

Novelties in the early management of acute heart failure syndromes

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Summary

The recent European Society of Cardiology (ESC) guidelines delineate the diagnosis and management of distinct categories of acute heart failure syndromes. However, physicians dealing with these patients may need guidance in choosing therapeutic alternatives as soon as the dyspneic patient arrives at the emergency department, until distinct categories of the ESC guidelines are identified. Hence, this manuscript summarizes practical recommendations for the very early management of patients with acute heart failure syndromes. The recommendations are based on a clinical classification system considering the initial systolic blood pressure and other symptoms. Early initiation of diagnostic and goal-directed treatment strategies are key factors in improving patient outcomes. Early and frequent reassessment is also imperative so that adjustments to the initial therapeutic approach can be made, as clinically indicated.

Key words: heart failure; acute; emergency treatment

Introduction

Acute heart failure (AHF) is defined as a gradual or rapid change in heart failure (HF) signs and symptoms, resulting in the need for urgent therapy. AHF is complex and encompasses multiple diagnoses and etiologies [1].

There are many novelties that were recently published, which might change methods to manage AHF in the near future [2–4]. The first novelty is that AHF is not a single disease but several “syndromes” arising from multiple clinical scenarios. The present review describes those scenarios that are identified by the initial level of systolic blood pressure (SBP) at admission. In addition, each scenario is linked to a primary physiopathologic problem. We think that in the emergency setting, physicians are left alone

with symptoms and vital signs of the patients. Herein, initiation of treatments based upon blood pressure is suggested, as patients may not be classified into distinct diagnostic categories of the European Society of Cardiology (ESC) guidelines within minutes of admission, though they may definitely be in need of urgent therapy. The present review insists on the initiation of the appropriate treatment as early as possible. Early treatment is defined as the pre-hospital phase and the first 6–12 hours after presentation [4]. The current paper is not intended to replace existing guidelines, rather implement them for facilitating *very early* clinical management of patients with AHF syndromes in a practical approach.

Rationale for early treatment of acute heart failure syndromes (AHFS)

The need for immediate treatment is obvious in conditions such as pulmonary edema or cardiogenic shock. Furthermore, a retrospective analysis from ADHERE evaluated the association between clinical outcomes and time to initiation of vasoactive therapy [5]. The authors observed an almost even distribution of patients who received vasoactive agents in the emergency department (ED) (n = 4096) as compared to the inpatient unit (n = 3499). The mean time to vasoactive therapy initiation was 1–2 hours when it was initiated in the ED, compared to 20–22 hours when it was given after admission. Early administration in the ED was associated with a shorter median length of stay in the hospital (4.5 days vs 7 days, $p < 0.0001$) and a lower in-hospital mortality rate (4.3% vs 10.9%, $p < 0.0001$) [5]. These data and others suggest that early initiation of treatment for AHFS is a key factor in improving outcomes among critically ill patients.

Diagnostic assessment to guide early management of AHFS

ECG and chest X-ray should be performed together with a clinical exam in order to designate perfusion and congestion status in all acute dyspneic patients admitted in the ED [6]. Of note, echocardiography is not needed in the

ED for most patients, but should be performed at the earliest appropriate time according to the mechanism of AHF and individual patient need [2]. Biological tests should include sodium, potassium, glucose, blood urea nitrogen or urea, serum creatinine, CK-MB and/or troponin T or I and a complete blood count.

The use of biomarkers to detect HF in the ED is based on the three observations: dyspnea is very frequent in the ED, AHFS is a major cause of acute dyspnea, and clinical signs such as ECG and chest X-ray may not always immediately rule AHFS in or out. Most of the diseases that lead to acute dyspnea need immediate and appropriate treatment: for example delaying antibiotic treatment and giving diuretics for a pulmonary infection may further harm the patient; optimal use of biomarkers can minimize harmful effect of mistreatment [7].

In the ED or in cardiology, natriuretic peptides (NPs; BNP and NT-proBNP as well as midregional proANP and proANP) are now considered as relevant quantitative markers of HF (and/or cardiac stress) that designate the extent of systolic and diastolic left ventricular dysfunction, valvular dysfunction, and right ventricular dysfunction, though they are not perfect [8]. The most recent ESC guidelines state that NPs are particularly useful in excluding HF with a reasonable negative predictive value [2]. In addition, the use of NPs improves medical and economic outcomes in patients with dyspnea [8]. Rational use of NPs in the emergency setting in patients presenting with dyspnea may help avoiding serious adverse events as well [7]. The accepted thresholds to confirm AHF were described recently [8] (fig. 1). However, there are still areas of uncertainty regarding the use of NPs in the emergency room. Indeed, the threshold of plasma NPs to differentiate between AHF and non-AHF is lower in obese patients and higher in chronic renal failure patients than the thresholds described above [9].

