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Understanding acute heart failure: pathophysiology and diagnosis

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Acute heart failure (AHF) is a relevant public health problem causing the majority of unplanned hospital admissions in patients aged of 65 years or more. AHF was historically described as a pump failure causing downstream hypoperfusion and upstream congestion. During the last decades a more complex network of interactions has been added to the simplistic haemodynamic model for explaining the pathophysiology of AHF. In addition, AHF is not a specific disease but the shared clinical presentation of different, heterogeneous cardiac abnormalities.
Persistence of poor outcomes in AHF might be related to the paucity of improvements in the acute management of those patients. Indeed, acute treatment of AHF still mainly consists of intravenous diuretics and/or vasodilators, tailored according to the initial haemodynamic status with little regard to the underlying pathophysiological particularities. Therefore, there is an unmet need for increased individualization of AHF treatment according to the predominant underlying pathophysiological mechanisms to, hopefully, improve patient's outcome.
In this article we review current knowledge on pathophysiology and initial diagnosis of AHF.

Introduction

Acute heart failure (AHF) is a relevant public health problem causing the majority of unplanned hospital admissions in patients aged of 65 years or more.[1] Despite major achievements in the treatment of chronic heart failure (HF) over the last decades, which led to marked improvement in long-term survival, outcomes of AHF remain poor with 90-day rehospitalization and 1-year mortality rates reaching 10–30%.[2] Persistence of poor outcomes in AHF might be related to the paucity of improvements in the acute management of those patients. Despite lacking evidence of beneficial effects on outcome, acute treatment of AHF still mainly consists of non-invasive ventilation in case of pulmonary oedema, intravenous diuretics and/or vasodilators. These interventions are tailored according to the initial haemodynamic status with little regard to the underlying pathophysiological particularities.[3–5]

Acute heart failure was historically described as a pump failure causing downstream hypoperfusion and upstream congestion. During the last decades a more complex network of interactions has been added to the simplistic haemodynamic model for explaining the pathophysiology of AHF.[6] In addition, AHF is not a specific disease but the shared clinical presentation of different, heterogeneous cardiac abnormalities. Therefore, there is an unmet need for increased individualization of AHF treatment according to the predominant underlying pathophysiological mechanisms to, hopefully, improve patient's outcome.

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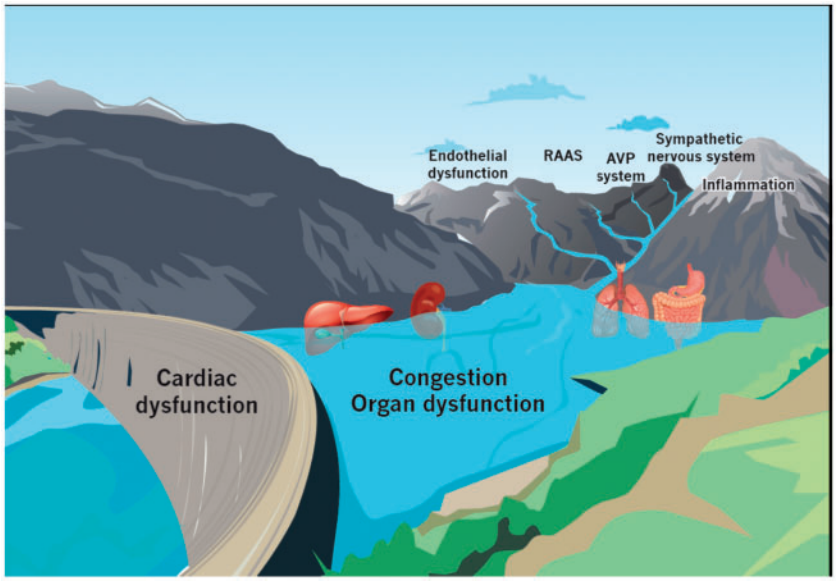

Figure 1 Congestion in heart failure.

Pathophysiology of acute heart failure

Acute heart failure is defined as new-onset or worsening of symptoms and signs of HF,[5] often requiring rapid escalation of therapy and hospital admission. The clinical presentation of AHF typically includes symptoms or signs related to congestion and volume overload rather than to hypoperfusion.[7] Since congestion plays a central role for the vast majority of AHF cases, understanding of the underlying pathophysiological mechanisms related to congestion is essential for treating AHF patients.[8] More importantly, the level of congestion and the number of congested organs have prognostic relevance in HF patients.[8]

Mechanisms of congestion: fluid accumulation and fluid redistribution

In presence of cardiac dysfunction, several neuro-humoral pathways, including the sympathetic nervous system, the renin-angiotensin-aldosterone system and the arginine-vasopressin system, are activated to counter the negative effects of HF on oxygen delivery to the peripheral tissues. Neuro-humoral activation in HF leads to impaired regulation of sodium excretion through the kidneys which results in sodium and, secondarily, fluid accumulation[9,10] (see *Figure 1*). Indeed, significantly increased cardiac filling pressures and venous congestion are frequently observed days or weeks before the overt clinical decompensation.[11-13]

Tissue oedema occurs when the transudation from capillaries into the interstitium exceeds the maximal drainage of the lymphatic system. Transudation of plasma fluid into the interstitium results from the relation between hydrostatic and oncotic pressures in the capillaries and in the interstitium as well as interstitial compliance. Increased transcapillary hydrostatic pressure gradient, decreased transcapillary oncotic pressure gradient and increased interstitial compliance promote oedema formation.

