Vena Cava Responsiveness to Controlled Isovolumetric Respiratory Efforts

Published version:

DOI:10.1002/jum.14235

Vena cava responsiveness to controlled isovolumetric respiratory efforts

Manuscript category: Original research

Anna Folino[1], Marco Benzo[3], Paolo Pasquero[2], Andrea Laguzzi[2], Luca Mesin[3], Alessandro Messere[1], Massimo Porta[2], Silvestro Roatta[1]

[1] Integrative Physiology Laboratory, Department of Neuroscience, University of Torino, Torino, Italy.

[2] Department of Medical Sciences, AOU San Giovanni Battista, University of Torino, Torino, Italy.

[3] Mathematical Biology and Physiology, Department of Electronics and Telecommunications, Politecnico di Torino, Torino, Italy.

Running title: IVC response to respiratory efforts

Corresponding author:

Silvestro Roatta

Dip. Neuroscienze, Università di Torino

c.so Raffaello 30, 10125 Torino, Italy

e-mail address: silvestro.roatta@unito.it

telephone number: +39 011 6708164

fax number: +39 011 6708174

ABSTRACT

Objective. Respirophasic variation of inferior vena cava (IVC) size is affected by large variability with spontaneous breathing. This study aims at characterizing the dependence of IVC size on controlled changes in intra-thoracic pressure.

Methods. Ten healthy subjects, in supine position, performed controlled isovolumetric respiratory efforts at functional residual capacity, attaining positive (5, 10, 15 mmHg) and negative (-5, -10, -15 mmHg) alveolar pressure levels. The isovolumetric constraint implies that equivalent changes are exhibited by alveolar and intrathoracic pressures during respiratory tasks.

Results. The IVC cross sectional area (CSA) equal to 2.88±0.43 cm^2 at baseline (alveolar pressure = 0 mmHg) was progressively decreased by both expiratory and inspiratory efforts of increasing strength, with diaphragmatic efforts producing larger effects than thoracic ones: - 55±15% decrease, at +15 mmHg of alveolar pressure ($p<0.01$), -80±33±12% at -15 mmHg diaphragmatic ($p<0.01$), -33±12% at -15mmHg thoracic. Significant IVC changes in size ($p<0.01$) and pulsatility ($p<0.05$), along with non significant reduction in the response to respiratory efforts, were also observed during the first 30 min of supine rest, detecting an increase in vascular filling, taking place after switching from the standing to the supine position.

Conclusion. This study quantified the dependence of IVC CSA on controlled intra-thoracic pressure changes and evidencd the stronger influence of diaphragmatic over thoracic activity. Individual variability in thoracic/diaphragmatic respiratory pattern should be considered in the interpretation of the respirophasic modulations of IVC size.

KEYWORDS Inferior vena cava; caval index; breathing pattern; alveolar pressure; IVC collapsibility; Valsalva Maneuver.

INTRODUCTION

Ultrasonographic monitoring of the inferior vena cava (IVC) is a noninvasive, widely adopted procedure to derive information about the volume status of patients as well as their possible responsiveness to fluid therapy (1-4). IVC diameter varies during the respiratory cycle due to pressure changes in the thorax and abdomen (5, 6) and depending on vessel compliance, which in turn depends on filling pressures and volume status (5). These variations are quantified by the caval index (CI), defined as the difference between expiratory and inspiratory IVC diameters divided by the expiratory diameter. However, proposed diagnostic cut-offs for spontaneously breathing patients vary considerably in the literature and caution in relying on CI for fluid therapy management is generally recommended (3, 5).

Several factors, mostly related to the variability of spontaneous breathing, may affect assessment of the CI and potentially undermine its reliability. 1) Spontaneous breathing is intrinsically irregular in both amplitude and frequency (7) and is affected by emotional status, pain, and pathology (8). 2) The respiratory pattern changes depending on gender and age (9, 10), also in terms of its thoracic/diaphragmatic components, which affect in different ways abdominal pressure and IVC diameter (6). 3) The IVC moves considerably during respiration (11), introducing errors in the assessment of CI, unless some advanced image analysis is implemented (12). 4) Often, the cross-section of the IVC is not circular, and may exhibit anisotropic changes in size due to modifications of filling pressure or breathing (11, 13). Consequently, the arbitrary choice of a given section for the measurement of IVC diameter may not be adequate to assess changes in its size and pulsatility and the assessment of the whole cross-sectional area has instead been proposed (14).

This study aims at characterizing the actual dependence of IVC size on changes in intrathoracic pressure, in the absence of the above described confounding factors.

To this aim IVC deformations were assessed in static conditions (short apnea), during controlled isovolumetric respiratory efforts and quantified in terms of changes in cross-sectional area (CSA).

In particular, attention was focused on 1) the IVC CSA response to controlled positive and negative changes in alveolar pressure, as produced by expiratory and inspiratory efforts, respectively, 2) the specific effect of thoracic/diaphragmatic involvement in inspiratory efforts, 3) testing whether such respiratory maneuvers may potentially be employed to detect changes in vascular filling, which spontaneously occur when switching from the standing to the supine position.

