Review

In-hospital journey of patients with heart failure

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ARTICLE INFO

Article history:

Received 7 July 2015

Received in revised form 7 August 2015

Accepted 10 August 2015

Available online 8 September 2015

Keywords:

Acute heart failure

Vasodilators

Diuretics

Treatment

ABSTRACT

The number of patients diagnosed with heart failure (HF) is gradually increasing as a result of the increase in the elderly population. As the proportion of patients admitted to the emergency room with the diagnosis of acute heart failure increases, the opinion of cardiologists who are interested in heart failure has gained more importance in both the in-hospital management of these patients during the acute period and also in post-hospital management. The current review aimed to help the clinicians determine the course of patients with HF, beginning with the time of admission, according to the current guidelines and expert opinions.

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Acute heart failure (AHF) is a life-threatening clinical syndrome that can develop as a result of worsening symptoms of existing heart failure (HF) or de novo development of these symptoms. Patients with AHF constitute a majority of the hospitalizations in cardiology clinics and intensive care units (ICU). Thus, the strategy for the management of these patients is critically important for both prognosis and for cost-effectiveness.

The rate of hospitalizations due to AHF has gradually increased within recent years and patients aged above 65 constitute more than 80% of these hospitalizations.¹ In large scaled HF registries, female gender accounts for 37–52% of the HF related hospitalizations, and while the female patient group is predominantly elderly, males remain relatively younger.^{2–4} Several studies have demonstrated that 23–44% of the patients, who are admitted to the hospital with the diagnosis of AHF, are

denovo AHF and approximately half of these have HF that are associated with acute coronary syndrome (ACS).^{5,6} It has been demonstrated that the in-hospital mortality of patients admitting with the diagnosis of AHF varies between 4% and 7% in different studies and this ratio has increased to 30–40% in patients admitted with cardiogenic shock (CS).^{4,7} In addition to in-hospital mortality, the duration of hospital stay and the rate of readmission are also considerably high in patients with AHF. The mean duration of hospital stay was nine days in the Euro Heart Failure Survey.⁴ The rates of rehospitalization were 20% within 30 days and 50% within the following six months.⁸ Hence, in the absence of evidence, experienced based medicine is essential in many aspects of HF management.

How to tackle first contact with the AHF patient?

Previous studies have particularly emphasized that the early management of patients with AHF is important, as is the case in other cardiovascular emergencies.^{9,10} Upon first contact with the patient with AHF

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Peer review under responsibility of The Society of Cardiovascular Academy.

in the hospital or emergency room (ER) before hospitalization, patients should be immediately evaluated and monitored for vitals including blood pressure, respiratory rate (RR), and noninvasive arterial oxygen saturation (with pulse oximeter) (If saturation drops below 95%, oxygen therapy should be weighed and individualized according to the clinical need. Patients with respiratory distress (RD) should be evaluated for noninvasive ventilation.¹¹ It has been demonstrated that transfer of the patient to a center with a cardiology clinic/coronary intensive care unit (CICU) and/or ICU in the shortest possible period has positive effects on the prognosis.¹²

How to determine in-hospital route of patients with HF?

The main goals in the treatment of AHF are to achieve improvement in hemodynamic status and oxygenation initially, and finally, relief of symptoms. In accordance with this purpose, the findings, obtained from the initial evaluation of the patient are quite important in the determination of the initial treatment strategy.¹¹ Therefore, it is recommended to tailor medical therapy by using nitrates and/or diuretics according to the blood pressure and to the degree of congestion.¹³

Firstly, the degree of cardiac and pulmonary stabilization should be assessed in patients with AHF. During this assessment, systolic and diastolic blood pressure, heart rate (HR) and rhythm, body temperature, and symptoms and signs of hypoperfusion, RR, the ability or inability to lie in the supine position, effort dyspnea, the degree of hypoxia, and the presence or absence of respiratory distress (RD) can provide information related to cardiac and pulmonary stabilization. At the end of these evaluations, unstable patients should be hospitalized in CICU or ICU and further evaluations should be continued after the stabilization of the vital signs of the patient.

After evaluating the degree of cardiopulmonary stabilization, the findings related to congestion such as peripheral edema, audible rales, and jugular venous pressure should also be evaluated and additional diagnostic tests should be performed thereafter.

