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Michael M. Kreusser, Philip Raake

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Michael M. Kreusser and Philip W. Raake

11.1 General Considerations

Patients with acute dyspnea resulting from acute heart failure should be rapidly assessed and stabilized. First, patients should be put in a seated posture and, if necessary, supplemental oxygen and ventilatory support (noninvasive or invasive, see below) should be provided [1]. After that, therapeutic aims should be focused on the correction of hemodynamic and intravascular volume abnormalities. Therapy has to be tailored to the individual situation, however, diuretics are the mainstay of therapy in the acute setting. Early intravenous vasodilator therapy is important for selected patients with the need of targeting systemic vascular resistance and left ventricular overload. This includes patients with severe hypertension, acute mitral regurgitation, or acute aortic regurgitation. The patient's hemodynamic and volume status determines how aggressive diuretic and vasodilator therapy has to be initiated. Acute heart failure therapy may be guided differentially in three stages of treatment: urgent/emergent care, hospitalization, and pre-discharge [2]. Therapies can be necessary to be used during any of these stages and are discussed in the following in detail. Monitoring and diagnostics in acute heart failure are discussed above.

11.2 Pharmacotherapy

11.2.1 Diuretics

Diuretics are the primary pharmacologic treatment for volume overload in patients with acute heart failure [3]. Patients presenting with volume overload usually receive intravenous loop diuretics (e.g. furosemide, torasemide, bumetanide) with a dose equivalent to 20–40 mg furosamide for patients without prior loop diuretic therapy. The dose should be adjusted/increased in the setting of renal dysfunction and chronic oral diuretic use. Loop diuretics should be administered intravenous, and if there is little or no response to the initial dose, the dose should be doubled at two-hour intervals as needed up to the maximum recommended dose.

In patients treated intravenously with loops diuretics, urine output needs to be carefully monitored, often by using a bladder catheter. In case of a significant volume overload (>5–10 l) or diuretic resistance, a continuous intravenous infusion is often necessary, usually furosemide 5–40 mg/h. In the recent DOSE trial Felker et al. found no differences in acute heart failure patients treated with loop diuretics as bolus or continuous infusion at low or high doses [3].

As noted below, vasodilators may increase diuresis and lower the need for high dose diuretics. Moreover, loop diuretics may be combined with another type of diuretics, such as thiazides (intravenous chlorothiazide or oral metolazone) or aldosteron antagonists (oral spironolactone, eplerenone) to increase diuresis. Patients under diuretic therapy have to be carefully monitored for hypotension, worsening renal function and electrolyte disturbances. Non-steroidal anti-inflammatory drugs should be avoided, because they can greatly reduce the efficiacy of diuretic drugs and can negatively influence kidney function. Patients with hypotension (<90 mmHg systolic blood pressure), severe hyponatremia and/or acidosis have to be carefully treated with diuretics and may not respond to diuretic therapy. If volume redistribution is more than volume overload the case of acute heart failure, e.g. in the case of hypertensive acute heart failure, aggressive diuretic therapy may be rather harmful.

M. M. Kreusser · P. W. Raake (✉)
University Hospital of Heidelberg, University of Heidelberg, Heidelberg, Germany
e-mail: Philip.Raake@med.uni-heidelberg.de

11.2.2 Vasodilators

Vasolidators are first line therapy for patients with acute heart failure, if hypotension is absent, and are recommended for patients with a systolic blood pressure >90 mmHg and the absence of serious obstructive valve disease [1]. Vasodilators have dual benefit by decreasing venous tone (to optimize preload) and arterial tone (decrease afterload), and thereby may increase stroke volume. Three types of vasodilators are currently available, all of which cause vasodilation by increasing intracellular cGMP, but each with distinct characteristics and indications.

Nitrates Nitrates are used for medical treatments since the 1870s, and the organic nitrates are one of the oldest treatments for acute heart failure. At low doses, nitrates dilate veins, produce rapid decrease in pulmonary venous and ventricular filling pressures and improve pulmonary congestion, dyspnoea and myocardial oxygen demand. At higher doses and in the presence of vasoconstriction, nitrates also dilate arteries and reduce afterload, and increase cardiac output.