In healthy individuals, increased total body sodium is usually not accompanied by oedema formation since a large quantity of sodium may be buffered by interstitial glycosaminoglycan networks without compensatory water retention.[14] Moreover, the interstitial glycosaminoglycan networks display low compliance which prevents fluid accumulation in the interstitium.[15]

In HF, when sodium accumulation persists, the glycosaminoglycan networks may become dysfunctional resulting in reduced buffering capacity and increased compliance. In AHF the presence of pulmonary or peripheral oedema correlates poorly with left- and right-sided filling pressures,[16,17] but in patients with dysfunctional glycosaminoglycan networks even mildly elevated venous pressures might lead to pulmonary and peripheral oedemas.[9] In addition, since a large amount of sodium is stored in the interstitial glycosaminoglycan networks and does not reach the kidneys, it escapes renal clearance and is particularly difficult to remove from the body.[9]

Moreover, persistent neuro-humoral activation induces maladaptive processes resulting in detrimental ventricular remodelling and organ dysfunction. Based on that, pharmacological therapies that inhibit the sympathetic and renin-angiotensin-aldosterone systems, including beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists and more recently the angiotensin receptor neprilysin inhibitor LCZ696 have become the mainstays of chronic HF therapy.[18-33]

Fluid accumulation alone cannot explain the whole pathophysiology of AHF. Indeed, the majority of AHF patients display only a minor increase in body weight (<1 kg) before hospital admission.[11-13]

In those patients, congestion is precipitated by fluid redistribution, rather than accumulation. Sympathetic stimulation has been shown to induce a transient vasoconstriction leading to a sudden displacement of volume from the splanchnic and peripheral venous system to the pulmonary circulation, without exogenous fluid retention.[34,35]

Table 1 Overview of congestion-induced organ dysfunction and clinical manifestations

Congested organ	Clinical manifestation	References
Heart	Third heart sound, jugular vein distension, positive hepato-jugular reflux Functional mitral and tricuspid regurgitation Elevated NPs: BNP >100 pg/mL, NT-proBNP >300 pg/mL, MR-proANP >120 pmol/L	83-85
Lung	Dyspnoea, orthopnoea, bendopnoea, paroxysmal nocturnal dyspnoea Auscultatory rales, crackles, wheezing; tachypnoea and hypoxia Pathological chest radiography (interstitial/alveolar oedema, pleural effusion) B-lines ('comets') on lung ultrasound	8,66
Kidney	Decreased urine output Elevated creatinine levels, hyponatraemia	44,45
Liver	Right-sided upper abdominal discomfort, hepatomegaly, icterus Elevated parameters of cholestasis	47,48
Bowel	Nausea, vomiting, abdominal pain Ascites, increased abdominal pressure Cachexia	46,51

Nonetheless, the prerequisite for fluid redistribution is the presence of a certain amount of peripheral and splanchnic congestion.

In physiological states, capacitance veins contain one fourth of the total blood volume and stabilize cardiac preload, buffering volume overload.[36,37] In hypertensive AHF, the primary alteration is a mismatch in the ventricular-vascular coupling relationship with increased afterload and decreased venous capacitance (increased preload).[38]

Fluid accumulation and fluid redistribution both produce an increase in cardiac load and congestion in AHF, but their relevance is likely to vary according to different clinical scenarios. While fluid accumulation might be more common in decompensations of congestive heart failure (CHF) with reduced ejection fraction, fluid redistribution might be the predominant pathophysiological mechanism in AHF with preserved ejection fraction.[39] Accordingly, the decongestive therapy should be tailored. While diuretics might be useful in presence of fluid accumulation, vasodilators might be more appropriate in presence of fluid redistribution to modulate ventricular-vascular coupling.

Furthermore, recent experimental data from human models suggest that venous congestion is not simply an epiphenomenon secondary to cardiac dysfunction but rather plays an active detrimental role in the pathophysiology of AHF inducing pro-oxidant, pro-inflammatory and haemodynamic stimuli that contribute to acute decompensation.[40] How these pathophysiological changes are induced remains incompletely understood but the biomechanical forces generated by congestion significantly contribute to endothelial and neuro-humoral activation. Indeed, endothelial stretch triggers an intracellular signalling cascade and causes endothelial cells to undergo a phenotypic switch to a pro-oxidant, pro-inflammatory vasoconstricted state.[41]

Congestion-induced organ dysfunction

Venous congestion significantly contributes to organ dysfunction in both chronic and acute HF (see *Table 1*).

