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Research Article

Perioperative Management of Patients with Heart Failure: A Review

Ana Isabel Pereira de Almeida[1] and Humberto S Machado[1,2]*

[1]*Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal*

[2]*Serviço de Anestesiologia, Centro Hospitalar Universitário do Porto, Porto, Portugal*

***Corresponding Author:** Humberto S Machado, Instituto de Ciências Biomédicas Abel Salazar and Serviço de Anestesiologia, Centro Hospitalar Universitário do Porto, Porto, Portugal.

Received: November 06, 2019; **Published:** July 30, 2020

Abstract

Introduction: Heart failure is an end-stage clinical syndrome based on a broad variety of underlying cardiac conditions. These patients still have an unacceptably high morbidity and mortality when undergoing surgeries, not only cardiac but also non-cardiac surgeries. Therefore, special care is required to maximize safety before, during and after surgery.

This literature revision aims to carry out a systematic review of the perioperative management strategies for patients with heart failure and provides the reader with new insight in diagnosis and treatment of heart failure.

Methods: A literature review based on studies published between 2005 and 2018, available on PubMed and Google.

Results: In order to prevent perioperative complications, several practices are suggested.

Preoperative: Echocardiography is well established for the diagnosis of heart failure and is superior to risk scores and biomarkers in risk stratification; therapeutic optimization using β-blockers, ACEIs/ARBs and diuretics is indispensable; and surgeries should be postponed if adequate medical treatment has not been established or if evidence of preoperative acute heart failure.

Intraoperative: Transoesophageal echocardiography is the gold-standard for monitoring; inotropic and vasopressor agents have been recommended and used for several years if evidence of hypotensive acute heart failure, but they remain controversial; vasodilators, most commonly nitroglycerin, should be the predominant treatment in hypertensive acute heart failure patients; and normotensive patients generally require significant diuresis with intravenous loop diuretics.

Postoperative: Reach the patient's preoperative levels is wanted; echo and electrocardiography monitoring should be maintained; and avoiding known triggers of acute heart failure.

Conclusion: Recent advances in the field of cardiovascular anesthesiology have been achieved, however there are variations in the perioperative period approach, and even lack of agreement on some topics, evidencing the need for large trials to clarify them.

Keywords: *Heart Failure; Systolic Dysfunction; Diastolic Dysfunction; Anesthesia; Perioperative Management*

Abbreviations

HF: Heart Failure; BUN: Blood Urea Nitrogen; CO: Cardiac Output; HR: Heart Rate; LV: Left Ventricle; MACE: Major Adverse Cardiac Events; ACC/AHA: American College of Cardiology/American Heart Association; AHF: Acute Heart Failure; CS: Cardiogenic Shock; ESC/ESA: European Society of Cardiology/European Society of Anaesthesiology; LVEF: Left Ventricular Ejection Fraction; HfpEF: Heart Failure Preserved

Ejection Fraction; HfmrEF: Heart Failure Intermediate Ejection Fraction; HfrEF: Heart Failure Decreased Ejection Fraction; MI: Myocardial Infarction; AF: Atrial Fibrillation; LVH: Left Ventricular Hypertrophy; ADHF: Acute Decompensation Of Heart Failure; RCRI: The Revised Cardiac Risk Index; IHD: Ischemic Heart Disease; TTE: Transthoracic Echocardiography; ACEIs: Angiotensin Converting Enzyme Inhibitors; Arbs: Angiotensin-Receptor Blockers; RCT: Randomized Controlled Trial; ADHERE: Acute Decompensated Heart Failure National Registry; PASP: Pulmonary Artery Systolic Pressure; EAE/ASE: European Association of Echocardiography and American Society of Echocardiography; SV: Stroke Volume; TEE: Transoesophageal Echocardiography; PAC: Pulmonary-Artery Catheter; CVP: Central Venous Pressure; SSC: Surviving Sepsis Campaign; PAOP: Pulmonary Artery Occlusion Pressure; PASP: Pulmonary Artery Systolic Pressure; ICU: Intensive Care Unit; AUC: Area Under The Curve; ROC: Receiver Operating Characteristic; HES: Hydroxyethyl Starch; MAP: Mean Arterial Pressure; CHF: Chronic Heart Failure; SBP: Systolic Blood Pressure; PH: Pulmonary Hypertension; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; LCOS: Low Cardiac Output Syndrome; IABP: Intra-Aortic Balloon Pump; CCB: Calcium Channel Blockers; DBP: Diastolic Blood Pressure; HMOD: Hypertension-Mediated Organ Damage; LA: Left Atrial; PACU: Postanesthetic Care Unit

Introduction

HF is a complex clinical syndrome caused by impaired ventricular performance. It can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood and it is the final common pathway for a variety of cardiovascular disease processes [1]. Unlike a normal ventricle, the ventricle in HF is no longer able to match the increases in venous return and cannot generate the pressure required for the rest of the body, leading to end-organ dysfunction. The body sees these insults as a decrease in intravascular volume and a cascade of neurohormonal responses is activated in order to compensate for the hypoperfusion, despite a normal fluid status. The perpetuation of these compensatory mechanisms, but poorly adapted, causes a vicious circle that leads to a progressive worsening of the cardiac function [2].

More than 4 million Americans suffer from HF, with an incidence of 500,000 new cases annually. After diagnosis, mean survival is 1.7 years for men and 3.2 years for women, with mortality rates of 50% at 2 years and 70% at 3 years [2]. HF is a disease of the elderly and, as more surgical procedures take place in elderly patients, anesthesiologists will more often face patients with diagnosed or even suspected HF in the perioperative period.

