Objective Assessment of Venous Pulse Wave Velocity in Healthy Humans

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Leonardo Ermini[a], Carlo Ferraresi[b], Carlo De Benedictis[b], Silvestro Roatta[a]

[a] Laboratory of Integrative Physiology, Department of Neuroscience, University of Torino, c.so Raffaello 30, 10125, Torino, Italy

[b] Department of Mechanical and Aerospace Engineering, Politecnico of Torino, c.so Duca degli Abruzzi 24, 10129, Torino, Italy

Corresponding author: Silvestro Roatta, c.so Raffaello 30, 10125, Torino, Italy. E-mail: silvestro.roatta@unito.it. Phone: +39 011 6708164

Abstract

Central venous pressure and volume status are relevant parameters for the characterization of the patient's hemodynamic condition; however, their invasive assessment is affected by various risks while non-invasive approaches provide limited and subjective indications. Here we explore the possibility to assess venous pulse wave velocity (vPWV), a potential indicator of venous pressure changes. In 8 healthy subjects, pressure pulses were generated artificially in the leg veins by rapid compression of the foot and their propagation detected at the level of the superficial femoral vein by Doppler ultrasound. Changes in leg venous pressure were obtained by raising the trunk from the initial supine position by 30 and 60 deg. The vPWV increased from 1.78 ± 0.06 m/s (supine) to 2.26 ± 0.19 m/s (60 deg) ($p<.01$) and exhibited an overall linear relation with venous pressure. These results show that vPWV can be easily assessed and constitute a non-invasive indicator of venous pressure changes.

Keywords: pulse wave velocity; central venous pressure; echo-Doppler; hemodynamics

Introduction

Central venous pressure and the volaemic status of the patient are relevant hemodynamic variables for the understanding of the patient condition and the management of fluid therapies (Monnet and Teboul 2018). Given the risk associated with invasive measurements, there is a compelling need for reliable non-invasive assessment techniques. Different non-invasive approaches have been proposed each suffering of some limitation (Uthoff et al. 2012). Analysis of pulsatility of the inferior vena cava is commonly adopted (Nagdev et al. 2010) although the caval index is affected by several confounding factors (Via et al. 2016) . The traditional assessment of the point of collapse of the jugular vein (Rizkallah et al. 2014; Xing et al. 2015) cannot be used in supine patients or in the presence of surgical interventions or treatments in the neck area. Compression of superficial veins has been recently proposed for assessing peripheral venous pressure (Crimi et al. 2016), which however only approximates central venous pressure in certain patient conditions (Rizkallah et al. 2014; Via et al. 2016). On this basis, it is appropriate to consider alternative/additional methodologies such the assessment of Pulse Wave Velocity (PWV) in the venous compartment. The PWV has been largely investigated in arteries and it is by now a well-established index of cardiovascular risk (Boutouyrie et al. 2009; Pereira et al. 2015) while investigations on the venous PWV (vPWV) are scanty, possibly due to the lack of a regular natural pulsation in the venous flux and to the small associated blood pressures changes. To our knowledge only two studies investigated vPWV in human subjects: one conducted on subjects with “prominent superficial veins”, the pressure pulse being generated by their digital compression/decompression (Mackay et al. 1967), the other based on the small natural pulsation of the venous flux detected by echo-Doppler at the level of subclavian and femoral arteries (Nippa et al. 1971). Although these early investigations consistently indicated a linear dependence of vPWV on venous blood pressure (Anliker et al. 1969; Mackay et al. 1967; Minten et al. 1983; Nippa et al. 1971) this line of research was not followed up, maybe because of ineffective methodologies.

Aim of this study was to develop a non-invasive and objective method to measure the vPWV as a preliminary step before carrying-out more thorough investigations on its reliability and sensitivity to hemodynamic challenges functional to possible future applications in the clinical setting. In order to work with clear cut and repeatable pulse waves these were externally generated by pneumatic compression of the foot and proximally detected at the level of the femoral vein by Doppler ultrasound while leg venous pressure (LVP) was modulated by changing reclination of the trunk.