The close interaction between cardiac and renal dysfunction is known as the cardio-renal syndrome.[42] Historically, renal dysfunction in HF was described as consequence of reduced cardiac index and arterial underfilling both causing renal hypoperfusion.[43] More recent data showed that venous congestion (assessed as increased central venous pressure) was the strongest haemodynamic determinant for the development of renal dysfunction and low cardiac index alone in AHF has minor effects on renal function.[44,45] However, the combination of elevated central venous pressure and low cardiac index is particularly unfavourable for renal function.

Visceral congestion may increase intra-abdominal pressure in HF, which further negatively affects renal function in HF. Recent data showed that reducing central venous and intra-abdominal pressures by decongestive therapy may ameliorate serum creatinine, presumably by alleviating renal and abdominal congestion.[46]

Cardiac dysfunction is frequently associated with liver abnormalities (cardio-hepatic syndrome) and negatively influences prognosis in AHF.[47,48] Cholestatic liver dysfunction is common in HF and is mainly related to right-sided congestion, while rapid and marked elevation in transaminases in AHF indicates hypoxic hepatitis related to hypoperfusion.[49,50] Finally, bowel congestion may contribute to development of cachexia in patients with advanced HF.[51]

Assessment of congestion

Detection of congestion at an early (asymptomatic) stage is still an unmet need. Improved diagnostic methods would be highly valuable to enable early initiation of appropriate therapy following the 'time to therapy' approach recently introduced into HF guidelines.[5] The guidelines emphasize the potentially greater benefit of early treatment in the setting of AHF, as has long been the case for acute coronary syndromes. Indeed, the congestive cascade often begins several days or weeks before symptom onset and includes a sub-clinical increase of cardiac filling and venous pressures ('haemodynamic congestion') which may further lead to redistribution of fluids within the lungs and visceral organs ('organ congestion') and finally to overt signs and symptoms of volume overload ('clinical congestion').[12,52] Clinical congestion may be the 'tip of the iceberg' of the

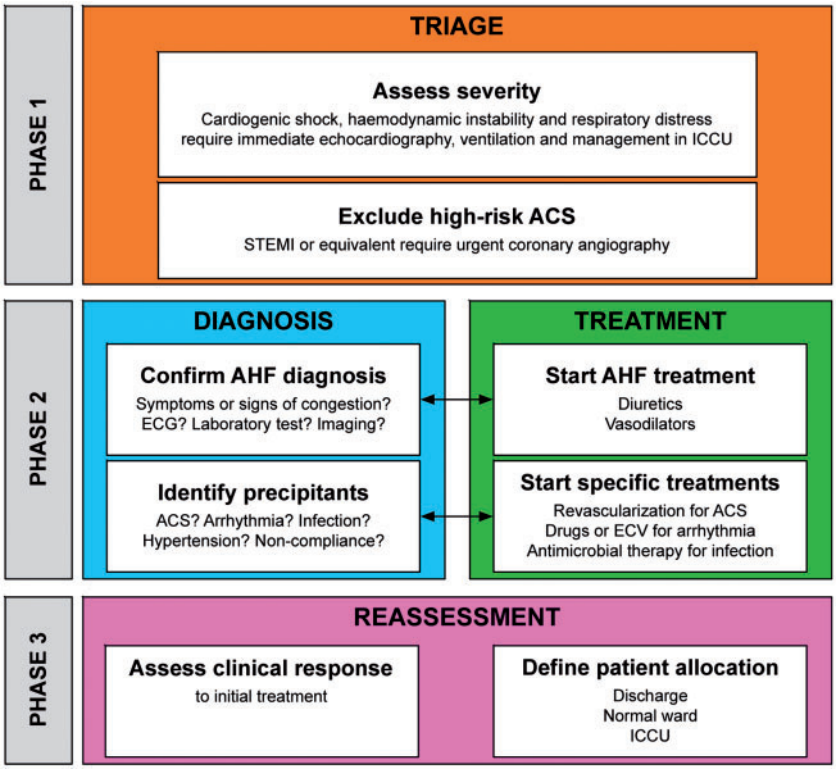

Figure 2 Early management of AHF.

congestive cascade[8]. Although organ congestion is usually related to haemodynamic congestion, this might not be always true: indeed, several mechanisms might prevent oedema formation despite increased venous pressures and conversely, oedema might develop even in absence of increased hydrostatic pressure.[53]

To achieve early detection of congestion, several strategies including cardiac biomarkers, intrathoracic impedance monitoring and implantable haemodynamic monitoring have been proposed.[54-59] However, the use of classical biomarkers, in particular natriuretic peptides (NPs), which are released by the failing heart, reflect the severity of myocardial dysfunction and only indirectly haemodynamic congestion.[60,61] Novel vascular biomarkers (e.g. soluble CD146, CA125) might better correlate with congestion than NPs.[62-65]

Diagnosis of acute heart failure

The early management of AHF should consist of three parts: triage, diagnosis and initiation of treatment, and reassessment (see *Figure 2*). Since AHF is a life threatening condition, current guidelines for the management of AHF recommend that diagnosis and initiation of treatment should occur as early as possible, optimally during the first 30–60 min after hospital admission.[3-5]

Clinical evaluation

The initial clinical evaluation of dyspnoeic patients should help to (i) assess severity of AHF (ii) confirm the diagnosis of AHF and (iii) identify precipitating factors of AHF.

