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IN DEPTH

Altered Hemodynamics and End-Organ Damage in Heart Failure

Impact on the Lung and Kidney

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ABSTRACT: Heart failure is characterized by pathologic hemodynamic derangements, including elevated cardiac filling pressures ("backward" failure), which may or may not coexist with reduced cardiac output ("forward" failure). Even when normal during unstressed conditions such as rest, hemodynamics classically become abnormal during stressors such as exercise in patients with heart failure. This has important upstream and downstream effects on multiple organ systems, particularly with respect to the lungs and kidneys. Hemodynamic abnormalities in heart failure are affected by processes that extend well beyond the cardiac myocyte, including important roles for pericardial constraint, ventricular interaction, and altered venous capacity. Hemodynamic perturbations have widespread effects across multiple heart failure phenotypes, ranging from reduced to preserved ejection fraction, acute to chronic disease, and cardiogenic shock to preserved perfusion states. In the lung, hemodynamic derangements lead to the development of abnormalities in ventilatory control and efficiency, pulmonary congestion, capillary stress failure, and eventually pulmonary vascular disease. In the kidney, hemodynamic perturbations lead to sodium and water retention and worsening renal function. Improved understanding of the mechanisms by which altered hemodynamics in heart failure affect the lungs and kidneys is needed in order to design novel strategies to improve clinical outcomes.

Heart failure (HF) is characterized by an inability of the heart to maintain organ perfusion at a rate commensurate with the needs of a body without the requirement of elevated filling pressures. Adverse outcomes in HF are often dictated by counter-regulatory responses to high filling pressures or inadequate perfusion, including activation of neurohumoral, inflammatory, and fibrotic pathways. It has been known for decades that systemic arterial hypertension causes end-organ damage across multiple systems, serving as a rationale for pharmacologic and nonpharmacologic treatment of elevated blood pressure. Similarly, there may be treatment targets to mitigate or prevent the development of end-organ damage related to hemodynamic perturbations in HF. This review focuses on the characteristic hemodynamic derangements that develop in HF at rest and during exercise, and their effect on lung and kidney function.

HF PHENOTYPES

HF is typically classified in 2 ways: HF with reduced left ventricular ejection fraction (EF) or HF with preserved left ventricular EF (HFpEF) and by the presence or absence

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of hemodynamic compensation.[1–4] Patients with decompensation present with abnormal hemodynamics at rest and often require hospitalization. Patients with compensation display normal filling pressures and cardiac output (CO) at rest but develop hemodynamic abnormalities during stressors such as exercise.[1–4] The pathophysiologic concepts relating abnormal hemodynamics to organ dysfunction described in this review are variably applicable to these different HF phenotypes, as summarized in Table 1.

FORWARD FAILURE: IMPAIRED CO

Normal CO

Normal CO ranges from 4 to 8 L/min at rest and varies with sex, age, metabolic rate, and body composition.[5–7] Normalizing to body surface area yields the cardiac index (normal values 2.2 to 4.0 L/min/m^2), facilitating comparison among individuals of different sizes. CO may increase by a factor of 4 to 6 from rest to maximal effort, to a degree that is highly dependent on training and fitness level.[8,9] To evaluate the adequacy of tissue perfusion (CO increase) with exercise, it is necessary to interpret CO with respect to the metabolic requirements of the tissues (oxygen consumption [$\dot{V}O_2$]). There is a linear correlation between CO and $\dot{V}O_2$, with a ≈6 mL/min CO increase needed for every 1 mL/min increase in $\dot{V}O_2$ under normal circumstances during exercise.[2,8] This is caused by the requirement for increased convective oxygen transport to and removal of CO_2 and other waste products from the exercising muscle.[10] Factors that regulate CO reserve to maintain this 6:1 relationship are not well understood, but CO is normally well maintained in this range, even under experimental

Table 1. Hemodynamic Alterations According to Heart Failure Phenotypes

Pathophysiologic Abnormality	Definition	Acute vs Chronic	HFrEF vs HFpEF	Comments
Cardiogenic shock	Cardiac index <1.8 to 2.2 L/min/m^2 + hypoperfusion signs	Acute	HFrEF >> HFpEF	EF may be preserved if nondilated ventricle; blood pressure may be preserved through vasoconstriction[14]
Low CO state (preshock)	Cardiac index <2.0 to 2.5 L/min/m^2 and no hypoperfusion signs	Both	HFrEF > HFpEF	May not be clinically evident from history
Impaired CO reserve	CO increase <6 times $\dot{V}O_2$ increase	Both	Both	Normally 6 mL/min CO increase per 1 mL/min $\dot{V}O_2$ increase[2,8]
Elevated PAWP at rest	≥15 mm Hg in supine position	Acute > chronic	Both	PAWP frequently normal in patients with HFpEF at rest[3]
Elevated exercise PAWP	≥25 mm Hg supine or ΔPAWP/ΔCO ratio >2 upright	Both	Both	Ultimate diagnostic criterion for heart failure[65–67]
Pericardial constraint and ventricular interdependence	Increased dependence between left- and right-sided filling pressure and volume	Both	Both	Common in patients with right-sided heart failure and cardiomegaly[71,72,119–121]
Ventilatory inefficiency	$\dot{V}_E/\dot{V}CO_2$ slope >30 to 35; increased V_D/V_T, low $PaCO_2$	Both	Both	More related to CO than filling pressures[26]; differential relations in HFpEF and HFrEF[27]
Periodic breathing	Cheynes-Stokes respiration pattern or oscillatory ventilation during exercise	Both	Both	Oscillatory ventilation during exercise reflects impaired CO reserve[32,122]
Pulmonary congestion or edema	Increased lung water content in setting of increased P_{cap}	Acute > chronic	Both	May develop acutely during exercise[89]
Pulmonary capillary stress failure	Inflammatory response extracellular matrix from increased P_{cap}	Both	Both	Repeated exposure impairs gas transfer[97–99]
Pulmonary vascular disease	mPAP >20 mm Hg, PVR ≥3 WU, and PAWP ≥15 mm Hg	Both	Both	Caused by pulmonary vascular constriction and remodeling[81,91,104,105]
Impaired venous function	Shift from the unstressed to the stressed venous volume	Acute > chronic	Both	Contributes to decompensation, may be worse in HFpEF[78]
Renal hypoperfusion	Low arterial blood pressure, high CVP, or vasoconstriction	Acute > chronic	Both	If prolonged or severe, may accelerate normal, age-related nephron loss[47,48]
Neurohumoral activation	Increased PRA, aldosterone, catecholamines, and AVP	Both	HFrEF >> HFpEF	Increases sodium reabsorption in the kidneys[49]

AVP indicates arginine vasopressin; CO, cardiac output; CVP, central venous pressure; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; P_{cap}, pulmonary capillary pressure; PRA, plasma renin activity; PVR, pulmonary vascular resistance; $\dot{V}CO_2$, carbon dioxide exhalation; V_D/V_T, ratio of pulmonary dead space to tidal volume; $\dot{V}_E$, minute ventilation; $\dot{V}O_2$, oxygen uptake; and WU, Wood units.

