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REVIEW ARTICLE

# The Venous Contribution to Cardiovascular Performance: From Systemic Veins to Left Ventricular Function - a Review

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## Abstract

The venous system contains ≈ 70 % of the total blood volume and is responsible in heart failure for key symptoms of congestion. It is active: it can increase or relax its tone with physiologic or pharmacologic stimuli. It is heterogeneous, behaves as a two-compartment model, compliant (splanchnic veins) and noncompliant (nonsplanchnic veins). It is dynamic in health and disease: in heart failure the vascular capacitance (storage space) is decreased and can result in volume redistribution from the abdominal compartment to the thoracic compartment (heart and lungs), which increases pulmonary pressures and precipitates pulmonary congestion. A noninvasive assessment of venous function, at rest and dynamically during stress, is warranted. The systemic haemodynamic congestion is assessed with inferior vena cava diameter and collapsibility. The pulmonary congestion is assessed with B-lines and pleural effusion. The contribution of left ventricular filling is assessed with end-diastolic volume, integrated with left ventricular function.

**Key words:** Venous return; Ventricular function; Central venous pressure; Mean systemic pressure.

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## Introduction

The venous system contains approximately ≈ 70 % of total blood volume and veins are 30 times more compliant than the arteries. Therefore, changes in blood volume within the veins are associated with relatively small changes in venous pressure.[1, 2] They are called capacitance vessels and serve as a reservoir of blood. The venous system is active: it can increase or relax its tone with physiologic or pharmacologic stimuli. It is heterogeneous: the venous system behaves as a two-compartment model, compliant (mainly splanchnic veins) and noncompliant (nonsplanchnic veins). The compliance of small venules and veins is almost 40 times greater than that of arterial vessels.[3-5] Thus, the total compliance of the circulation is dominated by the compliance of the systemic veins and venules. In humans, cardiac output (CO) is strongly governed by the amount of venous return, ie, blood flowing into the right atrium. According to the general equation of flow, three factors determine venous return: the right atrial pressure, the vascular resistance and the mean systemic pressure (MSP). Although the right atrial pressure and the venous resistance to flow are well considered by cardiologists, the MSP is less known, yet it is important, since MSP is the driving pressure competing against right atrial pressure to create a gradient that promotes a forward flow.

The concept of MSP dates back to the late 1800s when Bayliss and Starling surmised that if the circulation was transiently halted, arterial pressure would fall and venous pressure would rise.[3, 4] The


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pressure in the entire system during cardiac standstill would equilibrate at what they termed MSP. MSP must be independent of Mean Arterial Pressure (MAP) because it could be defined in the absence of cardiac pump function.

### Mean systemic pressure: its measurement and meaning

Let us imagine the heart is stopped for a relatively short period of time. Blood will not be flowing from the heart and toward the heart and pressure will be the same in all parts of the circulatory system. Such a pressure is called MSP.[6, 7] In dogs and presumably in healthy humans, MSP is approximately between 7 and 12 mmHg, whereas central venous pressure (CVP) is approximately 2-3 mmHg.[8-13] Thus, the gradient for venous return (VR) is somewhere between 5 and 10 mmHg and therefore the change in CVP of just by a few mmHg can have a considerable effect on venous return.[11]

## Pathophysiological basis

Although the cardiovascular circuit is a two-compartment model comprising both systemic and pulmonary circuits, > 60 % of the blood volume held in veins is in the systemic venous circulation with three-fourths of that in small veins and venules.[1, 2] The pulmonary veins contain only a small blood volume. For these reasons, the physiology of venous return can be described, in practical terms, as the physiology of venous return to the right atrium.