Since congestion is a typical feature of AHF, patient history and physical examination should primarily focus on the presence of congestion which would support the diagnosis of AHF. Left-sided congestion may cause dyspnoea, orthopnoea, bendopnoea, paroxysmal nocturnal dyspnoea, cough, tachypnoea, pathological lung auscultation (rales, crackles, wheezing) and hypoxia.[8] The absence of rales and a normal chest radiography do not exclude the presence of left-sided congestion. Indeed, 40–50% of patients with elevated pulmonary-artery wedge pressure may have a normal chest radiography.[66] Right-sided congestion may cause increased body weight, bilateral peripheral oedema, decreased urine output, abdominal pain, nausea and vomiting, jugular vein distension or positive hepato-jugular reflux, ascites, hepatomegaly, icterus.[8]

Symptoms and signs of hypoperfusion indicate severity and may include hypotension, tachycardia, weak pulse, mental confusion, anxiety, fatigue, cold sweated extremities, decreased urine output and angina due to myocardial ischaemia. The presence of inappropriate stroke volume and clinical and biological signs of hypoperfusion in AHF defines cardiogenic shock, the most severe form of cardiac dysfunction.[67] Cardiogenic shock is most frequently related to acute myocardial infarction and accounts for less than 10% of AHF cases but is associated with in-hospital mortality rates of 40–50%.[39,68]

However, given the limited sensitivity and specificity of symptoms and signs of AHF, the clinical evaluation should integrate information from additional tests.[69,70]

According to the presence of clinical symptoms or signs of organ congestion ('wet' vs. 'dry') and/or peripheral hypoperfusion ('cold' vs. 'warm'), patients may be classified in

four groups. [67,71] About two of three AHF patients are classified 'wet-warm' (congested but well perfused), about one of four are 'wet-cold' (congested and hypoperfused) and only a minority are 'dry-cold' (not congested and hypoperfused). The fourth group 'dry-warm' represent the compensated (decongested, well-perfused) status. This classification may help to guide initial therapy (mostly vasodilators and/or diuretics) and carries prognostic information.[70] Patients with cardiopulmonary distress should be managed in intensive cardiac care units.

Notably, the use of inotropes should be restricted to patients with cardiogenic shock or AHF resulting in hypotension and hypoperfusion to maintain end-organ function,[5] since their often inappropriate use is associated with increased morbidity and mortality.[72]

Acute heart failure usually consists of acute decompensation of chronic HF (ADHF) or, less frequently, may arise in patients without previous history of symptomatic HF (*de novo* AHF).[68] The distinction of these two scenarios is important because the underlying mechanisms leading to AHF are significantly different. Indeed, while pre-existing pathophysiological derangements predispose CHF patients to ADHF, *de novo* AHF is typically induced by severe haemodynamic alterations secondary to the initial insult. Common causes of *de novo* AHF include acute myocardial infarction, severe myocarditis, acute valve regurgitation and pericardial tamponade.[68] On the other hand, ADHF may be precipitated by several clinical conditions, while in some patients, no precipitant can be identified.[2,73–75]

Rapid identification of precipitants of AHF is crucial to optimize patient management. The most common precipitants are myocardial ischaemia, arrhythmias (in particular paroxysmal atrial fibrillation), sepsis and/or pulmonary disease, uncontrolled hypertension, non-compliance with medical prescriptions, renal dysfunction and iatrogenic causes. The identification of precipitants of AHF aims at detecting reversible or treatable causes and at assisting prognostication. Indeed, the initial management should include, in addition to vasodilators and/or diuretics, also specific treatments directed towards the underlying causes of AHF. In particular, early coronary angiography with revascularization is recommended in AHF precipitated by acute coronary syndrome, antiarrhythmic treatment and/or electrical cardioversion are recommended in AHF precipitated by arrhythmia, rapid initiation of antimicrobial therapy is recommended for AHF precipitated by sepsis.[76–79] Furthermore, identification of precipitants of AHF may allow risk stratification of patients with AHF. Indeed, AHF precipitated by acute coronary syndrome or infection is associated with poorer outcomes whereas outcomes tend to be better in AHF precipitated by atrial fibrillation or uncontrolled hypertension.[73,74]

Additional tests

Additional laboratory tests are helpful in the evaluation of patients with AHF. Natriuretic peptides, including B-type NP (BNP), amino-terminal pro-B-type NP (NT-proBNP) and mid-regional pro-atrial NPs (MR-proANP) show high accuracy and excellent negative predictive value in differentiating AHF from non-cardiac causes of acute dyspnoea.[80] Natriuretic peptide levels in HFpEF are lower than in HFrEF. Low circulating NPs (thresholds: BNP <100 pg/mL, NT-proBNP <300 pg/mL, MR-proANP <120 pmol/L) make the diagnosis of AHF unlikely. This is true for both HFrEF and HFpEF. A recent meta-analysis indicated that at these thresholds BNP and NT-proBNP have sensitivities of 0.95 and 0.99 and negative predictive values of 0.94 and 0.98, respectively, for a diagnosis of AHF.[80] MRproANP had a sensitivity ranging from 0.95 to 0.97 and a negative predictive value ranging from 0.90 to 0.97.[80]

