An alternative explanation for the phasic variations in venous flow

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ABSTRACT

Background: Phasic venous flow variation with respiration is surrounded by controversy and not well understood. The current concept assigns a major role to the "abdominal pump." According to this model, inspiratory increases in abdominal pressure compress the vena cava, increasing its internal venous pressure and propelling blood upstream. Some have assigned a secondary role to the "thoracic pump," with the negative intrapleural pressure aiding blood flow toward the heart. The aim of the present study was to examine the phasic changes in flow, pressure, and volume in the central veins and named tributaries.

Methods: Caliber area changes were measured using intravascular ultrasonography in 37 patients undergoing iliac vein stenting. The pressure was measured in 48 patients using transducer tip catheters with electronic zero calibration. Duplex ultrasound flow in the head and neck and truncal and limb veins during inspiration and expiration was measured in 15 normal volunteers.

Results: The caliber of the abdominal inferior vena cava had increased by 32% and its lateral pressure had decreased significantly during inspiration. Intravenous pressure in the central veins of the chest and right atrium was positive at 6 to 14 mm Hg. Negative pressures were rarely seen and then only transiently. The internal jugular vein displayed little phasic variation. The upper limb veins displayed weak inspiratory phasicity. Phase polarity was reversed in the lower limbs, with near flow stoppage during inspiration.

Conclusion: These observations conflict with the current notions of venous flow phasicity, which are based on push—pull pressure changes in the abdominal and thoracic veins. The paradoxical inspiratory inferior vena cava caliber increase probably explains the concurrent pressure decrease. Sustained negative pressures in the thoracic central veins and right atrium did not occur. We have proposed an alternate hypothesis for venous flow phasicity based on alternate stretching and relaxation of the mobile section of the great veins with respiratory movement. (J Vasc Surg: Venous and Lym Dis 2020;■:1-10.)

Keywords: Phasic venous flow; Phasicity; Venous flow

Phasic changes with cardiopulmonary action are characteristic of venous flow. Venous flow phasicity has long been a source of interest and several controversies. Early concepts of phasicity emphasized vis-a-fronte and vis-a-tergo by the heart pump.[1] The seminal works of Guyton on venous return has replaced the vintage cardiocentric concept with autonomous peripheral venous control. The heart is no longer considered an active suction pump but to function more like a sump pump, clearing the venous flow draining into it. A recent review by Magder[2] provides a succinct overview. In brief, venous outflow originates from central and peripheral venous reservoirs in which 70% of the blood volume resides. Approximately 20% of this volume is "stressed" (ie, held under tension by the stretched walls of the veins). This provides the driving force for flow, and the atrial contractions lower the pressure at the other end, increasing the gradient. The decrease and increase of atrial pressure with atrial filling and contraction are reflected as pressure waves in the central veins.

Progressive upstream flow and caliber increases occur in the coalescing venous tree. Pressure along the intermediate segments can vary in either direction, depending on the local caliber relative to the flow. A velocity decrease and pressure increase occurs in the flow when veins traverse the pressurized abdominal compartment. When the external pressure is negative, such as in the chest, limited conduit expansion occurs with little change in flow or pressure.[3,4]

Larger respiratory modulation of venous flow is thought to result from the negative and positive pressures prevailing in the thorax and abdomen, respectively. These pressures increase in their respective directions with

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inspiration.[5,6] Complimentary respiratory pressure changes in the two anatomic regions were considered to acting as a pull–push mechanism to aid venous drainage from the lower trunk into the heart. Some doubt on the efficacy of the thoracic pump arose with the finding that the central veins draining the upper trunk and limbs collapsed with inspiration as they entered the thoracic inlet.[7-9] This was attributed to "venous collapse"—a property of thin walled tubes that transit from a high pressure region to one of lower pressure as described by Holt.[10] The current concept still includes a role, albeit a muted one, to the thoracic pump for venous drainage from the upper trunk. For venous drainage from the lower trunk and limbs, the emphasis has shifted to the abdominal pump as the dominant modulator. In a series of canine experiments underpinning this concept, Guyton[8] showed that increased abdominal pressure compressed the abdominal inferior vena cava (IVC), increasing its internal pressure.

The availability of intravascular ultrasonography (IVUS) planimetry and catheter tip transducers has allowed for accurate measurements of phasic caliber and pressure changes during endovenous procedures. A surprising IVUS finding during such measurements was that the central veins in the abdomen expanded during inspiration rather than being compressed by the increased intra-abdominal pressure. Furthermore, the intravenous pressure in the iliac-caval veins decreased during inspiration, instead of increasing as expected.

We performed a single-center observational study with a retrospective analysis of prospectively collected data. The aim of the present study was to report the respiratory flow, caliber, and pressure changes at various levels of the superior vena cava and IVC and their major tributaries. From our observations, we have postulated an alternative mechanism of venous flow phasicity caused by the phasic stretching and relaxation of the vena cavae with respiratory movement.

ARTICLE HIGHLIGHTS

- **Type of Research:** A single-center, retrospective cohort study
- **Key Findings:** The intravascular ultrasound measure caliber of the inferior vena cava increased by a mean of 32% and the pressure decreased by ~4 mm Hg during inspiration, contradicting the "abdominal pump" theory. Also, sustained negative pressure in the right atrium was not seen.
- **Take Home Message:** A new hypothesis of venous flow phasicity is proposed.

METHODS

Patients

IVUS planimetry (n = 37) and venous pressure data (n = 48) acquired in separate series in the course of iliac-caval stent placement from 2012 to 2019 were analyzed.

Normal volunteers

The phasic changes in the diameter and flow velocity parameters in the IVC and large veins in the trunk and bilateral limbs were recorded in 15 normal volunteers using external color duplex ultrasonography.