The left heart plays a major role in the regulation of CO. Three of the four determinants of left heart CO, that is, preload, heart rate and contractility, are intrinsically cardiac-related indices.[14, 15] Cardiac function plays only an indirect role in the governance of the fourth determinant of CO, the venous return.[12] Under normal conditions and at rest the Frank–Starling mechanism primarily provides fine adjustment to cardiac function by making sure that the same volume that fills the ventricles on each beat leaves them.[3] During exercise, heart rate normally increases two- to three-fold, contractility three- to four-fold and systolic blood pressure by ≥ 50 %, while systemic vascular resistance decreases. LV end-diastolic volume (EDV) initially increase (increase in venous return) to sustain the increase in stroke volume through the Frank–Starling mechanism and later fall at high heart rates. CO during mild exercise is achieved by

*Table 1: Distribution of blood and pressures ranges for indicative aggregate data in the various components of the circulatory system at rest and during exercise or heart failure[2, 42, 46, 47, 49]*

| Distribution of blood | | REST CO ≈ 5 L/min | EX Health CO ≈ 20 L/min | HF CO ≈ 4 L/min |
|---|---|---|---|---|
| Systemic circulation | | | | |
| Veins | | 60 % | 12 % | 45 % |
| Arteries | | 25 % | 63 % | 12 % |
| Muscle | | 8 % | 58% | 3 % |
| Kidney | | 10 % | 2 % | 3 % |
| Skin | | 2 % | 1 % | 3 % |
| Brain | | 5 % | 2 % | 3 % |
| Pulmonary circulation | | 9 % | 14 % | 20 % |
| Heart | | 6 % | 11 % | 23 % |
| Total % blood volume distribution | | 100 % | 100 % | 100 % |
| **Pressure range (mmHg)** | | **REST CO ≈ 5 L/min** | **EX Health CO ≈ 20 L/min** | **HF CO ≈ 4 L/min** |
| Mean systemic venous pressure | | 7 – 12 | 7 – 12 | 6 – 18 |
| Central venous pressure | | 3 (0 – 5) | 3 (0 – 5) | 4 – 16 |
| RV pressure | systolic | 15 – 30 | 20 – 45 | 30 – 70 |
| | diastolic | 3 – 8 | 3 – 8 | 6 – 18 |
| Pulmonary artery | systolic | 15 – 30 | 25 – 45 | 30 – 70 |
| | diastolic | 8 – 12 | 14 – 22 | 20 – 40 |
| Pulmonary wedge pressure | | 3 (0 – 5) | 3 (0 – 5) | 4 – 16 |
| LV pressure | systolic | 100 – 140 | 170 – 220 | 95 – 111 |
| | diastolic | 3 – 12 | 5 – 14 | 16 – 24 |

*CO: Cardiac output; EX: Exercise; HF: Heart failure; LV: Left ventricle; RV: Right ventricle;*

an augmentation of both stroke volume and heart rate,[16] whereas the further increases in output during strenuous exercise result primarily from an increase in heart rate.[17] In healthy individuals, during peak aerobic exercise there is very little change in right atrial pressure with the very large increases in CO[7] and more venous return.[6, 10] An increase in sympathetic discharge during exercise leads to splanchnic arterial vasoconstriction leading to a decrease in flow, pressure and volume within the splanchnic veins and an increase in venous return, while splanchnic blood flow decreases from 1,500 mL/min to 350 mL/min. Altogether, these adaptations would have increased CO by 110 %. In heart failure (HF) at rest, as a result of neurohormonal imbalance, the venous vascular capacitance ("storage-space") is decreased and acute sympathetic nerve activation can result in acute volume redistribution from the abdominal compartment to the thoracic compartment (heart and lungs), which increases intra-cardiac pressures and precipitates HF symptoms. The splanchnic vascular compartment may be a key player in the volume dysregulation in acute and chronic HF, even in the absence of increases of total body fluid