Recently, van Diepen., *et al.* [3] determined that patients with symptomatic HF undergoing non-cardiac surgery have a perioperative 30-day mortality of 18.5%. Nevertheless, the same study determined that, even undergoing minor surgical procedures, these patients still exhibit a mortality rate of approximately 8%.

HF is not only a major risk factor for perioperative mortality, but also for MACE. In fact, compared to patients without a history of HF, patients with HF were 3.4 (95% CI: 2.0, 5.4) times more likely to experience MACE following non-cardiac surgery [4].

Generally speaking, perioperative risk is based on four categories: urgency of surgery, complexity of procedures involved, extent of medical comorbidities and severity of underlying heart disease. Each factor carries important independent prognostic information [5].

AHF in perioperative period is one of the most important sources of morbidity and mortality after non-cardiac surgery. Myocardial ischemia constitutes the most frequent cause of perioperative AHF, however, there are other less frequent causes including cardiac arrhythmias, acute or chronic heart valve insufficiencies, massive pulmonary embolism and pericardial tamponade [6].

Anesthetizing patients with HF requires knowledge of the disease state and likely response to titration and adjustment of therapy, as well as possible, hemodynamic consequences of anesthetization [4].

Objective of the Study

The objective of this study is to perform a systematized bibliographical review of the state of the art of the optimization of patients

with HF for surgery. Regarding the pre-, intra- and postoperative periods, individualized needs of these phases will be discussed, towards the safest surgical experience.

Methods

An online search was performed on PubMed and Google, between September 2018 and October 2018. The following keyword combinations were used:

- "Heart failure" and: "perioperative", "preoperative", "intraoperative", "postoperative"
- "Heart failure" and: "anesthesia"
- "Systolic dysfunction" and: "perioperative", "preoperative", "intraoperative", "postoperative"
- "Diastolic dysfunction" and: "perioperative", "preoperative", "intraoperative", "postoperative".

In this review, were eligible for inclusion articles written in English, published after 2005 inclusive. Also, only studies conducted in humans and in adults (age ≥ 19) were used.

Figure 1 shows inclusion/exclusion methodology of manuscripts.

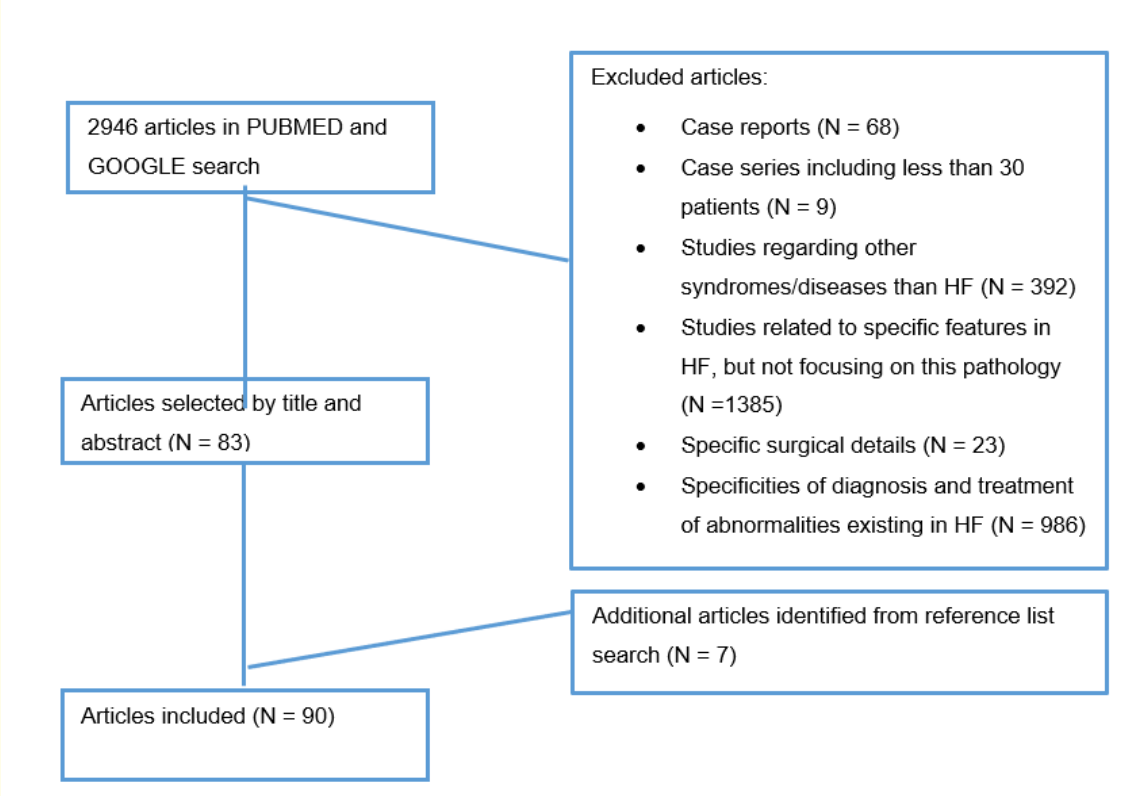

Figure 1: *Article selection methodology.*

Results

HF comprises a wide range of patients. In the latest ESC/ESA guidelines, three distinct categories of patients are defined based on LVEF: HFpEF, HFmrEF and HFrEF with a LVEF >50%, 49 - 40%, and < 40%, respectively [7].