Procedures

IVUS and pressure measurements were taken before balloon stenting (because of associated pain) with the patient in the supine position under light general anesthesia and spontaneous unassisted breathing through a laryngeal mask. The tidal volume was kept at not <400 cm^3 during the measurements by modulating the level of anesthetic.

IVUS measurements. An IVUS catheter (Visions PV 0.035; Philips Volcano Corp, San Diego, Calif) was used. The caliber perimeters of the IVC, common iliac vein, and external iliac vein were traced using an electronic pen. The machine planimetry software provided the area. The caliber area was measured at the height of inspiration and expiration when the phasic differences were maximum.

Pressure measurements. A catheter tip-mounted transducer was used (Mikro-Cath Pressure Catheter, 3.5F; Millar Inc, Houston, Tex). The catheter has an electronic zero calibration feature, which avoids the calibration and positional errors associated with the remote transducers in common use.

Duplex ultrasound examinations. A color duplex instrument (Logiq 9; GE Medical Systems, Waukesha, Wis) was used. A "hockey stick" probe (8-18 MHz; Logiq S8; GE Medical Systems), linear probe (8.5-10 MHz; Logiq S8; GE Medical Systems), and 5-Hz curvilinear probe (model C1-6; GE Medical Systems) were used according to the vessel depth. All major veins outside the thorax were examined with the participant quietly breathing in the supine position. The measured parameters ("flow metrics") were the phasic variations in vessel diameter, peak velocity, and time averaged velocity (TAV) and its duration. The phasic flow volume (cm^3) was calculated as follows: [area (πr^2)×TAV×TAV duration] using these measurements. Each of these flow metric values had a phasic variation. This phasic pattern is expressed as an inspiration/expiration ratio for each metric. The phasic dominance of each flow metric value was classified as inspiration dominant, expiration dominant, or neutral according to whether the respective flow metric values differed significantly.

An experienced technician examined the venous flow waveforms present during quiet breathing (Fig 1). The volunteers were not given any specific instructions regarding breathing and were not aware that the phasic

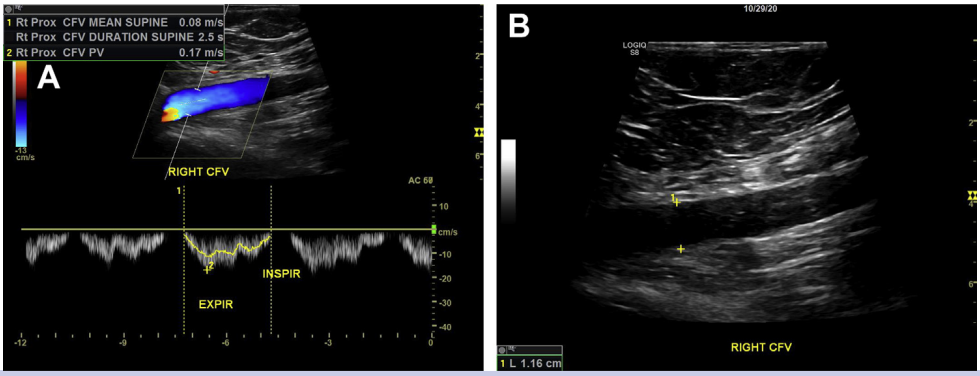


Fig 1. A, Standard duplex ultrasound machine setting, which yields a set of three waveforms per frame. The middle waveform was chosen by the technician as a representative sample for measurement of the duration, peak velocity (PV), and time averaged velocity (TAV). The machine software provided specific readouts as shown. See the text for details. **B,** The diameter of the vein was derived from the B-mode image. In some cases, a B-flow image provided a clearer boundary resolution for measurement. The phasic flow volume was calculated from the diameter and other flow metrics shown in **(A)**. *CFV,* Common femoral vein; *Expir,* expiration; *Inspir,* inspiration; *Rt Prox,* right proximal.

flow variations were being measured. This minimized any conscious variation in the breathing patterns. The standard machine setting yields three waveforms (breaths) per frame. Waveform-to-waveform variation has been rare in our experience. The technician chose a representative sample waveform with good definition and the least amount of scatter for analysis. The technician manually marked the boundary between inspiration and expiration, which was quite evident in most cases by the phase reversal. Most of the listed flow metric values were provided by the machine software as shown in Fig 1, except for the flow volumes, which were calculated.

Coefficient of variation for duplex flow measurements. The duplex flow measurements were repeated in five volunteers (21 vein segments per volunteer) after 6 to 12 weeks. The coefficient of variation (standard deviation divided by the mean) for the four parameters (peak velocity, TAV, TAV duration, and phasic flow volume) varied from 27% to 42%. In the upper limb, the phasic dominance changed from inspiration to neutral for 75% of the flow metric values each in the subclavian and axillary veins. The phasic dominance was neutral and remained unchanged for all flow metric values in the internal jugular vein. Flow dominance in the IVC changed from expiration to neutral for 50% of the flow metric values. In the lower limb, phasic dominance changed from expiration to neutral for 25% of the flow metric values each in the popliteal and profunda femoris veins. Phasic (inspiratory/expiratory) dominance was unchanged for the flow metric values in all other vein segments of the lower limb.

Statistical analysis

Data were extracted from contemporaneously entered electronic medical records. Two-tailed paired or unpaired *t* tests, as appropriate, were used to compare the phasic variations across the vessels. The χ^2 test was used to compare the ratios. All analyses were performed with commercial software (Prism Corp, Irvine, Calif). The values for the various observations described varied and are presented in context in the "Results" section.

