



# Systolic heart failure: diagnosis and therapy

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## Purpose of review

The present review highlights recent findings on perioperative systolic heart failure. It briefly summarizes the pathophysiology of heart failure and provides the reader with new insight in diagnosis and treatment of systolic heart failure. In addition, we review new therapeutic strategies with pharmacologic agents and mechanical assist devices to treat systolic heart failure.

## Recent findings

Left ventricular systolic heart failure is a high-risk disease for patients undergoing cardiac and noncardiac surgery and poses a high burden on the anesthesiologist in charge. Perioperative echocardiography is well established for urgent diagnosis in the operating room and is superior to biomarker-based diagnosis. Although cardiovascular disease associated mortality decreases, systolic heart failure related mortality remains at a high of 50% after 5 years. As a consequence, left ventricular assist device implantation rates grow rapidly and include approximately 30–40% patients with desperate clinical situation and destination therapy. Extracorporeal life support for acute heart failure needs further investigation to document possible indications and side-effects.

## Summary

Recent advances in the field of cardiovascular anesthesiology comprise advanced use of perioperative echocardiography, mechanical circulatory assist devices, and customized pharmacologic management.

## Keywords

cardiac surgery, echocardiography, left ventricular assist device, levosimendan, systolic heart failure

## INTRODUCTION

Heart failure is an end-stage clinical syndrome based on a broad variety of underlying cardiac conditions. With its high prevalence of over 5.7 million Americans older than 20 years of age and a projected rise of 46% from 2012 to 2030, resulting in more than 8 million people suffering from it in the USA [1,2] and more than 23 million worldwide, heart failure is of major significance for modern healthcare systems and has significant financial implications for healthcare systems. Heart failure is primarily a disease of the elderly and affects about 6.6% males and 4.8% females aged 60–79 years, with females leading the 80+ group (10.6% male vs. 13.5% female) [1,2]. Among all individuals (asymptomatic or validated clinical heart failure) the prevalence of left ventricular systolic dysfunction is 6% [3,4]. Left ventricular systolic dysfunction includes patients suffering from heart failure and a reduced left ventricular ejection fraction (HFrEF), compared with patients with diastolic heart failure and preserved ejection fraction (HFpEF), which is reviewed in another chapter in this issue of the journal.

The overall mortality remains high with 50% of patients dying 5 years after the diagnosis of heart failure [5], interestingly without significant differences in mortality between the groups HFrEF (EF < 40%), HFbEF (borderline ejection fraction 40–50%) and HFpEF (ejection fraction ≥ 50%) [6]. Physicians should be aware of the fact that acute decompensation of heart failure or intensification of chronic heart failure, is the most common cause of hospital admission among patients with heart failure. These patients frequently require invasive therapy and anesthesia during their hospital stay. Anesthesiologists are confronted with these patients in multiple locations including the operating room (OR) and outside-of-OR areas during a variety of interventions. Moreover, heart failure is

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**Curr Opin Anesthesiol** 2016, 29:55–60

DOI:10.1097/ACO.0000000000000270

## KEY POINTS

- Although mortality of cardiovascular disease (CVD) in total declines [34], 5-year survival of heart failure remains at approximately 50%.
- Undiagnosed and untreated patients with heart failure have a high risk of acute decompensation in the perioperative setting.
- Diagnosis and therapy must be handled with experience (inotropic treatment/mechanical assist) to provide best possible outcome.
- More patients receive continuous-flow left ventricular assist devices as destination therapy for disabling heart failure. Anesthesia care providers must be familiar with the management of the technical advances in this field (coagulation, TEE).

quite frequent in postoperative patients after cardiac surgery with an incidence of approximately 12% and is also the second most frequent reason for hospital readmission after an infection (approx. 16%) [7]. This shows that heart failure of different causes poses a huge challenge on healthcare providers, in particular those in acute care situations. We therefore review the latest literature for systolic heart failure (HFrEF) for the cardiovascular anesthesiologist with focus on new diagnostic and therapeutic approaches in the review period.