conditions where systemic blood flow is acutely reduced, as with the creation of an interatrial shunt.[11]

Impaired CO in HF

Cardiogenic Shock

CO may be normal or reduced in HF, depending on the clinical scenario (Figure 1). True cardiogenic shock represents one extreme, whereby CO is insufficient to meet the basic metabolic requirements needed to ensure proper organ function and integrity at rest. The latter component of this definition is crucial and is defined clinically by the presence of cool extremities, decreased urine output, altered mental status, or increased serum lactate level.[12] These organ-level perturbations may occur at different ambient levels of CO, which varies from individual to individual. As such, there is no universal CO cutoff that characterizes cardiogenic shock. Cardiac index <1.8 L/min/m^2 without support or cardiac index <2.2 L/min/m^2 with support have been used as part of the definition in clinical trials.[13] Hypotension is not an absolute prerequisite of cardiogenic shock, because arterial pressure may be maintained attributable to reflex-mediated vasoconstriction.[14]

Low CO State Without Shock

A low CO state without shock is considered to be present when cardiac index is <2.2 L/min/m^2 without obvious signs of hypoperfusion. Subtle signs of organ dysfunction may already be present in such patients, suggesting a continuum from preshock to mild, profound, and ultimately refractory shock. A minority of patients hospitalized with HF (<10%) present with a low CO state, and in the outpatient setting, this prevalence is even lower.[15,16] Thus, the majority of patients with HF have preserved CO at rest.

Impaired CO Reserve During Exercise

CO reserve with exercise is often impaired in HF, irrespective of the EF.[1,2,4,17–24] Exercise studies with invasive CO measurements have demonstrated that even among patients with HF with preserved CO at rest, there is an impaired ability to increase CO during exercise, illustrated by an average increase of only 80% during stress (Table 2). This is significantly lower when compared with healthy individuals, in whom CO increases by a much greater magnitude (≈300% to 500%). The range of CO reserve in HF is wide and some patients display preserved responses with exercise. The deficit in CO reserve with HF is related to both chronotropic incompetence and an inability to increase stroke volume.[18,25]

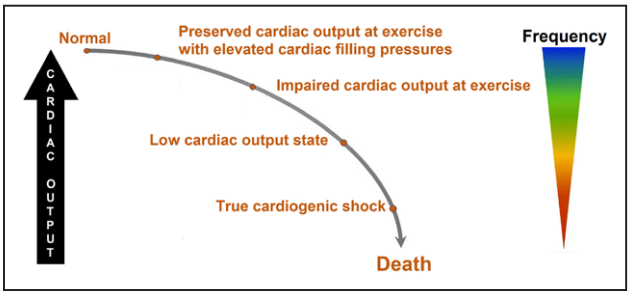

Figure 1. Stages of forward failure in heart failure.

The Effect of Impaired CO on Organ Dysfunction

Lungs: Exercise Ventilatory Inefficiency and Periodic Breathing

The lungs have 2 critical functions related to gas exchange: oxygenation or uptake of oxygen in erythrocytes and ventilation or removal of CO_2 from the blood. These functions proceed optimally when the lungs are dry and become impaired with pulmonary congestion or hypoperfusion. The effect of low CO on oxygenation is minimal in the absence of congestion, with arterial oxygen content typically being preserved, even in advanced HF. In contrast, impaired CO may exert significant influence on ventilation (Figure 2). Ventilatory efficiency is compromised in HF, requiring greater minute ventilation (V_E) to remove a given amount of CO_2, which is illustrated by an increased V_E/VCO_2 slope during exercise. There is a robust correlation between the V_E/VCO_2 slope and the ratio of pulmonary dead space to tidal volume (V_D/V_T ratio) in HF.[26] In patients with HF with reduced left ventricular EF, ventilatory inefficiency is more related to low $PaCO_2$, whereas in HFpEF, it is more strongly related to elevated dead space.[27] It is interesting that both V_E/VCO_2 slope and V_D/V_T ratio are more strongly related to CO than to cardiac filling pressures.[26] Low CO may increase the V_D/V_T ratio directly, both through expanding physiologic dead space and by reducing tidal volume. Elevated V_D/V_T is correlated with both higher resistance and lower compliance in the pulmonary vasculature in HF.[20] Reduced blood flow through the pulmonary circulation markedly increases ventilation–perfusion mismatch, increasing physiologic dead space.[28] Patients with HF frequently display a more rapid, shallow breathing pattern attributable to compromised respiratory muscle strength with underlying structural changes in the diaphragm.[29,30] Impaired CO is the hemodynamic feature that shows the strongest correlation with reduced respiratory muscle strength in HF.[31]

Cheynes-Stokes respiration or periodic breathing is a hallmark of low CO that is present in patients with HF with advanced disease. Oscillatory ventilation during exercise is strongly reflective of impaired CO reserve.[32] Decreased CO prolongs the circulation time for erythrocytes traveling from the lungs to peripheral chemoreceptors at the carotid bodies.[33] This delays the neural feedback loop from peripheral chemoreceptors to the brain, altering ventilatory control (Figure 2).[34] This effect on circulation time may be even more prolonged in the setting of blood and plasma volume expansion. In contrast, with acute reductions in central blood volume through venodilation, or increases in CO through afterload reduction,

Table 2. Exercise Studies With Invasive CO Measurement

Study	Population	N	CO_{rest}, L/min	$CO_{exercise}$, L/min
Borlaug et al (2010)[1]	HFpEF	32	2.8±0.6*	4.9±1.0*
Abudiab et al (2013)[2]	HFpEF	109	5.4±1.7	9.2±2.8
Degani-Costa et al (2015)[17]	Interstitial lung disease with pulmonary hypertension	15	4.5±0.4	9.3±0.6
Borlaug et al (2016)[18]	HFpEF	50	5.1±1.2	8.1±2.8
Malhotra et al (2016)[19]	HFpEF, HFrEF, pulmonary arterial hypertension	121	2.2±0.6*	4.5±1.2*
Obokata et al (2018)[20]	HFpEF	50	5.1±1.2	8.1±2.8
Gorter et al (2018)[21]	HFpEF ± pulmonary hypertension	161	2.5±0.6*	3.8±1.1*
Obokata et al (2018)[22]	HFpEF	38	5.0±1.2	7.7±2.4
Reddy et al (2018)[4]	HFpEF	134	4.9±1.4	8.4±3.0
Huang et al (2018)[23]	HFpEF	104	4.6±1.1	11.9±3.4
Wolsk et al (2019)[24]	HFpEF	108	5.6±2.0	8.7±3.0

CO indicates cardiac output; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.
*Indexed to body surface area.

periodic breathing in HF diminishes.[35] The combination of increased V_D/V_T ratio and interstitial lung congestion in HF activates pulmonary stretch receptors and cardiopulmonary receptors, contributing to a tendency for patients to exhibit a state of chronic hyperventilation on activity.[36,37] The resulting drop in arterial CO_2 is sensed with a delay and triggers an exaggerated apnea response. This in turn produces hypercapnia, resulting again in exaggerated hyperventilation and setting up a cyclic pattern of periodic breathing.[38] A diminished cerebrovascular response to hypocapnia in HF exacerbates this cycle.[39] Repeated and sustained exposure to these cardiopulmonary insults leads to increased sympathetic nervous system activation, systemic inflammation, and endothelial dysfunction.