Nitrates are preferentially used in patients with coronary artery disease and can be easily and immediately administered orally, sublingually or by spray. In a randomized study of 110 patients with fulminant pulmonary edema, patients treated with high dose nitrates were compared to low dose nitrate combined with high dose furosemid, and latter group were in disadvantage in terms of myocardial infactions and the need for mechanical ventilation [4]. Other studies provided evidence for beneficial effects of nitroglycerin on hemodynamics [5].

Nitroglycerine may be acutely administered sublingually (0.25–0.5 mg), buccally (isosorbide dinitrate 1–3 mg) or spray (0.4 mg or 2 puffs). Intravenous nitroglycerine is usually initially dosed 10–20 μg/min with up-titration in increments of 5–10 μg/min to blood pressure or symptom target. Inadequate up-titration is a common reason for failure of therapeutic efficacy. Nitroglycerine tolerance can develop within 24 h, and headache and symptomatic hypotension, the latter usually resolves within minutes, are fairly common adverse effect.

Sodium Nitroprusside Sodium nitroprusside induces a balanced vasodilation in veins and arteries and is easily titratable due to a very short half-life (seconds to a few minutes). It is intravenously administered and should be monitored by continuous blood pressure monitoring, or at least with automated blood pressure cuffs to guide dosage. Sodium nitroprusside very potently induces a dramatic decrease of left ventricular filling pressures and therefore is one of the most efficiant therapies, especially in the setting of elevated afterload (e.g., hypertensive acute heart failure). There are no randomized trials of nitroprusside in acute heart failure patients, but multiple studies demonstrated a dramatic reduction in pulmonary capillary wedge pressure and increases in cardiac output, as well as beneficial increases of diuresis, natriuresis and decreased neurohumoral activation [6] and also reduced mortality [7].

The initial dose of sodium nitroprusside is 0.3 μg/Kg/min with titration every 5 min up to 5 μg/Kg/min, a fast up-titration can cause profound hypotension. Nitroprosside is a prodrug and is rapidly metabolized to oxide and cyanide. Possible side effects are related to the cyanide metabolite and include nausea, abdominal dyscomfort, dissociative feelings and dysphoria. Cyanide rarely accumulates in patients, but physician discomfort with the potentially toxic metabolites may be the cause that nitroprusside is markedly underutilized (<1% of acute heart failure patients in Europe and the United States [8]). However, it has no arrhythmogenic properties, may improve myocardial oxygen demand by reducing afterload and wall stress and creates no significant electrolyte disturbancies.

Nesiritide B-type natriuretic peptide (BNP) may also be used for the treatment of acute heart failure. Nesiritide (recombinant human BNP) reduces venous and verntricular filling pressures by potent venous and arterial vasodilation and thereby mildly increases cardiac output, with subsequent improvement in symptoms of dyspnea. In one randomized trial with 489 patients with decompensated heart failure and dyspnoe at rest, patients were treated with placebo, nitroglycerin, or nesiritide for 3 h [5]. Patients receiving nesiritide had a significantly greater decrease in left ventricular filling pressure compared to nitroglycerine and placebo, and improvement in dyspnea compared with placebo.

Nesiritide may be administered with or without a bolus followed by an infusion of 0.015–0.03 μg/Kg/min. Hypotension more often occurs in patients with volume depletion, and consequently, nesiritide is indicated for patients with congestive signs and symptoms. Headache occurs less frequent as with nitroglycerin, and nesiritide is with limited need for frequent dose adjustments and an absence of tolerance. However, its high costs and lack of clear clinical benefit beyond other less expensive agents, and potential safety concerns, including higher mortality in some studies [9], have limited its use. Nesiritide is not available in many European countries.

11.2.3 Inotropes

Inotropes include agents that stimulate adrenergic receptors and thereby have varied effects on the vasculature, but all increase cardiac pump function (inotropy) and are reserved for selected situations of hypoperfusion or decreased blood

flow when other interventions are inappropriate or have failed. The concept of intermittend infusions of inotropes, or "inotrope holidays", cannot be recommended due to lacking supportive data.