MATERIALS AND METHODS

Subject selection

Subjects were recruited among PhD students and partly among amateur swimmers. Out of 16 subjects screened, 6 were excluded because of low quality of the ultrasonographic images (n=4), inability to correctly perform respiratory maneuvers (n=1), and for complete collapse of the IVC already at the low-pressure maneuvers (n=1). The study was then conducted on 10 healthy volunteers (4 males and 6 females, age 27 ±7, BMI 20.7±1.6). The study was approved by the Ethics Committee of Turin University. All participants gave their informed consent according to the principles of Helsinki Declaration.

Experimental setup

During the whole experimental procedure, participants maintained a supine position with head slightly raised with respect to the body. They were asked to either relax and breathe normally or perform respiratory efforts. The upper part of the IVC was visualized by subxyphoid or right lateral intercostal approach by a single echographer (PP), taking into account anatomical landmarks as the left portal branches and the ligamentum venosum.

Video clips of the IVC were recorded in the transversal plane (see below) with an ultrasonographic unit (Mylab25 Gold ESAOTE; Genoa, Italy) equipped with a 2-5 MHz convex probe.

Air pressure during respiratory maneuvers was measured at the mouth level by a pressure monitor (BP-1 pressure monitor, World Precision Instruments, Florida, USA) equipped with a mouthpiece, providing no air leakage. In the absence of airflow, the pressure measured at the mouth during respiratory efforts coincides with the alveolar pressure, provided the glottis remains open. The analog output of the device was digitally acquired (sampling frequency 200 Hz, CED 1401micro, and Spike2 acquisition software, Cambridge, UK) and displayed on a monitor to provide a visual feedback to the subject. In order to synchronize the recording of alveolar pressure signal with the IVC video clip, a digital trigger signal generated by the program (Spike2, CED, UK) was acquired with alveolar pressure and fed to the ECG input of the echograph, thus being displayed and recorded in the video clip.

Respiratory maneuvers

In a preliminary session, the subjects were invited to practice diaphragmatic and thoracic breathing and learned to perform the controlled isovolumetric respiratory efforts while maintaining the glottis open. Respiratory maneuvers consisted of isovolumetric respiratory efforts conducted at functional residual capacity (FRC) as follows. At the end of a spontaneous expiration a trigger signal was manually generated by the experimenter and, after 4 s of apnea (basal condition), the subjects performed the controlled expiratory/inspiratory effort through the mouthpiece according to pre-defined positive/negative target levels, and maintained them for 10 seconds (Fig. 1). At the end of each maneuver, the mouthpiece was removed and the subject could relax and breathe normally. While during expiratory efforts both abdominal and thoracic muscles were simultaneously recruited, inspiratory efforts were performed by selectively activating the diaphragm or thoracic muscles. The accuracy of the inspiratory maneuver was checked by the experimenter based on visual inspection of thoracic and abdominal movements.

Protocol

A resting period of 30 minutes in supine position was allowed to stabilize transcapillary fluid exchange. During this time, respiratory efforts at -5 and +5 mmHg were performed (at 0, 15 and 30 min) with the aim of testing the effect of possible changes in blood volume with time. To the same purpose, 30-s video clips of IVC cross section were recorded during spontaneous breathing.

After this time, a sequence of both thoracic and diaphragmatic inspiratory efforts at -5, -10 and -15 mmHg was performed along with isovolumetric expiratory efforts at 5, 10, and 15 mmHg according to the diagram in Fig. 2. Twenty-second video clips in the transversal plane of the IVC were taken at each respiratory maneuver, allowing to monitor its cross-section before and during the maintained change in alveolar pressure. Resting intervals of at least 30 s were allowed between consecutive maneuvers.

Image processing

All videos were processed by a custom-made software (implemented in Matlab 2015a, The Mathworks) based on automated detection of the IVC wall, providing continuous assessment of the IVC cross sectional area (CSA, Fig. 3) (manuscript in preparation). The CSA was estimated for each frame and a time series obtained with sampling frequency equal to the video frame rate, between 11 Hz and 19 Hz (depending on current echographic settings).

The trigger signal recorded in the video clip was automatically detected and used to re-align in time the CSA signal with the alveolar pressure recording, separately acquired. The CSA signal was then low-pass filtered with cut-off frequency of 2 Hz (Butterworth anti-causal IIR filter of order 4), which preserved both cardiac and respiratory oscillatory components and re-sampled at 200 Hz, as the alveolar pressure signal.

The responses to respiratory maneuvers were analyzed in terms of changes in IVC CSA.. Average CSA was computed over 4-s intervals, before (baseline) and during the respiratory effort (effect), after alveolar pressure reached the target level (see Fig. 1). In baseline intervals, for each heartbeat, the cardiac caval index was calculated as: CCI = (max(A)-min(A))/max(A), where A is the IVC-CSA computed by the algorithm. An average CCI was then obtained for each interval.

Responses to the respiratory maneuvers were calculated as relative changes referred to baseline [(effect-baseline)/baseline].

Assessment of the “classical” caval index, CI= [max(D)-min(D)]/max(D), D being the IVC diameter, was computed off-line by the same echographer (PP), from the 30s video clips recorded during spontaneous breathing using the “frame-by-frame” method, as the average of 3 measurements collected on 3 different respiratory excursions (MyLabDesk, Esaote).