Kidneys: Neurohumoral Activation and Increased Sodium Avidity

The kidneys fulfill multiple important functions relevant to HF, including clearance of waste products, maintenance of volume and electrolyte homeostasis, and activity as a neuroendocrine sensor and effector. The glomerular filtration rate (GFR) reflects the filtration function of the kidneys, which is most relevant to the first component. Filtration depends on the number of functional nephrons, the surface and permeability characteristics of the glomerular basement membrane, and Starling forces within the glomerulus. The effect of CO on these factors is indirect, explaining why GFR can remain relatively preserved even in the setting of severely depressed CO (Figure 3).[40,41] The kidneys are continuously adjusting renal blood flow by modulating vascular resistance (autoregulation). Stretch-sensitive receptors within the afferent arteriolar wall adapt resistance tone to maintain intraglomerular pressure constant within a range of mean arterial pressures between 70 and 150 mm Hg.[42] Activation of the renin-angiotensin system by hypotension causes angiotensin II–mediated efferent arteriolar vasoconstriction, increasing renal vascular resistance and promoting increased intraglomerular pressure.[43] Severely reduced CO may be accompanied by a relatively preserved arterial blood pressure when systemic vasoconstriction is present, which also helps to maintain intraglomerular pressure.[14] This explains why pronounced hypotensive episodes are more strongly associated with a

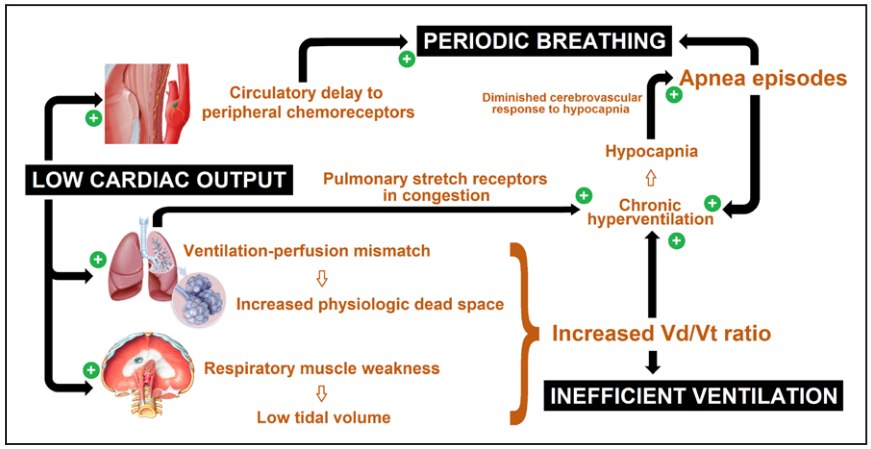

Figure 2. The effect of low cardiac output on ventilatory efficiency and occurrence of periodic breathing patterns.
V_D/V_T ratio indicates the ratio of pulmonary dead space to tidal volume.

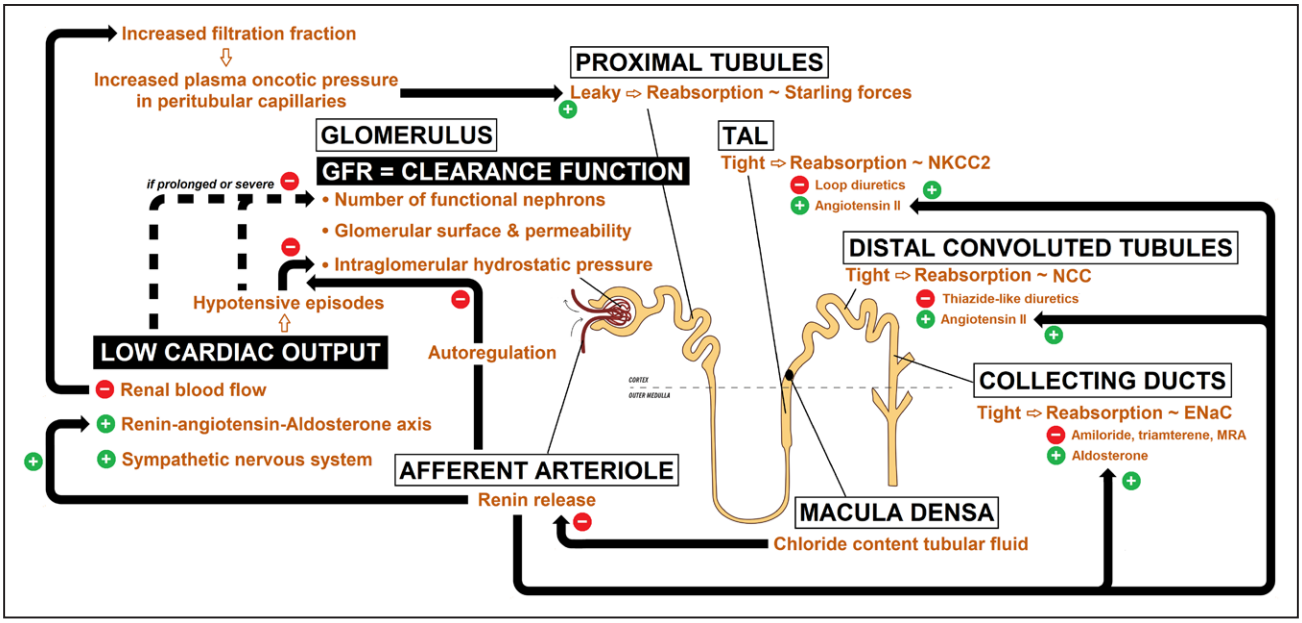

Figure 3. The effect of low cardiac output on glomerular filtration, neurohumoral activation, and sodium reabsorption.
ENaC indicates epithelial sodium channel; GFR, glomerular filtration rate; MRA, mineralocorticoid receptor antagonism; NCC, natrium–chloride cotransporter; NKCC2, sodium–potassium–chloride cotransporter; and TAL, thick ascending limb of the loop of Henle.

fall in the GFR during an episode of acute HF than reductions in CO.[44,45] Angiotensin II also promotes mesangial cell contraction, which decreases the glomerular surface and permeability of individual nephrons, leading to hyperfiltration in others while stressing the podocytes of the glomerular basement membrane.[46] Many of the same factors that decrease renal perfusion will simultaneously increase relative renal oxygen consumption (eg, angiotensin II) because increased sodium reabsorption requires substantial adenosine triphosphate consumption. The outer renal medulla is prone to ischemia because of the countercurrent system in its vasa recta. Prolonged or severe hypoperfusion of the kidneys may therefore accelerate the pace of normal, age-related nephron loss that is already augmented in HF.[47,48]

Low CO may contribute to HF through effects on neurohumoral activation, promoting salt and water retention by the kidneys (Figure 3).[49] Viewed through the framework of arterial underfilling, low CO may contribute to activation of the sympathetic nervous system and the renin–angiotensin–aldosterone axis. The relevance of this paradigm to HF pathophysiology is difficult to prove, because arterial filling is more of a concept than a measurable quantity. In animal models, low renal blood flow leads to an increased filtration fraction to maintain GFR.[49] Filtration fraction was elevated to 27% to 37% (normal value 20%) in the few studies of human patients with HF in which it was measured reliably through radionucleotide tracer methods.[50,51] However, in the study by Smilde and colleagues,[51] filtration fraction did not increase at lower renal blood flow, potentially indicating that findings from animal models do not always translate to patients with HF.