### Pathophysiology and cause of systolic heart failure

Different pathophysiologic models have been proposed in the last decades, altogether describing the mechanisms of heart failure. The hemodynamic model from 1967 defines heart failure as a pathological state in which an abnormality of myocardial function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues during ordinary activity [8]. This was supported by data showing that intrinsic cardiac muscle contractility was reduced during hemodynamic load. The associated ventricular remodeling occurs in both types of heart failure with a high impact on hemodynamic stability [9]. As a consequence, patients with HFrEF typically present with dilated left ventricular cavity and a normal or reduced ratio of end-diastolic volume. The extracellular matrix hereby determines the ventricular architecture and provides a basis for efficient pumping. Myocardial injury leads to remodeling of the extracellular matrix through fibroblast proliferation, which results in ventricular

thinning and impairment of systolic function. The cardiorenal model refers to the close functional relationship between the heart and kidneys. Renal sodium and water retention are then leading to the clinical symptoms of dyspnea and edema [10]. This form of heart failure is treated primarily by diuretics and dietary sodium restriction. The associated neurohumoral activation results in sympathetic nervous activation, increased contractility, vasoconstriction, elevated blood pressure, and long-term maladaptive remodeling with progressive worsening of myocardial injury. Proof of this neurohumoral model was provided through drug-mediated interference with the adrenergic and renin-angiotensin-aldosterone system with significantly improved survival in patients with heart failure [11–14]. The role of the  $\text{Ca}^{2+}$  metabolism through the ryanodin receptor and the SERCA2a pump in the development of heart failure was also highlighted in several studies [15,16]. Other approaches focus on cardiac myocyte cell death through necrosis and apoptosis because of excessive adrenergic activity, inflammation, oxidative stress or toxic substances [17–19]. At least genome wide association studies aim to identify heart failure syndrome-related gene candidates in order to help understand the mechanisms by which genetic aberration can affect cardiac function [20,21]. All these approaches describe the complex pathophysiological picture of heart failure and are reflected in the current treatment guidelines of the ACCF and AHA [22].

### Recent advances in heart failure diagnosis

A prospective trial by O'Meara *et al.* [23] investigated the role of renal disease, interleukins, and specific left ventricular remodeling processes in patients with HFrEF with/without anemia by comparing clinical, echocardiographic, and circulating biomarker profiles with a control group. This study found a strong association between anemia, heart disease markers, and the level of renal dysfunction in patients with HFrEF, represented by increased myocardial remodeling, inflammation, and volume overload. The HFrEF group with anemia showed significantly higher NT-proBNP levels and more often elevated troponin T levels than the nonanemic group. Furthermore, patients with anemic HFrEF showed more advanced chronic kidney disease (CKD) than those without anemia, reaching control-group levels of GFR (those with diagnosed CKD). Inflammatory cytokines IL-6 and IL-10 were higher in the anemia group, and the echocardiographic markers left ventricular mass, mitral regurgitation, and left atrial end-systolic volume index. All these echocardiographic markers were elevated

in patients with anemic HFrEF representing a greater left ventricular remodeling process. Altogether this study demonstrates that patients suffering from HFrEF and anemia have a complex pathophysiology and have a more advanced and active heart disease than nonanemic patients. This finding should be noticed by anesthesiologists for preoperative evaluation and patient blood management.

### Echocardiography in the evaluation of perioperative pump function

Recent recommendations from the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association summarized the perioperative use of ultrasound imaging [24]. Transthoracic and transesophageal echocardiography (TTE, TEE) is a standard tool in the intraoperative and postoperative hemodynamic assessment of patients following cardiac surgery. Postoperatively TTE should be performed first but will often be supplemented by TEE because of poor quality of the transthoracic acoustic window in these patients. Postoperative complications of systolic function include pericardial collection and cardiac tamponade. Suboptimal intraoperative myocardial protection and long bypass times during complex heart surgery often cause significant myocardial depression. A diagnostic approach to assess systolic cardiac function should include inspection of the first 2–4 cm of the coronary arteries, which are accessible to the TEE. Imaging of the right ventricle should also be performed. For that matter tricuspid annular plane systolic excursion (TAPSE) is a validated parameter of global right ventricular function and should be measured intraoperatively as a reference value for postoperative assessment. TAPSE is easily obtainable, correlates well with other standardized parameters of right ventricular function and is furthermore an independent predictor of poor outcome in patients with acute right heart failure [25]. Echocardiography for cannula placement and device implementation is essential and has a vital role in excluding nonheart failure causes of cardiorespiratory failure. Guidelines from the American Society of Anesthesiologists (Practice Guidelines for Perioperative Transesophageal Echocardiography; update in 2016 and estimated publication 2017) describe the perioperative use of echocardiography in detail [26].