Population-based studies have shown that approximately half of the patients with HF have a normal LVE [1,7-9]. In addition, the prevalence of HFpEF, relative to HFrEF, is growing by 10% per decade - a trend that may make the HFpEF the most common form of HF in the future [9].

Differentiation of patients with HF based on LVEF is important due to different underlying aetiologies, demographics, co-morbidities and response to therapies [7].

Coronary artery disease, with or without history of MI, is the major risk factor for developing HFrEF [1]. On the other hand, patients with HFpEF are more likely to be older, female, hypertensive with AF, and less likely to have coronary artery disease [1,9].

In addition, it should be noted that systolic and diastolic dysfunction are not mutually exclusive, that is, most patients with HFrEF also have diastolic dysfunction, and subtle abnormalities of systolic function have been shown in patients with HFpEF [7].

The MAGGIC meta-analysis, using individual patient data, found that patients with HFpEF have a lower risk of death than patients with HFrEF, and this difference is seen regardless of age, gender, and aetiology of HF. Irrespective of this recent finding, several studies have shown that mortality associated with HFpEF is unacceptably high [10].

Anesthesiologists frequently see asymptomatic patients with diastolic dysfunction or with non-specific symptoms that can be similar to those of chronic obstructive pulmonary disease. Nevertheless, most physicians pay attention to LVEF for preoperative echocardiographic evaluation of the systolic function, but diastolic function is not routinely evaluated in patients undergoing surgery. Therefore, left ventricular diastolic dysfunction is an underestimated disease in the perioperative period [8].

Preoperative management

In the preoperative period, it is important to identify patients who may have or be at risk of HF. For this, is necessary a preoperative evaluation that involves a complete history and physical examination and the subsequent evaluation and stratification of the perioperative risk, based on factors related to the patient and surgery. Additionally, it is crucial to prevent situations that may lead to ADHF [11].

In the latest guidelines of ESC/ESA there is a strong recommendation (Class 1, Level A) to adequately examine patients with suspected or already diagnosed HF, and who are scheduled for non-cardiac surgery, using TTE and to measure the actual BNP or NT-pro-BNP [12].

In a prospective derivation study, performed in high-risk patients undergoing major non-cardiac surgery, BNP was shown to have sensitivity and specificity of 87% in predicting cardiovascular events for non-cardiac vascular surgery [13].

A meta-analysis of 15 studies confirmed the association between elevated preoperative BNP and NT-pro-BNP levels with a postoperative OR of 19.77 (95% CI, 13.18 - 29.65) for MACE and an OR of 9.28 (95% CI, 3.51 - 24.56) for short-term mortality within 43 days of surgery [14].

Systolic dysfunction

In 2010, a retrospective study revealed that a severely reduced LVEF (< 30%), obtained by echocardiographic evaluation in patients with HF undergoing non-cardiac surgery of medium and high risk, is associated with worsened outcomes [5].

In patients with HF, the importance of continuation of therapy with chronic β-blockers in the perioperative period seems to be consensual among the different studies [2,4]. Looking at the results by Andersson., *et al.* [15], in patients with HF, the use of β-blockers preoperatively was associated with a significantly lower risk of MACE (HR 0.78; 95% CI, 0.67 - 0.90) and all-cause mortality (HR 0.80; 95% CI, 0.70 - 0.92). In these patients, the outcomes were similar for urgent and elective surgery.

In 2014, both the ESC/ESA and ACC/AHA guidelines encourage the continuation of β-blockade therapy in patients with HF during the perioperative period [11,12].

However, the question arises as to the safety of initiating β-blockade in the perioperative period in patients at risk for major adverse cardiac events [2]. About that, the remaining recommendations offered by current guidelines remain weak [11,12].

Four major observational trials were more frequently cited: studies by Andersson., *et al.* [15], Jørgensen., *et al.* [16], Lindenauer., *et al.* [17] and London., *et al* [18].

According to Andersson., *et al.* [15], in patients with IHD who underwent non-cardiac surgery, the use of β-blockers was associated with a lower risk of 30-day MACE and mortality only among those with HF or recent MI. Jørgensen., *et al.* [16] found that antihypertensive treatment with a β-blockers may be associated with increased risks of MACE and all-cause mortality in patients with uncomplicated hypertension (without renal or cardiac disease). Both Lindenauer., *et al.* [17] and London., *et al.* [18] reported that preoperative β-blockers initiation in high-risk patients (RCRI score ≥ 2 and undoubtedly, ≥ 3) is associated with a reduced risk of all-cause mortality, but not in the low-risk ones.

Current ESC/ESA, but not ACC/AHA, perioperative guidelines recommend the use of atenolol or bisoprolol if the initiation of β-blockers is needed before surgery (Class 2, Level B), based on a few observational studies. Nevertheless, no randomised head-to-head comparison of β-blocker subtypes exists in a perioperative setting [12].

Regarding the use of ACEIs/ARBs, there is still more controversy. The different guidelines vary in the recommendations and the evidence is limited [11,12,19].

Several studies have shown that continuing therapy with ACEIs/ARBs in chronic users before non-cardiac surgery is associated with a clear increase in the incidence of intraoperative hypotension [11,12,19,20]. For instance, an international prospective cohort study from 2007 to 2011 conducted by Roshanov., *et al*. found that patients in whom ACEIs/ARBs were suspended within 24 hours before non-cardiac surgery had a lower adjusted risk of clinically important intraoperative hypotension (aRR 0.80; 95% CI, 0.72 - 0.93). What is new in this study is that these patients were less likely to suffer from 30-day all-cause death, stroke or myocardial injury (18% aRR reduction) [20].