In animal models, when an increased filtration fraction occurs, the plasma oncotic pressure rises in peritubular capillaries that are located in series after the glomerular capillary network. The increase in plasma oncotic pressure creates a suction force driving sodium, chloride, and water reabsorption in the proximal renal tubules.[49,52] Consequently, tubular fluid with decreased chloride content is delivered downstream to the macula densa, which responds by stimulating renin release at the afferent arteriole. The resulting activation of the renin–angiotensin–aldosterone axis promotes sodium and chloride reabsorption through different pumps and channels along the entire length of the nephron (Figure 3).[49] Much of this pathophysiologic paradigm relating CO and filtration fraction has been characterized poorly in humans and requires further study. In a study using endogenous lithium clearance to query proximal tubular sodium reabsorption, there was no difference between patients with HF and controls without HF.[53] Nonetheless, sodium avidity has been emerging as a powerful prognostic parameter in HF and most successful HF treatments have been demonstrated to increase natriuresis.[54–56]

BACKWARD FAILURE: ELEVATED CARDIAC FILLING PRESSURES

Normal Cardiac Filling Pressures

Left-Sided Cardiac Filling Pressure: Pulmonary Arterial Wedge Pressure

Through its characteristic twisting–untwisting motion during contraction and relaxation, the left ventricle is able to create a suction gradient that allows chamber

filling at low pressure during diastole.[57] A normal pulmonary arterial wedge pressure (PAWP) is 5 to 13 mm Hg at rest in the supine position (range indicating 2 standard deviations below to above the mean, thus comprising 95.8% of the normal population). With exercise, viscoelastic suction is increased in the healthy heart, allowing enhanced filling of the left ventricle to accommodate a larger preload volume in a shorter period (attributable to tachycardia), without significant increase in PAWP.[57,58] With normal aging, there is a slight increase in exercise PAWP in the supine position, but the totality of evidence indicates that PAWP remains <25 mm Hg in patients without HF during exercise.[59,60] The latter value also coincides with the capillary hydrostatic pressure in the lung at which pulmonary congestion develops in animal preparations.[61] For these reasons, PAWP values ≥25 mm Hg during exercise or ≥15 mm Hg at rest are used to diagnose HFpEF in the supine position.[1,3,4]

In upright exercise, there is no apparent age-related increase in the upper limit of normal PAWP.[62] However, similar PAWP at maximal exercise in healthy elderly versus younger individuals comes with a lower CO. There may be greater flow dependency of PAWP with upright exercise that is less pronounced in the supine position (where venous return is maximized owing to gravitational effects). The flow dependency of PAWP is especially evident in healthy adults operating at very high levels of exercise intensity.[63] To account for this potential flow dependency, Eisman and colleagues[64] have recently proposed a PAWP/CO slope >2 with upright exercise as a complementary measure to help guide the diagnosis of HF, based on evidence of poorer peak V_{O_2} and increased risk for cardiovascular hospitalization at 5 years in patients with these values.

Right-Sided Cardiac Filling Pressure: Central Venous Pressure

Normal central venous pressure (CVP) at rest in the supine position is 0 to 6 mm Hg. Because of the low-resistance, high-compliance features of pulmonary circulation, the walls of the right ventricle are much thinner and more distensible compared with the left ventricle. As such, CVP is usually <60% of PAWP. However, because the right and left heart chambers are connected in series and influence one another in parallel because of their shared location within the pericardial space, and because both are affected by volume status, there is a close relationship between CVP and PAWP. Under normal conditions, every 1 mm Hg increase in CVP is coupled to a 1.5 mm Hg increase in PAWP during exercise (Figure 4).[1,63]

Elevated Cardiac Filling Pressures in HF

PAWP ≥15 mm Hg at rest in the supine position is recommended by guidelines as the diagnostic criterion for

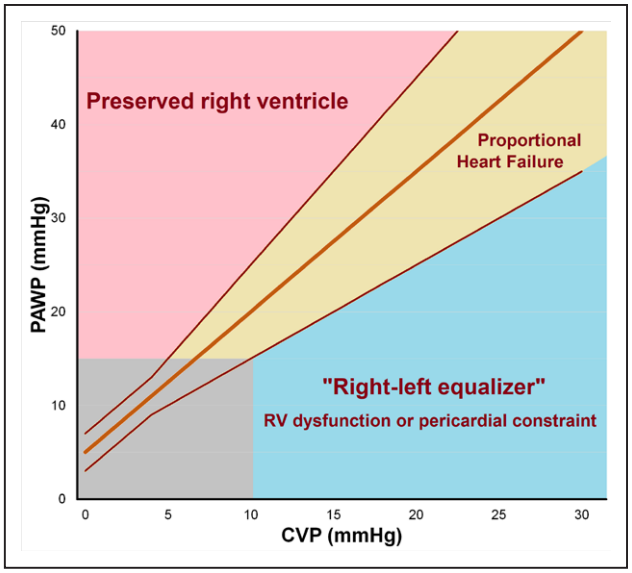

Figure 4. The central venous pressure (CVP)–pulmonary arterial wedge pressure (PAWP) relationship and its relationship with right ventricular (RV) function/pericardial constraint.

left-sided HF.[1,3,4,65–67] This partition value is 2 mm Hg higher than the 98th percentile of normal for pragmatic reasons to account for measurement error. PAWP approximates left atrial pressure but is not a perfect surrogate of downstream end-diastolic left ventricular pressure, which is often slightly higher but may also be lower in patients with a prominent V-wave.[68] Elevated PAWP has been found to better predict outcomes in patients with HF as compared with left ventricular end-diastolic pressure, because it more accurately reflects downstream pressure that opposes flow through the pulmonary arteries.[69] Measurement of left ventricular end-diastolic pressure may be challenging because it may be difficult to ascertain, especially when using fluid-filled catheters and during tachycardia. By definition, PAWP ≥15 mm Hg confirms the hemodynamic diagnosis of HF, but has reduced sensitivity (56%) and negative predictive value (52%), because many patients display elevated PAWP only during exercise.[3] Therefore, it is necessary to evaluate PAWP during exercise to exclude the possibility of HF reliably, especially in patients with normal or borderline PAWP values at rest.