Statistical analysis

Data are expressed as mean±SD in the text and displayed as mean±SEM in bar diagrams. Statistical significance of respiratory effects was assessed by repeated-measures one-way ANOVA (factor: pressure level), for expiratory efforts, by two-way ANOVA (factors: pressure level and diaphragmatic/thoracic pattern) for inspiratory efforts, with Bonferroni correction for multiple comparisons, and by the Dunnett's test for comparison with the basal value. Statistical significance of changes during the stabilization phase with respect to initial condition (t=0) was assessed with the Dunnett's test. The significance cut-off was $p<0.05$. All analyses were carried out with GraphPad Prism version 6.0c (GraphPad Software, San Diego California, USA).

RESULTS

The effect of controlled isovolumetric respiratory efforts was tested after 30 min in supine position. An example of the ensuing changes in IVC CSA is shown in Fig. 4, for a representative subject. Coherent tracings of CSA and alveolar pressure are plotted during expiratory (A) and thoracic and diaphragmatic inspiratory efforts (B, C). It can be observed that the maneuver produced immediate changes in both average size and pulsatility of IVC strictly related in their time course to changes in alveolar pressure. Furthermore, larger effects appear to be produced by diaphragmatic than thoracic inspiratory efforts at -5 mmHg, while even smaller effects are produced by the expiratory effort at +5mmHg (C).

Response to inspiratory efforts

On average, the inspiratory maneuvers induced progressive reduction in CSA with decreasing alveolar pressures ($p<0.001$), the effect being significantly larger with diaphragmatic than thoracic efforts ($p<0.05$) (Fig. 5).

In particular, the average CSA was 2.88±0.43 cm^2 in basal conditions (Fig. 5, dashed line), decreased to 2.0±0.4 cm^2 (n.s.) and to 0.53±0.20 cm^2 ($p<0.01$) during thoracic and diaphragmatic inspiratory efforts at -15 mmHg, respectively. (Fig. 5). Dunnett's test indicates that while thoracic inspiration did not provoke any statistically significant change from basal condition, diaphragmatic inspiration induced significant changes at all pressure levels.

In relative terms, the decrease of CSA ranged from 39±11% to 80±10% in diaphragmatic and up to 33±12% in thoracic maneuvers.

In some subjects, collapse of the IVC up to complete occlusion was observed during the maneuver. This occurred more frequently at increasing negative pressures and during diaphragmatic efforts (number of subjects: 1 at -5 mmHg; 5 at -15 mmHg).

Response to expiratory efforts

Expiratory efforts induced a progressive decrease in the IVC CSA with increasing positive alveolar pressure ($p< 0.05$, Fig. 6). In relative terms, the CSA decreased by 15 ± 6% (n.s., at +5mmHg) and by 55±15% (at +15 mmHg, $p<0.01$).

In 3 subjects, complete collapse of the IVC was observed at +15 mmHg.

Changes occurring in the stabilization phase

Here we discuss the possible blood volume changes occurring during the first 30 min in the supine position (stabilization phase) on the different variables measured, a complete set of recording being achieved in 8 subjects (in two subjects some of the recordings were excluded from the analysis due to delays in following the protocol).

During the stabilization phase, the IVC CSA (measured in resting conditions at functional residual capacity) was dependent on time, increasing from 2.37±0.2cm^2 (t0) to 2.90±0.21cm^2 (t30, $p<0.01$) (see Fig. 7A), where t0 and t30 refer to the conditions at the beginning of the protocol and after 30 min, respectively, as indicated in Fig. 2. Assessment of CSA at the end of the protocol

($2.89\pm0.2 cm^2$ at about 45 min) revealed that no further changes occurred during the last part of the protocol.

The CCI exhibited a specular trend: from $0.22\pm0.01\ cm^2$ (t0) to $0.19\pm 0.01\ cm^2$ (t30, $p<0.05$, Fig. 7B).

The response to respiratory efforts also exhibited a decreasing trend during the first 30 minutes (Fig. 7D). IVC collapse produced by a 5-mmHg diaphragmatic inspiratory effort decreased from 60±12% at t0 baseline to 40±11% at t30. A similar trend was exhibited by the response to thoracic inspiratory efforts (-5 mmHg, Fig. 7E), decreasing from 20±15 % at t0 to 1±10% at t30, and expiratory efforts (+5 mmHg, Fig. 7F), decreasing from 23±15% (t0) to 15±5% (t30), although not reaching statistical significance.

The standard cross-sectional CI, measured manually during spontaneous breathing, confirmed the same trend decreasing from 0.41±0.19 to 0.31±0.13 ($p<0.05$) (Fig. 7C).

DISCUSSION

With this study we show that controlled isovolumetric respiratory efforts produce consistent changes in IVC CSA. During inspiratory efforts, these effects are strongly dependent on whether a thoracic or diaphragmatic effort is made. In particular, diaphragmatic inspiratory efforts produced the largest decreases in CSA (averaging across subjects, from 30% to 80% of basal condition, at -5 mmHg and -15 mmHg, respectively), while changes during thoracic inspiration were less than a half. Expiratory efforts also decreased CSA (up to 65% at +15 mmHg). Preliminary results collected during the stabilization phase in the supine position indicated that the response to standardized respiratory efforts, along with other parameters including the IVC CSA and the cardiac and respiratory CI, are potential indicators of changes occurring in the vascular volume.

