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PERSPECTIVE

Vascular phenotypes of acute decompensated vs. new-onset heart failure: treatment implications

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Abstract

Aims Acute heart failure (HF) is a frequent and life-threatening syndrome with heterogeneous clinical, haemodynamic, and neurohormonal features. This article describes the vascular phenotypes associated with acute decompensated chronic HF (ADCHF), and new-onset acute HF (NOAHF).

Data Synthesis Worsening of chronic HF occurs with full activation of adaptive mechanisms that maintain blood pressure (BP) and systemic perfusion. Rapid onset of HF in the setting of previous normal functioning heart not only does not allow full activation of adaptive mechanisms but also generates inappropriate responses from systemic endothelium leading to low BP/hypotension. Consequently, the treatment of ADCHF is based on diuretics and vasodilators, while in NOAHF, vasoconstrictors may be required to maintain BP to allow the correction of the acute cardiac disease.

Conclusions Patients with ADCHF and NOAHF present different vascular phenotypes with treatment implications.

Keywords Acute decompensated chronic heart failure; New-onset acute heart failure; Vascular phenotypes; Treatment

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Case Presentation A: A 65-year-old man with previous myocardial infarction was admitted to the emergency department for increasing severity of dyspnoea in the last week. He referred an increased sodium intake associated with travelling. At admission, he presented with blood pressure (BP) of 120/90 mmHg; heart rate was 95 b.p.m. with weak carotid pulses and peripheral oxygen saturation (SpO_2) of 92%, with congestion rales in lower pulmonary fields and leg oedema. The electrocardiogram revealed Q-waves in leads V1–V5 and left ventricular ejection fraction was estimated in 35% by echocardiogram. High-sensitivity cardiac troponin T was 54 ng/L, amino-terminal pro B-type natriuretic peptide (NT-proBNP) 7044 pg/mL, lactate 1.6 mmol/L, and creatinine 1.38 mg/dL. Haemodynamic monitoring was consistent with acute heart failure (AHF) (*Table 1*).

Case Presentation B: A 65-year-old man, apparently healthy, was admitted to the emergency department for sudden dyspnoea. At admission, he presented with BP of 90/65 mmHg; heart rate was 110 b.p.m. and SpO_2 of 85%, with diaphoresis, cool extremities, rales, and wheezing in the entire pulmonary fields. The electrocardiogram revealed ST-segment elevation in leads V2–V6, and left ventricular ejection fraction was estimated in 40% by echocardiogram. High-sensitivity cardiac troponin T was 19 ng/L, NT-proBNP 201 pg/mL, lactate 3.8 mmol/L, and creatinine 0.85 mg/dL. Haemodynamic monitoring was consistent with AHF (*Table 1*).

Introduction

Heart failure (HF) is a major contributor for the burden of cardiovascular mortality and morbidity worldwide.[1–3] Each year, more than 1 million people are hospitalized for acute HF (AHF) in Europe, and similar relative numbers are observed in the USA.[1,4]

Acute HF refers to rapid onset or worsening of symptoms and/or signs of HF.[3] Patients with AHF usually present with the haemodynamic triad of reduced cardiac output (CO), increased cardiac filling pressure (CFP), and augmented systemic vascular resistance (SVR).[5] The pathophysiology of AHF can be captured as a single but complex set of interactions between the heart, kidney, autonomic nervous system, peripheral

Table 1 Haemodynamic parameters of case presentations

Haemodynamic parameters	Case A	Case B
Clinical assessment	Profile C (wet and cold)	Profile C (wet and cold)
Mean arterial blood pressure (mmHg)	102	73
Pulmonary-capillary wedge pressure (mmHg)	30	25
Cardiac index (L/min/m^2)	1.6	1.8
Systemic vascular resistance (dyn s/cm^5)	2105	1333