Permissions

Data were collected from normal volunteers as a part of an institutional review board (IRB)–approved registry. The IRB approved all procedures and ancillary or incidental data acquired during the procedures, and the volunteers and patients provided written informed consent. The IVUS data from the patients were collected during 2012 and 2013. Pressure data from patients were collected during 2017 to 2019. The relevance of the IVUS data to the present study was not apparent until after the final retrospective analysis of the collected pressure data. The IRB approved the inclusion of the earlier IVUS data in the present report.

RESULTS

The demographics of the normal volunteers and patients are presented in Supplementary Table I (online only). None of the volunteers had a history of previous venous disease or duplex ultrasound evidence of venous disease. The patient characteristics reflected features from larger series of patients undergoing iliac vein stenting. The volunteers had a normal body mass index (BMI), and the patients had an elevated BMI, similar to a large fraction of the general population in our area.

Phasic flow metric values. We found no differences in phasic flow between the right and left side veins, except for two flow metric values for the internal jugular vein (Supplementary Table II, online only). The duplex flow metrics measured during inspiration and expiration for the central and large peripheral veins in each limb are presented in the Table, with differing regional patterns apparent:

Table. Phasic flow parameters in normal subjects

Variable	Inspiration	Expiration	Phasic variation ratio[a] (inspiratory/expiratory)	Dominant flow[b]
Head and neck				
Internal jugular vein (n = 30)				
PV (cm/s)	51.3 ± 32.9	48.8 ± 26.1	1:1	Neutral
TAV, cm/s	14.9 ± 10.4	13.9 ± 8.8	1:1	Neutral
Flow duration, seconds	2.3 ± 1.0	2.5 ± 0.9	1:1	Neutral
Phasic flow volume, cm^3	263.1 ± 277.2	243.7 ± 207.4	1:1	Neutral
Upper limbs				
Subclavian vein (n = 20)				
PV, cm/s	55.2 ± 21.5[c]	34.5 ± 21.1	2:1	Inspiration
TAV, cm/s	13.6 ± 6.1[d]	7.3 ± 5.8	2:1	Inspiration
Flow duration, seconds	2.5 ± 0.8	2.4 ± 0.9	1:1	Neutral
Phasic flow volume, cm^3	198.4 ± 116.6[e]	89.1 ± 60.9	2:1	Inspiration
Axillary vein (n = 20)				
PV, cm/s	36.0 ± 20.2[f]	30.0 ± 20.3	1:1	Inspiration
TAV, cm/s	10.7 ± 12.8[e]	8.7 ± 11.1	1:1	Inspiration
Flow duration, seconds	2.0 ± 0.8	2.6 ± 0.9[f]	1:1	Expiration
Phasic flow volume, cm^3	86.7 ± 82.5	84.1 ± 69.4	1:1	Neutral
Abdominal central veins				
IVC (n = 10)				
PV, cm/s	27.4 ± 37.5	51.3 ± 18.4[f]	1:2	Expiration
TAV, cm/s	10.1 ± 11.0	18.0 ± 5.1[f]	1:2	Expiration
Flow duration, seconds	1.8 ± 1.2	3.4 ± 1.3[e]	1:2	Expiration
Phasic flow volume, cm^3	538.3 ± 1047.0	1334.0 ± 704.7	1:2	Neutral
CIV (n = 20)				
PV, cm/s	2.4 ± 4.0	19.4 ± 9.4[d]	1:8	Expiration
TAV, cm/s	1.3 ± 2.3	9.5 ± 3.4[d]	1:7	Expiration
Flow duration, seconds	1.2 ± 1.1	4.0 ± 1.5[d]	1:3	Expiration
Phasic flow volume, cm^3	16.2 ± 45.5	459.1 ± 228.4[d]	1:28	Expiration
EIV (n = 20)				
PV, cm/s	1.2 ± 3.8	26.7 ± 20.3[d]	1:22	Expiration
TAV, cm/s	0.6 ± 1.7	12.2 ± 11.3[c]	1:20	Expiration
Flow duration, seconds	1.1 ± 1.0	3.8 ± 0.9[d]	1:3	Expiration
Phasic flow volume, cm^3	9.4 ± 34.2	642.6 ± 616.1[c]	1:68	Expiration
Lower limbs				
CFV (n = 20)				
PV, cm/s	5.5 ± 7.4	23.4 ± 8.5[d]	1:4	Expiration
TAV, cm/s	1.9 ± 3.3	9.7 ± 3.4[d]	1:5	Expiration
Flow duration, seconds	1.4 ± 1.2	4.0 ± 1.6[d]	1:3	Expiration
Phasic flow volume, cm^3	50.3 ± 110.1	540.2 ± 404.7[d]	1:11	Expiration
FV (n = 20)				
PV, cm/s	6.0 ± 8.1	23.9 ± 8.6[d]	1:4	Expiration
TAV, cm/s	1.6 ± 2.3	11.1 ± 4.9[d]	1:7	Expiration
Flow duration, seconds	1.8 ± 1.1	3.8 ± 1.6[d]	1:2	Expiration
Phasic flow volume, cm^3	10.4 ± 16.0	136.2 ± 65.5[d]	1:13	Expiration
PFV (n = 20)				
PV, cm/s	3.4 ± 6.7	21.0 ± 8.3[d]	1:6	Expiration
TAV, cm/s	1.1 ± 2.3	10.5 ± 7.0[d]	1:10	Expiration

Table. Continued.