In 2018, a meta-analysis involving 9 studies (5 RCTs and 4 cohort studies, including the study by Roshanov., *et al*.) confirmed the current observation that perioperative continuation of ACEIs/ARBs is associated with an increased incidence of intraoperative hypotension. However, it did not demonstrate an association between perioperative administration of ACEIs/ARBs and mortality or MACE [19].

Conversely, some studies have shown that the preoperative administration of ACEIs may also protect the kidney in vascular surgical patients [21]. This is potentially important considering that an analysis of over 118000 patients from the ADHERE database confirmed the high prevalence (91%) of renal dysfunction in patients with AHF [22].

Diuretics are recommended to reduce the signs and symptoms of congestion in patients with HFrEF. On the subject of maintaining diuretics until the day of surgery, the ESC/ESA guidelines do not provide recommendations and these drugs are not addressed in the ACC/AHA guidelines [11,12].

The increased risk of hyperkalemia associated with taking this class of diuretics, namely eplerenone and spironolactone, is documented in several studies [12].

Another electrolyte disturbance that should be considered in any patient receiving diuretics, like loop diuretics, is hypokalemia. According to the ESC/ESA guidelines, hypokalaemia is reported in up to 34% of patients undergoing surgery (mostly non-cardiac) [12].

Diastolic dysfunction

The latest ESC/ESA guidelines recommend, based only on the absence of evidence-based studies, similar perioperative management of patients with HFpEF, emphasizing parameters beyond LVEF, like general clinical condition, evidence of volume overload, and increased levels of natriuretic peptides. In the ACC/AHA guidelines there is no differentiation between HFrEF and HFpEF for the perioperative management [12].

According to Flu., *et al.* [23], in patients undergoing open vascular surgery, even if asymptomatic, isolated diastolic dysfunction is associated with 30-day cardiovascular events (OR 1.8; 95% CI, 1.1 - 2.9) and long-term cardiovascular mortality (HR 3.0; 95% CI, 1.5 - 6.0). These data suggest that preoperative risk stratification should include, not only HF symptoms, but also routine preoperative echocardiography to stratify open vascular surgery patients' risk.

In 2014, a retrospective study elucidated that a ratio of E-wave velocity (measured at the mitral valve in the fast filling stage by pulsed Doppler) and the E´-wave velocity (measured by tissue Doppler at the interventricular septum or lateral wall of the left ventricle) - E/E'- > 15; PASP > 35 mmHg and LVH in preoperative TTE predicted postoperative pulmonary oedema in patients with diastolic dysfunction. Likewise, E/E′ > 15 predicted MACE in these patients who underwent low or intermediate-risk non-cardiac surgery [24].

The EAE/ASE has suggested a practical algorithm to classify diastolic function based on the E/E' ratio and other parameters. This classification includes 3 grades: mild or grade I (impaired relaxation pattern), moderate or grade II and severe or grade III (restrictive filling) [25].

Hence, as stated by Nicoara., *et al.* [8] and Gelzinis [9], patients with grade I and II may benefit from β-blockers and rate-slowing agents or require, during anesthetic management, fluid administration to increase LA pressure. In contrast, patients with grade III have a fixed SV, so the administration of diuretics may have a salutary effect. Still, the administration of diuretics and venodilators should be made with caution in these patients, since they are particularly susceptible to excessive preload reduction.

Many factors including uncontrolled hypertension, AF, myocardial ischaemia, anaemia, renal failure, and non-compliance with treatment may precipitate overt systolic and diastolic HF [28]. However, as noticed by Zannad., *et al.* [27] uncontrolled hypertension is involved in more than 50% of the cases of acute (decompensated) diastolic HF.

Intraoperative management

In 2013, a review of 400,000 cases of patients undergoing total hip or knee arthroplasty observed a significantly lower incidence of mortality among neuraxial and combined neuraxial-general anesthesia groups compared with those undergoing surgery under general anesthesia. Incidence rates of in-hospital complications (including for pulmonary embolism, pneumonia, cerebrovascular events, and acute renal failure) were generally lower among the neuraxial and combined neuraxial-general groups than the general group. However, no differences in the rate of acute MI were seen between groups [28].

In 2018, a retrospective analysis of 75,319 patients undergoing carotid endarterectomy indicated that when local/regional anesthesia is performed, there was no difference in mortality or neurological adverse events. Still, general anesthesia was associated with a 2-fold

increased risk of MI (aOR 1.95; 95% CI, 1.06 - 3.59, P = 0.03), a 4-fold increased risk of ADHF (aOR 3.92; 95% CI, 1.84 - 8.34, P < 0.001) and 1.5 times higher hemodynamic instability (aOR, 1.54; 95% CI, 1.44 - 1.66, P < 0.001) compared to the local/regional group [29].

Agreeing with several authors, TEE is the most effective clinical tool for monitoring patients with HFrEF and HFpEF during the intraoperative period. It can even give indications about the haemodynamic profile of the patient, preload estimation through the measurement of left ventricular end diastolic area, and estimation of fluid responsiveness by dynamic indicators that allow real-time guidance for volume therapy [1,8].

A study to compare therapy guided by a PAC with standard therapy (not guided by a PAC) in 1,994 elderly and high-risk patients (American Society of Anesthesiologists class III or IV risk) undergoing surgery was performed. This multicentre RCT observed that in-hospital mortality was similar in the two groups: 7.7% (95% CI, 6.1 - 9.6) in the standard-care group compared with 7.8% (95% CI, 6.2 - 9.7) in the catheter group. There were also no differences in mortality rates at 6 and 12 months in both groups [30].