vasculature, and a variety of neurohormones, vasoactive and inflammatory circulating mediators generating a range of clinical and haemodynamic profiles[6,7] (*Figure 1*). In line with these aspects, AHF is a heterogeneous clinical syndrome with several previous clinical contexts, precipitating factors, clinical and haemodynamic features, and prognosis.[6,8] Indeed, the disease comprises patients with new-onset AHF (NOAHF) or acute decompensated chronic HF (ADCHF); the primary involvement of coronary arteries, valves, myocardium, or pericardium in the failing heart; and a wide spectrum of BP from severe hypertension to haemodynamic collapse leading to in-hospital mortalities ranging from 1.5% in hypertensive HF to 39.6% in cardiogenic shock.[3,4,6,8] On the other hand, treatment tools include apparently paradoxical antagonistic strategies like vasodilators vs. vasoconstrictors and decongestive therapy vs. fluid support.[2,3,8,9]

This article describes two different phenotypes of AHF associated with the NOAHF and ADCHF due to specific interactions of the pathogenic players and the consequent therapeutic implications.

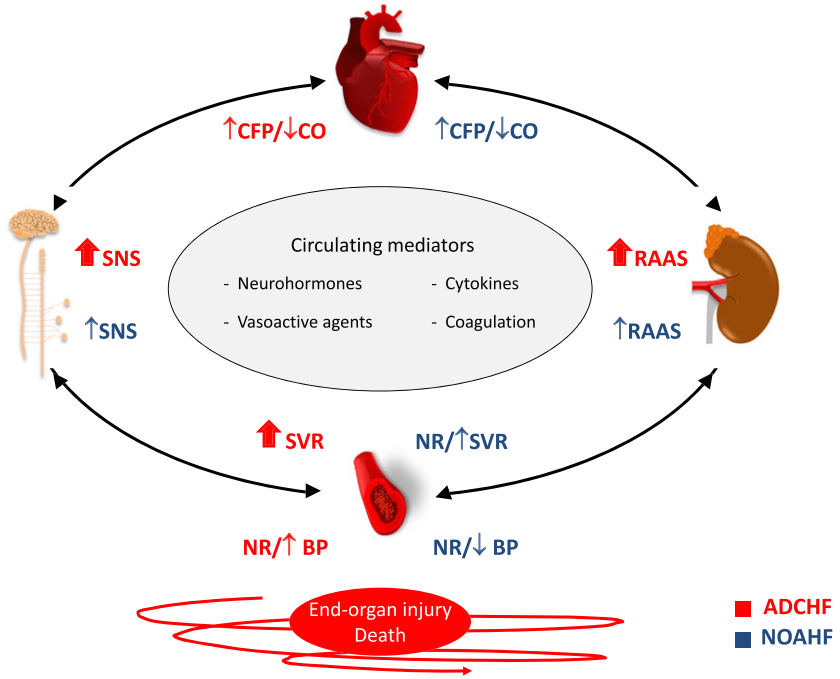
Vascular phenotypes of acute heart failure

In every three patients admitted for AHF, two present with ADCHF and one with NOAHF.[8,9] In the EuroHeart Failure Survey II, only minor differences were observed in demographic characteristics between ADCHF and NOAHF, but comorbidities were more common in patients with ADCHF.[8] Valvular disease (44%) and dilated cardiomyopathy (25%) were more prevalent in patients with ADCHF, and acute myocardial infarction (AMI) (35%) was more frequent in NOAHF.

Acute decompensated chronic heart failure

Patients with ADCHF present with intense activation of adaptive mechanisms, including overactivity of the sympathetic

Figure 1 Pathophysiology of acute heart failure. ADCHF, acute decompensated chronic heart failure; BP, blood pressure; CFP, cardiac filling pressure; CO, cardiac output; NOAHF, new-onset acute heart failure; NR, normal range; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; SVR = systemic vascular resistance.



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nervous system[10–12] and overexpression of the renin–angiotensin–aldosterone system[11,13] leading to a significant compensatory increase in the SVR that preserves BP and systemic perfusion, even in the presence of sharp reduction of CO associated with advanced stages of HF (*Table 2*).

