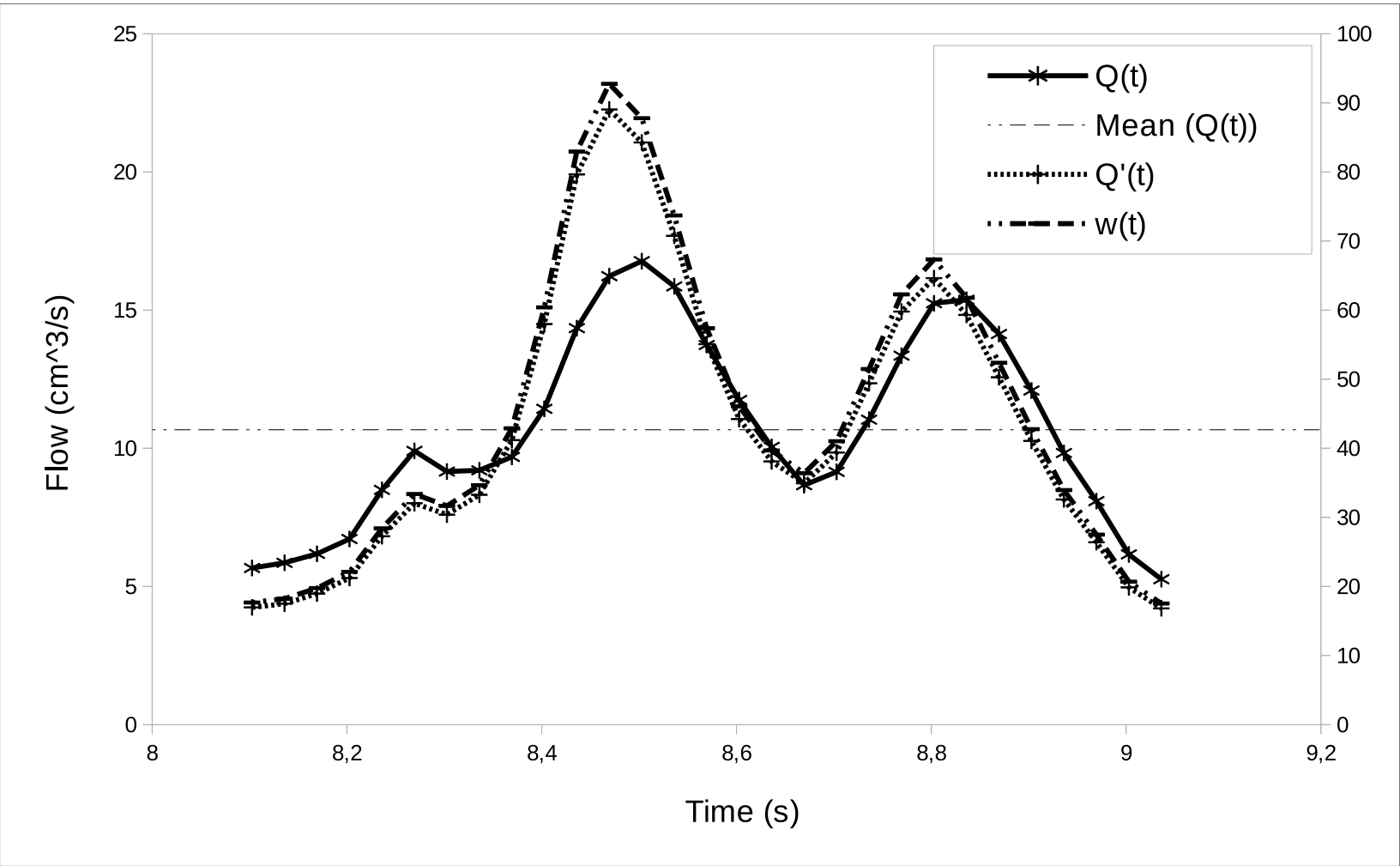

Figure3

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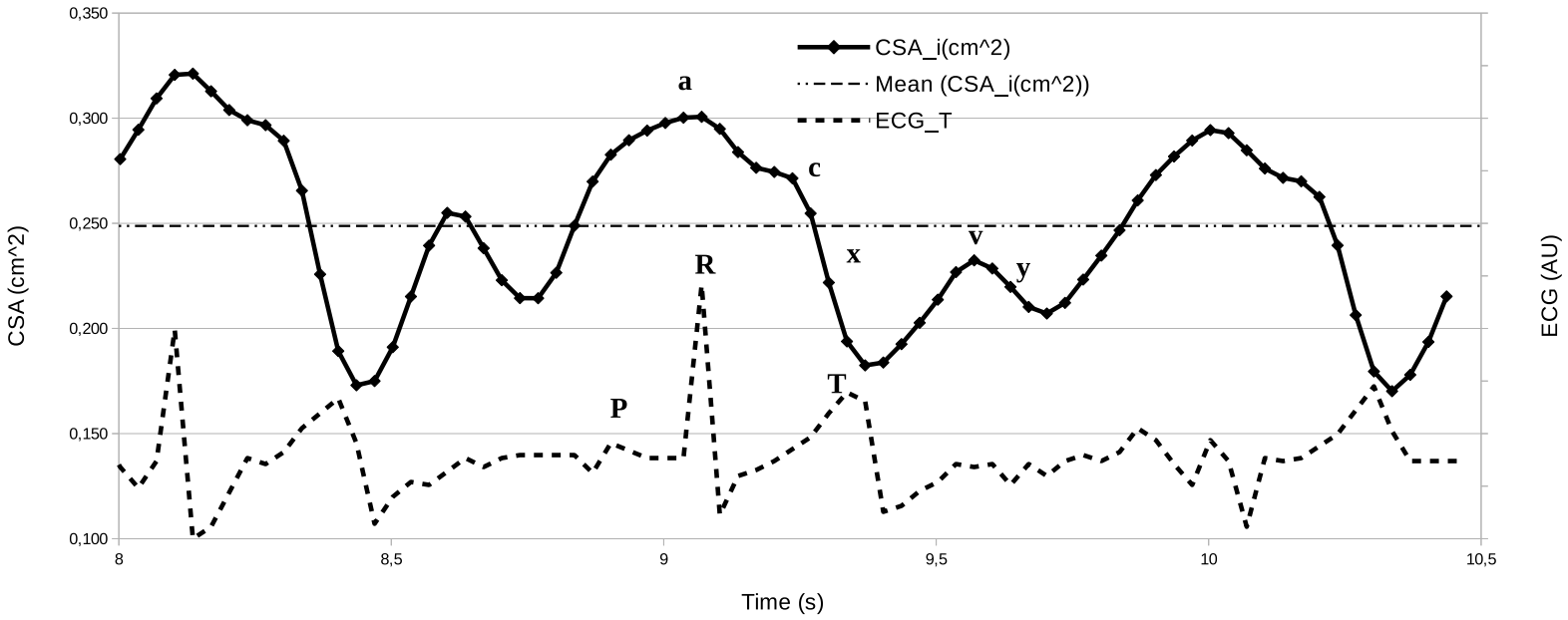

Figure4

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