In this study we adopted an approach that excludes most of the confounding factors affecting the CI, the classical index of IVC collapsibility. 1) ***Breath-to breath variability***, i.e., the amplitude of the respiratory movements from breath to breath. Tobin et al (7) observed a coefficient of variation in breath-to-breath tidal volume of 30% and 44% and in respiratory frequency of 20 and 28% in young and old subjects, respectively. Since amplitude and speed of respiratory movements directly affect intra-thoracic and abdominal pressures, their variability is expected to directly translate into CI variability. Variability of spontaneous breathing was prevented in this study in which IVC size changes were assessed in response to standardized respiratory maneuvers performed at constant lung volume (functional residual capacity). 2) ***Thoracic/diaphragmatic breathing.*** Variability of the respiratory pattern also concerns the relative proportion of thoracic vs. diaphragmatic activation (in the inspiratory phase), which also exhibits breath-to-breath variability (CoV= 22-31%) (7) as well as dependence on gender and age (9, 10). Although it is well known that thoracic and diaphragmatic breathing affect abdominal pressure differently (15) and thus also the CI (6), it is impossible to control for this confounder in patients because some self-consciousness and training are required for thoracic or diaphragmatic respiration to be correctly performed. Preliminary training was necessary for the healthy subjects of this study. Possibly, because of this difficulty, the issue is generally overlooked and its implications ignored in the interpretation of the CI. 3) ***Respiratory movements of the IVC.*** Longitudinal displacement of the IVC in the order of 2 cm in cranio-caudal direction has been shown (11) and this may introduce an error of up to 30% in the estimate of the CI, depending on the shape of the IVC (12). This error affects transversal as well as M-mode longitudinal measurements, although the latter were recently indicated as the most sensitive indicators of changes in volume status (16). These artifacts were prevented in the present study, because all measurements were taken in static conditions (short apnea). 4) ***Non circular IVC cross-sectional shape.*** The CI and other similar indices of collapse are always computed on the basis of maximum and minimum IVC diameters, which is a misrepresentation, because the IVC usually presents a non-circular cross-sectional shape. Thus, the choice of a given "diameter" is arbitrary and its temporal changes may not be representative of the behavior of the whole vessel. In fact, in hypovolemic patients undergoing fluid replacement, Murphy et al (13) showed that the minor axis exhibited a five-fold increase as compared to a 5% increase of the major axis (of IVC imaged in transversal section), which they called anisotropic behavior of the IVC. This problem was prevented here by assessing changes in the cross-sectional area of IVC rather than in a single, arbitrarily chosen diameter, following the approach proposed by Nakamura et al. (14).

IVC changes in thoracic vs. diaphragmatic inspiratory efforts.

IVC size varies in response to changes in transmural pressure (i.e., the difference between internal and external pressures), according to its compliance (defined as the incremental variation of vessel volume induced by a change of transmural pressure). Transmural pressure may change due to changes in 1) internal pressure (i.e., central venous pressure, CVP) which directly depends on changes in intra-thoracic pressure and 2) external (abdominal) pressure which may increase due to contraction of the diaphragm (e.g., during diaphragmatic inspiration or inspiratory efforts) or of abdominal expiratory muscles (e.g., during forced expiration or expiratory efforts). In this study, the subjects engaged in isovolumetric respiratory efforts, attaining selected positive and negative levels of alveolar pressure that, in the absence of airflow, could be measured at the mouth-piece. Since all maneuvers were performed at the same lung volume (FRC), we can assume unchanged transpulmonary pressure, which implies that changes in alveolar pressure produced equivalent changes in intrathoracic pressure, affecting the CVP.

In light of these considerations, the results can be interpreted as follows. Diaphragmatic inspiratory efforts produced both a reduction of blood pressure in the IVC (by decreased intrathoracic pressure) and an increase of abdominal pressure (by diaphragm contraction). These effects concurred to markedly decrease IVC transmural pressure, resulting in the observed marked decrease in IVC CSA. The latter was roughly proportional to the intensity of the effort performed (Fig. 5, black columns). Conversely, thoracic inspiratory efforts only affected intrathoracic pressure, with virtually no effect on abdominal pressure, resulting in comparably lower reductions in IVC CSA. These were negligible at -5 mmHg and did not further decrease for -10 to -15 mmHg of alveolar pressure (Fig.

5, white columns). This suggests that lowering intrathoracic pressure has a limited collapsing effect on the IVC, compared to increasing abdominal pressure.

This interpretation fits with other data in the literature. The thoracic/diaphragmatic respiratory pattern also affects venous return, which is impaired by increased abdominal pressure. In fact, Miller et al. (15) elegantly showed that abdominal pressure increases (+ 6 cmH_2O) and venous return (observed at the femoral vein) is arrested during the inspiratory phase of diaphragmatic breathing, the same effects being produced by manually compressing the abdomen. On the contrary, thoracic inspiration facilitates venous return (15). Gutzeit et al. (17) recently reported that forced inspiration (“suction against resistance” at -20 mmHg) decreased venous return from inferior with respect to superior vena cava. Although they did not control for thoraco/diaphragmatic inspiratory patterns, it is likely that the diaphragm was activated to some extent, thus impairing venous return in the IVC. In uncontrolled breathing at increasing inspiratory effort (0, -5, -10 mmHg) Gignon et al. (18) showed that the increased CI was highly correlated with diaphragm displacement. To our knowledge, specific thoraco/diaphragmatic effects on IVC size were only investigated by Kimura et al. (6), who reported that diaphragmatic breathing is associated with increased IVC excursions and CI, with respect to thoracic breathing at comparable tidal volumes. Based on a different approach (isovolumetric efforts at comparable levels of blood volume and alveolar pressure), we show here that increasing inspiratory diaphragmatic efforts progressively decreased IVC size down to complete collapse in 5/10 subjects. Notably, intrathoracic pressure changes during spontaneous breathing are in the order of 2-3 cm H_2O, well below 5 mmHg. On this basis, the data presented here support the notion that abdominal pressure is a major determinant of IVC size and further emphasize that an uncontrolled breathing pattern may confound volume status assessment based on measured CI (6, 18).