The excessive retention of sodium and water generates symptomatic pulmonary and systemic congestion but ensures an appropriate increase in the preload, essential to exploit the increase in CO conditioned by the Frank–Starling mechanism.[14,15] Cardiac remodelling with ventricular hypertrophy and dilatation that occurs in chronic HF[16] ensures an increase in CO in patients with severe ventricular systolic dysfunction. The acute decompensation is usually triggered by a non-cardiac (e.g. infection, thyroid dysfunction, anaemia, and increased sodium intake) or a superimposed precipitating cardiovascular condition (e.g. arrhythmia, myocardial ischaemia, and pulmonary embolism)[2,3] in the setting of a severe but stable cardiac condition (e.g. myocardial, valvular, or pericardial diseases).

Case presentation A illustrates this vascular phenotype dominated by normal/increased BP conditioned by a sharp increase in SVR generated by excessive sympathetic nervous system and renin–angiotensin–aldosterone system activation. Despite the pronounced increase in CFP, which generates a significant pressure gradient between the veins (30 mmHg) and pulmonary alveoli (negative pressure), the alveolar oedema is scarce at rest in orthostatic position owing to a significantly thicker alveolar–capillary barrier.[17]

Blood biomarkers released or accumulated as a consequence of myocardial injury [cardiac troponins (cTn)] and stretch {brain natriuretic peptide (BNP) and its biologically inert amino-terminal pro-peptide [N terminal pro BNP (NT-proBNP)]}, tissue hypoxia (lactate), or comorbidities (e.g. creatinine) play a significant role in the diagnosis, risk stratification and therapy guidance in patients with AHF. Patients with ADCHF frequently present with abnormal levels of cTn and very high levels of BNP/NT-proBNP, which are associated with worse prognosis.[18,19] Tissue hypoperfusion can generate some degree of renal dysfunction[19] but is usually insufficient to produce high levels of lactate.[20]

Clinical and haemodynamic data from the LIDO study, which mainly enrolled patients with deterioration of severe chronic HF despite optimum oral therapy, are consistent with this vascular phenotype.[21] Mean value of BP was normal (114/70 mmHg) despite the sharp reduction of CO (3.7 L/min) conditioned by a marked increase in mean SVR (1960 dyn·s/cm^5). Despite the high mean pulmonary-capillary wedge pressure (25 mmHg), its chronic nature did not trigger overt pulmonary oedema.

New-onset acute heart failure

Patients with NOAHF usually present with SVR inadequately elevated for the level of CO, which produces low normal BP or even hypotension[22–24] (*Table 2*). The Frank–Starling mechanism is limited to the venoconstriction-based increase in the preload, because retention of sodium and water needs time to expand the *volemia*. The absence of cardiac remodelling exacerbates the reduction of CO even in patients with moderately reduced ejection fraction.[25] The deficiency of these adaptive mechanisms can be amplified by inappropriate responses of the hypoperfused endothelium, such as overexpression of inducible nitric oxide synthase and inflammatory cytokines (tumour necrosis factor-alpha and interleukin-6)[23,26] that reduce catecholamine responsivity, decrease myocardial contractility, and further depress perfusion pressure. Consequently, many patients have impending or even cardiogenic shock[8] with a vicious circle of ischaemia, hypotension, and myocardial dysfunction.[25]

The AHF is usually triggered by an acute severe cardiac disease (e.g. myocardial infarction, myocarditis, valve dysfunction, tamponade, and massive pulmonary embolism)[3] in a previously healthy subject or with a non-cardiac comorbidity.