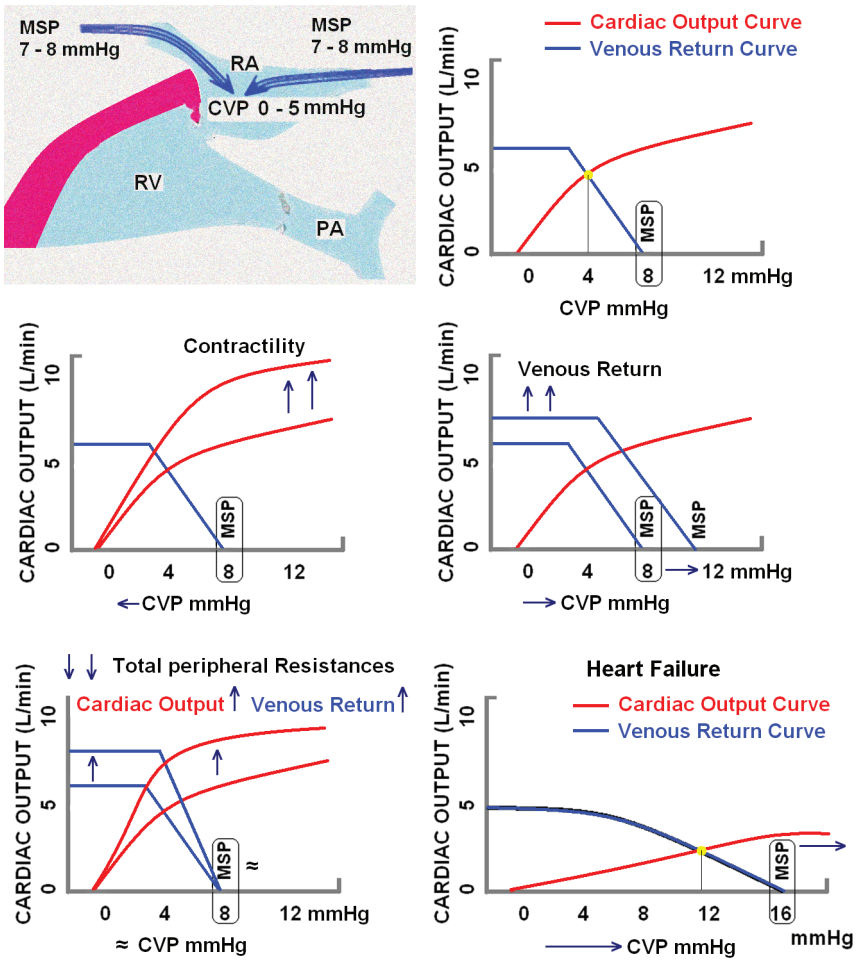


*Figure 1: Venous return, cardiac output, operating point of the heart.*[8, 10, 20, 37]

***Left upper panel:*** *Mean systemic pressure (MSP) is a pressure that drives the blood inside the veins to full the right atrium (RA). MSP must be higher than pressure inside the right atrium or central venous pressure (CVP). In the normal subject MSP is 7-8 mmHg and CVP is between 0 and 5 mmHg. When MSP increases more blood comes back to right atrium; when the MSP decreases less blood comes back to right atrium.*

*RV: Right ventricle; PA: Pulmonary artery.*

***Right upper panel:*** *Relationship between CVP and Cardiac Output (CO). CO = red curve. Venous return = blue line and it is higher when the CVP pressure is = 0; at increasing CVP venous return starts decreasing until a point where return becomes 0: at this point CVP equals MSP and zero blood is coming back to right atrium. The point where venous return curve intercepts the x-axis identifies the MSP, normally = 7-8 mmHg. The point where venous return and CO curves cross each other shows the operating point of the heart (yellow circle): CO and venous return are equal at this point: the heart is pumping out all the blood that is coming back as venous return. A straight line down the operating point measures the CVP value = 4 mmHg = normal.*

***Left middle panel:*** *Increased contractility (arrows) increases CO, without pre-load changes. Changing the contractility does not change the MSP and mildly decreases the CVP.*

***Right middle panel:*** *If the volume of vein blood increases (arrows), venous return increases: the operating point shifts up and on the right: the CO increases but also the CVP and the MSP increase to 6 and 12 mmHg respectively.*

***Left lower panel:*** *When total peripheral resistances decrease (arrows) venous return, CO and the operating point are shifted up: without changes of CVP and MSP. That's occurs during exercise with dilation of arterioles in the skeletal muscles.*