Materials and Methods

Subjects

The experiment was conducted on 8 healthy volunteers (age 31±9) with no exclusion criteria. The study was approved by the ethics committee of the University of Torino (March 23, 2015) and all participants gave their informed consent according to the principles of the Helsinki Declaration.

Measurement set-up

An overview of the experimental set-up is given in Fig. 1. A rapid compressive stimulus is delivered to the foot by rapid inflation (peak pressure: 200 mmHg, duration: 1 s, inflation time: 400 ms) of a pneumatic cuff (49 x 15 cm, GIMA, Gessate, Italy). This is achieved by a custom PC-controlled system previously developed for the investigation of the compression-induced rapid dilatation in skeletal muscles (Messere et al. 2017b; Messere et al. 2018). Adapted, semi-rounded plastic foam paddings were applied under the sole and above the dorsum of the foot in order to achieve a quasi-cylindrical shape, adequate to be wrapped by the cuff. The trigger for the stimulus is provided by the subject himself by acting on a hand-held button. The foot compression generates a pressure pulse that propagates proximally along venous vessels and can be detected by Doppler ultrasound (MyLab 25 Gold, ESAOTE, Genova, Italy; equipped with linear probe LA523) at the level of the superficial femoral vein (SFV), distal to the inguinal ligament. Venous blood velocity is recorded by means of a linear probe, with transversal approach and incident angle of about 60 deg

(Messere et al. 2017a). The cuff pressure was continuously monitored by a pressure sensor placed at the cuff outlet (Pressure monitor BP-1, WPI, Sarasota, FL, USA) and the corresponding electrical signal was acquired by the acquisition system (Micro 1401 IImk, CED, Cambridge, UK, with Spike2 software), along with the Doppler signal and the signal from the button. The same digital board provided the trigger for cuff inflation by the pneumatic system.

Vessel size and peripheral venous pressure

The cross-sectional area of the SFV was calculated from a transversal echographic scan in B-mode, the linear probe oriented at 90 deg with respect to the vein axis. The leg venous pressure (in mmHg) in the SFV was estimated as the hydrostatic load relative to the vertical distance (*vd*, in cm) between the venous point of collapse, i.e., the point in which venous pressure approaches 0 mmHg, and the leg (its mid height), horizontally laying on the bed: LVP = 1.05 * 1.36 * *vd*. The venous point of collapse was echographically sought along the jugular vein (Rizkallah et al. 2014; Xing et al. 2015) when the trunk was reclined at 30 and 60 deg and along the basilic vein, when the subject was completely supine (trunk angle of 0 deg), the right arm being transiently and passively raised vertically to this purpose. The venous point of collapse was visualized with a second dedicated ultrasound machine (Mylab 25 XView, Esaote, Genova, Italy, with linear array LA 523).

Experimental protocol

The subject remained supine for at least 30 min (Folino et al. 2017; Hagan et al. 1978) before starting with the measurements then the subject assumed three different positions: the legs were maintained horizontal while the trunk was reclined to 0, 30 or 60 deg, in random order, thus affecting LVP due to modification of the hydrostatic load (Uthoff et al. 2012; Xing et al. 2015). While breathing normally, the subject was asked to periodically (approximately every 20-30 s) press the hand-held button at the end of the expiratory phase, thus triggering the delivery of the pressure pulse. This allowed to focus the measurement in the most reproducible respiratory condition (functional residual capacity) and exclude the potential interference of respiratory activity on vPWV, given its effects on venous blood pressure and flow (Folino et al. 2017). The control unit

made sure that consecutive pulses were at least 20 s apart, ignoring the button signal otherwise. A serie of 15 pulses were delivered in each position, to assess vPWV 15 times consecutively. After a serie was completed, the vessel cross-sectional area was measured and the LVP estimated (see above).