However, elevated levels of NPs do not automatically confirm the diagnosis of AHF, as they may also be associated with a wide variety of cardiac and non-cardiac causes. Among them, atrial fibrillation, age, and renal failure are the most important factors impeding the interpretation of NP measurements. On the other hand, NP levels may be disproportionally low in obese patients and in those with flash pulmonary oedema. Natriuretic peptides should be measured in all patients with suspected AHF upon presentation to the emergency department or intensive cardiac care units.[3–5]

Cardiac troponin may be helpful to exclude myocardial ischaemia as precipitating factor of AHF. However, cardiac troponin, in particular when measured with high-sensitive assays, is frequently elevated in patients with AHF, often without obvious myocardial ischaemia or an acute coronary event. Indeed, AHF is characterized by accelerated myocardial necrosis and remodelling. Troponin measurement may be considered for prognostication as elevated levels are associated with poorer outcomes.[81] Numerous clinical variables and biomarkers are independent predictors of in-hospital complications and longer-term outcomes in AHF syndromes, but their impact on management has not been adequately established. The easy-to perform AHEAD score based on the analysis of co-morbidities has been shown to provide relevant information on short and long term prognosis of patients hospitalized for AHF.[82]

An electrocardiography (ECG) may be helpful to identify potential precipitants of AHF (e.g. arrhythmia, ischaemia) and to exclude ST-elevation myocardial infarction requiring immediate revascularization. However, ECG is rarely normal in AHF patients. Current guidelines do not recommend immediate echocardiography in all patients presenting with AHF.[3–5] However, all patients presenting with cardiogenic shock or suspicion of acute life-threatening structural or functional cardiac abnormalities (mechanical complications, acute valve regurgitation, aortic dissection) should receive immediate echocardiography. Early echocardiography should be considered in all patients with *de novo* AHF and in those with unknown cardiac function, however, the optimal timing is unknown (preferably within 24–48 h from admission).[3–5]

Thoracic ultrasound and chest X-ray may both be useful to assess the presence of interstitial pulmonary oedema. While chest X-ray may also be helpful to rule-out alternative causes of dyspnoea (e.g. pneumothorax, pneumonia), both techniques provide complementary information about the presence of pulmonary oedema or pleural effusion. Abdominal ultrasound may be useful to measure inferior vena cava diameter and collapsibility and exclude the presence of ascites.[3–5]

Reassessment and allocation

Most of the patients presenting with AHF require hospital admission. The level of care (discharge, observation, ward, telemetry and intensive cardiac care unit) should be based on history (including symptom severity, precipitating factors), physical examination (haemodynamic and respiratory status, degree of congestion) and biomarkers (NPs, cardiac troponin, renal function, serum lactate). Forty to 50% of AHF patients require admission to intensive cardiac care units.[39,68] Low risk AHF patients (those with slightly elevated NP levels, normal blood pressure, stable renal failure, normal troponin) and with good response to initial therapy may be considered for early discharge. Follow-up plans must be in place prior to discharge and clearly communicated to the primary care team.[3–5]

Pathophysiology-based management

According to current knowledge on the pathophysiology of AHF, the initial treatment of AHF patients should include decongestive therapy (e.g. vasodilators and/or diuretics) and specific therapy directed towards the underlying causes of AHF (e.g. revascularization, antiarrhythmic treatments, antimicrobial drugs). Moreover, early administration of oral disease-modifying HF therapy (beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and mineralocorticoid receptor antagonists), before hospital discharge is recommended in all patients with AHF.