***Right lower panel:*** *The venous engorgement of congestive HF: reduced gradient between MSP and CVP, both increased with resulting decreasing venous return. The steady-state operating point (yellow circle) shifts down and CO is blunted despite increased preload.*

*CO: Cardiac output; CVP: Central venous pressure; MSP: Mean systemic pressure; PA: Pulmonary artery; RA: Right atrium; RV: Right ventricle.*

volume.[13] In cardiac failure, the heart is the limiting factor in the circulation and will determine the upper limit of CO. However, in subjects without HF venous return can be seen as the limiting factor, because the heart can only pump out the amount of blood it receives.

### Practical considerations

Pulmonary compliance and volume shifts between systemic and pulmonary circuits.

Normally, the mean pressure in the pulmonary artery is about 15 mmHg at rest. Increased blood pressure in the capillaries of the lung causes pulmonary hypertension, leading to interstitial oedema if the mean pressure increases to above 20 mmHg and to pulmonary oedema at mean pressures above 25 mmHg. Total pulmonary compliance is only one-seventh of total systemic vascular compliance[5] and the pulmonary circuit does not contain a lot of volume that can be shifted to the systemic circulation. It also cannot take up a lot of volume without causing a large increase in pulmonary venous pressure and a major disturbance to pulmonary gas exchange. Even maximal sympathetic stimulation results in only a small shift from the pulmonary circuit to the systemic circulation.[15, 18] Accumulation of volume in the pulmonary vasculature is especially a problem in patients with marked left ventricular diastolic dysfunction. The higher left ventricular filling pressure increases pulmonary capillary filtration and leads to pulmonary oedema and respiratory failure. If volume is removed to treat the respiratory failure, CO deceases and the kidneys fail. If volume is then added to improve renal perfusion, respiratory failure occurs.

### Venous return

The heart does not actively suck blood. The pressure gradient between MSP and CVP determines venous return.[19]

The greater the difference between MSP and CVP, the greater the venous return will be. Guyton et al[20] showed in their experiments in dogs that when CVP is elevated, CO and venous return are reduced. When CVP is increased further and further, venous return declines until it ultimately ceases. The value that CVP reaches at zero flow is the MSP. On the other hand, with decreasing CVP, venous return increases. The pressure gradient between MSP and CVP is the driving force for venous return and consequently CO.

## Diagnostic testing

### Measurements of venous pressure

Measurement of CVP is a critical component of the complete haemodynamic assessment of a patient. CVP is considered equivalent to right atrial pressure (RAP) when the *vena cava* is continuous with the right atrium.[21] CVP reflects the amount of blood returning to the heart and the ability of the heart to pump the blood back into the arterial system. Central venous catheterisation is the gold standard measurement of CVP and RAP. Noninvasive techniques to estimate CVP play a crucial role in promoting a more widespread CVP evaluation in clinical practice.

The inferior *vena cava* (IVC) is a compliant vessel whose size and shape vary with changes in CVP and intravascular volume. Therefore, sonographic measurement of the IVC represents an effective and noninvasive method of estimating CVP.[22-24] For simplicity and uniformity of reporting, specific values of RAP, rather than ranges, should be used in the determination of systolic pulmonary artery pressure. IVC diameter < 2.1 cm that collapses > 50 % with a sniff suggests normal RAP of 3 mmHg (range, 0–5 mmHg), whereas IVC diameter > 2.1 cm that collapses < 50 % with a sniff suggests high RAP of 15 mmHg (range, 10–20 mmHg). In scenarios in which IVC diameter and collapse do not fit this paradigm, an intermediate value of 8 mmHg (range, 5–10 mmHg) may be used. This estimate should be used in estimation of the pulmonary artery pressure on the basis of the tricuspid regurgitant jet velocity, rather than assuming a constant RAP for all patients.[25, 26] More difficult is the measure of MSP ie, the pressure that drives the blood inside the veins to full the right atrium. This means that MSP must be higher than pressure inside the right atrium otherwise they would not move blood towards right atrium. In a healthy person MSP is around 7-12 mmHg and the right atrial pressure is somewhere between 0 and 5 mmHg.