Initial biological tests also help to assess organ dysfunction associated with acute dyspnea. AHF may worsen organ function, particularly renal and liver function. Impaired end-organ function should be considered as an alarming sign to intervene, because impaired renal function worsens the prognosis of patients with AHF [10, 11]. Concerning liver function abnormalities, elevated AST, ALT and lactate were shown to influence outcomes in patients with HF [2]. Hence, evidence of poor organ perfusion along with low cardiac output and low SBP may indicate the urgent need for inotropic therapy in these patients [4].

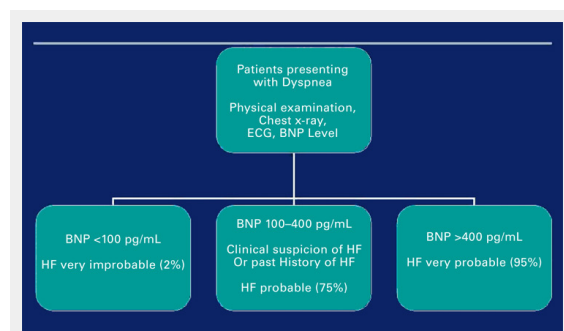


Figure 1
Algorithm of BNP use at presentation for acute dyspnea.

Early management of AHFS primarily based on systolic blood pressure

The ESC guidelines were the first to classify patients with AHFS into distinct clinical conditions [2]. These include: i) acute decompensated HF, de novo or decompensated chronic HF; ii) hypertensive AHF; iii) pulmonary edema; iv) cardiogenic shock; v) AHF secondary to ACS; and vi) right HF [2]. However, this classification is a mixture of the clinical phenotype and disease severity on presentation and there is significant overlap among the different conditions. Of note, accurate and timely diagnosis of AHF secondary to ACS is of paramount importance, since timely revascularization could save myocardium, and hence influence prognosis dramatically. However, it is important to remember that troponins are of little benefit in differential diagnosis in this setting, as HF is also associated with an increase in troponins de novo by itself [12]. Hence, symptoms suggestive of ACS should be investigated thoroughly.

Although the above mentioned ESC classification is the optimal approach to treat heart dysfunction, *very early* ED management of AHFS is primarily based on signs and symptoms. SBP was repeatedly described as the most important predictive factor of morbidity and mortality [4]. Classification by levels of SBP at admission, regardless of other parameters such as previous treatment, can markedly facilitate early risk stratification of AHFS patients. Actually, in the landmark study showing performance of perfusion and congestion based evaluation (clinical judgment classifying patients into one of four categories: dry and warm, dry and cold, wet and warm and wet and cold) in HF, perfusion was mainly based on derivatives of blood pressure (Compromised perfusion was assessed by the presence of a narrow proportional pulse pressure [systolic diastolic blood pressure/systolic blood pressure <25%], pulsus alternans, symptomatic hypotension [without orthostasis,]) plus cool extremities, and/or impaired mentation [6].

Monitoring of cardiac output and filling pressures, for instance with a PAC, is suggested in haemodynamically unstable patients who are not responding in a predictable fashion to traditional treatments or who are refractory to initial therapy, who have a combination of congestion and hypoperfusion, whose volume status and cardiac filling

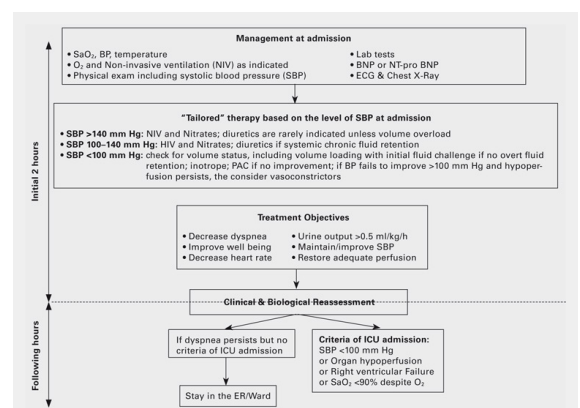


Figure 2
Initial management of acute heart failure syndromes [modified from 4].

pressures are unclear, or who have clinically significant hypotension and worsening renal function during therapy [4].

The SBP cut-offs of 100 and 140 mm Hg were recently proposed by ED, intensive care unit (ICU) and cardiology experts in AHFS and based on published literature (see reference 4 for details). Among patients with dyspnea and/or congestion, at a SBP of >140 mm Hg, left ventricular systolic function is likely preserved, at SBP of 100–140 mm Hg left ventricular systolic function is limited, and some patients with impaired left ventricular systolic function exhibit SBP <100 mm Hg and combination of the two designates the group with poor prognosis [13]. Indeed, clinical judgment is extremely important for the management of all patients with AHFS [6]. SBP guided early therapy upon clinical judgment might provide a modern way to treat AHFS (fig. 2). It is based on “tailored” therapies given as early as possible to the appropriate patient. Further details are given in the following paragraphs.