Variable	Inspiration	Expiration	Phasic variation ratio[a] (inspiratory/expiratory)	Dominant flow[b]
Flow duration, seconds	1.6 ± 1.2	3.8 ± 1.5[d]	1:2	Expiration
Phasic flow volume, cm^3	7.1 ± 15.7	163.2 ± 145.7[c]	1:23	Expiration
GSV (n = 20)				
PV, cm/s	3.2 ± 11.2	13.1 ± 5.3[c]	1:4	Expiration
TAV, cm/s	0.8 ± 1.6	4.9 ± 2.6[d]	1:6	Expiration
Flow duration, seconds	2.0 ± 1.7	3.3 ± 1.1[c]	1:2	Expiration
Phasic flow volume, cm^3	1.7 ± 3.3	38.0 ± 36.5[c]	1:22	Expiration
Popliteal vein (n = 20)				
PV, cm/s	0.3 ± 1.1	13.7 ± 5.5[d]	1:46	Expiration
TAV, cm/s	0.2 ± 0.5	6.3 ± 3.4[d]	1:32	Expiration
Flow duration, seconds	2.2 ± 1.3	3.2 ± 1.4[e]	1:1	Expiration
Phasic flow volume, cm^3	1.6 ± 6.0	86.1 ± 49.3[d]	1:54	Expiration

CFV, Common femoral vein; *CIV,* common iliac vein; *EIV,* external iliac vein; *FV,* femoral vein; *GSV,* great saphenous vein; *IVC,* inferior vena cava; *PFV,* profunda femoris vein; *PV,* peak velocity; *TAV,* time averaged velocity.
Data presented as mean ± standard deviation.
[a]Rounded to nearest integer.
[b]Phasic dominance determined if parameter values differed significantly; if not, they were rated as neutral.
[c]$P < .001$, significant increase in either inspiration or expiration.
[d]$P < .0001$, significant increase in either inspiration or expiration.
[e]$P < .01$, significant increase in either inspiration or expiration.
[f]$P < .05$, significant increase in either inspiration or expiration.

Head and neck

The internal jugular vein displayed little phasic variation.

Upper limbs

The subclavian flow metrics were significantly higher during inspiration compared with during expiration, except for the flow duration, which was neutral without a significant phasic variation. The axillary flow metrics were dominant during inspiration, except for the flow duration, which was significantly longer during expiration. Thus, the phasic flow volume was neutral, with little phasic variation. Overall, the phasic variations were weakly inspiration dominant in the axillary subclavian veins.

Abdominal central veins

Abdominal IVC

The inspiratory/expiratory ratio in the abdominal IVC was ~1:2. The phasic flow volume was reduced during inspiration compared with expiration but not significantly.

Common iliac veins

The peak velocities and TAV were eight and seven times greater during expiration compared with inspiration, respectively, and the flow duration increase was less at three times. This was reflected by 97% of the flow occurring during expiration, with only 3% occurring during inspiration.

External iliac veins

The peak velocities and TAV were 22 and 20 times greater during expiration compared with inspiration, respectively. The flow duration was three times greater during expiration vs inspiration. Again, 99% of the flow occurred during expiration, and only 1% occurred during inspiration.

Lower limb veins

Common femoral vein

The phasic variation was ~1:4, with 91% of the flow volume occurring during expiration.

Lower limb peripheral veins

Flow in the femoral vein and below was shown to come to a virtual stop during inspiration. The femoral vein, profunda femoris vein, great saphenous vein, and popliteal vein exhibited 93%, 96%, 96%, and 98% of flow volume occurring during expiration, respectively.

Venous pressures. The phasic variations in venous pressure for all central veins in the abdomen and chest are shown in Fig 2. The inspiratory and expiratory pressures are presented as paired data from the same subject for all 45 patients. For 21 of these patients, paired data were available for all the segments shown in Fig 2. For the other 24 patients, paired data for one or more segments were missing.

The venous pressures were lower by 2 to 6.5 mm Hg during inspiration vs expiration in all segments above and below the diaphragm. The phasic variation was ~3 mm Hg in the abdomen and increased to ~7 mm Hg in the chest. The phasic pressure variation (inspiration vs expiration) in all segments above and below the diaphragm was significant (Fig 2). The *P* values shown in Fig 2 are for comparisons of the pressure at the

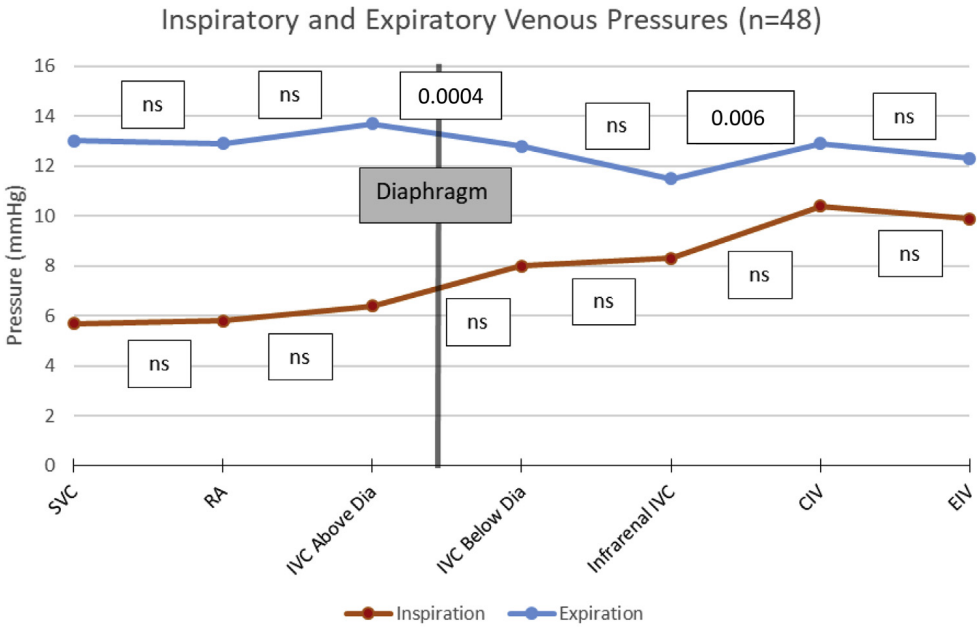


Fig 2. Inspiratory and expiratory pressure profile in the central veins of the abdomen and chest. Significant differences from the previous caudal segment shown in boxes. The inspiratory pressures were also significantly lower than the expiratory pressures at every segment ($P < .001$), in contrast to the abdominal pump theory. The mean inspiratory venous pressures in the chest were positive, not negative. See text for details. *CIV,* Common iliac vein; *Dia,* diaphragm; *EIV,* external iliac vein; *IVC,* inferior vena cava; *ns,* not significant; *RA,* right atrium; *SVC,* superior vena cava.

indicated segment with the segment caudal to that segment. The average pressures in the right atrium and vena cavae were ~6 mm Hg during peak inspiration and ~14 mm Hg during peak expiration.