IVC changes during expiratory efforts

Attaining a positive alveolar pressure at constant lung volume results in equivalent increase in intrathoracic pressure, which in turn should increase blood pressure in the IVC and increase its size. However, the expiratory effort requires contraction of both thoracic and diaphragmatic expiratory muscles and results in increased abdominal pressure (19), which per se produces the opposite effect on IVC transmural pressure and size. On this basis, predicting the outcome on IVC size is not trivial and may depend on both lung volume and how the maneuver is actually performed (20). Grant et al. (20) observed reduction of the IVC in 100% of males and 50% of females performing a Valsalva maneuver. In a recent study, IVC deformation by the Valsalva maneuver was reinvestigated with computed tomography (21) and a systematic decrease of IVC size was reported (to 22% of resting CSA, on average). However in none of these studies was the maneuver controlled or standardized in terms of exerted pressure. The authors did not measure abdominal pressure simultaneously with IVC size. Since it averaged about 80 mmHg, the expiratory effort was presumably close to maximal in the second study (21). In this study, rather low pressure values (5, 10 and 15 mmHg) were attained at the mouthpiece, as compared to the 40 mmHg commonly employed for the Valsalva maneuver (22), but a progressive and significant decrease in IVC size was observed, again indicating that abdominal pressure prevails on intra-thoracic pressure.

Detection of volume changes during the stabilization phase

A fluid shift from the extravascular to the intravascular compartment is known to occur when switching from the orthostatic to the clinostatic position (23). The increase in plasma volume, often assessed on the basis of the accompanying decrease in protein concentration and hematocrit (so called postural pseudoanemia (24)), was reported to be in the order of 8% and 12% after 15 and 60 min from changing posture (23). Other studies have substantially confirmed these figures, indicating volume shifts of about 400 ml within 30 min from postural change, from lying to standing or vice versa (24, 25). Such increase in plasma volume presumably occurred in the present study, during the stabilization phase. In agreement with this hypothesis, a significant increase in IVC CSA was detected, along with other effects indicating decreased IVC compliance, such as the decrease in cardiac and respiratory CI and a trend to decrease in the IVC CSA response to inspiratory efforts. These results emphasize the importance of allowing for a stabilization phase in the supine position before starting experimental protocols and that failing to do so may introduce large errors in the measurement of IVC variables. The response to a standardized respiratory maneuver has the potential to reveal changes in blood volume; however further studies and larger population samples are needed to characterize the sensitivity of the different parameters to the actual changes in blood volume occurring in this and other conditions.

Limitations

Although maneuvers were performed at constant lung volume, some movement of the diaphragm could still occur at the onset of inspiratory and expiratory efforts (although not during measurements), resulting in longitudinal displacements of the IVC that may not have been adequately compensated for by the operator. In addition, some residual movements of the diaphragm during thoracic inspiration, or of the thorax during abdominal inspiration, may have occurred. This, however, did not prevent detection of large differences in the IVC responses to the two breathing patterns.

The subjects involved were selected for echogenicity and for their ability to correctly perform the respiratory maneuvers required by the protocol. They were partly recruited among amateur swimmers, often characterized by a particularly large IVC (26), and this may account for the relatively high average IVC CSA and low CI observed.

A further limitation concerns the applicability of this approach to the clinical setting. The implementation of these respiratory maneuvers required well-trained subjects and may be unfeasible with poorly collaborative patients.

Conclusions

We describe for the first time IVC responses to positive and negative changes in alveolar pressure, producing equivalent changes in intrathoracic pressure. The results indicate that diaphragmatic activation, affecting abdominal pressure, is a major determinant of IVC size and suggest that individual variability in the thoracic/diaphragmatic respiratory patterns may account for the large variability normally observed in the respiratory CI. Implementation of isovolumetric controlled maneuvers proved effective in probing IVC compliance in the absence of the confounding effects otherwise introduced by spontaneous breathing and potentially adequate to detect changes in volume status. Further studies are required to test this possibility and to make the procedure compatible with the clinical setting.

ACKNOWLEDGMENTS

This work was supported with grants from University of Torino.

REFERENCES

1. Barbier C, Loubieres Y, Schmit C, Hayon J, Ricome JL, Jardin F, et al. Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. *Intensive Care Med* 2004; 30:1740-1746.

2. Nagdev AD, Merchant RC, Tirado-Gonzalez A, Sisson CA, Murphy MC. Emergency department bedside ultrasonographic measurement of the caval index for noninvasive determination of low central venous pressure. *Ann Emerg Med* 2010; 55:290-295.

3. Zhang Z, Xu X, Ye S, Xu L. Ultrasonographic measurement of the respiratory variation in the inferior vena cava diameter is predictive of fluid responsiveness in critically ill patients: systematic review and meta-analysis. *Ultrasound Med Biol* 2014; 40:845-853.