Management of AHFS with normal or high blood pressure

The three main tools used to treat AHFS with normal or high SBP are non-invasive ventilation, diuretics and vasodilators, and the decision to administer any of three, alone or in combination, is made by congestion status (see fig. 2).

Oxygen and non-invasive ventilation (NIV)

Oxygen is recommended as early as possible to achieve an arterial oxygen saturation \Rightarrow 95% in AHF patients [2]. In chronic obstructive pulmonary disease (COPD) patients, the target is rather an arterial oxygen saturation of 90% in order to avoid hypercapnia. NIV with positive end-expiratory pressure (PEEP) is recommended as early as possible in most AHF patients, especially patients with acute cardiogenic pulmonary oedema and hypertensive AHF. In those patients, early application of NIV reduces both the need for intubation and short-term mortality [2]: This has been recently challenged by the 3CPO, a large randomised controlled trial, which showed that NIV improved clinical parameters but not mortality [16, 17].

Diuretics

Loop diuretics, especially furosemide, are the first line agents around the world for the treatment of patients with AHFS. However, only a few studies have evaluated short and long term clinical outcomes. In addition, AHFS patients with a long lasting history of increased blood pressure and chronic treatment with diuretics, are likely to be systemically euvolemic or hypovolemic. High dose diuretics in these patients may be detrimental. Intravenous diuretics are therefore recommended in AHFS patients in the presence of symptoms secondary to congestion and volume overload. The recommended initial dose is a bolus of furosemide 20–40 mg IV (0.5–1 mg of bumetanide; 10–20 mg of torasemide) at admission [2]. Urine output of patients should be assessed frequently in the initial phase. The dose of diuretics should be repeated once after 45–60 minutes in case of lack of urine. The placement of a bladder catheter is usually desirable in order to monitor urinary output and rapidly assess treatment response. The dose of i.v. fur-

osemide may be increased according to renal function and a history of chronic oral diuretic use. In any case, in order to avoid side effects, the total furosemide dose should remain <100 mg in the first 6 hours and 240 mg during the first 24 hours [2]. In case of diuretic resistance, thiazides (hydrochlorothiazide 25 mg po) and aldosterone antagonists (spironolactone, eplerenone 25–50 mg po) can be used together prior to loop diuretics in order to make sequential nephron blockade. Ultrafiltration may be considered in patients who fail to respond to diuretic therapy, or may be an alternative [14]. However, there is still some room for placing it into routine practice.

Vasodilators

Intravenous vasodilators are recommended at an early stage for AHFS patients without symptomatic hypotension, SBP <90 mm Hg or serious obstructive valvular disease [2]. Indeed, intravenous vasodilators (nitroglycerin, isorbide mononitrate, isorbide dinitrate, sodium nitroprusside and nesiritide) decrease SBP, decrease left and right heart filling pressures and systemic vascular resistance, and improve dyspnoea while maintaining or increasing coronary blood flow [2]. The initial recommended dose of intravenous nitroglycerin is 10–20 μ g/min, increased in increments of 5–10 μ g/min every 3 to 5 minutes as needed [2]. Intravenous nesiritide may be initiated with or without a bolus infusion with infusion rates from 0.015–0.03 μ g/kg/min. Noninvasive blood pressure measurements are usually adequate. Tachyphylaxis is common after 24–48 hours, necessitating incremental dosing with nitrates. Although intravenous nitrates are strongly recommended in AHFS by several multinational guidelines [2–3], their use is mostly limited to the ED or the coronary care unit (CCU)/ICU, in most western countries, and their intravenous administration is often stopped when patients are transferred to the ward. Whether vasodilators, especially nitrates should be used for a longer period of time (during the entire hospitalization or longer), or in a non-intravenous form, remains unclear, though a recent pilot study showed promising results [15].

Although the aim of NIV is to improve oxygen saturation and intravenous diuretics aim to improve urine output, the clinical target and the length of administration of vasodilator therapy has not been described in recent guidelines. Accordingly, a multicentre Swiss trial, named GALACTIC, conducted by C. Mueller aims to assess the efficacy and safety of 1) non-intravenous forms of vasodilators – namely combining transdermal nitrates and oral hydralazine – in non-ICU AHFS patients, 2) early administration of high dose vasodilators, soon after presentation and 3) maintenance of non-invasive forms of high-dose vasodilators for at least seven days. GALACTIC has already included patients from three Swiss centers (Basel, Aarau, Luzern) and is scheduled to be extended to European centers.