Sustained negative pressures in the right atrium and vena cavae in the chest did not occur in any of the patients. When it did occur, it was transient, lasting <2 seconds during the height of inspiration (Fig 3). A transient pressure of 0 mm Hg was observed in one or more veins in the chest or right atrium in six patients. A transient pressure <0 mm Hg was found in one or more veins in the chest or right atrium in only two patients.

IVUS planimetry. The partially collapsed IVC during expiration was seen to expand with inspiration (Fig 4; Supplementary Video). The iliac veins were already full at the prevailing pressures (Fig 4, *C*) and expanded much less. The phasic cross-sectional caliber changes with respiration of the IVC and iliac veins measured using IVUS are shown in the tabular data in Fig 4. Inspiration produced a marked caliber increase (~32%) in the IVC. The iliac veins also expanded, albeit to a smaller extent (<5%).

The caliber changes in the IVC at the diaphragmatic transit point and above the diaphragm are presented in Supplementary Table III (online only). The caliber became smaller (stenotic) at the diaphragm during inspiration in 50%, remained unchanged in 17%, and became larger in 33%. The caliber of the thoracic IVC above the diaphragm (n = 41) became smaller during inspiration in 24% and was unchanged in 76%. A complete "collapse" of the IVC at or near the diaphragmatic passage was not seen in any of the subjects during either phase of respiration.

DISCUSSION

Key findings

The results from the present study have added new details to aspects of venous phasicity with respiration. Although considerable intra- and interpatient variation exists in respiratory metrics, the phasic dominance

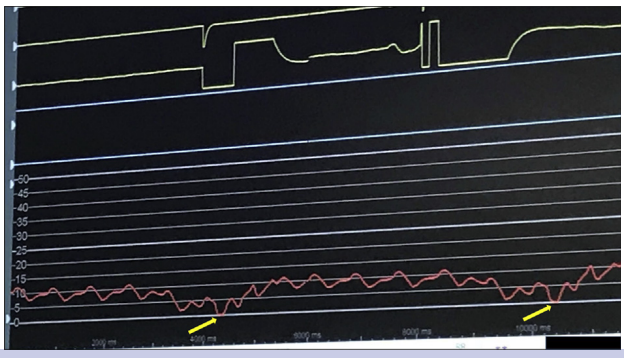
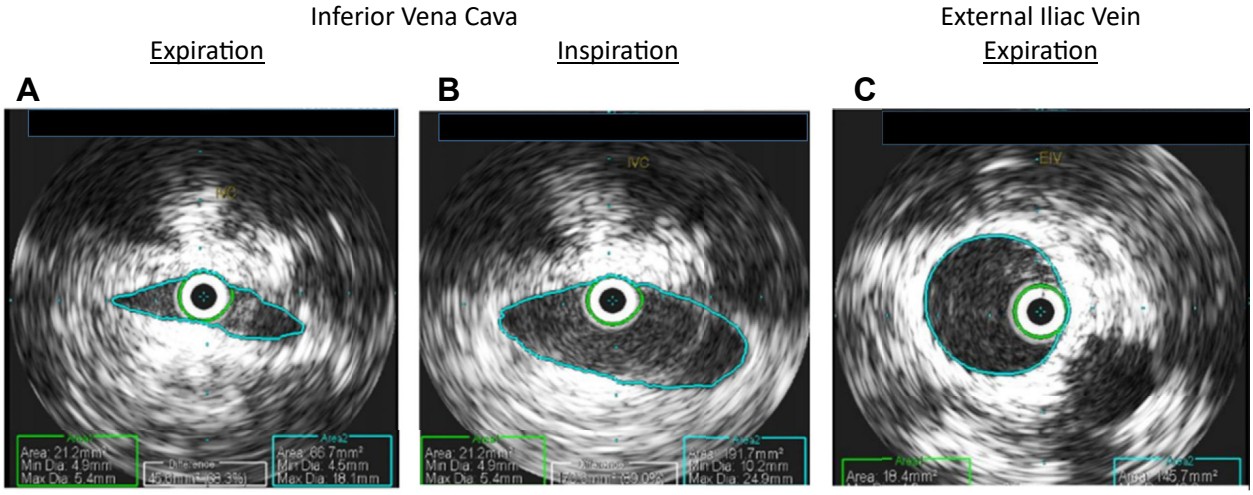


Fig 3. Right atrial pressure tracing. Larger respiratory waves are superimposed after six to seven smaller atrial pressure waves. The pressure nadir might transiently decrease to less than zero, as shown in the present example. Sustained negative pressures were not seen in the right atrium and great veins of the chest. Even the occurrence of transient negative pressure was only seen in a small fraction of cases. See text for details.