Data analysis

The Doppler signal was sampled at a rate of 10 kHz and it was exported from Spike2 (Fig. 2a) to Matlab for an off-line analysis: a custom-made algorithm was developed to extract the maximum velocity profile from the time-frequency representation of the signal and to identify the footprint of that profile (Boutouyrie et al. 2009). As first step the signal was cut into epochs of 1 sec, using the instant at which the control unit delivered the trigger for cuff inflation (t_0) as reference time, in order to isolate only portions of the entire recording in which the passage of the PW was present for sure. Then, the signal was digitally band-pass filtered with cut-off frequencies of 100 and 2000 Hz (approximately equivalent to 3-60 cm/s in terms of blood velocity). Afterwards, the signal was transformed to be analyzed in the time-frequency plane by means of the Wavelet Synchro Squeezed Transform (WSST). We choose this technique because, besides being a Continuous Wavelet Transform (CWT) and therefore appropriate to deal with signals whose frequency spectrum varies rapidly over time (Boashash 2015), it presents a reduced energy smearing with respect to classic CWTs and preserves the native resolution in the time domain (Thakur et al. 2013). These two latter properties were very useful in the present case, due to the low intensity of the venous flow and due to the need to precisely localize the reference point in time, respectively. Once the signal was transformed (Fig. 2b) the maximum velocity profile was extracted by linking all the maximum energy points along the time axis. The profile was subsequently smoothed by a local regression using the weighted linear least squares method and a 1st degree polynomial model applied by a sliding window of 200 ms. Finally, the footprint was identified as the instant t_1 at which the second derivative of the velocity profile reaches its maximum (Fig. 2c). The PW transit time, from ankle to insonation site, was computed as $\Delta t = t_1 - t_0 - Lat$, where t_0 is the time at which the control unit

delivered the trigger for cuff inflation and *Lat* is latency between t_0 and the time at which the PW can be detected along the great saphenous vein at the ankle level. This latency, which mostly accounts for the mechanical delays in the pneumatic circuit, was set to 50 ms, based on measurements carried out in preliminary experiments. The vPWV is then calculated as the ratio of the travelled distance (Δx = ankle-probe distance) and the PW transit time: vPWV = $\Delta x / \Delta t$. Occasional odd vPWV values, attributed to failure of the algorithm due to low signal-to-noise ratio of the Doppler signal, were automatically identified as the values beyond three times the Mean Absolute Deviation and removed.

The intra-subject variability of the vPWV measurements was quantified by the coefficient of variation (CoV = STD / mean * 100), then the average vPWV value was computed for each condition. The effect of trunk position on vPWV was then assessed by a paired one-way ANOVA, followed by Tukey-Kramer post-hoc test. The same was done for LVP and vessel cross-sectional area. Finally, the correlation between LVP and vPWV was assessed by the Pearson's coefficient.

All the values reported in the results section are expressed in terms of MEAN ± STD.

Results

Body posture significantly affected blood pressure ($p<0.01$) and volume ($p<0.01$) of the leg venous compartment. The estimated LVP increased from 8 ± 3 to 26 ± 2 mmHg and the cross-sectional area of the superficial femoral vein from 34 ± 22 to 67 ± 34 mm^2, when the trunk was reclined from 0 (supine position) to 60 deg. The change in posture also affected PW transit time (Δt) ($p<0.01$) which decreased from 0.384 ± 0.038 s (supine) to 0.303 ± 0.021 s (60 deg), therefore the vPWV increased from 1.78 ± 0.06 m/s (supine) to 2.26 ± 0.19 m/s (60 deg). The cuff-probe distance (Δx) variability was 0.68 ± 0.07 m. These results are graphically summarized in Fig. 3. Notably, vPWV exhibits a linear dependence on venous pressure ($r=0.82$). On the contrary, vessel size exhibits a curvilinear pattern suggestive of increasing vessel stiffness with increasing pressure.