Case presentation B is the paradigm of this vascular phenotype dominated by low BP due to inadequate increase of SVR for the impaired CO. Despite the absence of expanded volemia, even a moderate increase in CFP/venous pulmonary pressures generates significant alveolar oedema[8] due to absence of alveolar–capillary barrier remodelling.[17,22]

Table 2 Spectrum of clinical, haemodynamic, and neurohormonal features of acute decompensated chronic heart failure and new-onset acute heart failure

Clinical, haemodynamic, and neurohormonal features	Acute decompensated chronic heart failure	New-onset acute heart failure
Blood pressure	Normal/hypertension	Low normal/hypotension
Systemic congestion	Moderate/severe	Absent/mild
Pulmonary congestion	Mild to severe	Mild to severe
Cardiac output	Depressed	Depressed
Cardiac filling pressure	Increased	Increased
Systemic vascular resistance	Very increased	Normal to increased
Sympathetic nervous system	Very increased	Increased
Renin–angiotensin–aldosterone system	Very increased	Increased
Cytokines/vasodilator mediators	Mild increase	Moderate/high increase

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Baseline biomarkers of myocardial injury/stretch may be only slightly elevated in early presenters with NOAHF, even in the setting of AMI. Indeed, the release kinetics of cTn and BNP/NT-proBNP are time dependent after the onset of symptoms.[27,28] The development of significant tissue hypoperfusion generates increased levels of lactate,[29] but baseline serum creatinine may underestimate the effective glomerular filtration rate and the extent of renal injury.[30]

Haemodynamic data from the SHOCK Trial Registry[31] in patients with AMI and the study from Dekker and colleagues[32] in patients with acute mitral regurgitation are consistent with this vascular phenotype. Mean value of BP was 89/54 and 61/38 mmHg, CO was 3.86 and 2.03 L/min, and SVR was 1257 and 2051 dyn·s/cm^5, respectively, in the SHOCK Trial Registry and in the Dekker study.

Overlap of vascular phenotypes

The spectrum of clinical, haemodynamic, and neurohormonal features generates possible overlap phenotypes in patients with ADCHF and NOAHF (*Table 2*). Indeed, a patient with chronic HF may present with low BP/hypotension in the setting of a septic precipitating cause (e.g. pneumonia).

On the other hand, a patient with prior mitral valve prolapse and chronic renal failure may be admitted for NOAHF with significant systemic congestion caused by acute mitral regurgitation due to rupture of chordae tendineae.

Clinical haemodynamic profiles

The American and European guidelines for HF[2,3] recommend the clinical assessment of haemodynamic status with the 2 × 2 table based on the degree of congestion ('dry' vs. 'wet', if absent vs. present) and peripheral hypoperfusion ('warm' vs. 'cold', if absent vs. present) in patients with AHF for guiding therapy. Although these clinical profiles are based on the four haemodynamic Forrester classes, defined by pulmonary artery catheterization (pulmonary-capillary wedge pressure $\leq$18 vs. $>$18 mmHg and cardiac index $>$2.2 vs. $\leq$2.2 L/min/m^2) with significant prognostic impact in patients with AMI,[33] their ability to estimate prognosis is contradictory.[34–36]

The majority of patients with ADCHF fit in the profiles B (wet and warm) and A (dry and warm), whereas patients with NOAHF can be placed in the profiles B and C (wet and cold).[35,36] Nevertheless, patients with ADCHF and NOAHF may present with any of all four clinical haemodynamic profiles and together with case presentations are illustrative of the extensive overlap of clinical haemodynamic assessment. This inadequate phenotyping of patients with AHF underscores the subjective nature of clinical assessment of haemodynamic profiles and may lead to ineffective or inappropriate treatments.[37]

Treatment implications

Treatment of AHF is aimed to correct the haemodynamic derangements responsible for the symptoms and signs, identify and treat the precipitating/underlying cause, and implement therapeutic measures to prevent disease progression.[2,3,5]

Acute decompensated chronic heart failure

Decongestive therapy with loop diuretics is the cornerstone in the treatment of patients with ADCHF[2,3] (*Table 3*). Vasodilators are also a first-line therapy, because they improve all the haemodynamic features of AHF. Indeed, they reduce SVR, which increases CO, and the final balance is unchanged BP with improved systemic perfusion. On the other hand, they reduce CFP and venous pressures, which translates into reduced fluid transudation and improvement in pulmonary/peripheral oedema.