Data suggest that only 50% of critically ill patients respond to a fluid challenge. For this reason, investigators have been looking for indices of fluid responsiveness that can be used to predict the response to a fluid challenge [31].

CVP has been used to guide fluid challenges for over 40 years. However, over the past few years, studies with several patient groups have repeatedly shown that changes in CVP and PAOP have a very poor or totally missing correlation with changes in CO. Additionally, CVP measurement has only minimal predictive power in determining intravascular volume status [32].

Despite this, according to the SSC guidelines of 2016, a CVP of 8-12 cm H2O in the first 6 hours is recommended in sepsis with signs of hypoperfusion [31].

According with several authors, because the body covers a high oxygen demand in the tissues by increasing CO physiologically, the efficacy of a resuscitative therapy can be better assessed by continuous CO monitoring [32,33]. The most important feature of CO monitoring, in order to be used during the fluid challenge is the ability to measure small changes in SV in real time [33].

If the main target of a fluid challenge is an increase in SV, the primary safety limit is the failure to increase the SV [33]. Regarding the study by Monnet., *et al.* [34], involving 51 patients with acute circulatory failure, oxygen delivery increased significantly in volume-responsive patients (+32% ± 16%, P < 0.0001). However, in nonvolume-responsive group, delivery oxygen decreased by 4% ± 7% (P < 0.001), probably due to hemodilution with consequent hematocrit decrease. This, in turn, demonstrates that a fluid challenge should be seen as a one-time attempt if alternative markers remain unchanged.

Systolic dysfunction

Recent evidence suggests that there is no universal target blood pressure value to define intraoperative arterial hypotension. But, MAP < 65 mmHg or reductions in MAP > 20% (in relation to preoperative pressure) are related to myocardial and kidney injury [34].

In the latest ESC/ESA and ACC/AHA guidelines, there is still a recommendation for intravenous inotropic support (Class 2b, Level C and Class 1, Level C, respectively) in patients with CS (defined as hypotension - SBP <90 mmHg - and/or sign/symptoms of hypoperfusion despite the adequate filling status) [7,35].

In fact, the available inotropics have been associated with harm, though the evidence base is small and inconsistent [36]. In this context, in a study by Mebazaa., *et al.* [37], the use of intravenous catecholamines was associated with 1.5-fold increase in-hospital mortality rate for dopamine or dobutamine use and a 2.5-fold increase for use of noradrenaline or adrenaline. Upon that, catecholamines should be used cautiously as it has been seen that they actually increase the risk for in-hospital mortality.

In terms of vasopressors, studies have not found the best agent yet [37]. For instance, SOAP II, a multicentre RCT, elected 1,679 shock patients to receive dopamine (20 μg/kg/min) or noradrenaline (0.19 μg/kg/min) as first-line vasopressor therapy to restore and maintain blood pressure. The results showed that dopamine compared to noradrenaline was associated with an increase in the 28-day death rate among patients with CS (N = 280), but not among patients with septic shock (N = 1,044) or with hypovolemia shock (N = 263) (P = 0.03, P = 0.19, P = 0.84, respectively). In addition, there were more arrhythmic events among dopamine-treated patients than among those treated with noradrenaline (24.1% vs. 12.4%, P < 0.001, respectively) [38].

The OPTIME-CHF study randomized 949 patients with systolic dysfunction and ADHF, of whom 51% had ischemic HF and 49% had non-ischemic HF, to receive 48 to 72 hours of intravenous milrinone or placebo. In this study, in-hospital mortality for milrinone-treated patients with ischemic HF was 5.0% versus 1.6% for placebo (P = 0.04). Meanwhile, patients with non-ischemic HF demonstrated evidence of benefit with milrinone therapy compared with placebo: 2.6% versus 3.1%, respectively (P = 0.04) [39].

Four major studies have reported the use of levosimendan in AHF: LIDO [40], RUSSLAN [41], REVIVE-II [42] and SURVIVE [43]. The first two studies encourage the use of levosimendan in this context, reporting a decrease in mortality rate when compared to dobutamine (LIDO) or placebo (RUSSLAN). While the last two, did not show this benefit in survival. However, some authors pointed out the characteristics of the patients selected as implicated in these results [44].

Re-analysis of the REVIVE-II mortality data identified low blood pressure at baseline (SBP < 100 mmHg or DBP < 60 mmHg) as a factor associated with increased mortality risk with the use of levosimendan [44].

On the other hand, a new way of looking at SURVIVE results reveals that the stratification of patients according to the presence/absence of CHF and the use/non-use of β-blockers at baseline influenced 5-day mortality. In fact, it was lower for levosimendan than for dobutamine: 3.4% vs 5.8% (P = 0.05) in the CHF group and 5% vs 5.1% (P = 0.01) in the β-blockers group [45].

In 2015, a meta-analysis of randomized trials published in the last 20 years, found no difference in mortality between patients who received inotropics/vasopressors and the control group (OR 0.98; 95% CI, 0.96 - 1.01). However, the only drug associated with improvement in survival was levosimendan, although it has not yet been shown to improve survival in large, multicentre RCTs [46].

Although it is associated with poor prognosis, particularly when hypoperfusion is also present, only 5% to 8% of all patients have low SBP (< 90 mmHg, hypotensive AHF). In most cases, patients with AHF present with either preserved (90-140 mmHg) or elevated (140 mmHg, hypertensive AHF) SBP [7,36].