Specific treatment of low cardiac output or cardiogenic shock

Inotropic agents

Inotropic agents are still used inappropriately in many European countries and throughout the World. Many surveys show inappropriate high usage of inotropes in AHFS. Inotropic agents should be used in a small number of patients, mainly those with signs of low cardiac output or cardiogenic shock, and vasopressor agents should be used in the presence of low SBP on top of low cardiac output. They are not recommended in patients with high blood pressure. In case of evidence for the use of inotropes, it is advised to administer inotropes as early as possible [4]. Thus, traditional inotropes [dobutamine, milrinone] or the new inodilator levosimendan should be used early in patients with evidence of poor organ perfusion (patient is cold, clammy, or vasoconstricted; or patient has renal impairment, liver dysfunction, or impaired mentation) and low cardiac output, low SBP, and high filling pressures (as detected by physical examination and symptoms), who are not responding to other therapies [2, 4]. Again, these patients account for the minority of AHFS hospitalizations. Inotropes may stabilize patients at risk of progressive haemodynamic collapse or serve as a life-sustaining bridge to more definitive therapy such as mechanical circulatory support, ventricular assist devices, or cardiac transplant. Recent evidence suggests that, in case an inotrope is needed, levosimendan should be the preferred treatment in patients with previous history of heart failure and/or under beta-blockers [18].

In very few cases, norepinephrine is recommended alone or in combination with an inotrope or cardiac enhancer in order to increase SBP in the situation of persistent organ hypoperfusion (e.g., low urine output clearly related to low blood pressure). If no improvement in perfusion is observed, then advanced haemodynamic monitoring should be used. If blood pressure remains low (<100 mm Hg), then a vasoconstrictor should be considered after optimizing preload. The recommended dose for norepinephrine is 0.2 to 1.0 µg/kg/min. It may be started on a peripheral line, but a central line should be placed for its infusion as soon as feasible. Epinephrine is not recommended as a first line therapy. It is used as a rescue therapy in cardiac arrest. There is no evidence of a renal benefit with low-dose dopamine, though preliminary findings from DAD-HF trial using low dose dopamine and low dose diuretic yielded promising results.

Device therapy

An intraaortic balloon pump could be the first line device for patients with AHF syndromes [4, 19]. It can be rapidly placed in the cardiac catheterization laboratory or in the CCU/ICU. It is associated with some risks, including compromised blood flow to the leg, and dissection (particularly in patients with peripheral vascular disease). An intraaortic balloon pump only provides a temporary solution for AHFS. It may be implemented more quickly in patients with suspected ongoing ischemia. In a very recent meta-analysis [20] comparing IABP with percutaneously implanted left ventricular assist devices (LVAD) such Impella and Tandem Heart, it was shown that, though percutaneous

LVADs provide superior haemodynamic support in patients with cardiogenic shock compared with IABP, the use of novel devices did not improve early survival. Hence, they can not be suggested in the front line for these patients.

Early mechanical device therapy may be useful in patients who have not responded to other therapies during the first 6–12 hours after presentation. Patients who may be candidates for device therapy include those with severe and persistent hypotension or hypoperfusion despite the use of inotrope, urine output <30 mL/hour, decreasing oxygen saturation, persistent ischemia, or cold or mottled skin. When implemented early, the use of these devices may promote recovery in some patients [2–4, 19].

Managing comorbidities and chronic heart failure medications during AHFS episode

The majority of patients with AHFS have multiple comorbidities. These conditions may contribute to the development of AHFS, and they should be controlled as soon as possible after presentation. Examples include atrial fibrillation with rapid ventricular response, ventricular arrhythmias, bradycardia, severe anemia, and infection. On the other hand, worsening renal function can negatively influence both in and out of hospital outcomes [11]. However, cardiorenal syndrome is large enough to be a discussion of another paper. In addition, concomitant medications can exacerbate HF and precipitate AHFS. These medications should be stopped immediately after presentation. Examples include non-steroidal anti-inflammatory drugs, COX-2 inhibitors, thiazelinediones, sympathomimetics, tricyclic antidepressants, Class I and III antiarrhythmics (except amiodarone), and non-dihydropyridine calcium channel blockers. By contrast, unless the patient is in cardiogenic shock, beta-blockers can be safely continued during acute decompensations according to a recent study [21].

Conclusion

Patients presenting with AHFS are a complex and heterogeneous population at high risk of short term morbidity and mortality. Early classification of patients according to their clinical presentation is a key step in determining the appropriate initial treatment. These categories, based on the initial SBP at presentation along with clinical judgment, identify patients according to the primary pathophysiological problem, so that early goal directed therapy can be implemented. Early initiation of diagnostic and goal-directed treatment strategies are key factors in improving patient outcomes. Early and frequent reassessment is also imperative so that adjustments in the initial therapeutic approach can be made as clinically indicated.

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