Supporting elements for the determination of the route; diagnostic tests

Electrocardiography is generally abnormal in patients with AHF and it is recommended to evaluate ECG in all patients with HF, as it could provide information related to the etiology of HF and the factors precipitating AHF.¹⁴ Furthermore, it is known that wide QRS in patients with HF is associated with increased in-hospital mortality and increased mortality during the follow-up period.¹⁵

Chest X-rays are among the routine tests in patients who are suspected to have HF. It gives clues for cardiomegaly, pulmonary congestion and for other reasons that could lead to dyspnea. Of note, a normal chest X-ray does not exclude AHF.¹⁶

Laboratory findings: routine tests including hemogram, blood glucose, urea, creatinine, electrolytes, and liver enzymes should be performed in all patients who are admitted to the hospital with the suspicion of AHF. In addition to providing information related to the factors precipitating AHF, these parameters are also helpful in the selection of the most appropriate treatment regime. In particular, creatinine and electrolytes should be closely followed up in AHF patients. It has been shown that renal function worsens in 25% of the patients who are treated for AHF and this worsening might potentially be associated with poor prognosis unless it is transient and mild.¹⁷ The liver function tests are abnormal in 75% of the patients with AHF and this situation is most frequently consistent with the severity and the clinical findings of AHF.¹⁸ As troponin levels can be above normal values in patients with AHF, the diagnosis of ACS could not be excluded by only measuring troponin levels; however, the high levels of troponin are important, as troponin is a marker of poor prognosis in patients with HF.¹⁹ Blood gas analysis, preferably venous, could be performed to evaluate the metabolic or respiratory acidosis in patients with persistent RD who did not benefit

from initial therapy with oxygen or noninvasive ventilation.²⁰ D-Dimer test could be ordered in patients with suspected pulmonary embolism. Furthermore, it is necessary to evaluate thyroid hormones in AHF patients in order not to overlook hypo/hyperthyroidism.

Natriuretic peptides (NP): although atrial natriuretic peptides (ANP), B-type natriuretic peptides (BNP), and C-type natriuretic peptides are members of the natriuretic peptide family, BNP family is the most frequently studied one. BNP is secreted as a response to ventricular wall tension. Another form of BNP that is inactive and could be measured in blood is NT-pro BNP. According to the current guidelines, during the initial evaluation of AHF, BNP < 100 pg/ml, and NT-pro BNP < 300 pg/ml excludes the diagnosis of AHF.²¹ Although, there is no evidence related to the benefit of in-hospital monitorization of NP, it has been demonstrated that 30–50% decrease in NT-pro BNP or an absolute level below 350 pg/ml at the time of discharge is associated with good prognosis.²²

Emergency detailed echocardiography might not be necessary during the initial evaluation except in patients in CS. However, recent data suggest that emergency bed-side focus echocardiography including basic evaluation of heart and lungs might help triaging of these patients. After stabilization of the patient, it is important to perform echocardiography at any time during the hospitalization period, especially in denovo AHF patients.

Site selection during the in-hospital journey: triaging for HF patient

AHF patients who are admitted to the ER, should first be evaluated according to whether they have shock criteria or not. If the patient is diagnosed with CS, cardiopulmonary stabilization should be immediately achieved and then emergency echocardiography should be performed to help determine the etiology of the shock. If there is clinical, electrocardiographic, and echocardiographic findings that support ACS, the patient should immediately be taken to the catheterization laboratory; otherwise the patient should be hospitalized directly in the CICU or ICU (Fig. 1).

CS is a clinical condition characterized with hypoperfusion (oliguria; urine output < 0.5 ml/kg/h for at least 6 h; impaired mental status; livedo reticularis accompanied by cold extremities; blood lactate level > 2 mmol/l; metabolic acidosis; SvO₂ < 65%) and low SBP (< 90 mmHg for longer than 30 min in spite of sufficient fluid replacement).²³ CS might develop as a result of low cardiac output during end-stage of chronic HF, and also it might develop in ST elevation myocardial infarction or in acute valvular pathologies.