Paradoxical IVC Expansion During Inspiration				
	Expiration Area mm² (±SD)	Inspiration Area mm² (±SD)	% Change	P value
IVC (n=37)	168 (±83)	222 (±87) ****	32% increase	<0.0001 ****
CIV (n=35)	151 (±54)	158 (±54) ****	5% increase	<0.0001 ****
EIV (n=35)	135 (±50)	140 (±51) ****	4% increase	<0.0001 ****

-Significant *increase* as noted. **** p<0.0001

Fig 4. Intravascular ultrasound (IVUS) images of inferior vena cava (IVC) during expiration **(A)** and inspiration **(B)**. The IVC caliber expanded by ~32% during inspiration, instead of the expected compression, possibly explaining the pressure decrease. **C,** IVUS image of an external iliac vein. The iliac veins were already "full" at the prevailing pressures owing to a steeper pressure—volume curve than in the IVC. The inspiratory expansion was, therefore, less with <5%. IVUS volumetric changes in the central veins of the abdomen with respiration shown in the tabular data. See text for details. *CIV,* Common iliac vein; *EIV,* external iliac vein; *SD,* standard deviation.

(inspiration, expiration, or neutral) was largely uniform. The inspiratory/expiratory duration ratio in the upper limbs and internal jugular vein was 1:1. This duration ratio tended to increase to 1:2 or even more in the abdominal and lower limb veins.

The internal jugular vein showed little phasic variation in most flow metric values with the subject in the supine position (Table). The upper limb venous flows were weakly inspiration dominant or neutral. We found a reversal of phase polarity in the abdominal IVC. All flow metrics, except for the phasic flow volume, become expiration dominant in the IVC. The flow metrics were uniformly expiration dominant in all vein segments caudal to the IVC.

Phasic polarity became reversed (from inspiration to expiration dominant) in all the veins below the diaphragm. This antiphase was most marked in the lower limb, with flow nearly coming to a standstill during the height of inspiration. Almost all the flow occurred during expiration. Thus, phasic variation was most marked in the veins below the IVC.

We found no IVUS evidence of inspiratory compression of the abdominal central veins, as suggested by the abdominal pump theory. In contrast, the paradoxical inspiratory volume increase and pressure reduction noted in the abdominal cava found in the present study calls into question the abdominal pump concept as currently conceived.

The volumetric expansion of as much as 32% in caliber of the abdominal IVC during the inspiratory phase would explain the concurrent pressure decrease. We considered other possible explanations for the volume increase. Constriction of the IVC by the diaphragm at the transit point during inspiration, as noted in 50% (Supplementary Table III, online only), could have been a contributory factor in some. It is known that the renal and hepatic veins do not drain during inspiration, ruling out compressive ejection of blood from these large viscera as a cause of the paradoxical volume expansion.[11] Grant et al,[12] using color duplex ultrasonography in 25 patients, found maximum expansion of the IVC at the end of inspiration, just as in the present study.

Another heretical finding from the present study was that the mean pressure in the right atrium and central veins was positive during the respiratory cycle and rarely decreased to less than zero, except transiently in a few cases (Fig 2). The datum for venous pressure measurement is the phlebostatic axis at the level of the tricuspid valve. This zero set point is often confused with the true atrial pressure. The normal central venous pressure

is ~7 mm Hg.[13] The reported normal mean right atrial pressure in heart catheterization texts is 3 mm Hg (range, 3-7 mm Hg).[14] The pressure can transiently reach zero level at the nadir of the "x" and "y" waves; however, persistent negative pressures were not noted.[14]

Contradictory findings in the literature

Very few human volumetric or pressure data of the IVC related to respiratory phasicity are available. Murphy et al,[15] using IVUS in 10 patients, reported that the smallest diameter of the IVC occurred during inspiration. However, the patients had been intubated under general anesthesia and mechanically ventilated. Thus, the negative inspiratory pleural pressure was converted into positive, likely reversing the phase in venous outflow.

Many of the reported findings in conflict with our data are probably related to the use of the canine model from which many of the current concepts have evolved. Dogs are chest breathers; however, abdominal respiration is dominant in humans with a higher intra-abdominal pressure (~2 mm vs ~7 mm Hg).[11,16] Most canine experiments have involved open thoracotomy, which abolishes the negative pressure, substituting positive atmospheric pressure in its place. The natural tendency of veins to collapse from wall tension is thereby unopposed and further enhanced. In the experiments by Guyton et al,[17] a right heart bypass was used to derive the venous curves. They simulated negative atrial pressures up to −10 mm Hg, which were incorporated into the venous return curves.[17] The vena cavae collapsed with this degree of artificially induced negative pressure, seemingly supporting the "venous collapse theory."[8] It seems highly unlikely that sustained negative pressure in the central veins and right atrium ever occurs in intact normovolemic individuals.[3] The vena cavae have a dynamic flow of ~100 cm^3/s connected to a highly compliant venous reservoir; any vacuum created will be quickly filled. Thus, the air embolisms often attributed to negative pressure in the central veins probably occur by the Venturi effect.[3]

Venous collapse theory. Holt[10] demonstrated that that thin walled conduits, such as veins, passing from a pressurized chamber to a lower pressure environment tend to collapse at the transition point. The collapse is associated with exotic flow phenomena not seen in Poiseuille flow.[12,18,19] The collapse will not occur if the outflow pressure is greater than that in the pressure chamber.[10,20,21] This would be the case with the positive mean atrial pressures reported in the present study. The inspiratory decrease across the diaphragm is not of an order that would indicate "collapse" (Fig 2). The inspiratory pressure in the thoracic IVC is ~6 mm Hg, well above the zero expected in hydrodynamic "collapse." Others have noted that the "collapse" does not occur when the right atrial pressure is elevated.[9] No caval collapse was seen using IVUS in the present study.

An alternative hypothesis. Many of the findings in the present report are not consistent with the current concepts of venous flow phasicity. We have proposed an alternative explanation based on the phasic respiratory changes on the longitudinal tension of the central veins of the chest and abdomen (Fig 5). The proposed theory is congruent with the anomalous findings we have reported.