### Mean systemic venous pressure using inspiratory holds

Mean systemic venous pressure can be estimated with a method based on the haemodynamic effects of mechanical ventilation: mechanical ventilation with positive airway pressures increases intrathoracic pressures, causing an increase in CVP and a decrease in venous return and CO. With the use of inspiratory holds (inspirato-

ry hold = a ventilating manoeuvre in which the delivered volume of gas is held in the lung for a while before expiration) haemodynamic steady-state conditions were met to assure that venous return and CO were equal. CVP and pulmonary artery flow were measured at the end of each inspiratory hold. Pinsky confirmed this validation in dogs, measuring mean systemic venous pressure during ventricular fibrillation and estimating mean systemic venous pressure by extrapolation of the relationship between stroke volume and CVP.[27, 28] Measurement of MSP at the bedside allows the physician to gain knowledge about other haemodynamic parameters such as resistance for venous return, compliance and stressed volume. This allows to describe whether a specific vasoactive agent affects primarily the arterial or the venous side of the circulation.

The pulmonary wedge pressure or PWP, or cross-sectional pressure is the pressure measured by wedging a pulmonary catheter with an

*Table 2: Invasive vs noninvasive measurement of blood volume distribution*[2, 24, 47, 49]

| Total blood volume (TBV) 100 % | Distribution of TBV | Invasive/ Radionuclide | Noninvasive/ Radiation free |
|---|---|---|---|
| Systemic circulation 85 % | Veins 60 % | Radionuclide Plethysmography | Bioimpedance |
| | Arteries 25 % | Thorax and abdomen gamma camera | Ultrasound-Doppler |
| | - Muscle | Thermo dilution; Green dye infusion; 133 Xenon; PET | Ultrasound-doppler; MRI; Laser-doppler; Electromagnetic flow |
| | - Kidney | 133 Xenon radionuclide | Ultrasound-doppler; Magnetic resonance |
| | - Skin | Radioactive isotopes; Xenon-133 clearance | Plethysmography; Laser doppler |
| | - Brain | Radionuclide brain Flow testing | Ultrasound-doppler; Magnetic resonance |
| Pulmonary circulation 9 % (TPBV) | Pulmonary arteries 30-40 % of TPBV | Electromagnetic pulmonary artery flow; Thermo-dilution | Encoding phase subtraction MRI |
| | Pulmonary capillaries 20 % of TPBV | Breath-holding method | Contrast bubble echocardiography |
| | Pulmonary veins 40-50 % of TPBV | Venous return catheter (LA dye curve) | MRI; Ultrasound-doppler |
| Heart 6 % | | Contrast angiography; Radionuclide imaging | Transthoracic echocardiography |

*LA: Left atrium; MRI: Magnetic resonance imaging; PET: Positron emission tomography; TBV: Total blood volume; TBV = Plasma volume/1-haematocrit; TPBV: Total pulmonary blood volume; TPBV = Cardiac index x mean transit time from pulmonary artery to left atrium;*

*Table 3: Invasive vs noninvasive measurement of pressure ranges*[24, 19, 41, 46, 47]

| Pressure | | Invasive | Noninvasive |
|---|---|---|---|
| Mean systemic pressure | | Circulatory arrest (cardiac surgery, ICD implant) | Inspiratory holds when a patient is on a mechanical ventilator |
| Central venous pressure | | Right atrium catheter | Inferior vena cava diameter Ø; Ultrasound |
| Right ventricular pressure | systolic | Swan-Ganz catheter | Tricuspid regurgitation peak velocity; Doppler-ultrasound |
| | diastolic | Swan-Ganz catheter | Pulmonary regurgitation peak velocity; Doppler-ultrasound |
| Pulmonary artery pressure | systolic | Swan-Ganz catheter | Tricuspid regurgitation peak velocity + RA pressure |
| | diastolic | Swan-Ganz catheter | Pulmonary regurgitation end-diastolic velocity + RA pressure |
| Pulmonary wedge pressure | | Inflated balloon into a small pulmonary arterial branch | (1.24 x E/è) + 1.9 doppler-ultrasound |
| LV pressure | systolic | LV catheter | Brachial SBP x 0.9 |
| | diastolic | LV catheter | EDV (E/é) |