In the latest ESC/ESA and ACC/AHA guidelines, there is a recommendation for intravenous loop diuretics (Class 1, Level C and Class 1, Level B, respectively) and intravenous vasodilators (Class 2a, Level B and Class 2b, Level A, respectively) in patients with normotensive AHF [7,35].

Both guidelines recommend a dose of 20 - 40 mg of intravenous diuretics in patients with new-onset AHF and, for those on chronic diuretic therapy, an initial intravenous dose at least equivalent to the oral dose, without however mentioning the most appropriate doses [7,35]. About this, a RCT with 308 patients with ADHF comparing low intravenous dose of furosemide (equivalent to the patient's previous oral dose) with high dose (2.5 times the previous oral dose) found that larger doses resulted in more diuresis and improvement in dyspnea over the first 72 hours, but also increased the likelihood of creatinine elevation. In addition, no difference was observed in the administration of bolus diuretics or continuous infusion [47].

Similar results are reported in a recent meta-analysis of 10 RCTs in which no differences were found in continuous administration of loop diuretic versus bolus injection in terms of safety and efficacy in ADHF patients [48].

Compared with the general population, only about 15 - 20% of the furosemide dose is delivered into the tubular fluid in patients with chronic kidney disease, stage 5. Therefore, to achieve the desired effect, higher doses or an increased frequency of treatment with furosemide are required [36].

Another strategy to investigate optimal diuretic therapy is to evaluate its combination with other agents. Cotter., *et al.* [49] compared a vasodilator focused strategy (high dose nitrates with low dose diuretics) with a diuretic focused strategy (high dose diuretics and low dose nitrates) in 104 patients with ADHF and acute pulmonary oedema and found that the vasodilator focused strategy led to significantly lower incidence of the need for mechanical ventilation (13% vs 40%, P = 0.0041) and of MI (17% vs 37%, P = 0.047).

Diastolic dysfunction

Approximately half of the patients hospitalized with AHF present hypertension (SBP ≥ 140 mmHg). Therefore, avoiding acute systemic hypertension is important during surgery [36].

The most common causes of intraoperative hypertension include inadequate analgesia and superficial anesthesia for the degree of surgical manipulation [29].

Schwartzenberg., *et al.* [50] compared hemodynamic responses to vasodilator therapy in patients with HFrEF and HFpEF and noted that patients with HFpEF experience a reduction 2.6-fold in SBP (P < 0.0001) and a 60% less improvements in SV and CO (P < 0.0001) as compared to patients with HFrEF. Similar reduction in PAOP was observed. These data underscore the fundamental differences in pathophysiology in HFpEF versus HFrEF and suggest that alternative treatment strategies targeted to ventricular-vascular stiffening rather than afterload reduction may have greater likelihood of benefit in HFpEF.

As noted previously for the treatment of patients with normotensive AHF, the guidelines strongly recommended intravenous loop diuretics in all patients with AHF with signs of fluid overload and congestion in the absence of signs of hypoperfusion (Class 1). However, they provide little support for the use of vasodilators as first-line therapy in hypertensive AHF (Class 2a and 2b) [7,35].

As mentioned by Collins., *et al.* [51], vasodilator therapies are often underused in managing these patients and diuretics are more likely to be administered inappropriately when volume overload plays little or no role in symptomatic pulmonary congestion.

The VMAC trial failed to demonstrate statistically significant improvement of PAOP or self-reported dyspnea at 3 hours after the initiation of nitroglycerin infusion compared with placebo. However, the median dose of nitroglycerin administered over the first 3 hours was 42 µg/min. and 29 µg/min (among catheterized and non-catheterized patients, respectively) - much lower than that seen in prospective studies of nitrates in hypertensive AHF [51]. According to Elkayam., *et al.* [52], the lack of effect shown in the VMAC study was probably related to a decrease in vasodilatory response to nitroglycerin (nitrate resistance) that suggests the need to use larger doses (>120 µg/min.) to achieve a significant improvement of hemodynamic parameters.

In 2007, another study conducted in patients with hypertensive AHF, compared continuous infusion of intravenous nitroglycerin followed by subsequent high doses of nitroglycerin (2mg every 3 to 5 minutes) with continuous single infusion of nitroglycerin. In this trial, patients who received high doses of nitroglycerin required endotracheal intubation, non-invasive ventilation and ICU admission less frequently than controls who received continuous single nitroglycerin infusion (13.8% vs 26.7%; 6.9% vs 20.0% and 37.9% vs 80.0%, respectively). However, it is important to note that this is a nonrandomized, open-label study which can introduced the potential for selection bias and imbalances in groups' composition [53].

In 2017, a retrospective observational cohort study stated that early administration of high-dose nitroglycerin by intermittent boluses (2 mg every 3 to 5 minutes) in patients with hypertensive AHF is associated with lower admission rates to the ICU and shorter hospitalization as compared with continuous infusion (P < 0.0001 and P = 0.02, respectively) [54].

Nesiritide is an alternative to nitroglycerin. Although some studies have shown that intravenous infusion of nesiritide has beneficial hemodynamic effects in patients with ADHF, it failed in an RCT - ASCEND-HF. This trial compared nesiritide with placebo in patients admitted with ADHF (N = 7141) and found no relative benefit or harm associated with nesiritide in terms of mortality or hospital readmission (9.4% vs 10.1%, P = 0.31 for nesiritide and placebo, respectively) or dyspnea improvement (44.5% vs. 42.1%, P = 0.03 for nesiritide and placebo, respectively) [55].