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References

1. Townsend N, Nichols M, Scarborough P, Rayner M. Cardiovascular disease in Europe–epidemiological update 2015. *Eur Heart J* 2015;**36**:2696–2705.
2. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CSP, Sato N, Shah AN, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;**63**:1123–1133.
3. Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, Ristic AD, Lambrinou E, Masip J, Riley JP, McDonagh T, Mueller C, deFilippi C, Harjola V-P, Thiele H, Piepoli MF, Metra M, Maggioni A, McMurray JJV, Dickstein K, Damman K, Seferovic PM, Ruschitzka F, Leite-Moreira AF, Bellou A, Anker SD, Filippatos G. Recommendations on pre-hospital and early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine - short version. *Eur Heart J* 2015;**36**:1958–1966.
4. Mebazaa A, Tolppanen H, Mueller C, Lassus J, diSomma S, Baksyte G, Cecconi M, Choi DJ, Cohen-Solal A, Christ M, Masip J, Arrigo M, Nouira S, Ojji D, Peacock F, Richards M, Sato N, Sliwa K, Spinar J, Thiele H, Yilmaz MB, Januzzi J. Acute heart failure and cardiogenic shock: a multidisciplinary practical guidance. *Intensive Care Med* 2016;**42**:147–163.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members, Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
6. Mentz RJ, O'connor CM. Pathophysiology and clinical evaluation of acute heart failure. *Nat Rev Cardiol* 2016;**13**:28–35.
7. Costanzo MR, Jessup M. Treatment of congestion in heart failure with diuretics and extracorporeal therapies: effects on symptoms, renal function, and prognosis. *Heart Fail Rev* 2012;**17**:313–324.
8. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JEA, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, Van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJV, Filippatos G, European Society of Cardiology, European Society of Intensive Care Medicine. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail* 2010;**12**:423–433.
9. Nijst P, Verbrugge FH, Grieten L, Dupont M, Steels P, Tang WHW, Mullens W. The pathophysiological role of interstitial sodium in heart failure. *J Am Coll Cardiol* 2015;**65**:378–388.
10. McKie PM, Schirger JA, Costello-Boerrigter LC, Benike SL, Harstad LK, Bailey KR, Hodge DO, Redfield MM, Simari RD, Burnett JC, Chen HH. Impaired natriuretic and renal endocrine response to acute volume expansion in pre-clinical systolic and diastolic dysfunction. *J Am Coll Cardiol* 2011;**58**:2095–2103.
11. Yu C-M, Chan JY-S, Zhang Q, Omar R, Yip GW-K, Hussin A, Fang F, Lam KH, Chan HC-K, Fung JW-H. Biventricular pacing in patients with bradycardia and normal ejection fraction. *N Engl J Med* 2009;**361**:2123–2134.
12. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. *Circulation* 2007;**116**:1549–1554.
13. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, Aranda JM, Abraham WT, Smart FW, Stevenson LW, Kueffer FJ, Bourge RC. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation* 2008;**118**:1433–1441.
14. Titze J, Shakibaei M, Schafflhuber M, Schulze-Tanzil G, Porst M, Schwind KH, Dietsch P, Hilgers KF. Glycosaminoglycan polymerization may enable osmotically inactive Na+ storage in the skin. *Am J Physiol Heart Circ Physiol* 2004;**287**:H203–H208.
15. Guyton AC. Interstitial fluid pressure. Pressure-volume curves of interstitial space. *Circ Res* 1965;**16**:452–460.
16. Breidthardt T, Irfan A, Klima T, Drexler B, Balmelli C, Arenja N, Socrates T, Ringger R, Heinisch C, Ziller R, Schifferli J, Meune C, Mueller C. Pathophysiology of lower extremity edema in acute heart failure revisited. *Am J Med* 2012;**125**:1124.e1–1124.e8.
17. Zile MR, Adamson PB, Cho YK, Bennett TD, Bourge RC, Aaron MF, Aranda JM, Abraham WT, Stevenson LW, Kueffer FJ. Hemodynamic factors associated with acute decompensated heart failure: part 1–insights into pathophysiology. *J Card Fail* 2011;**17**:282–291.
18. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;**334**:1349–1355.
19. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
20. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–2007.
21. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Böhm M, Anker SD,