Normal quiet breathing in humans is mostly abdominal. During inspiration, the diaphragm moves down ~4 to 5 cm, along with vital structures (eg, heart, liver, kidneys). The great veins adjacent to the diaphragm are mobile, moving with the diaphragm. The central veins are fixed by fascial structures at either end of the mobile mid-section at the thoracic inlet and infrarenal vena cava. Inspiratory movement produces relaxation of the cava below the diaphragm, allowing it to expand and stretching the superior vena cava and tributaries in the upper chest. A small "bucket handle" upward movement of the first rib during inspiration likely augments the stretching at the upper end.

When relaxation of the IVC in the upper abdomen is present, wall tension is relieved, allowing it to expand from the prevailing venous pressure. An illustrative example is the volume and pressure changes seen when a long inflated balloon is alternatively stretched and relaxed by pulling the ends. When stretched, the narrowest portion is near the ends. When relaxed, the widest lumen is in the center.

The stretching at the upper end likely reduces the lumen caliber of upper superior vena cava and tributaries, which disproportionately increases flow resistance ($1/\pi r^4$). This could explain the seemingly weak phasic inspiratory flow and phase amplitude in the veins of the upper trunk and limbs despite a large pressure gradient. During expiration, little favorable gradient is present to attract flow. The narrowing of the large veins at the thoracic inlet and first rib has been attributed to the "collapse" theory.[7] However, it might result from stretching of the veins.

Little doubt exists that the intra-abdominal pressure increases with inspiration, as shown by measurements by multiple investigators. The marked flow reduction in the abdominal IVC is a well-recognized flow dynamic phenomenon, shown when collapsible tubes are subjected to external pressure.[3,4] This results in near flow stoppage in all the lower limb veins during inspiration. The findings from the present study are in agreement with these conventional concepts. However, an expected increase in the venous pressure of the abdominal veins or compression of the vena cava was not found. In contrast, the IVC pressure significantly decreased with a significant increase in its caliber. This was remarkable because the mean BMI in the patient cohort was quite elevated and the intra-abdominal pressure is known to be elevated in those with an increased BMI.[22] The IVC

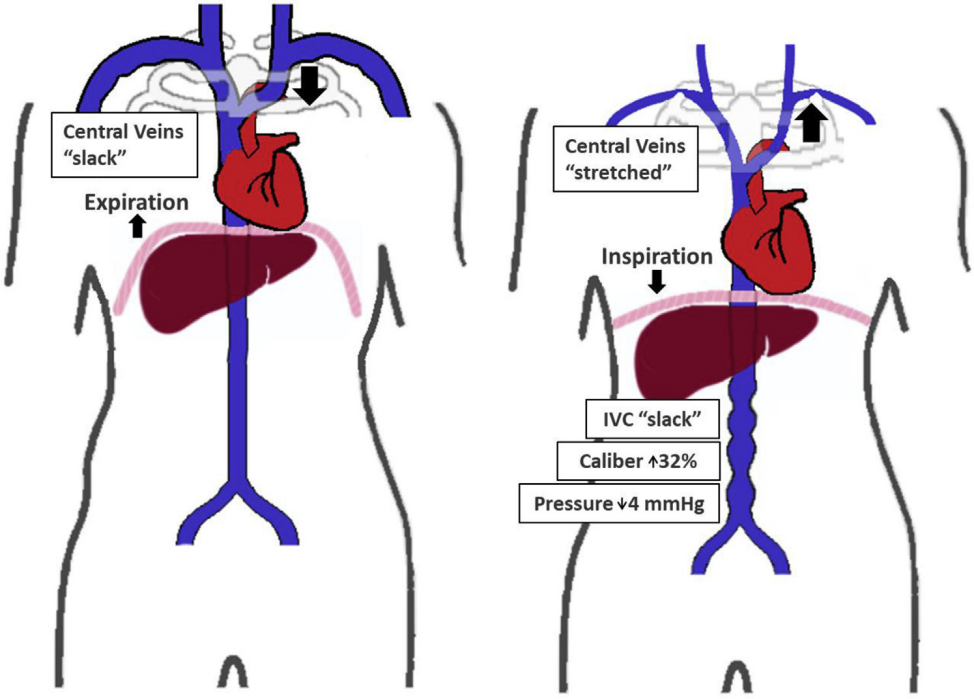


Fig 5. A hypothesis of the origin of respiratory phasicity in venous flow. The mid-section of the central veins extending down from the level of the right auricle to the renal veins is highly mobile. They move down ~4 cm with the attached viscera during inspiration. The great veins above and below the mobile section are fixed by fascial structures. The inspiratory volume expansion of the inferior vena cava (*IVC*) likely results from a sudden slack in wall tension. Portions of the superior vena cava and tributaries are likely stretched during inspiratory excursion of the diaphragm, reducing their caliber and increasing their flow resistance. The inspiratory "collapse" of the great veins at the thoracic inlet could be the result of traction, rather than the "collapse" phenomenon. See text for details.

pressures should be elevated as well, instead of decreased. Teleologically, the pressure reduction might be an effort to shield vital outflow from the abdominal viscera and shield the coronary circulation from the phasic high pressures that would otherwise result.

Study limitations

The respiratory duration and inspiratory/expiratory ratio are under voluntary control for a short duration of a few minutes. The amount of data variance that might have resulted is unknown, although an effort was made to keep the volunteers unaware of their breathing. The extent of systemic bias resulting from this in our study was unknown.

The pressures and volume observations were performed in patients who were under general anesthesia, which affects a wide range of cardiopulmonary parameter values. The resultant measurements might not represent normal values. The degree of data skewing, especially in post-thrombotic limbs is unknown. The IVUS and pressure measurements were not concurrent observations on the same subjects. Thus, a possible relationship between the two was not suspected until after the retrospective analysis had been completed. Measurement of both parameters simultaneously would have increased the procedure time significantly.