Apart from the patients with AHF and CS, patients with severe symptoms and signs such as RR > 25/min, SaO₂ < 90% or those with intubation, SBP < 90 mmHg or hypoperfusion (confusion, oliguria, metabolic acidosis, cold extremities, mixed venous oxygen saturation < 65%) should be hospitalized in the CICU/ICU. Patients with AHF not having any of these findings could be followed up in the ER or in the ward. Approximately 80% of AHF patients who are admitted to ER are hospitalized.²⁴ It is thought that approximately 50% of the patients who are hospitalized after being admitted to the ER could be safely discharged after a short period of follow-up.²⁵ Presence of low risk criteria in AHF patients such as normal oxygen saturation in room air, normal heart rate and rhythm, absence of troponin elevation, absence of orthostatic hypotension, absence of worsening renal and/or liver function, and normal urine output along with a good response to treatment in the form of improved dyspnea could help discharge patients rapidly from the ER.

Main factor that determines the duration of the in-hospital journey of patients with HF: selection of an appropriate treatment strategy

Patients with low SBP and low cardiac output due to systolic dysfunction constitute only 5–10% of the patients who are hospitalized due to AHF. The majority of them are patients with clinical findings due to systemic and/or pulmonary congestion.

Fig. 1. Time related algorithm for acute heart failure.

Diuretics, vasodilators and vasopressors constitute the basic treatment protocol in AHF patients who have symptoms related to tissue congestion caused by hypervolemia that is also named as “wet”. Inotropic agents should be the first choice in patients in whom hypotension and tissue hypoperfusion-related symptoms are caused by low cardiac output. When findings of both congestion and hypoperfusion are present, the combined use of diuretics, vasodilators and inotropic agents in a tailored manner gains importance.

The goal of *diuretic therapy* is to achieve euvolemia, thus dry weight, with the minimum possible dose. During the administration of diuretic therapy in HF, urine output of 40 ml/h and daily weight loss of 1–1.5 kg is usually targeted. Furosemide, which is the most frequently used diuretic in Turkey and around the world, could be initiated as a small intravenous dose that is equal to the routinely used oral dose or as an intravenous high dose that is 2.5-folds of the routinely used oral dose. In addition to the low dose and high dose protocols, the effects and benefits of bolus and infusion routes in patients with HF have been compared in the DOSE (Diuretic Optimization Strategies Evaluation Trial) study, and no significant difference was detected between different treatment strategies.²⁶ In a meta-analysis of small-scaled studies comparing the infusion and bolus routes, no significant difference was detected between the two groups; however, it has been demonstrated that diuresis is more effective by infusion.^{27,28} If sufficient diuresis could not be achieved in spite of a dose increase of the loop diuretic, furosemide, a second diuretic agent could be added in the form of consecutive nephron blockade. Although the thiazide group of diuretics are commonly used, the evidence related to the use of high dose spironolactone is increasing.²⁹ Furthermore, a meta-analysis demonstrated that improved weight loss, decreased duration of hospital stay, and decreased rates of rehospitalization and mortality could be achieved with the combined use of furosemide and hypertonic saline infusion in patients with insufficient diuresis through diuretic therapy and in those who have extracellular fluid accumulation.³⁰ DAD HF II and ROSE studies have demonstrated that diuretic therapy combined with low dose dopamine infusion, which has been used as another alternative in patients with insufficient diuresis, has no additional benefit for increasing diuresis and protecting renal functions.^{31,32} Another alternative for diuretic therapy in HF patients with hyponatremia is tolvaptan, which is a vasopressin 2 receptor antagonist. The EVEREST study demonstrated that tolvaptan has no effect on mortality and hospitalization; however, it improves urine output and by increasing sodium, improves congestive findings such as dyspnea and edema.³³

Ultrafiltration is also another treatment option to improve congestive findings in hypervolemic patients. Ultrafiltration that is added to standard therapy has been compared to standard therapy alone in the RAPID-CHF (relief for acutely fluid-overloaded patients with decompensated CHF) study and no significant difference was detected between the two groups in terms of efficacy and safety.³⁴ The results of studies on this subject are controversial.^{35,36} These data have been

evaluated in recent HF guidelines, and in the ESC 2012 HF guideline, ultrafiltration was included among the controversial issues, as there is no sufficient evidence and a distinct recommendation has not been given. However, the ACC/AHA guideline recommends a Class IIb drug for decreasing congestion in hypervolemic patients.