Thompson SG, Poole-Wilson PA, SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;**26**:215–225.
22. The Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;**316**:1429–1435.
23. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;**325**:293–302.
24. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigattors. *N Engl J Med* 1992;**327**:685–691.
25. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klinger GH, Neaton J, Sharma D, Thiyagarajan B. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial–the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;**355**:1582–1587.
26. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667–1675.
27. Maggioni AP, Anand I, Gottlieb SO, Latini R, Tognoni G, Cohn JN, Val-HeFT Investigators (Valsartan Heart Failure Trial). Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol* 2002;**40**:1414–1421.
28. Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K, CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–776.
29. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, Riegger GAJ, Malbecq W, Smith RD, Guptha S, Poole-Wilson PA, HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009;**374**:1840–1848.
30. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM, TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**:1383–1392.
31. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321.
32. Zannad F, McMurray JJV, Krum H, Van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
33. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, the PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
34. Sánchez-Marteles M, Rubio Gracia J, Giménez López I. Pathophysiology of acute heart failure: a world to know. *Rev Clin Esp* 2016;**216**:38–46.
35. Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure–re-distribution and other mechanisms beyond fluid accumulation. *Eur J Heart Fail* 2008;**10**:165–169.
36. Greenway CV, Lister GE. Capacitance effects and blood reservoir function in the splanchnic vascular bed during non-hypotensive haemorrhage and blood volume expansion in anaesthetized cats. *J Physiol (Lond)* 1974;**237**:279–294.
37. Greenway CV. Role of splanchnic venous system in overall cardiovascular homeostasis. *Fed Proc* 1983;**42**:1678–1684.
38. Viau DM, Sala-Mercado JA, Spranger MD, O'leary DS, Levy PD. The pathophysiology of hypertensive acute heart failure. *Heart* 2015;**101**:1861–1867.
39. Rudiger A, Harjola V-P, Müller A, Mattila E, Säila P, Nieminen M, Follath F. Acute heart failure: clinical presentation, one-year mortality and prognostic factors. *Eur J Heart Fail* 2005;**7**:662–670.
40. Colombo PC, Onat D, Harxhi A, Demmer RT, Hayashi Y, Jelic S, LeJemtel TH, Bucciarelli L, Kebschull M, Papapanou P, Uriel N, Schmidt AM, Sabbah HN, Jorde UP. Peripheral venous congestion causes inflammation, neurohormonal, and endothelial cell activation. *Eur Heart J* 2014;**35**:448–454.
41. Colombo PC, Doran AC, Onat D, Wong KY, Ahmad M, Sabbah HN, Demmer RT. Venous congestion, endothelial and neurohormonal activation in acute decompensated heart failure: cause or effect?. *Curr Heart Fail Rep* 2015;**12**:215–222.
42. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008;**52**:1527–1539.
43. Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure. Relationship of cardiac index to kidney function. *Drugs* 1990;**39 Suppl 4**:10–21.
44. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, Yancy CW, Califf RM, Stevenson LW, Hill JA. Cardiorenal interactions: insights from the ESCAPE trial. *J Am Coll Cardiol* 2008;**51**:1268–1274.
45. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WHW. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* 2009;**53**:589–596.
46. Verbrugge FH, Dupont M, Steels P, Grieten L, Malbrain M, Tang WHW, Mullens W. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. *J Am Coll Cardiol* 2013;**62**:485–495.
47. Poelzl G, Ess M, Mussner-Seeber C, Pachinger O, Frick M, Ulmer H. Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. *Eur J Clin Invest* 2012;**42**:153–163.
48. Nikolaou M, Parissis J, Yilmaz MB, Seronde M-F, Kivikko M, Laribi S, Paugam-Burtz C, Cai D, Pohjanjousi P, Laterre P-F, Deye N, Poder P, Cohen-Solal A, Mebazaa A. Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure. *Eur Heart J* 2013;**34**:742–749.
49. Ebert EC. Hypoxic liver injury. *Mayo Clin Proc* 2006;**81**:1232–1236.
50. Henrion J, Schapira M, Luwaert R, Colin L, Delannoy A, Heller F. Hypoxic hepatitis: clinical and hemodynamic study in 142 consecutive cases. *Medicine (Baltimore)* 2003;**82**:392–406.
51. Valentova M, Haehling von S, Bauditz J, Doehner W, Ebner N, Bekfani T, Elsner S, Sliziuk V, Scherbakov N, Murin J, Anker SD, Sandek A. Intestinal congestion and right ventricular dysfunction: a link with appetite loss, inflammation, and cachexia in chronic heart failure. *Eur Heart J* 2016;**37**:1684–1691.
52. Picano E, Gargani L, Gheorghiade M. Why, when, and how to assess pulmonary congestion in heart failure: pathophysiological, clinical, and methodological implications. *Heart Fail Rev* 2010;**15**:63–72.
53. Arrigo M, Huber LC. Eponyms in cardiopulmonary reflexes. *Am J Cardiol* 2013;**112**:449–453.
54. Bourge RC, Abraham WT, Adamson PB, Aaron MF, Aranda JM, Magalski A, Zile MR, Smith AL, Smart FW, O'shaughnessy MA, Jessup ML, Sparks B, Naftel DL, Stevenson LW, COMPASS-HF Study Group. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. *J Am Coll Cardiol* 2008;**51**:1073–1079.
55. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, Phillips CO, Hodshon BV, Cooper LS, Krumholz HM. Telemonitoring in patients with heart failure. *N Engl J Med* 2010;**363**:2301–2309.
56. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, Brachmann J, Lewalter T, Goette A, Block M, Kautzner J, Sack S, Husser D, Piorkowski C, Sogaard P, IN-TIME study group. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. *Lancet* 2014;**384**:583–590.
57. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS, CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011;**377**:658–666.
58. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GYH, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis

and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787–1847.
59. Troughton R, Michael Felker G, Januzzi JL. Natriuretic peptide-guided heart failure management. *Eur Heart J* 2014;**35**:16–24.
60. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC, Grinfeld L, Udelson JE, Zannad F, Gheorghiade M, EVEREST Trial Investigators. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J* 2013;**34**:835–843.
61. Sabatine MS, Morrow DA, de Lemos JA, Omland T, Desai MY, Tanasijevic M, Hall C, McCabe CH, Braunwald E. Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. *J Am Coll Cardiol* 2004;**44**:1988–1995.
62. Gayat E, Caillard A, Laribi S, Mueller C, Sadoune M, Seronde M-F, Maisel A, Bartunek J, Vanderheyden M, Desutter J, Dendale P, Thomas G, Tavares M, Cohen-Solal A, Samuel J-L, Mebazaa A. Soluble CD146, a new endothelial biomarker of acutely decompensated heart failure. *Int J Cardiol* 2015;**199**:241–247.
63. Kubena P, Arrigo M, Parenica J, Gayat E, Sadoune M, Ganovska E, Pavlusova M, Littnerova S, Spinar J, Mebazaa A, GREAT network. Plasma levels of soluble CD146 reflect the severity of pulmonary congestion better than brain natriuretic peptide in acute coronary syndrome. *Ann Lab Med* 2016;**36**:300–305.
64. Núñez J, Llàcer P, Núñez E, Ventura S, Bonanad C, Bodí V, Miñana G, Santas E, Mascarell B, Fonarow GC, Chorro FJ, Sanchis J. Antigen carbohydrate 125 and creatinine on admission for prediction of renal function response following loop diuretic administration in acute heart failure. *Int J Cardiol* 2014;**174**:516–523.
65. Arrigo M, Truong QA, Onat D, Szymonifka J, Gayat E, Tolppanen H, Sadoune M, Demmer RT, Wong KY, Launay JM, Samuel JL, Cohen-Solal A, Januzzi JL, Singh JP, Colombo PC, Mebazaa A. Soluble CD146 is a Novel Marker of Systemic Congestion with Prognostic Role in Severe Heart Failure Patients: An Experimental Mechanistic and Transcardiac Prognostic Study. *Clin Chem* 2016; in press.
66. Chakko S, Woska D, Martinez H, de Marchena E, Futterman L, Kessler KM, Myerberg RJ. Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. *Am J Med* 1991;**90**:353–359.
67. Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, Stevenson LW. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol* 2003;**41**:1797–1804.
68. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola V-P, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L. EuroHeart Survey Investigators, Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;**27**:2725–2736.
69. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 1989;**261**:884–888.
70. Drazner MH, Hellkamp AS, Leier CV, Shah MR, Miller LW, Russell SD, Young JB, Califf RM, Nohria A. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. *Circ Heart Fail* 2008;**1**:170–177.
71. Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. *JAMA* 2002;**287**:628–640.
72. Arrigo M, Mebazaa A. Understanding the differences among inotropes. *Intensive Care Med* 2015;**41**:912–915.
73. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'connor CM, Pieper K, Sun JL, Yancy CW, Young JB, OPTIMIZE-HF Investigators and Hospitals. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. *Arch Intern Med* 2008;**168**:847–854.
74. Arrigo M, Tolppanen H, Sadoune M, Feliot E, Teixeira A, Laribi S, Plaisance P, Nouira S, Yilmaz MB, Gayat E, Mebazaa A, Network OBOTG. Effect of precipitating factors of acute heart failure on readmission and long-term mortality. *ESC Heart Fail* 2016;**3**:115–121.
75. Arrigo M, Gayat E, Parenica J, Ishihara S, Zhang J, Choi DJ, Park JJ, AlHabib KF, Sato N, Miro O, Maggioni A, Zhang Y, Spinar J, Cohen-Solal A, Iwashyna TJ, Mebazaa A. Identification of precipitating factors to predict short-term outcome of acute heart failure: a report from the intercontinental GREAT registry. *Eur J Heart Fail*; in press.
76. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. *N Engl J Med* 1999;**341**:625–634.
77. Santoro GM, Carrabba N, Migliorini A, Parodi G, Valenti R. Acute heart failure in patients with acute myocardial infarction treated with primary percutaneous coronary intervention. *Eur J Heart Fail* 2008;**10**:780–785.
78. Arrigo M, Jaeger N, Seifert B, Spahn DR, Bettex D, Rudiger A. Disappointing success of electrical cardioversion for new-onset atrial fibrillation in cardiosurgical ICU patients. *Crit Care Med* 2015;**43**:2354–2359.
79. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J-D, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent J-L, Angus DC. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;**315**:801–810.
80. Peacock WF, De Marco T, Fonarow GC, Diercks D, Wynne J, Apple FS, Wu AHB, ADHERE Investigators. Cardiac troponin and outcome in acute heart failure. *N Engl J Med* 2008;**358**:2117–2126.
81. Roberts E, Ludman AJ, Dworzynski K, Al-Mohammad A, Cowie MR, McMurray JJV, Mant J, NICE Guideline Development Group for Acute Heart Failure. The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting. *BMJ* 2015;**350**:h910.
82. Spinar J, Jarkovsky J, Spinarova L, Mebazaa A, Gayat E, Vitovec J, Linhart A, Widimsky P, Miklik R, Zeman K, Belohlavek J, Malek F, Felsoci M, Kettner J, Ostadal P, Cihalik C, Vaclavik J, Taborsky M, Dusek L, Littnerova S, Parenica J. AHEAD score–Long-term risk classification in acute heart failure. *Int J Cardiol* 2016;**202**:21–26.
83. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AHB, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA, Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;**347**:161–167.
84. Januzzi JL, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, Tung R, Cameron R, Nagurney JT, Chae CU, Lloyd-Jones DM, Brown DF, Foran-Melanson S, Sluss PM, Lee-Lewandrowski E, Lewandrowski KB. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol* 2005;**95**:948–954.
85. Maisel A, Mueller C, Nowak R, Peacock WF, Landsberg JW, Ponikowski P, Möckel M, Hogan C, Wu AHB, Richards M, Clopton P, Filippatos GS, Di Somma S, Anand I, Ng L, Daniels LB, Neath S-X, Christenson R, Potocki M, McCord J, Terracciano G, Kremastinos D, Hartmann O, Haehling von S, Bergmann A, Morgenthaler NG, Anker SD. Mid-region pro-hormone markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *J Am Coll Cardiol* 2010;**55**:2062–2076.