CONCLUSION

The results from the present study have shown that the flow in the peripheral veins in the lower body and limbs nearly ceases during inspiration, although the phasic decrease is less in the upper body and limbs. The venous pressure in the heart and central veins was positive during respiration; sustained negative pressure did not occur. The venous pressure in the central veins of the abdomen paradoxically (against current concepts) declined with inspiration, and the volume increased. We hypothesized that phasic physical stretching and relaxation of the great veins in the chest and abdomen, along with the diaphragm, during respiration might explain these paradoxical findings.

AUTHOR CONTRIBUTIONS

Conception and design: SR
Analysis and interpretation: SR, WW, CN, RK, TP
Data collection: SR, WW, CN, RK
Writing the article: SR, WW, CN, RK, TP
Critical revision of the article: SR, WW, CN, RK, TP
Final approval of the article: SR, WW, CN, RK, TP
Statistical analysis: SR, WW, CN, RK, TP
Obtained funding: SR
Overall responsibility: SR

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Volume ■, Number ■

Supplementary Table I (online only). Demographics

Demographics	Normal subjects	Patients
Persons (limbs), No.	15 (30)	85 (85)
Male/female ratio	1:4	1:3
Age, years		
Median	38	57
Range	22-57	23-96
Right/left ratio	1:1	3:2
BMI, kg/m^2	27.7 ± 4.2	33.9 ± 16.5[a]

BMI, Body mass index.
[a]Of adults living in Mississippi in 2019, 40.8% were obese (BMI >30 kg/m^2); U.S. average BMI 29.1 kg/m^2 according to data from the Centers for Disease Control and Prevention [available at: cdc.gov]).

Supplementary Table II (online only). Mean values for flow metrics in normal subjects[a]

Variable	Inspiration		Expiration	
	Right	Left	Right	Left
Head and neck				
Internal jugular vein (n = 20)				
PV (cm/s)	60.8	54.8	51.5	52.0
TAV (cm/s)	17.7	15.8	15.3	14.9
Flow duration (s)	2.1	2.9[b]	2.9	2.5
Phasic flow volume, cm^3	627[b]	382	525	332
Upper limbs				
Subclavian vein (n = 20)				
PV, cm/s	51.6	58.7	36.3	32.7
TAV, cm/s	12.0	15.2	7.6	6.9
Flow duration, seconds	2.7	2.3	2.5	2.2
Phasic flow volume, cm^3	283	327	160	124
Axillary vein (n = 20)				
PV, cm/s	38.2	33.8	31.7	28.2
TAV, cm/s	13.8	7.5	10.5	6.8
Flow duration, seconds	1.9	2.1	2.7	2.4
Phasic flow volume, cm^3	189	146	137	127
Abdominal central veins				
IVC (n = 10)	—	—	—	—
PV, cm/s				
TAV, cm/s				
Flow duration, seconds				
Phasic flow volume, cm^3				
CIV (n = 20)				
PV, cm/s	2.6	2.1	18.1	20.6
TAV, cm/s	1.6	1.0	9.9	9.1
Flow duration, seconds	1.6	0.8	3.8	4.1
Phasic flow volume, cm^3	64	62	564	453
EIV (n = 20)				
PV, cm/s	1.4	1.0	31.8	21.5
TAV, cm/s	0.6	0.5	16.1	8.3
Flow duration, seconds	1.1	1.2	3.8	3.7
Phasic flow volume, cm^3	37	35	954	460
Lower limbs				
CFV (n = 20)				
PV, cm/s	5.9	5.1	22.0	24.7
TAV, cm/s	2.5	1.3	9.9	9.5
Flow duration, seconds	1.4	1.5	4.0	4.1
Phasic flow volume, cm^3	175	69	603	476
FV (n = 20)				
PV, cm/s	6.1	5.8	23.9	23.9
TAV, cm/s	1.9	1.2	12.2	9.9
Flow duration, seconds	1.9	1.6	3.6	3.9
Phasic flow volume, cm^3	31	19	174	151
PFV (n = 20)				
PV, cm/s	3.4	3.3	21.7	20.3
TAV, cm/s	1.2	1.0	12.5	8.4
Flow duration, seconds	1.5	1.7	3.6	4.1
Phasic flow volume, cm^3	22	36	218	163
GSV (n = 20)				
PV, cm/s	5.7	0.6	13.7	12.5
TAV, cm/s	1.0	0.5	5.4	4.4
Flow duration, seconds	1.9	2.1	3.1	3.5
Phasic flow volume, cm^3	12	9	42	51
Popliteal vein (n = 20)				
PV, cm/s	0.0	0.5	13.7	13.6
TAV, cm/s	0.0	0.3	7.2	5.4
Flow duration, seconds	2.4	2.0	2.9	3.5
Phasic flow volume, cm^3	0	9	140	95

CFV, Common femoral vein; *CIV,* common iliac vein; *EIV,* external iliac vein; *FV,* femoral vein; *GSV,* great saphenous vein; *IVC,* inferior vena cava; *PFV,* profunda femoris vein; *PV,* peak velocity; *TAV,* time averaged velocity.

[a]No significant difference was found between right and left sides, except for the internal jugular vein.

[b]$P < .05$, significant difference between right and left sides.

Journal of Vascular Surgery: Venous and Lymphatic Disorders
Volume ■, Number ■

Supplementary Table III (online only). Caliber change of IVC at diaphragm and thorax during inspiration

Caliber change	No. (%)
Diaphragmatic hiatus	24
Smaller	12 (50)
No change	4 (17)
Larger	8 (33)
Thoracic IVC	41
Smaller	10 (24)
No change	31 (76)

IVC, Inferior vena cava.