### Perioperative treatment of the patient with systolic heart failure

#### Inotropic treatment

In the situation of low cardiac output in a patient with a failing ventricle and typical clinical signs of

systolic heart failure, it is of vital interest to improve the cardiac performance. A recent study from Sponholz *et al.* [27] evaluated the use of catecholamines during heart surgery in Germany and reported, that 80–100% of all individuals enrolled in this study received vasopressors during the perioperative period. First-line therapy in the case of hypotension caused by low cardiac output was dobutamine, which was administered by 32% of all care providers, followed by epinephrine with 30%. Only 8% applied primarily a phosphodiesterase inhibitor (PDEI). Vasoplegia was treated with norepinephrine by 96% of all physicians reported in this study. Second-line treatment was performed by PDEI (50%), epinephrine (42%), and levosimendan (22%).

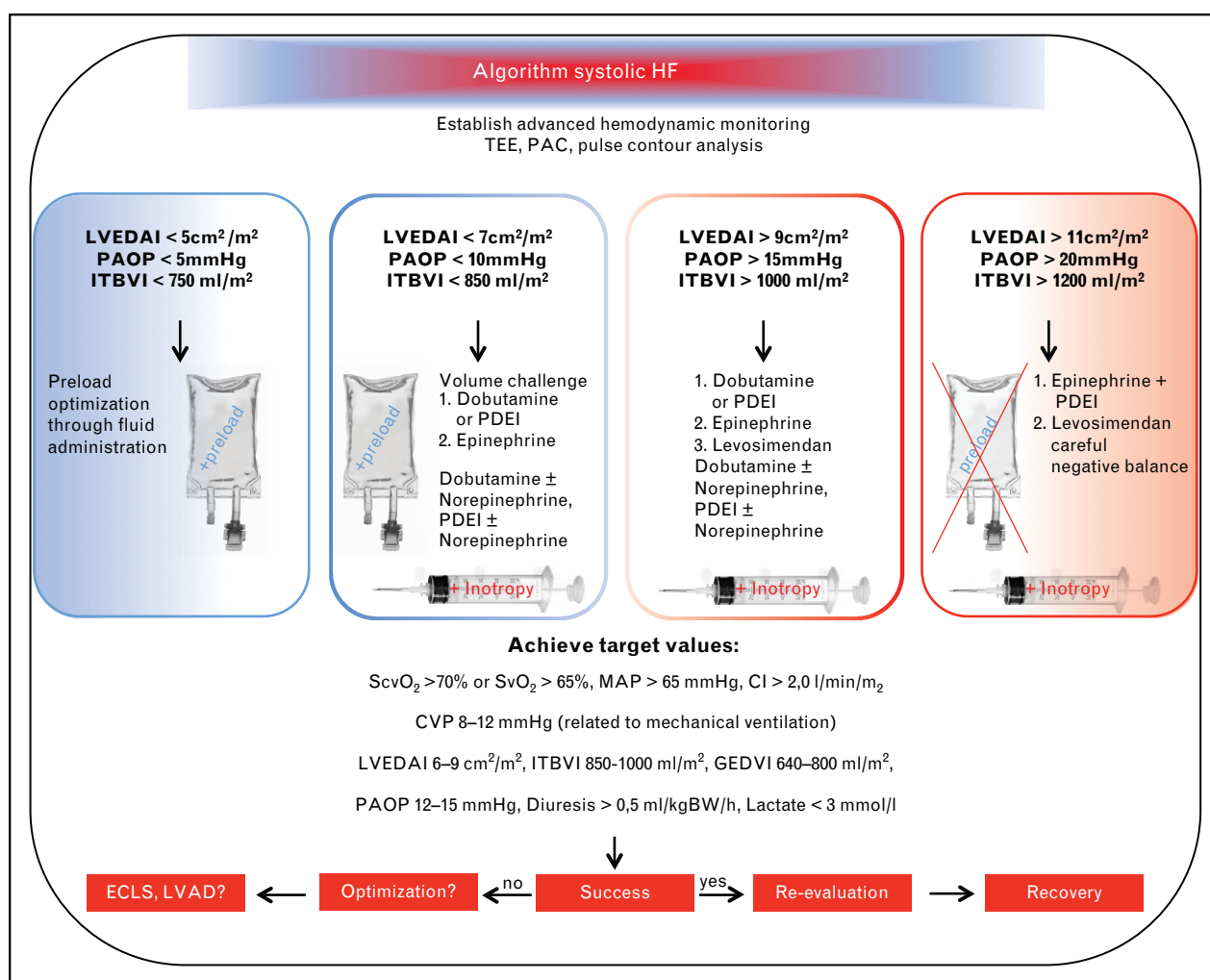
A propensity score-matched analysis in 2340 patients by Nielsen *et al.* investigated the association between intraoperative and postoperative use of inotropes, mortality, and postoperative complications in heart surgery patients [28]. Results showed a strong association between the intraoperative and postoperative use of inotropes, increased mortality, and major postoperative morbidity. Inotropic therapy was independently linked to postoperative myocardial infarction (adjusted OR, 2.1; 95% CI, 1.4–3.0), stroke (adjusted OR, 2.4; 95% CI, 1.4–4.3), and renal replacement therapy (adjusted OR, 7.9; 95% CI, 3.8–16.4). Recent years have seen the advent of the calcium-sensitizer Levosimendan, which is still under extensive clinical investigation (LICORN, *soon reporting*, NCT 02184819; LEVO-CTS, *recruiting*, NCT 02025621; HSR-LEVO, *recruiting*, NCT00994825; Intracoronary administration of levosimendan in cardiac surgery patients, *recruiting*, NCT01500785; prophylactic administration of levosimendan in patients undergoing coronary surgery, *soon reporting*, NCT01318460). The latest European expert opinion on the preoperative and perioperative use of Levosimendan in cardiac surgery summarizes the growing body of knowledge [29] and stated that levosimendan effectively improves general and pulmonary hemodynamics in patients undergoing cardiac surgery. It thereby reduces the need for inotropic and mechanical support with benefit for renal and hepatic function, even though pronounced vasodilation frequently raises vasopressor demand. It can effectively reduce the length of stay on both ICU and hospital. Preoperative administration of levosimendan is recommended in patients who have a generally compromised myocardial function, including right ventricular dysfunction. Bolus administration of levosimendan out of the OR is not advisable, instead a continuous infusion of 0.1 µg/kg/min for 24 h was considered the optimal dose. If not possible, bolus dose after induction of anesthesia is feasible.