Dobutamine Dobutamine is the most commonly used positive inotrope in the United States and Europe [2]. However, there are data that dobutamine may be associated with increased mortality. Dobutamine increases cardiac output through direct inotropy, decreasing afterload and increasing heart rate. It is indicated for patients with acute heart failure due to low output. Dobutamine is administered as an infusion without a loading dose starting at 2–3 μg/Kg/min and can be up-titrated to doses of 15–20 μg/Kg/min. A need for increasing doses may occur with infusions over 24–28 h. Adverse effects of dobutamine include tachycardia, increasing occurrence of atrial and ventricular arrhythmias, myocardial ischemia and possible direct toxic effects on the myocardium inducing necrosis. Lower doses of dobutamine improve renal perfusion and in general, dobutamine (or dopamine) is the preferred inotrope in patients with hypotension and in the setting of renal dyfunction, given the renal excretion of milrinone. Beta-blocker therapy results in competitive antagonism of the effects of dobutamine and may require higher doses of dobutamine and/or the substitution of milrinone. Dobutamine should be gradually weaned off under carefully clinical re-evaluation and adaption of comedication with each dose adjustment.

Dopamine Dopamine was in both the United States and Europe as often used as dobutamine, especially for patients with renal insufficiency because of its renal vasodilation effect. However, a meta-analysis suggested that dopamine may only mildly increase urinary output on the first day with no effect on creatinine clearance and a trend toward increased adverse events [10]. In the initial phase of titration, dopamine can induce tachycardia and atrial and/or ventricular arrhythmias. Intermediate to high doses can cause significant vasoconstricion, leading to worsening of heart failure and poor perfusion.

Epinephrine and Norepinephrine Epinephrine is a potent inotropic agent with balanced vasodilator and vasoconstrictor effects. Norepinephrine is also a potent inotropic agent, but can also cause marked vasoconstriction, potentially inducing end-organ hypoperfusion and tissue necrosis. Both of these agents are given to raise blood pressure and redistribute blood to the vital organs at the expense of an increase in left ventricular afterload and therefore are reserved for profound hypotension or for cardiac resuscitation.

Phosphodiesterase Inhibitors (PDEI) Phosphodiesterase III is found in cardiac and smooth muscle and degrades the signaling molecule cAMP to AMP. cAMP increases inotropy (contractile function), chronotropy (heart rate) and lusitropy (myocardial relaxation). This signaling pathway being downstream of adrenergic receptors bypasses beta-adrenergic receptor desensitization and antagonism by betablockers in heart failure patients. PDEI cause significant peripheral and pulmonary vasodilation, reduce afterload and preload and increase inotropy.

Milrinone is the most commonly used PDEI, but only used in 1–3% of acute heart failure patients [8, 11]. Milrinone has adverse effects as marked hypotension, as well as atrial and ventricular arrhythmias. In one study, 951 patients with acute heart failure not requiring intravenous inotropic support were randomized to receive milrinone or placebo [12]. In the milrinone-treated group, there were found increased sustained hypotension and new atrial arrhythmias, as well as increased mortality in a post-hoc sub-group analysis for patients with ischemic heart disease who received milrinone [13]. Therefore, administration, titration, and withdrawal of milrinone has to be done very carefully.

Enoximone is a PDEI that is available in Europe and is metabolized by the liver into renally cleared active metabolites and needs to be reduced in the setting of either renal or hepatic insufficiency.

Calcium Sensitizers The calcium sensitizer levosimendan acts via multiple mechanisms, including cardiac myofilament calcium sensitization by calcium-dependent binding of troponin C, activation of ATP-sensitive vascular smoth muscle potassium channels and mild PDEI activity. These actions increase myocardial contractility and produce peripheral vasodilation. Levosimendan is used in about 4% of acute heart failure patients [8], mainly for patients with reduced left ventricular systolic function and the absence of severe arterial hypotension. Clinical trials demonstrated beneficial hemodynamic effects and relief of dyspnea [14]. However, randomized trials found more episodes of atrial fibrillation in levosimendan-treated patients and ambiguous effects on survival [15]. Levosimendan has gained popularity in Europe, were it is used as an alternative to adrenergic agens, preferably to reverse the effect of beta-blockade if beta-blocker is thought to be contributing to hypoperfusion in acute heart failure. Levosimendan may be administered with an initial loading dose of 3–12 μg/Kg during 10 min, although many clinicians avoid a loading dose to prevent hypotension. Levosimendan is then continuously given with a rate of 0.1 μg/Kg/min and may be up- or down-titrated between 0.05 and 0.2 μg/Kg/min, adjusted to the clinical need. Levosimendan has a half-life of over 80 h, and has hemodynamic effects even days after discontinuation of the infusion.