*EDV: End-diastolic volume; ICD: Implantable cardioverter defibrillator; LV: Left ventricular; RA: Right atrium; SBP: Systolic blood pressure;*

inflated balloon into a small pulmonary arterial branch.[29, 30] It estimates the left atrial pressure. Physiologically, distinctions can be drawn among pulmonary artery pressure, pulmonary capillary wedge pressure, pulmonary venous pressure and left atrial pressure, but not all of these can be measured in a clinical context. Because of the compliance of pulmonary circulation, it provides an indirect measure of the left atrial pressure. Physiological pressure is 2–15 mmHg.

## Plasma volume in patients with chronic heart failure

In HF, at rest, as a result of neurohormonal imbalance, the venous vascular capacitance ("storage and pulmonary lung congestion-space") is decreased and acute sympathetic nerve activation can result in acute volume redistribution from the abdominal compartment to the thoracic compartment (heart and lungs), in the presence or even in the absence of increased of total body fluid volume.[13, 18] This could result in the acute translocation of as much as 1 L of fluid without a net change in body weight. Here, vasodilator therapy would be more appropriate than aggressive diuretic intervention. In both cases, increased blood volume in the pulmonary compartment should be assessed by B-Lines (see further).[31] Body weight-driven diuretic therapy can lead to treating weight increase without lung congestion with adverse effects on kidney function and to miss treatment of lung congestion present in spite of lack of weight changes and clinical signs of congestion.

## Ultrasound lung comets (B-lines)

In pulmonary congestion, the presence of both air and water generates a peculiar acoustic fingerprint. Lung ultrasound shows B-lines, comet-like signals arising from a hyper-echoic pleural line with a to-and-from movement synchronised with respiration. Increasing extravascular lung water accumulation sub-pleural oedema with multiple B-lines, or a white lung pattern (alveolar pulmonary oedema) with coalescing B-lines.[31] The number and spatial extent of B-lines on the antero-lateral chest allows a semi-quantitative estimation of extravascular lung water. The simplified 4-site scan is much less time-consuming and equally sensitive than the 28-site scan. With the simplified 4-site scan only 4 sites are scanned on the third intercostal space, symmetrically on the right and left hemithorax, from mid-axillary to anterior axillary and from anterior axillary to mid-clavicular line. Each of the 4 sites is scored from 0 (normal horizontal A-lines pattern in a black lung) to 10 (coalescent vertical B-lines with white lung). B-lines score is the sum of the 4 sites and ranges from normal values (≤ 1) to mildly (2 to 4), moderately (5 to 9) and severely abnormal (≥ 10) values. The higher the B-lines score at rest and during stress, the more profound the functional impairment and the worse the outcome in patients with known or suspected coronary artery disease and/or HF. Wet B-lines are made by water and decreased by diuretics, which cannot modify dry B-lines made by connective tissue. Cardiologists can achieve much diagnostic gain with little investment of technology, training and time. B-lines represent 'the shape of lung water'. They allow noninvasive detection, in real time, of even subclinical forms of pulmonary oedema with a low cost, radiation-free approach. They allow a better way to follow congestion and titrate diuretics than simple weight control, which cannot separate fluid accumulation elsewhere in the body and pulmonary congestion which is the real target of diuretic therapy. In fact, a lung-ultrasound guided therapy in heart failure provides a clear symptom and possibly survival benefit compared to a standard therapy based on body weight as shown by randomised controlled trials.[31-34] Still, the whole story cannot be told by B-lines alone, since pulmonary congestion can arise from body volume overload or fluid redistribution from splanchnic to systemic circulation.