Vasodilators are also the main components of AHF treatment, as is diuretic therapy. It is thought that nitrovasodilator (nitroglycerine and nitroprusside) therapy has an important role in the improvement of hemodynamic status in patients with AHF. There are data supporting that the use of these agents is associated with low mortality rates.¹⁰ Nitroglycerine treatment is started with 10–20 µg/min and can be increased in a stepwise fashion up to 200 µg/min in AHF patients by observing hemodynamic response. Nitroprusside can be initiated with a dose of 0.3 µg/kg/min and increased up to 5 µg/kg/min under close hemodynamic monitorization. The duration of nitro-vasodilator therapy is 24–48 h. Beyond this time, tachyphylaxis or tolerance to nitroglycerin or intoxication from nitroprusside may occur. It is recommended to use IV nitrovasodilators by considering the abovementioned dose and duration, to improve hemodynamic status by decreasing pulmonary capillary wedge pressure (PCWP) and LV filling pressures in patients with AHF who have SBP > 110 mmHg.³⁷ Other agents for vasodilatation are Serelaxin and Ularitide. These agents are currently being investigated in phase III clinical trials.

Although used less frequently than vasodilators and diuretics, *positive inotropic agents* are also among the drugs that might be necessary to treat AHF. These drugs are mostly used in patients with low cardiac output and hypotension due to systolic dysfunction or in patients with CS; this patient group constitutes 5–10% of the patients admitted with AHF. These agents increase myocardial contractility and cardiac output and decrease ventricular filling pressure and PCWP, and thus enable symptomatic and hemodynamic stability.³⁸ As they increase ischemic provocation and arrhythmias, limited and short-term use is recommended. The inotropic effects of *dopamine* start at doses of 3–5 µg/kg/min, and increase systemic vascular resistance at higher doses. Its use in patients with severe hypotension and/or CS is appropriate. *Dobutamine* is an inotropic agent that is effective via B1 receptors which is preferred dopamine in patients who have normal or close to normal blood pressure and low cardiac output.³⁹ It could be used at a dose range of 2–20 µg/kg/min and as the dose increases, attention should be given to heart rate increase and arrhythmias. Tolerance development 24–48 h after initial administration and decreased effect in patients using beta blockers are its disadvantages. *Levosimendan* leads to vasodilatation by opening ATP dependent potassium channels in the vascular smooth muscles and thus decreases cardiac preload and afterload, in addition to its inotropic effect by increasing calcium-dependent myocardial contractile proteins.⁴⁰ It has been demonstrated that levosimendan enables hemodynamic improvement when compared with dobutamine.⁴¹ Levosimendan is administered as a 24-h IV infusion at a dose of 0.05–0.2 µg/kg/min following the administration of a loading dose of 6–12 µg/kg/min in 10 min. Levosimendan is

not recommended in cases with a systolic BP <85 mmHg. It has been observed that inotropic agents increase cardiac output more when they are used together. A low dose dopamine and dobutamine combination is frequently used in routine daily practice. Furthermore, a dobutamine and levosimendan combination could also be preferred in resistant cases.⁴²

Vasopressor agents are used to preserve organ perfusion in situations where severe life-threatening hypotension develops and blood pressure cannot be increased in spite of fluid support and/or inotropic agents such as CS. *Epinephrine* is generally used at a dose of 0.05–0.5 µg/kg/min. It can be used in clinical practice if hypotension cannot be controlled. Unless there is no serious hypotension, it is not recommended in decompensated HF. *Epinephrine* is not recommended as an inotropic and vasopressor agent for CS. *Norepinephrine* is a strong vasoconstrictor but a weak inotropic agent. In general, it is used to increase BP. It is generally used at doses of 0.2–1.0 µg/kg/min but it is not recommended for decompensated HF.