Inotropic therapy with intrinsic vasodilation effect agents (inodilators) should be considered in patients with resistance to diuretic and/or vasodilator therapy. Actually, a poor diuretic response identified by a low weight loss indexed to diuretic use was associated with poorer prognosis[38] and may be used to select patients for ultrafiltration.[2,3]

Treatment of a correctable underlying precipitating factor is essential for the success of therapy.

Table 3 Treatment strategies for acute decompensated chronic heart failure and new-onset acute heart failure

Acute decompensated chronic heart failure	New-onset acute heart failure
Decongestive therapy	Vasopressor
Loop diuretics	Norepinephrine
Renal replacement therapy	Dopamine
Vasodilator	Intrathoracic positive pressure
Nitrates	Non-invasive ventilation
Nitroprusside	Mechanical ventilation
Nesiritide	Fluid challenge
Inodilator	Circulatory assist device
Dobutamine	Intra-aortic balloon pump
Levosimendan	ECMO
Milrinone, enoximone	Ventricular assist device
Treatment of the precipitating cause	Treatment of the underlying cause

ECMO, extracorporeal membrane oxygenation.

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New-onset acute heart failure

The treatment strategy of NOAHF is based on the immediate clinical stabilization of the patient to allow early percutaneous/surgical correction of the underlying acute severe cardiac disease, followed by supportive measures until the recovery.

Vasopressors (norepinephrine preferable over dopamine)[39] should be used in the presence of persistent hypotension. These catecholamines offer appropriate inotropic support,[5] and dobutamine should be used cautiously or even avoided owing to its vasodilation effect. In line with this vascular phenotype, the use of beta-blockers, angiotensin-converting enzyme inhibitors, nitrates, and morphine can precipitate shock.[40–43]

The cardiogenic respiratory failure should be managed with positive intrathoracic pressure provided by non-invasive or invasive mechanical ventilation. Some patients may need a fluid challenge to compensate the associated reduction in venous return[44] and the absence of systemic congestion.

The refractory cases to this standard management, presenting with persistent hypotension and/or systemic hypoperfusion, may be considered for mechanical circulatory support either before the correction of the acute underlying cardiac disease or after, as a bridge to recovery. Supportive measures may include renal replacement therapy and antibiotics to treat intestinal ischaemia-induced gram-negative bacteraemia. Failure of pharmacological therapies targeted to endothelial dysfunction (e.g. tilarginine), inflammation (e.g. pexelizumab and anti-CD18), and myocardial protection (e.g. delcasertib) in patients with AMI may represent a limitation of the simplistic view of its pathophysiology.[45]

The recognition that AHF is not a single disease but rather a set of clinical entities, even with different haemodynamic patterns, may contribute to a better understanding of failed clinical trials and to improve their future design.[6,46]

Patients with ADCHF usually present with failure of adaptive mechanisms in the setting of progressive heart disease, which is associated with higher mortality.[47] It is unlikely that a therapy used for a few hours/days during the acute phase could modify the natural history of heart disease, especially in the context of significant structural remodelling. On the other hand, the correction of the underlying cardiac disease in patients with NOAHF can modify the natural history of heart disease, as demonstrated by early myocardial revascularization in patients with AMI complicated by cardiogenic shock.[48]

Conclusions

Patients with ADCHF and NOAHF present with the haemodynamic hallmark of AHF—reduced CO and increased CFP and SVR. However, worsening of chronic HF occurs in a patient with full activation of adaptive mechanisms that maintain BP and systemic perfusion. On the other hand, rapid onset of HF in the setting of previous normal functioning heart not only does not allow full activation of adaptive mechanisms but also generates inappropriate responses from systemic endothelium leading to a further BP drop.

Consequently, two different vascular phenotypes can be described for ADCHF (moderate to severe systemic congestion and very increased SVR generating normal BP/hypertension) and NOAHF (absence of significant systemic congestion and inadequately high SVR for the level of CO leading to low BP/hypotension).

As a corollary, the treatment of ADCHF targets systemic congestion (diuretics) and SVR (vasodilators), while in NOAHF, vasoconstrictors may be required to maintain BP to allow the correction of the underlying cardiac disease, whenever possible.

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