## Pulmonary congestion with and without body (wet) weight increase

Obviously, diuretic therapy is the mainstream in presence of body volume overload. In the second case how to redistribute volume from heart-pulmonary circulation to splanchnic reservoir? In the first-in-man study,[18] the authors aimed to modulate the splanchnic sympathetic tone through a minimally invasive regional nerve block, which resulted in a marked reduction in intra-cardiac filling pressures and increase in CO, primarily driven by a significant reduction in systemic vascular resistances and improved vascular capacitance (increasing volume redistribution to the splanchnic volume) more effective than depletion of total circulation volume through diuretics. Not all volume overload is the same and the measurement of intravascular volume identifies heterogeneity to guide tailored therapy.[35]

# From vein to left ventricular preload

## The venous side of the pulmonary circulation

The Frank-Starling relationship generally has been examined with filling pressure as the index of preload, resulting in a curvilinear function that plateaus at higher filling pressures: and difficult to quantify.[36, 37] In the 1960s Eugene Braunwald and colleagues evaluated the Starling law in human patients. This group sewed metallic markers into ventricles and measured ventricular volume by cineradiography. Braunwald used the large beat-to-beat variation in filling during atrial fibrillation to show that stroke volume varies as a function of left ventricular end diastolic volume.[38] It was seen that the mechanical activity of the left ventricle during each contraction could be related to the left ventricular end-diastolic segment length, just preceding the onset of the contraction under consideration. Similarly, he showed that right ventricular systolic excursion varied with ventricular filling during Valsalva maneuver. The data demonstrated that filling and stretch of the ventricles increase the stroke volume. All of the preceding experiments confirmed that the heart has the intrinsic ability to accommodate changes in venous preload, both in the systemic (right atrium) and in the pulmonary (left atrium) venous conduit; increasing diastolic volume and stretch increase the force of contraction. Elevated cardiac pressure only increases the force of contraction and stroke volume if the experimental conditions permit the filling pressure to be an accurate proxy for end-diastolic volume.[39, 40]

# Clinical models

## The Starling mechanism in clinical practice

The relative flatness of human myocardial resting length-tension curves with small degrees of stretching is of importance in limiting the rise of ventricular end-diastolic pressure and therefore of atrial and venous pressures, for any given augmentation of myocardial length. Conversely, the relative steepness of the curve relating resting tension to active tension indicates that substantial augmentation of the force developed by the ventricle during systole is possible with relatively small increases in resting tension. The investigations of Braunwald demonstrated the Frank-Starling principle in the intact human right and left ventricle, ie, the dependence of the mechanical activity of the heart on the ventricular end-diastolic volume and the fundamental importance of ventricular end-diastolic volume, instead of pressure, in the regulation of the contractile activity of the human heart.[20, 30] Starling's text, in fact, does not suggest that right atrial pressure is an independent variable that controls stroke volume or myocardial work. The actual independent variable of his experiments was the amount he opened the valve that resisted flow into the right atrium: for the return of blood to the heart under a set of defined circumstances. Clinicians should also consider using CVP measurement instead of volume or flow because it can be obtained non-invasively. However, an isolated measurement of CVP, like any other single haemodynamic variable, cannot describe the state of the circulation.

# Perspectives

## A) The concept of preload-recruitable stroke work

The traditional teaching of cardiac physiology has focused almost exclusively on the left side of the heart. However, this focus ignores the critical role of the right heart and venous system in regulating venous return in states of haemodynamic compromise and shock.[41] As regarding the traditional pressure related assessment of diastolic venous return to ventricles, the conventional approach has been to ignore ventricular fibre length and to use E/e' as a surrogate of LV filling pressures.[42] Unfortunately, E/e' is only poorly correlated to invasively measured LV filling pressures at rest and, even more, during stress and is not readable in the majority of patients during stress.[42] A more feasible index of LV preload is LV EDV, which can be usefully combined with E/e' when available and with B-lines to gain insight into diastolic function. The relationship between stroke work (y-axis) and preload expressed by EDV (x-axis) is linear. A flat slope, that is a low preload-recruitable stroke work relationship, indicates that increased preload produces relatively little increase in stroke work because of the reduced contractility.[40] The relationship takes both preload and afterload into account and is applicable in a wide variety of cardiac diseases. During stress, it is the slope of the