Pericardial Restraint and Venous Distribution

The CVP versus PAWP relationship may be appreciated to assess right ventricular function and pericardial constraint indirectly (Figure 4).[70–72] With increasing pericardial restraint and enhanced ventricular interdependence, which often accompanies right-sided HF, CVP may be disproportionately high and make an important contribution to elevated left-sided filling pressure.[73] This is because CVP approximates pericardial pressure and

can therefore be taken as an estimate of the extramural pressure applied to the left heart. In other words, PAWP may be high because of increased external pressure on the left ventricle rather than an increase in distending pressure. This pathophysiology plays an important role in patients with HFpEF, particularly in the setting of obesity and in patients with exercise-induced pulmonary hypertension, where ventricular interaction becomes amplified because of right ventricular–pulmonary arterial uncoupling with exercise.[35,74,75] In some patients, left ventricular transmural filling pressure (approximated by PAWP–CVP) is actually low despite high PAWP, which contributes to impaired left ventricular stretch and filling, hence lower stroke volume and CO.[73] Some patients with severe right HF may display elevation in CVP and PAWP, with both values exceeding 15 mm Hg, and it remains unclear whether such patients should be identified as having left-sided HF, because the increase in PAWP may be caused by ventricular interdependence rather than left heart pathology.

In addition to total blood volume and right heart compliance, venous capacitance is another important determinant of CVP and cardiac preload.[76] Between 60% and 75% of total blood volume is contained within the venous circulation at rest. The distribution of venous blood can be described in terms of the stressed and unstressed volumes. The unstressed volume refers to the amount of blood necessary to fill the venous vascular space at a pressure of 0, whereas the stressed volume describes the volume that contributes to elevation in venous pressure that augments right atrial filling. At rest, most venous blood contributes to the unstressed volume, pooled in venous capacitance veins. However, with sympathetically mediated venoconstriction as occurs during exercise, this volume can be mobilized rapidly to the central circulation. This venoconstriction is crucial to maintain circulatory homeostasis in the normal heart but may become detrimental in patients with HF, where the ability to translate preload recruitment to increases in CO is lost. Such alteration in venous tone may contribute to elevations in both PAWP and CVP, as occurs during HF decompensation.[77] Venous regulation remains understudied in HF, but there is some evidence that venous compliance is more severely impaired in patients with HFpEF as compared with HF with reduced left ventricular EF.[78]

The Effect of Elevated Cardiac Filling Pressures on Organ Dysfunction

Lungs: Pulmonary Edema, Capillary Stress Failure, Altered Gas Exchange, and Vascular Remodeling

The combination of myocardial dysfunction and volume retention in HF causes elevation of the pulmonary capillary pressure (P_{cap}). This alters Starling forces across the capillary, favoring development of edema in the pulmonary interstitial and alveolar space when lymphatic resorption capacity is exceeded by the amount of fluid filtered (Figure 5). PAWP, which is measured clinically, is closely related but not equivalent to P_{cap}. This is because the pulmonary venules and veins also resist blood flow, introducing a pressure drop from the pulmonary capillaries to left atrium. In normally perfused canine lungs, 60% of the distribution of pulmonary vascular resistance resides on the arterial side, whereas 40% is related to capillary plus venous resistance. As such, P_{cap} in normal dogs may be approximated by the formula P_{cap} = PAWP + 0.4 (mPAP – PAWP).[79] When lungs are perfused with very high flow to simulate exercise, the distribution of resistances is altered such that upstream resistance decreases, leading to an underestimation of the true P_{cap} by this formula.[80] Moreover, any condition influencing the distribution of resistances alongside the length of the pulmonary vascular tree may affect this relationship dramatically. Recently, Fayyaz and colleagues[81] showed in a histopathologic study that venous intimal thickening is observed frequently in human HF, and the extent of venous remodeling is associated with hemodynamic indicators of pulmonary vascular disease severity. Therefore, it seems likely that some patients with HF display varying distributions of arterial and venous vasoconstriction and remodeling, which may require different treatments, but this question has not been explored adequately.

Conditions involving elevated pulmonary venous resistance lead to a greater underestimation of P_{cap} by PAWP. In addition to patients with HF, this is particularly relevant in sepsis, acute respiratory distress syndrome, high-altitude pulmonary edema, or neurogenic pulmonary edema.[82–84] A higher pulmonary venous resistance also may contribute to an increased risk of pulmonary edema after adjusting for left-sided filling pressures in older adults.[85] Total pulmonary resistance increases from 1 mm Hg × min/L to 2.5 mm Hg × min/L with healthy aging, leading to a greater P_{cap} for any given PAWP.[59,86]

Fluid flux (J_V) across the pulmonary capillary wall may be estimated by the Starling equation ($J_V = K_{PC}$ [($P_{cap} - P_{interstitium}$) – σ ($\pi_{cap} - \pi_{interstitium}$)]; Figure 5). In this equation, K_{PC} is equal to the product of the pulmonary capillary hydraulic conductivity and the capillary surface area and σ is the reflection coefficient from 0 to 1 that indicates microvascular impermeability to proteins. P_{cap}, $P_{interstitium}$, π_{cap}, and $\pi_{interstitium}$ represent the classic Starling forces across the capillary wall that govern fluid transit (ie, hydrostatic and oncotic pressures). P_{cap} is the most important factor influencing J_V in this equation. Gradual increases in P_{cap} up to 25 mm Hg may be compensated by increased lymph flow in normal lungs, provided that π_{cap} is normal.[61,87] Above this value, pulmonary edema develops and lung compliance decreases. Extrapolation from animal experiments in dogs suggests that lymph flow may increase by a factor of 20 to 30 under