Postoperative

Regarding a study published in 2016, the magnitude of association between congestive HF and postoperative adverse outcomes was higher for cardiac arrest, followed by mortality, unplanned intubation, and ventilator dependence > 48 hours (95% CI; P < 0.001). Excessive fluid volume administration and decreased CO during the perioperative period may explain these complications [32].

A meta-analysis of 18 studies confirmed that elevated postoperative BNP and NT-pro-BNP levels are strongly associated with an increased mortality or nonfatal MI (OR 3.7; 95% CI, 2.2 - 6.2; P < 0.001). Effectively, additional postoperative BNP and NT-pro-BNP measurement enhanced risk stratification after non-cardiac surgery compared to a preoperative BNP and NT-pro-BNP measurement alone [56].

Several authors have pointed out the importance of postoperative TEE performed as early as possible in patients with suspected or already diagnosed HF [1,8,57]. Hunter., *et al.* [36] have reported that cardiac ultrasonography discriminates AHF from other causes of dyspnea with sensitivities ranging from 77 to 83% and specificities ranging from 74 to 90%. Additionally, Janda., *et al.* [58] have shown that TTE has a sensitivity of 83% and specificity of 72% for the diagnosis of PH.

Severe postoperative pain is reported in 5 - 10% of patients [12]. In 2014, a meta-analysis of 125 RCTs reported that in patients undergoing general anesthesia, concomitant epidural analgesia (with local anesthetics, and maintained for at least 24 hours postoperatively), reduces postoperative mortality and improves cardiovascular, respiratory, and gastrointestinal morbidity, compared with patients who received standard systemic analgesia (OR 0.6, 95% CI, 0.39 - 0.93) [59]. In accordance to this, the ESC/ESA and ACC/AHA guidelines state that postoperative epidural analgesia may be considered (Class 2b, Level B) [11,12].

In 2013, a meta-analysis of 639 RCTs demonstrated an increase in MACE by about one-third and a significant risk of vascular death in patients taking coxibs (RR 1.37; 95% CI, 1.14-1.66; P = 0.0009 and RR 1.58; 95% CI, 1 - 2.49; P = 0.0103, respectively) or diclofenac (RR 1.41; 95% CI, 1.12 - 1.78; P = 0.0036 and RR 1.65; 95% CI, 0.95 - 2.85; P = 0.0187, respectively) compared with placebo. Furthermore, HF risk was roughly doubled by all NSAIDs [5].

Systolic dysfunction

Current ESC/ESA and ACC/AHA guidelines encourage the restart of HF medication in postoperative period, as soon as clinical conditions allow [11,12].

In cases where β-blocker therapy is initiated preoperatively, both guidelines alert that, the optimal duration of postoperative β-blockade, cannot be derived from RCTs, as it depends on the morbidity of the surgery and its final outcome. Moreover, a target resting HR of 60 - 70 beats/min and SBP >100 mmHg are also recommended in patients undergoing β-blocker therapy [11,12].

Postoperative LCOS is the most common and most serious complication and is associated with increased morbidity and mortality in the short and long-term. It is more frequent in high-risk cardiac patients, especially those with preoperative systolic dysfunction, compared with patients with normal LVEF [60].

There is no consensus definition of what constitutes LCOS, but some authors define it as mixed venous saturations < 60%, cardiac index < 2.2 L/min/m^2 and PAOP > 18 mmHg [60].

In some studies it has been reported that the postoperative administration of levosimendan in patients with LCOS reduces mortality, the requirement for another inotropic, the use of vasopressors and the requirement for IABP use [60,61].

Still, in 2017 a multicentre RCT (CHEETAH) found that in patients with postoperative LCOS a low-dose infusion of levosimendan did not result in lower 30-day mortality (HR 1.02; 95% CI, 0.65 - 1.59; P = 0.94) nor did it positively affect any secondary-outcome (such as durations of mechanical ventilation, UCI and hospital stays) compared to placebo. This study differs from all previous ones, since it was not used a loading dose and the mean continuous infusion dose of levosimendan was 0.07 μg/Kg/min., which is lower than the 0.1 μg/Kg/min. used in other studies [62].

Diastolic dysfunction

In patients with diastolic dysfunction, hypoxemia and/or AF are the most common complications in the postoperative period [9]. Furthermore, postoperative pain may induce tachycardia and hypertension with the potential of triggering acute (decompensated) diastolic HF [8].

All of these are particularly important in patients with HFpEF, since they may be more susceptible to volume overload and tachycardia because of the stiffness of the LV wall and the smaller size of the LV chamber [8].

Recent ESC/ESA and ACC/AHA guidelines for the management of AF, recommended the use of β-blockers and CCB (verapamil, diltiazem) to control HR in AF patients with LVEF ≥40% (Class 1, Level B in both guidelines). Besides this, they refer these drugs should be preferred over digoxin, because of their rapid onset of action and effectiveness at high sympathetic tone [64]. Likewise, guidelines for the management of HF also recommend oral β-blockers if there is no distressing HF symptoms, while in patients with marked congestion, digoxin is preferred [7,35].

In addition, β-blockers have been shown to accelerate the conversion of AF to sinus rhythm in the ICU after non-cardiac surgery (95% CI, 1.046 - 7.8; P = 0.049) [63].