Relaxin Relaxin is a naturally occurring peptide vasodilator. Serelaxin, recombinant human relaxin-2 was investi-

gated in the RELAX-HF trial that included 1161 patients with acute heart failure and included patients with decreased and preserved left ventricular ejection fraction [16]. Serelaxin improved one measure of dyspnea and reduced the length of index hospital stay. Interestingly the serelaxin group displayed a lower rate of cardiovascular death and all-cause mortality. However, additional studies are required to confirm efficiacy and safety of this new agent.

11.2.4 Others

Morphine Opiate therapy in patients with acute heart failure should be avoided, because observational studies suggested that morphine and its analogs may increase the likelihood of admission to the intensive care unit and intubation, and may prolong hospital stay [17]. However, to relieve anxiety, distress, and dyspnoea it may be recommended for selected patients under careful monitoring.

Anxiolytics and Sedatives Anxiolytics or sedatives may be needed in patients with agitation or delirium. Cautious use of benzodiazepines (diazepam, lorazepam) is recommended as the safest approach.

Venous Thromboembolism Prophylaxis Thromboembolism prophylaxis is recommended for hospitalized patients with heparin or other anticoagulant agents unless contraindicated or unnecessary.

Sodium Restriction Sodium restriction is suggested for all patients with heart failure.

Vasopressor Receptor Antagonists Vasopressin receptor antagonists such as tolvaptan block the action of arginine vasopressin (AVP) at the V2 receptor in renal tubules and promote aquaresis. These agents are a rarely used option for patients with volume overload and severe hyponatremia (i.e. serum sodium <120 mmol/l). The EVEREST (The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial showed no benefit regarding long-term mortality or heart failure morbidity related to tolvaptan treatment in patients hospitalized for worsening of heart failure [18].

11.3 Renal Replacement

Ultrafiltration involves the removal of plasma water across a semipermeable membrane in response to a transmembrane pressure gradient. In the UNLOAD trial ultrafiltration was related to an intensified weight loss and fewer rehospitaltisations in patients with acute heart failure [19]. However, renal insfficiency and/or diuretics resistance were not a prerequisite for study inclusion. In the CARRESS-HF trial only patients with acute decompensated heart failure, worsening renal function and congestion were included. In this trial ultrafiltratrion was even inferior to pharmacologic therapy regarding change in serum creatinine level and body weight and was associated with more adverse events [20]. As such, there is no evidence favouring ultrafiltration over intensification of diuretics as first-line therapy in the setting of acute heart failure [20] and therefore ultrafiltration is not recommended in general and should be restricted to patients who fail to respond to diuretic-based therapies. Current guidelines recommend the following criteria to indicate the need for renal replacement therapy in patients with refractory volume overload: severe hyperkalaemia ($K^+ > 6.5$ mmol/l), severe acidaemia (pH < 7.2), serum urea level >25 mmol/l (150 mg/dl) and serum creatinine >300 µmol/l (>3.4 mg/dl) [1]. Renal replacement will be further discussed below (see chapter on cardiorenal syndrome).

11.4 Non-Invasive Ventilation (and Oxygen Supplementation)

In the presence of decreased oxygen in the blood (hypoxemia; $SaO_2 < 95\%$ or $SaO_2 < 90\%$ in patients with chronic obstructive pulmonary disease (COPD) to avoid ventilation-perfusion mismatch and suppressing of ventilation), administration of oxygen is recommended, although it has not been studied rigorously. In the absence of hypoxemia, supplemental oxygen may cause hyperoxia-induced vasoconstriction and thereby may worsen acute heart failure [21].