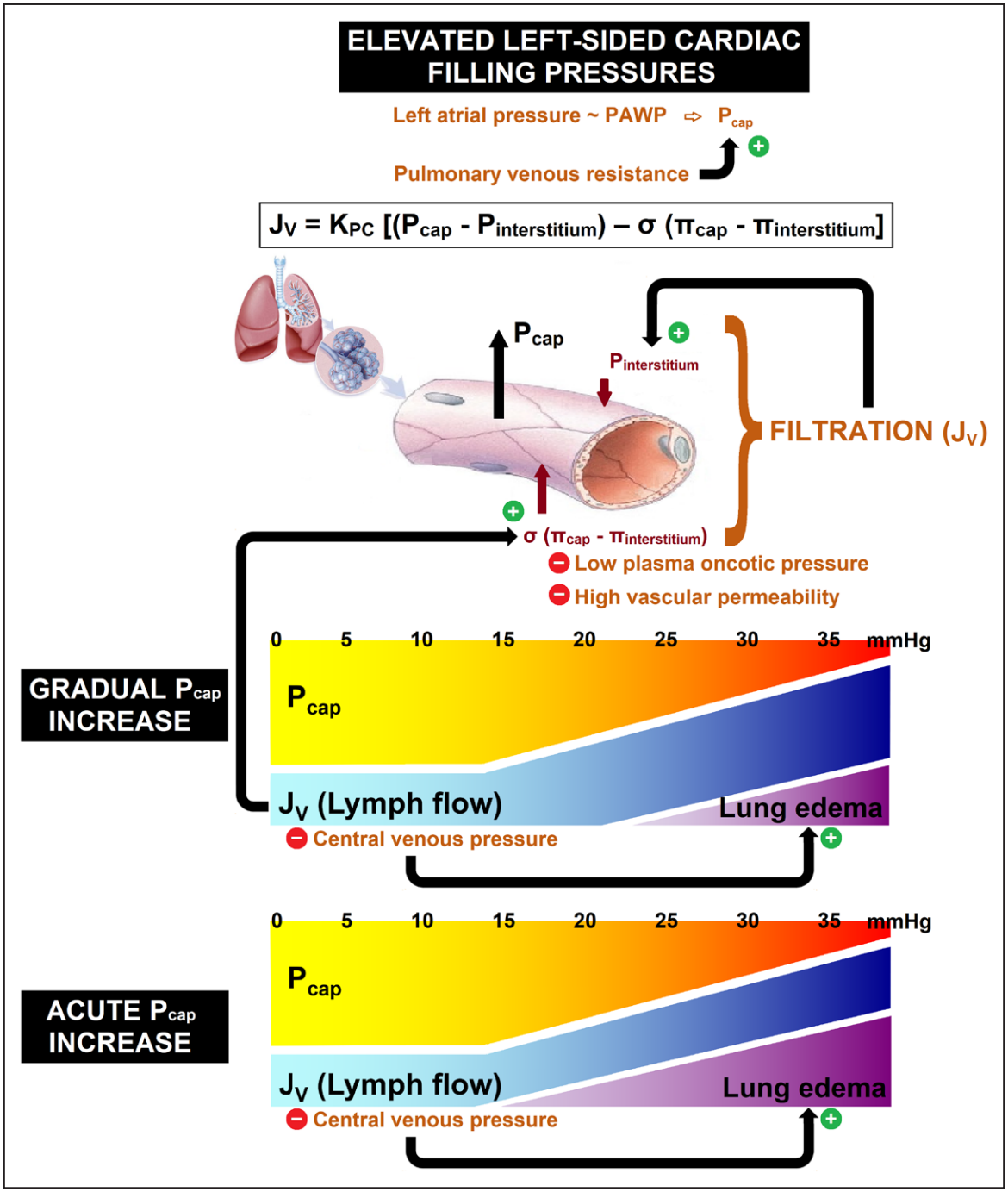

Figure 5. Central role of elevated left-sided cardiac filling pressure in the occurrence of lung edema.
J_V indicates fluid flux or filtration; K_{PC}, pulmonary capillary hydraulic conductivity; PAWP, pulmonary arterial wedge pressure; P_{cap}, pulmonary capillary hydrostatic pressure; π_{cap}, pulmonary capillary colloid osmotic pressure; $\pi_{interstitium}$, interstitial colloid osmotic pressure; $P_{interstitium}$, interstitial hydrostatic pressure; and σ, reflection coefficient from 0 (completely permeable to proteins) to 1 (completely impermeable to proteins).

sustained conditions of increased filtration attributable to elevated P_{cap}.[88] These adaptations develop gradually over time, explaining how patients with HF with chronically elevated PAWP often display no lung edema on chest auscultation or imaging, whereas patients with acute increases in P_{cap}, as with myocardial infarction or acute mitral regurgitation, overwhelm lymphatic reserve. Increased lymph flow not only compensates for increased filtration but also reduces filtration directly through its effect on $\pi_{interstitium}$ (Figure 5). Increased lymph flow washes out interstitial proteins, increasing the oncotic gradient that counteracts filtration. This effect is reduced in patients with high vascular permeability (low σ) or low π_{cap}, which is the case, for example, in systemic inflammation that is often present in HF. These data from animal models support an important role for

the pulmonary lymphatics, but this area remains understudied in human HF.

Elevated right-sided cardiac filling pressures (high CVP) may impede lymph flow. Patients with the most dramatic elevation in CVP, often out of proportion to PAWP, tend to develop more severe pleural effusions owing to reduced lymph flow, with less increase in lung parenchymal congestion, because P_{cap} is less elevated. Although right-sided HF has traditionally been regarded as a condition of dry lungs, recent data have shown that the presence of elevated biventricular filling pressures is the most important determinant of lung edema. In an invasive study, Reddy and colleagues[89] demonstrated that the combination of elevated CVP and PAWP synergistically promote lung congestion during exercise among patients with HFpEF. CVP elevations in this study were intimately related to abnormalities in right heart function and right ventricular to pulmonary arterial coupling, providing important new insight on how the presence of right-sided HF may worsen lung function in patients with apparent left-sided predominance. In contrast, elevations of CVP in the absence of high P_{cap} (as in pulmonary arterial hypertension) do not cause lung edema.

Imbalances of Starling forces in HF are accompanied by the disruption of local cellular pathways involved in fluid reabsorption at the alveolar and endothelial levels. The effects of progressive increases in P_{cap} on the capillary and alveolar wall have been studied in animal preparations of alveolar–capillary stress failure, reproducing the transition from leakage of protein toward the interstitium (low permeability stage) to leakage of protein and erythrocytes toward the alveolar lumen (high permeability stage).[90] The continuous fluid clearance from alveoli to the interstitium (and subsequently to the lymphatic system) is crucial to maintain dry lungs, ensuring high conductance of the alveolar membrane for gas exchange. This vital process occurs primarily through specific epithelial sodium channels, located at the luminal surface of alveolar type II cells, which are activated or inhibited by β-agonists and amiloride, respectively. Secondary active sodium transport generates an osmotic gradient required for water to follow passively, hence removing excess intra-alveolar fluid. In a small randomized study, the β-agonist albuterol improved pulmonary vascular reserve in patients with HFpEF, which could be attributable in part to promotion of alveolar fluid clearance, in addition to direct effects on vascular smooth muscle and endothelium.[91] A similar effect with albuterol has been observed in human HF with reduced left ventricular EF.[92]

When these stress adaptations in the lung become overwhelmed, development of edema triggers a cascade of inflammatory responses, leading to activation of metalloproteinases and the degradation of matrix proteoglycans that can contribute to progressive pulmonary disease or the propensity to develop future episodes of pulmonary edema. This alters the composition of the plasma membrane of endothelial cells, causing increased membrane fluidity (Figure 6). The weakened tensile strength of the endothelial membrane potentiates stress failure and dysfunction, with inhibition of nitric oxide synthesis as well as activation of endothelin and adrenomedullin neurohormonal pathways.[93–95] Longstanding mechanical and inflammatory injury in the lung microcirculation from repeated and sustained elevations in P_{cap} provokes interstitial thickening and fibrosis. In animal models, this leads to pulmonary venous remodeling that effectively protects the pulmonary capillaries from left atrial hypertension, but at the cost of an increase in the venous component of pulmonary vascular resistance.[96] In addition, there is basement membrane thickening and remodeling of the alveolar–capillary interface that also protects against pulmonary edema formation but impairs gas diffusion. This is detected in human HF by measuring lung diffusion capacity, particularly gas diffusion membrane and capillary components, which are abnormal at rest and during exercise in patients with HF and are independently associated with adverse outcomes.[97–99]