If vasodilation emerges, treatment with norepinephrine or vasopressin is recommended, possibly supplemented by the inotrope dobutamine. At last a recent study from Greco *et al.* [30<sup>\*</sup>] was mentioned, in which commonly used inotropes (dobutamine, phosphodiesterase inhibitors) were compared to levosimendan. Interestingly, only levosimendan was associated with a decrease in mortality when compared with placebo (OR = 0.48; 95% CI, 0.28–0.80). The expert panel and the authors of this study agreed upon the need for large-scale RCTs to support this finding.

Therapy for heart failure can be guided according to the last practical guidelines released from the Scientific Medical Societies in Germany (AWMF), which are currently under revision. Figure 1 (algorithm for systolic heart failure) illustrates hemodynamic management in patients with low cardiac

output and proposes a stepwise therapeutical approach using parameters of cardiac preload. The left ventricular end-diastolic area index (LVEDAI) is such a marker and can be monitored by echocardiography in the mid-papillary region on short axis view, thus being a powerful alternative to catheter-based pressure measurements with faster handling and superior global hemodynamic assessment.

Global end-diastolic volume (GEDV) measurement and the closely related intrathoracic blood volume (ITBV) are a set for volumetric estimates of cardiac preload that can be obtained using transpulmonary thermodilution from a cold injectate of saline via a central venous catheter. The GEDV measures the largest volume of blood in the four chambers of the heart and can be used by clinicians to estimate the total cardiac preload, being a stronger static preload marker than central venous



**FIGURE 1.** Graphic illustration of the recommended algorithm for intensive care therapy in patients with low cardiac output syndrome. Edited by The Association of the Scientific Medical Societies in Germany and published in April 2010 (currently under revision). CI, cardiac index; CVP, central venous pressure; GEDVI, global end-diastolic volume index; ITBVI, intrathoracic blood volume index; LVEDAI, left ventricular end-diastolic area index; MAP, mean arterial pressure; PAOP, pulmonary artery occlusion pressure; PDEI, phosphodiesterase inhibitor; ScvO<sub>2</sub>, central venous oxygen saturation; SvO<sub>2</sub>, venous oxygen saturation.



pressure (CVP) or pulmonary artery occlusion pressure (PAOP). Placement of a pulmonary artery catheter allows intermittent recording of the PAOP as an indirect marker of left ventricular preload. The intrathoracic blood volume (ITBV) comprises the GEDV and the blood volume from the pulmonary vasculature and plays a similar role in preload assessment, but is more difficult to measure (double-indicator transpulmonary thermodilution) and has to be corrected by computation. However, ITBV assessment allows further calculation of extravascular lung water as a diagnostic criterion for acute lung injury and the acute respiratory distress syndrome in critical care patients.

### Mechanical assist

Ever since the first LVAD was approved by the US Food and Drug Administration (FDA) in 1994, the field evolved rapidly and device implantation rates constantly grow according to The Interagency Registry for Mechanically Assisted Circulatory Support (Intermacs). Intermacs currently lists 158 participating hospitals in the USA and Canada and a total of 14 039 patients (21.2% female; 78.6% male) in their first quarterly report from 2015 [31]. Out of this population 8762 individuals (62.2%) received a mechanical circulatory assist device as a bridge-to-transplantation and 5084 individuals (36.2%) as destination therapy. Only 102 patients (0.7%) were bridged to recovery and 78 patients (0.5%) received a device for extracorporeal cardiopulmonary resuscitation. LVADs account for 92.5% and BiVADs for 5.2% of all registered device implantations with LVADs being the group of devices with the highest expansion rate. Survival rate from prospective implantation of state-of-the-art continuous flow LVADs between June 2006 to March 2015 is 81% after 1 year and decreases by approximately 10%/year. LVAD implantation prolongs and improves life for patients with heart failure; however, recent reports demonstrate a significant issue concerning the development of pump thrombosis with a relevant impact on survival of patients having the HeartMate II LVAD [32\*,33]. Starling *et al.* describe an incidence-increase of pump thrombosis from initially reported 2.2%, 3-months after implantation before March 2011 through 8.4% by January 2013 with occurrence peak 1-month after implantation. Six-month mortality did not differ between patients who had pump thrombosis and were treated with device replacement or transplantation, compared with patients without pump thrombosis, yet untreated patients with pump thrombosis showed an alarming mortality of 48.2% after 6 months [32\*]. So far experiences show that this

technology is capable to improve and prolong patient life on the one hand, but has to be subjected to superior monitoring on the other hand in order to screen for life threatening adverse events. Moreover considering ethical issues, maximum care providers must be aware that one-third of all patients with LVAD have the device implanted as DT when it comes to complications (DT 2006–2007: 14.7% vs. DT 2011–2013: 41.6%). More than ever consent in treatment and end-of-life care must be met through the patient and all participating specialties before futile situations occur.

### CONCLUSION

We conclude that patients with diminished cardiac pump function demand full attention from the entire perioperative team. Not only must the patient be well prepared for surgery, including adequate diagnosis of the underlying cardiac condition and pharmacologic pretreatment, but also care providers must cooperate best possible to achieve acceptable outcomes. Therefore, current standards of care must be met in the use of the TEE device, pharmacologic agents, and knowledge of the circuit in any hemodynamic situation, especially while implementing mechanical assist devices. At last levosimendan could favor the outcome of patients in the perioperative course of cardiac surgery.

### Acknowledgements

*The authors thank the staff of the Cardiothoracic Division of the Department of Anesthesiology and Intensive Care Medicine, for their outstanding work with patients and their commitment to teaching young residents.*

### Financial support and sponsorship

*Internal funding from the Medical Faculty of the Eberhard-Karls-University Tübingen to J.H. (fortune Program Nr. 2228-1-0).*

### Conflicts of interest

*There are no conflicts of interest.*

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