Single measurements of vPWV exhibited little intra-subject variability, as expressed by the CoV: 5.6 ± 2.5 % when averaged across all subjects and conditions. Individual values of vPWV were also quite similar in the supine condition (CoV=3.1 %) but did spread over a wider range at increased LVP (see error bars in Fig. 3a).

Discussion

The present study provides a proof of concept for a new methodology for the assessment of vPWV in human subjects. Although the reported vPWV values could be slightly overestimated, since we did not subtract the average blood velocity from the measurement, the results are compatible with other studies performed in different models and with different techniques, reporting values in the range 1-3 m/s in supine position (Anliker et al. 1969; Minten et al. 1983; Nippa et al. 1971) while 4 to 15 m/s were reported at venous pressures of 20 to 80 mmHg in the arm (Mackay et al. 1967). The linear dependence of vPWV with LVP (Fig. 3a) is also in line with the literature (Anliker et al. 1969; Mackay et al. 1967; Minten et al. 1983; Nippa et al. 1971) and reflects the increase in vessel stiffness at increasing trans-mural pressure, which is also demonstrated by the dependence of the vessel size on LVP (Fig. 3b). With respect to previous studies, new and relevant achievements may be evidenced: 1) the automatic detection of the footprint of Doppler signal associated to the pulse wave, thanks to the synchronization between the pulse delivery and the signal acquisition and to the implementation of specific signal processing algorithms; 2) the high precision of the measurement (CoV≈6%) compared to previous reports (CoV=14%) (Nippa et al. 1971). Several reasons have contributed to the latter result: 1) the sharpness of the externally-generated pulse wave compared to natural oscillations of venous flow and pressure; 2) the large distance between delivery and detection of the pulse wave (above 60cm in the present case) and 3) the synchronization of the measurement with the respiratory activity, which cyclically modulates venous pressure (Minten et al. 1983; Nippa et al. 1971).

In the present implementation we included a single Doppler measurement assuming the delay in the generation of the pressure pulse to be the same in all subjects. While a measurement based on two simultaneous Doppler readings, at the ankle and at the thigh, would be more precise, the present approach has the advantage of requiring a simpler set-up and measuring procedure. Future studies will help to shape the best trade-off or to design dedicated measuring devices.

Simultaneous measurement of vPWV and invasive CVP in patients with central venous access may be one way to investigate the direct relation between the two variables. On the other hand vPWV may turn out to be particularly sensitive to detect changes in hemodynamic conditions, as observed by Felix et al. (Felix et al. 1971) in dogs exposed to progressive blood losses. In addition, the possibility to use vPWV to implement automatic and long-term monitoring of the status of the venous compartment is particularly attractive. However, further technical improvements may have to be implemented and additional studies will be necessary to assess reliability and validity of this methodology before recommending its possible clinical application.

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Conflict of Interest

A patent application on the measurement of venous pulse wave velocity has been submitted.

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Figure captions list

Fig. 1. Experimental set-up. Electrical and pneumatic connections are indicated by dashed and solid lines, respectively.

Fig. 2. Representative recording and processing. a) Venous pulse wave as detected by Doppler Ultrasound (upper trace), at the superficial femoral vein, after delivery of a compressive stimulus to the foot (lower trace) at time t_0. Post-processing of the 1-sec epoch indicated by the dashed line is shown on the right: b) Wavelet Synchro Squeezed Transform (WSST) of the Doppler signal; c) the smoothed normalized maximum energy profile of WSST (solid line) and its normalized second derivative (dashed line), whose maximum identifies the footprint of the profile (t_1).

Fig. 3. Average effects of trunk position. The effects on venous pulse wave velocity (a) and on vessel size (b) are displayed as a function of the effects on the venous pressure in the leg (LVP). Grey lines (a) represent the individual responses. The dashed lines indicate the best linear (a) and quadratic (b) fitting. Error bars represent standard deviation. *: $p<0.05$; **: $p<0.01$.