Longstanding exposure to left atrial hypertension may lead to an increase in pulmonary vascular resistance and excessive reduction in pulmonary arterial compliance, or combined postcapillary and precapillary pulmonary hypertension. Patients with combined postcapillary and precapillary pulmonary hypertension display unique characteristics as compared with patients with left atrial hypertension and isolated postcapillary pulmonary hypertension, including poorer right ventricular reserve, greater ventricular interdependence, and more dramatic abnormalities in right ventricular to pulmonary arterial coupling. This is related in part to the fact that the increased venous return to the right heart during exertion cannot be circulated through the diseased pulmonary vasculature, attributable to both vascular remodeling and right ventricular dysfunction.[21] The right ventricular dilation that accompanies exercise in these patients may further impair left ventricular filling and stroke volume, because right heart engorgement causes reduction in left ventricular volumes through enhanced ventricular interdependence.[21,73,100] Therapies that reduce pulmonary vascular resistance with exercise conversely have been shown to improve left ventricular transmural distending pressure and CO responses to exercise in HFpEF, with the improvement in transmural pressure being correlated with the reduction in pulmonary vascular resistance.[91] The dynamic abnormalities in right ventricular to pulmonary arterial coupling in this setting are associated with impaired functional capacity and increased risk for adverse events.[21,101–103]

Part of the increase in pulmonary vascular resistance in combined postcapillary and precapillary pulmonary

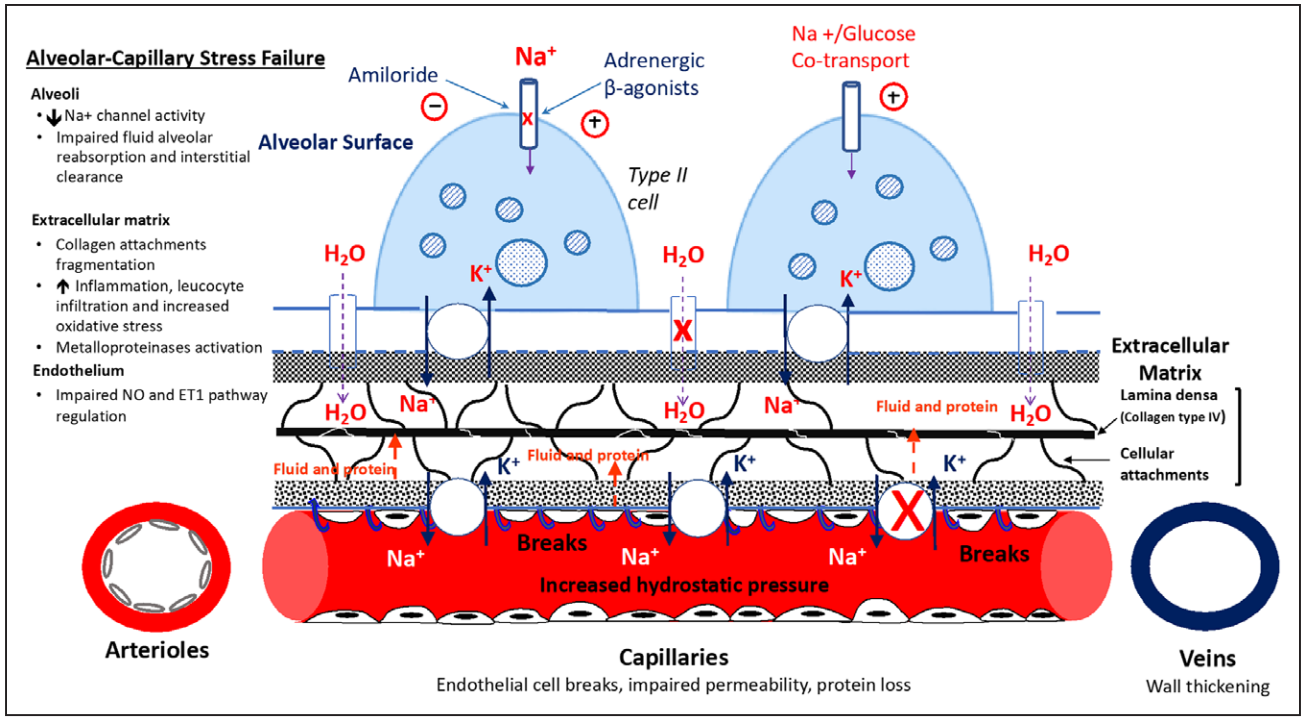

Figure 6. Concept of alveolar–capillary stress failure.

hypertension is related to vasoconstriction, because administration of pulmonary vasodilators such as nitrates or β-agonists improves pulmonary vascular resistance, but part is related to structural remodeling in the vessels themselves.[81,91,104,105] There are no adequate methods to distinguish between these 2 entities, but the potential treatment implications (eg, antiproliferative versus vasodilatory approaches) suggest an important need for such methods. A reasonable approach seems to be performing provocative testing with pulmonary vasodilators, whereby patients with a significant acute reduction in pulmonary vascular resistance can be deemed to display some element of vasoconstriction that is reversible.

Elevated Right-Sided Cardiac Filling Pressure: Impact on Kidney Function

Renal venous congestion exerts a significant effect on the GFR, and CVP elevations are reflective (although not a perfect surrogate) of renal venous pressure (Figure 7).[106] Because the kidneys are encapsulated organs, renal venous hypertension causes an increase in renal interstitial pressure and the hydrostatic pressure in the tubular system, opposing filtration forces in Bowman capsule.[107] A similar effect on the hydrostatic pressure inside the glomerular capillaries may partly counterbalance this effect.[108] Nevertheless, GFR is reduced in patients with renal venous hypertension because of vasoconstriction and vascular redistribution causing a decrease in filtration area and hydraulic conductivity.[108]

CVP is 1 of the 3 hemodynamic determinants of renal perfusion (along with arterial blood pressure and renal vascular resistance).[41] Whereas renal autoregulation mechanisms serve to maintain renal blood flow and GFR in the face of a changing arterial blood pressure, there is little evidence that similar autoregulatory forces are able to adapt to the presence of elevated CVP. Neither a compensatory increase in arterial blood pressure nor a vasodilatory response in the renal vasculature occurs in HF to maintain renal perfusion in response to elevated renal venous pressure. This explains why renal venous hypertension impedes renal blood flow with an immediate effect of decreased urine production.[109,110] Intrarenal Doppler ultrasound studies have demonstrated complete abrogation of flow in diastole when CVP is markedly elevated, and this correlates with reduced diuretic response and adverse prognosis.[111,112] The combination of low arterial blood pressure and high right-sided cardiac filling pressure is especially harmful for the kidneys, because both may contribute to reduced renal blood flow, although this has not been measured directly in human HF.[50] Over time, these processes are believed to lead to an accelerated and irreversible loss of nephrons, hastening deterioration in GFR.[48,113]

At the tubular level, high renal venous pressure associated with systemic venous hypertension promotes salt and water reabsorption, mainly in the proximal segments (Figure 7). These segments are freely permeable to water and electrolytes, so Starling forces between the peritubular capillaries and the renal interstitial compartment determine reabsorption rates. High venous pressure increases the hydrostatic pressure in both compartments to a similar extent, essentially leading to a null effect.[107] However, increased renal interstitial pressure