relationship that shows various degrees of LV dysfunction, with steeper slope indicating better contractile reserve (higher function with lower volume) and flat slope indicating worse contractile reserve (lower functional reserve with higher ventricular volumes).[43, 44] Changes in EDV reflect relaxation capacity of the myocardium and adequacy of upstream venous return, in the same way as changes in ESV reflect contraction capacity of the myocardium and downstream afterload changes.

### B) Testing venous dysregulation

Venous function cannot be easily measured and no surprise if it has been overlooked until now. It is possible that venous dysregulation will be increasingly recognised as a significant pathogenetic player and a potential therapeutic target in some cardiovascular conditions, including HF,[13, 18] vaso-vagal syndrome or cardiac arrest.[45] In view of the better understanding of the role of venous system in several cardiovascular conditions a set of noninvasive, simple, widely available examinations should be developed and validated. As always, also the parameters of venous interest are more informative when tested both at baseline and during stress, since alterations occur in resting conditions can show-up under dynamic real life loading conditions.[46-48] At an early stage of disease, the function is not altered at rest but the possibility to increase function during stress can be already impaired. This is true for instance for left ventricular contractile reserve testing the myocardium, on the basis of its contraction capability, or coronary flow reserve testing the coronary microcirculation on the basis of vasodilatory capacity. It is our educated guess that the same is true for the venous system, but at present we miss a toolbox of parameters, stresses and normal values for venous stress echocardiography.[16, 24, 42]

### C) Therapeutic applications in HF patients

Recent papers[13, 18] highlightened how the abdominal vascular compartment is the main storage of intravascular blood volume and decreased abdominal vascular capacitance has been proposed as a major contributor to the complex pathophysiology of HF. In HF, as a result of a neurohormonal imbalance, the vascular capacitance (storage space) is decreased and acute sympathetic nerve activation can result in acute volume redistribution from the abdominal compartment to the thoracic compartment (heart and lungs), which increases intracardiac pressures and precipitates HF dyspnoea symptoms. The abdominal compartment may redistribute the splanchnic volume to the thoracic volume, playing a key role in the volume dysregulation in acute and chronic HF, even in the absence of increases of total body fluid volume.[49, 50] In a first-in-man study, Fudim et al[18] aimed to modulate the splanchnic sympathetic tone, which resulted in a marked reduction in intra-cardiac filling pressures and increase in CO, primarily driven by a significant reduction in systemic vascular resistances and increasing volume redistribution to the splanchnic volume, more effective than depletion of total circulation volume through diuretics.

## Conclusions

- Preload, heart rate and contractility, are three determinants of cardiac output.
- The heart plays only an indirect role in the fourth determinant, the venous return.
- The veins contain ≈ 70 % of blood and are responsible of congestion in heart failure.
- Volume redistribution to splanchnic veins is effective in congestive heart failure.
- A noninvasive assessment of venous function, at rest and dynamically is warranted.

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### Legal Notices and Disclaimer

All methods, applications and clinical data are provided for qualified medical professionals and educational purposes only. We do not guarantee the accuracy of the calculators and scores. All data must be confirmed according to standard clinical guidelines before use. Whilst the advice and information in this publication is believed to be true and accurate at the time of publication, neither the author nor the publisher assume any legal responsibility or liability for any error or omission that may have been made.

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TB had the original idea and drafted the manuscript and approved the submitted version.

## List of abbreviations

CO = Cardiac output
CVP = Central venous pressure
EDV = End-diastolic volume
HF = Heart failure
IVC = Inferior vena cava
MAP = Mean arterial pressure
MSP = Mean systemic pressure
PWP = Pulmonary wedge pressure
RAP = Right atrial pressure
VR = Venous return

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