Non-invasive ventilation has further developed in recent years and provides the possibility to relieve symptoms of dyspnoe and improve oxygenation of the blood without intubation by using multiple different face-mask based modalities such as continuous positive airway pressure (CPAP) and bi-level positive pressure ventilation (PPV). Meta-analyses have suggested that non-invasive ventilation reduced the need for invasive ventilation and short-term mortality. However, a randomized, controlled clinical trial of 1069 patients with acute cardiogenic edema demonstrated no effect on short-term mortality, but improved symptoms and the associated metabolic and hemodynamic abnormalities [22]. In Europe, over 30% of patients with pulmonary edema received non-invasive ventilation [8]. Mechanical ventilation needs to be performed in about 4–5% of all patients, with a high risk for patients with muscle fatigue and myocardial infarction [8].

11.5 Temporary Mechanical Support

For patients with acute heart failure and INTERMACS (The Interagency Registry for Mechanically Assisted Circulatory support level 1 or 2), short-term mechanical support systems include percutaneous cardiac support devices, extracorporal life support (ECLS) and extracorporal membrane oxygenation (ECMO). These systems can be used to support patients with left or biventricular failure until cardiac and other organ functions have recovered, but typically are restricted to a few days or weeks. In addition, these mechanical support systems can be used as a "bridge to decision".

Intra-Aortic Ballon Pump The intra-aortic ballon pump (IABP) was originally used for temporary left ventricular support before surgical corrections of specific acute mechanical problems (e.g., acute mitral regurgitation or interventricular septal rupture), during severe acute myocarditis and in selected patients with acute myocardial infaction before, during and after percutaneous or surgical revascularization. Benefits of IABP support were found in the era of thrombolysis of acute myocardial infarction [23] In this regards, the recent SHOCK II (The Intraaortic Balloon Pump in Cardiogenic Shock II) trial found no additional benefit in IABP treatment in paitents in cardiogenic shock due to myocardial infarction undergoning percutaneous revascularization [24, 25].

Percutaneous Microxial and Centrifugal Pumps Two different systems may be distinguished: microaxial (e.g. Impella pump Abiomed) and centrifugal pumps (e.g. Tandem Heart, Tandem Life). All systems can be placed percutenously, except the Impella 5 l/min requires surgical cutdown in the groin. The Impella pump draws blood in the left ventricle and via a microxial pump the blood is transported into the ascending aorta above the aortic valve; it performs according to size 2.5–5.0 l/min. The centrifugal Tandem Heart consists of a transseptal cannula introduced blood in the left atrium for suction, a centrifugal pump and an arterial femoral cannula for return of oxygenized blood. Both systems are capable of unloading the left heart. The efficiency of the Impella microaxial pump and the centrifugal Tandem Heart were shown in smaller studies [26, 27]. However, a meta-analysis collecting these smaller studies found no advantage of these two systems over IABP usage in cardiogenic shock [28]. Larger multicenter, controlled, randomized studies are certainly needed to provide more solid data and finally draw conclusions. However, in situations of refractoy cardiogenic shock these systems may provide temporary support for decision making. Due to lacking data it should only be used on an individual basis.

Extracorporal Life Support Extracorporal life support systems (ECLS) allow full cardiopulmonary support including oxygenation. Access is veno-arterial. A venous suction cannula is placed in or close to the right atrium via inferior or superior caval vein. The venous blood is accelerated via a roller pump, oxygenized and returned via a femoral artery cannula. First single center studies could show safety and effectiveness in infarct-related cardiogenic shock [29]. Still evidence is more than weak to support general usage in cardiogenic shock, particularly, as ECLS treatment does not unload the left heart and instead increases left ventricular afterload. It is considered as a rescue strategy in individual patients with refractory cardiogenic shock [1]. Chen et al. could demonstrate that ECLS supported resuscitation was superior to standard of care in inhospital cardiac arrest regarding outcome [30]. However, more evidence is needed and larger multicenter, prospective, randomized studies are still pending.

11.6 Other Interventions

In patients with acute heart failure and pleural effusion, pleurocentesis and fluid evacuation may be considered in order to alleviate dyspnea. In patients with ascites, ascites paracentesis with fluid evacuation may be considered to alleviate symptoms and may also, by decreasing intra-abdominal pressure, partially normalize the transrenal pressure gradient and thereby improve renal function.

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