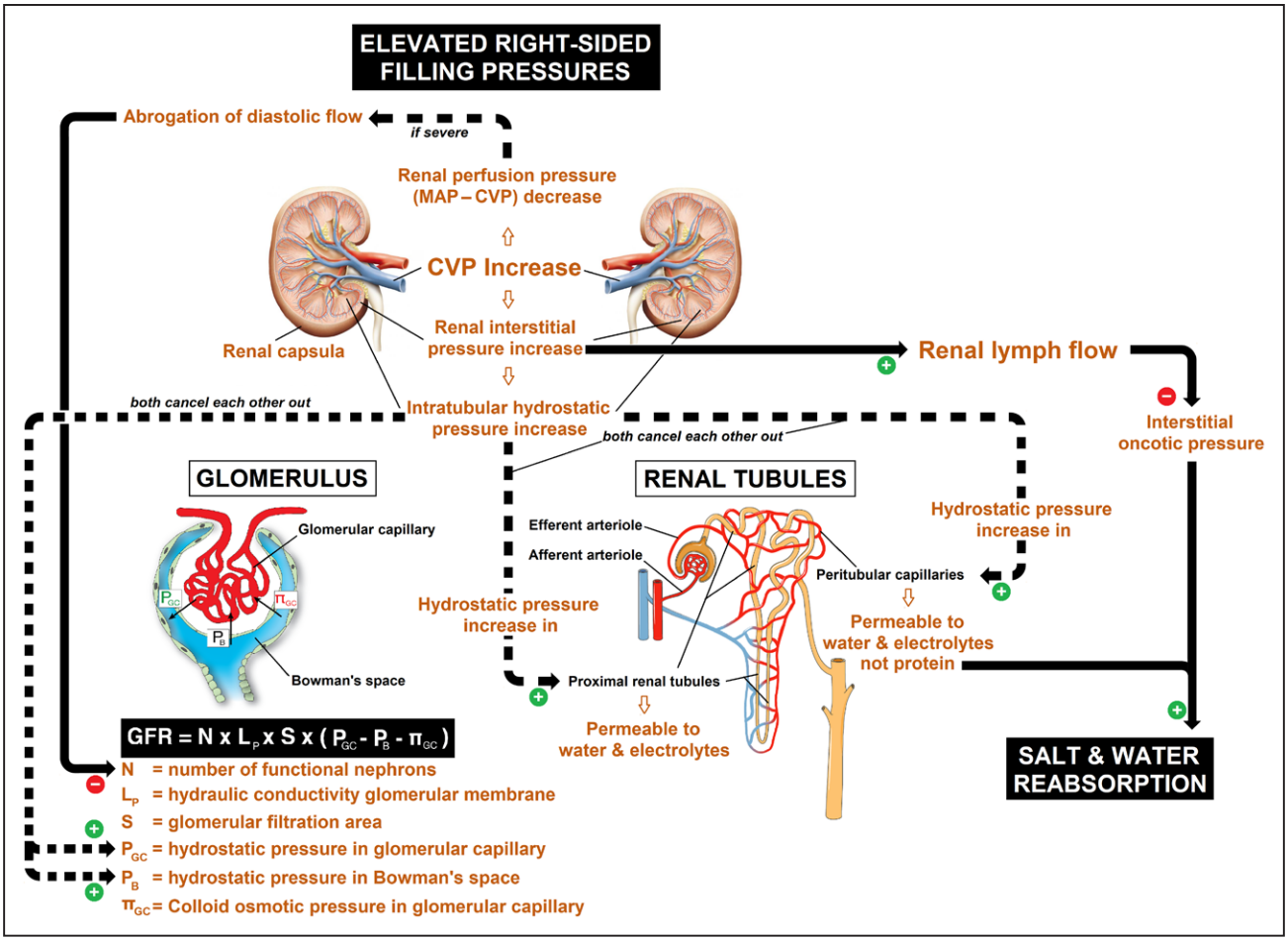

Figure 7. The effect of elevated right-sided cardiac filling pressure on the GFR and tubular reabsorption.
CVP indicates central venous pressure; GFR, glomerular filtration rate; and MAP, mean arterial pressure.

markedly enhances lymph flow, washing out interstitial proteins and decreasing the colloid osmotic pressure in the renal interstitial compartment. It has been demonstrated that renal lymph flow massively increases, even exceeding urine flow in the ureter, in a state of renal venous hypertension.[114,115]

The peritubular protein concentration and hence colloid osmotic pressure is elevated in HF because of an increased filtration fraction related to low CO. Peritubular capillaries, although highly permeable to water and electrolytes, are virtually impermeable to plasma proteins, which explains why their colloid osmotic pressure remains high.[116] The resulting colloid osmotic pressure gradient strongly favors reabsorption.[52] The combination of low GFR and increased proximal reabsorption is a potential cause for further activation of the renin–angiotensin–aldosterone axis and diuretic resistance against most commonly used agents that act distally in the nephron (ie, loop and thiazide-like diuretics; Figure 3).[49,54]

Just as excessive increases in P_{cap} may trigger lung edema formation (Figure 5), excessively rapid reduction in intravascular volume may be observed with treatments such as ultrafiltration for patients with congestion. The plasma refill rate describes the rate at which intravascular volume is reconstituted from the interstitial space during treatment. The plasma refill rate cannot be measured directly, but can be estimated by the degree of hemoconcentration during treatment for congestion. Testani et al.[117] and Mentz et al.[118] have shown that hemoconcentration is associated with favorable outcomes, even despite a reduction in the GFR, but it is likely that decongestion that greatly exceeds the plasma refill rate (as with high ultrafiltration rates) may lead to neurohormonal activation that can worsen renal and clinical outcomes.

CONCLUSIONS

Characteristic hemodynamic features define the HF syndrome irrespective of the EF. Low CO at rest is present in <1 in 10 patients with symptomatic HF, but impaired CO reserve during exercise is much more frequent. In the lungs, inadequate CO exacerbates ventilation–perfusion mismatch and leads to respiratory muscle weakness, which reduces ventilatory efficiency

and causes periodic breathing patterns. Impaired CO is an important driver of neurohumoral activation and sodium avidity in the kidneys that plays a crucial role in the occurrence of congestion. Elevated cardiac filling pressures play an even greater role in altering lung and kidney function in terms of gas exchange, vascular loading, and filtration/reabsorption capacity. In the field of systemic hypertension, multiple studies have demonstrated clearly how therapies targeting high blood pressure may mitigate end-organ damage to improve clinical outcomes. Whereas HF is less common than hypertension, the hemodynamic derangements induced by cardiac failure may be just as damaging, particularly to organ beds directly upstream of the heart. Further study is required to improve the understanding of mechanisms by which altered hemodynamics in HF affect the lungs and kidneys in order to design and test novel strategies to improve clinical outcomes. Indeed, widely used HF therapies, such as renin–angiotensin system blockers, mineralocorticoid receptor antagonists, and angiotensin receptor neprilysin inhibitors, may partly exert their beneficial effects on clinical outcomes through protective effects on end organs such as the lung and kidneys.

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Disclosures

None.

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