4. Muller L, Bobbia X, Toumi M, Louart G, Molinari N, Ragonnet B, et al. Respiratory variations of inferior vena cava diameter to predict fluid responsiveness in spontaneously breathing patients with acute circulatory failure: need for a cautious use. *Crit Care* 2012; 16:R188.

5. Bodson L, Vieillard-Baron A. Respiratory variation in inferior vena cava diameter: surrogate of central venous pressure or parameter of fluid responsiveness? Let the physiology reply. *Crit Care* 2012; 16:181.

6. Kimura BJ, Dalugdugan R, Gilcrease GW, 3rd, Phan JN, Showalter BK, Wolfson T. The effect of breathing manner on inferior vena caval diameter. *Eur J Echocardiogr* 2011; 12:120-123.

7. Tobin MJ, Mador MJ, Guenther SM, Lodato RF, Sackner MA. Variability of resting respiratory drive and timing in healthy subjects. *J Appl Physiol (1985)* 1988; 65:309-317.

8. Borges-Santos E, Wada JT, da Silva CM, Silva RA, Stelmach R, Carvalho CR, et al. Anxiety and depression are related to dyspnea and clinical control but not with thoracoabdominal mechanics in patients with COPD. *Respir Physiol Neurobiol* 2015; 210:1-6.

9. Romei M, Mauro AL, D'Angelo MG, Turconi AC, Bresolin N, Pedotti A, et al. Effects of gender and posture on thoraco-abdominal kinematics during quiet breathing in healthy adults. *Respir Physiol Neurobiol* 2010; 172:184-191.

10. Parreira VF, Bueno CJ, Franca DC, Vieira DS, Pereira DR, Britto RR. Breathing pattern and thoracoabdominal motion in healthy individuals: influence of age and sex. *Rev Bras Fisioter* 2010; 14:411-416.

11. Blehar DJ, Resop D, Chin B, Dayno M, Gaspari R. Inferior vena cava displacement during respirophasic ultrasound imaging. *Crit Ultrasound J* 2012; 4:18.

12. Mesin L, Pasquero P, Albani S, Porta M, Roatta S. Semi-automated tracking and continuous monitoring of inferior vena cava diameter in simulated and experimental ultrasound imaging. *Ultrasound Med Biol* 2015; 41:845-857.

13. Murphy EH, Arko FR, Trimmer CK, Phangureh VS, Fogarty TJ, Zarins CK. Volume associated dynamic geometry and spatial orientation of the inferior vena cava. *J Vasc Surg* 2009; 50:835-842; discussion 842-833.

14. Nakamura K, Tomida M, Ando T, Sen K, Inokuchi R, Kobayashi E, et al. Cardiac variation of inferior vena cava: new concept in the evaluation of intravascular blood volume. *J Med Ultrason (2001)* 2013; 40:205-209.

15. Miller JD, Pegelow DF, Jacques AJ, Dempsey JA. Skeletal muscle pump versus respiratory muscle pump: modulation of venous return from the locomotor limb in humans. *J Physiol* 2005; 563:925-943.

16. Celebi Yamanoglu NG, Yamanoglu A, Parlak I, Pinar P, Tosun A, Erkuran B, et al. The role of inferior vena cava diameter in volume status monitoring; the best sonographic measurement method? *Am J Emerg Med* 2015; 33:433-438.

17. Gutzeit A, Roos JE, Hergan K, von Weymarn C, Walti S, Reischauer C, et al. Suction against resistance: a new breathing technique to significantly improve the blood flow ratio of the superior and inferior vena cava. *Eur Radiol* 2014; 24:3034-3041.

18. Gignon L, Roger C, Bastide S, Alonso S, Zieleskiewicz L, Quintard H, et al. Influence of Diaphragmatic Motion on Inferior Vena Cava Diameter Respiratory Variations in Healthy Volunteers. *Anesthesiology* 2016; 124:1338-1346.

19. Hackett DA, Chow CM. The Valsalva maneuver: its effect on intra-abdominal pressure and safety issues during resistance exercise. *J Strength Cond Res* 2013; 27:2338-2345.

20. Grant E, Rendano F, Sevinc E, Gammelgaard J, Holm HH, Gronvall S. Normal inferior vena cava: caliber changes observed by dynamic ultrasound. *AJR Am J Roentgenol* 1980; 135:335-338.

21. Laborda A, Sierre S, Malve M, De Blas I, Ioakeim I, Kuo WT, et al. Influence of breathing movements and Valsalva maneuver on vena caval dynamics. *World J Radiol* 2014; 6:833-839.

22. Pstras L, Thomaseth K, Waniewski J, Balzani I, Bellavere F. The Valsalva manoeuvre: physiology and clinical examples. *Acta Physiol (Oxf)* 2016; 217:103-119.

23. Fawcett JK, Wynn V. Effects of posture on plasma volume and some blood constituents. *J Clin Pathol* 1960; 13:304-310.

24. Jacob G, Raj SR, Ketch T, Pavlin B, Biaggioni I, Ertl AC, et al. Postural pseudoanemia: posture-dependent change in hematocrit. *Mayo Clin Proc* 2005; 80:611-614.

25. Hagan RD, Diaz FJ, Horvath SM. Plasma volume changes with movement to supine and standing positions. *J Appl Physiol Respir Environ Exerc Physiol* 1978; 45:414-417.

26. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23:685-713; quiz 786-688.