Assist device therapy should be kept in mind for patients with AHF who have no response to medical therapy, including inotropic therapy. Intra-aortic balloon pump (IABP) is the most frequently used left ventricle assist device (LVAD).⁴³ However, in a recently performed IABP-SHOCK II study, it has been demonstrated that IABP application in patients with acute myocardial infarction and CS, did not improve the results.⁴⁴ Furthermore, in a meta-analysis of seven randomized controlled studies with IABP, it has been demonstrated that IABP caused positive changes in hemodynamic parameters; however, it had no effect on survival of the patients.⁴⁵ In patients who had no response to standard therapy and IABP, other percutaneous LVADs (TandemHeart {Cardiac Assist, Pittsburgh, PA, USA} and Impella LP 2.5 {Abiomed Europe GmbH, Aachen, Germany}) are recommended.^{26,46} However, recent data related to these devices are limited. However, short-term mechanical support, including extracorporeal membrane oxygenation, could be used in patients with CS patients who had no response to maximal medical therapy.⁴⁷

Evidence-based in-hospital management of chronic oral therapy in patients with HF

Oral treatment for HF should not be terminated in patients with AHF as long as there is no hemodynamic instability (SBP <85 mmHg; heart rate <50/min), hyperkalemia (potassium >5.5 mg/dl), or severe renal dysfunction.³⁷ In such situations, the daily oral dose could be decreased or it could be discontinued until the patient is stabilized. In patients taking angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), if SBP is <85 mmHg, the treatment should be discontinued. If SBP is between 85 mmHg and 100 mmHg, the dose should be decreased or the treatment should be discontinued. Normotensive or hypertensive patients could be reevaluated and the dose could be increased. Furthermore, if creatinine is >2.5 mg/dl and estimated glomerular filtration rate (eGFR) is <30 ml/min/1.73 m², the treatment should be discontinued. In patients who are on mineralocorticoid receptor antagonist (MRA) therapy, if SBP is <85 mmHg, creatinine is >2.5 mg/dl, or eGFR is <30 ml/min/1.73 m² and/or potassium is >5.5 mg/dl, treatment should be discontinued. If potassium is <3.5 mg/dl, increasing the dose of MRA could be an option. Related to the diuretic therapy regime, if SBP is <85 mmHg, diuretic therapy should be discontinued; if SBP is between 85 mmHg and 100 mmHg, the dose should be decreased. If potassium is >5.5 mg/dl when eGFR is >30 ml/min/1.73 m² or if potassium is >5.5 mg/dl when creatinine is <2.5 mg/dl, reevaluation of the patient and increasing the diuretic dose could be an option. The beta blocker therapy should be arranged according to the blood pressure and HR of the patient. If HR and SBP are appropriate, beta blockers could be safely continued in AHF except CS.⁴⁸ If SBP is <85 mmHg and/or HR <50/min, beta blocker therapy should be discontinued; if SBP is 85–100 mmHg and/or HR is 50–60/min, decreasing the dose could be an option.

When does the in-hospital journey of a patient with HF be stopped? Which patients can be discharged?

Although it is attempted to limit the duration of hospital stay in all patients, discharge that is too early might cause repeated rehospitalizations. It is necessary for patients with AHF to be discharged in stable, euvolemic hemodynamic state, under optimal oral therapy for at least 24 h and along with stable renal functions; otherwise discharge should be delayed.¹¹ Although the opinions related to NP measurement before discharge is debated, the recommendation of the ACC/AHA guidelines as clinical risk-prediction tools and/or biomarkers can be used to identify patients at higher risk for post-discharge clinical events (Class IIa recommendation Level of Evidence: B).²¹ Furthermore, patients with AHF should be evaluated as a whole by considering comorbidities, psychological and social factors, and the patient and the caregivers should be informed in detail about HF. The information should include the etiology of the disease; the drugs that the patient should use; diet; water and salt consumption; other factors that could lead to decompensation of HF; the symptoms and signs of HF; monitorization of weight, blood pressure, and HR; and the exercises that the patient can perform.

In conclusion, the most important factor that would correctly guide the patient with HF in his/her difficult in-hospital journey is the decision of the physician in charge during follow-up. It is clear that continuing the journey according to the route that has been developed by key opinion leaders who are specialized in HF, in light of scientific and recent data, would decrease the mortality and rehospitalization rates in patients with HF.

Conflict of interest

None

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