FIGURES

Figure 1: Visual feedback. At the bottom, the visual feedback of alveolar pressure (black) and the target level to be reached (grey). At the top, the trigger signal fed to the echograph for synchronization. Dashed lines indicate the 4-s intervals used in the analysis, identifying “baseline” and “effect”.

Figure 2. Experimental protocol. Bars of different height indicate expiratory (positive, grey) and inspiratory (negative) diaphragmatic (black) and thoracic (white) efforts of different magnitudes (5, 10 and 15 mmHg). Squared brackets indicate whether maneuvers were used to characterize the effects of respiratory efforts on IVC or to detect possible changes in blood volume over the first 30 min in the supine position.

Figure 3. Representation of the automated detection of the IVC wall.

Figure 4. IVC response to respiratory efforts, in a representative subject. Recordings of the cross-sectional area of the inferior vena cava (IVC CSA, upper trace) in response to controlled changes in alveolar pressure (lower trace) are shown in an expiratory effort at +5 mmHg (A) and a thoracic (B) and adiaphragmatic (C) inspiratory effort at -5 mmH. Note that different effects are produced in terms of changes in CSA and pulsatility by the different maneuvers.

Figure 5. Average IVC response to inspiratory efforts. Cross sectional area of inferior vena cava (IVC-CSA) during diaphragmatic (black) and thoracic (white) inspiratory efforts at different pressure levels. The dashed horizontal line represents the average basal value (pre-maneuver) of IVC-CSA and the grey band and error bars represents standard error. Symbols on single columns indicate significant difference from baseline. *) $p<0.05$; #) $p<0.01$.

Figure 6. Average IVC response to inspiratory efforts. Cross sectional area of inferior vena cava (IVC-CSA) during the expiratory efforts at different pressure levels. The dashed horizontal line represents the average basal (pre-maneuver). Other notations as in Fig. 5.

Figure 7. Changes observed during the first 30 min in supine position. A) Cross sectional area of inferior vena cava (IVC-CSA). B) Cardiac caval index (CCI). C) Respiratory caval index assessed by the echographer. Response to diaphragmatic (D) and thoracic (E) inspiratory efforts at -5 mmHg and to expiratory efforts (+5 mmHg, F), expressed in terms of % change in CSA with respect to baseline; *) significantly different from t0, $p<0.05$. #) significantly different from t0, $p<0.01$.

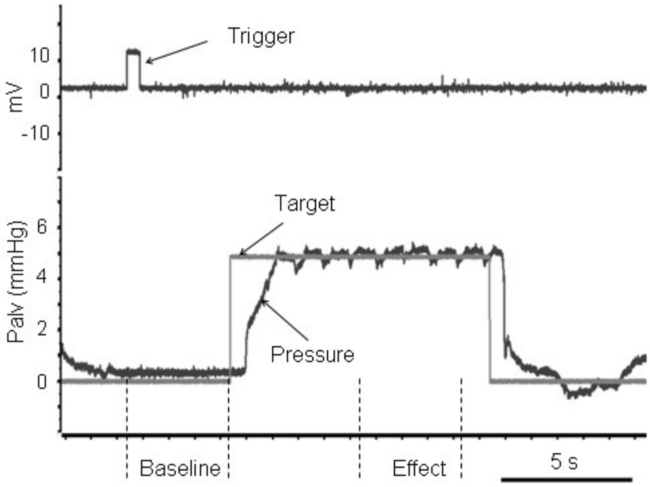
Trigger
10
0
-10
mV
Target
6
4
2
0
Palv (mmHg)
Pressure
Baseline
Effect
5 s

FIG.1

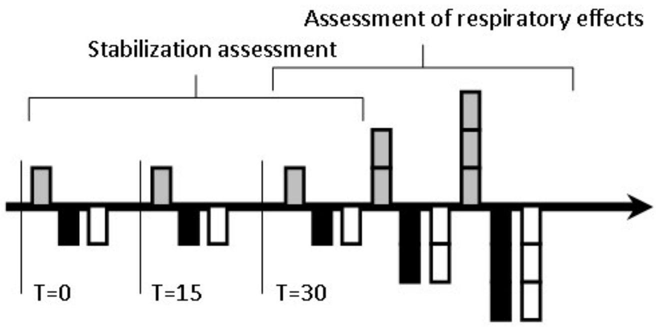
Assessment of respiratory effects
Stabilization assessment
T=0
T=15
T=30

FIG.2

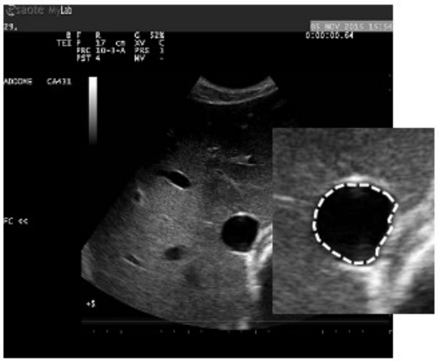
esaote MyLab
29.
05 NOV 2015 15:54
0:00:00.64
B F R G 52%
TEI F 17 cm XV C
FRC 10-3-A PRS 3
FST 4 MV -
ADDOME CA431
FC <<
+5

FIG.3

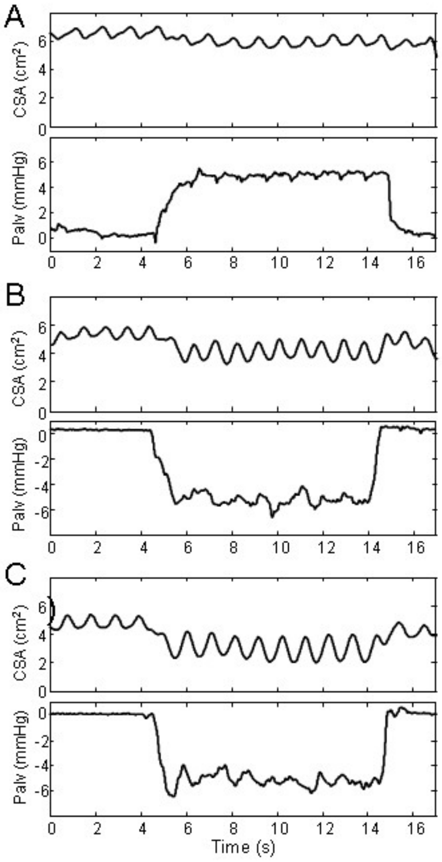
A
CSA (cm²)
0
2
4
6
Palv (mmHg)
0
2
4
6
0 2 4 6 8 10 12 14 16
B
CSA (cm²)
0
2
4
6
Palv (mmHg)
0
-2
-4
-6
0 2 4 6 8 10 12 14 16
C
CSA (cm²)
0
2
4
6
Palv (mmHg)
0
-2
-4
-6
0 2 4 6 8 10 12 14 16
Time (s)

FIG.4

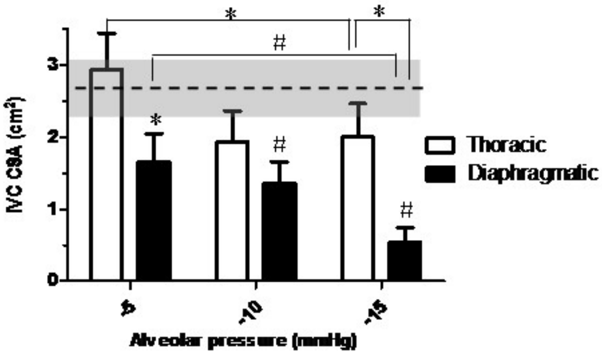
*
*
#
3
2
1
0
IVC CSA (cm^2)
*
#
#
Thoracic
Diaphragmatic
-5
-10
-15
Alveolar pressure (mmHg)

FIG.5

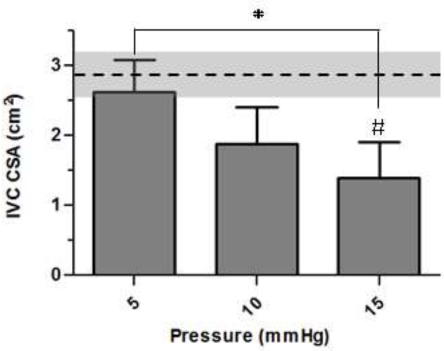

FIG.6

477

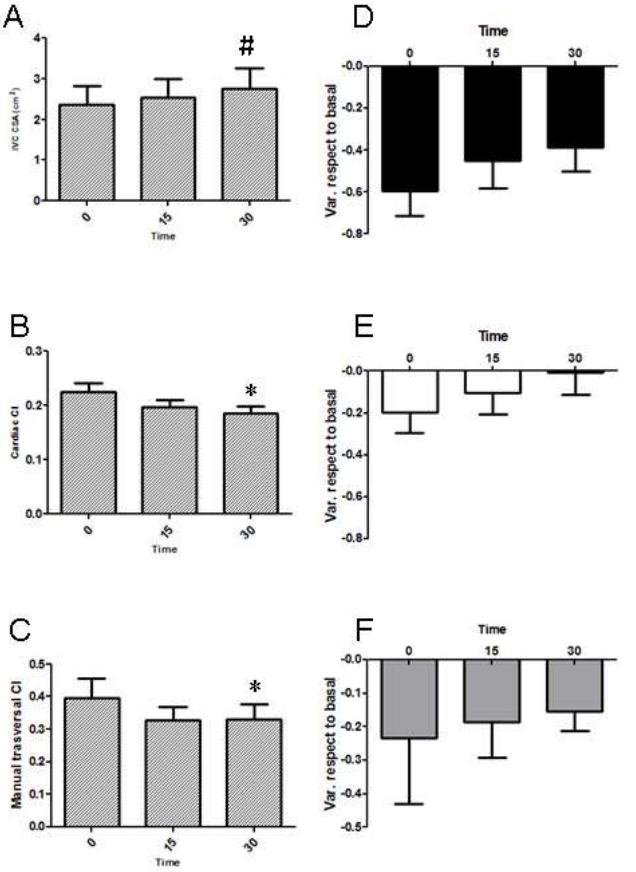
A
IVC CSA (cm²)
4
3
2
1
0
#
0
15
30
Time
D
Time
0
15
30
-0.0
-0.2
-0.4
-0.6
-0.8
Var. respect to basal
B
Cardiac CI
0.3
0.2
0.1
0.0
*
0
15
30
Time
E
Time
0
15
30
-0.0
-0.2
-0.4
-0.6
-0.8
Var. respect to basal
C
Manual trasversal CI
0.5
0.4
0.3
0.2
0.1
0.0
*
0
15
30
Time
F
Time
0
15
30
-0.0
-0.1
-0.2
-0.3
-0.4
-0.5
Var. respect to basal

FIG.7