Hypertensive emergencies are defined by the presence of severe hypertension/grade 3 - SBP ≥ 180 mmHg and/or DBP ≥110mmHg - associated with acute HMOD. These situations are often life-threatening and require immediate but careful intervention to reduce blood pressure, usually with intravenous therapy [64,57].

In the latest ESC/ESA and ACC/AHA guidelines for the management of arterial hypertension, there is a recommendation for the use of nitroprusside or nitroglycerine intravenous as first-line treatment in patients with severe hypertension associated with AHF. Since these situations are accompanied by acute cardiogenic pulmonary oedema, the association with loop diuretics is necessary [64,65].

Some authors also mention the use of intravenous CCB, such as nicardipine or nitrendipine. ACEIs are not useful in the acute phase, because of their slower onset of action [26].

Discussion

Preoperative management

In what concerns to the preoperative evaluation of the surgical risk, several risk scores were developed. However, although risk scores are useful in elective surgeries, several clinical variables, such as LVEF and clinical stability, are important for risk stratification [23,24]. Effectively, it is agreed that risk models do not dictate management decisions, but are tools for physicians in relation to the need for cardiac evaluation, drug treatment, and additional assessment of risk for cardiac events [11,12].

Taking into account the various articles analysed, it is possible to infer that patients undergoing very low-risk surgery (e.g. ophthalmologic surgery), even with multiple risk factors, would have a low risk of MACE; whereas a patient undergoing major vascular surgery with few risk factors would have an elevated risk of MACE [11].

TTE is recommended in all patients with suspected or already diagnosed HF and who are scheduled for non-cardiac intermediate or high-risk surgery [11,12]. Effectively, echocardiography is the gold standard for the assessment of cardiac structure and function and their findings are important parameters in surgical risk stratification of patients with systolic and/or diastolic dysfunction[5]. Although, evaluation of BNP or NT-pro-BNP is also recommended in these cases [11,12], these biomarkers have been used less frequently in the context of perioperative medicine [24].

Despite several studies have demonstrated the benefit of BNP and NT-pro-BNP in preoperative cardiac risk stratification [14,15]. BNP-guided therapy has not been prospectively tested in perioperative medicine [24].

In addition, if the cut-off points obtained in the PROBE-HF study for the purpose of preoperative screening in patients with moderate to high HF risk are supported by other authors [7,35], on the other hand, the ability of natriuretic peptides to discriminate risk among HF patients, who may have chronically elevated levels, has not yet been examined [5]. Furthermore, as stated by Pirracchio., *et al.* [26] mildly elevated values of BNP may not differentiate between systolic and diastolic HF.

In case of emergent surgery and evidence of preoperative AHF the surgical procedure should be postponed whenever possible until cardiac compensation and euvolemia are achieved [1].

Systolic dysfunction

Regarding the use of β-blockers before surgery, two important questions arise. Should β-blockers be maintained in the perioperative in patients with HF? Should β-blockers be started in the perioperative in patients at risk for HF? [1,2]. Data from trials of β-blockers use to reduce perioperative cardiac complications are conflicting - perhaps, because of differences in patients, surgery and β-blocker type, timing of onset, duration and dose titration [69].

Answering the first question, several studies have documented the reduction of mortality when chronic β-blocker therapy was continued in patients with HFrEF [15]. Moreover, the results of these studies are cited and supported by several other review studies [2,4] and by the most recent guidelines [12,35]. Therefore, and given the potential acute-hemodynamic effect of β-blocker withdrawal, these agents should be continued during the perioperative period and removed only in the setting of hypotension or severe symptomatic bradycardia [4,12,35].

Reviewing the available literature, there seems to be a general trend that low-risk patients (low RCRI or uncomplicated hypertension) may be at harm with perioperative β-blockers, intermediate-risk patients (mid-RCRI, combined risk factors or isolated IHD) may or may not benefit from treatment, whilst high-risk patients (high RCRI or HF) may be at reduced risk of mortality if receiving perioperative β-blockers [11,12].

It is unanimous that a large RCT is needed to determine the appropriate perioperative management of ACEIs/ARBs, especially in relevant subgroups, such as, patients with known HF or cardiovascular disease. Nonetheless, two points seem to be consensual when ACEIs/ARBs are continued preoperatively: the association with an increased incidence of intraoperative hypotension and organ-protective benefits, namely, cardiac and kidney protection, since these patients seem to experience a lower reduction in CO and glomerular filtration rate. Unfortunately, no significant differences in mortality or MACE were observed with continuation/suspension of these drugs preoperatively [19,21].

Therefore, in patients with HFrEF, who are in a stable clinical condition, it seems reasonable to continue ACEIs/ARBs therapy under close monitoring during the perioperative period [11,12].

Concerning the preoperative maintenance of diuretics in patients with HF, few investigations were found, however some review studies and also the ESC/ESA guidelines support the maintenance of diuretics until the day of surgery. Even so, numerous authors alert for the

importance of electrolytic monitoring, in order to avoid/immediately correct any ionic imbalance and avoid arrhythmias [12].

Diastolic dysfunction

Despite being associated with adverse outcomes in patients undergoing cardiac and non-cardiac procedures, diastolic dysfunction is neglected [8].

Looking at the literature, the E/E' ratio proved to be a reliable indicator of LV filling pressures with good correlations with invasively measured pressures. Moreover, LA volume serves as a morphological marker and reflects the chronicity of diastolic dysfunction and its severity - the adaptive response of the LA translates into its dilatation [8,25].

As in systolic dysfunction, an approach according to the predominant underlying diastolic defect/grade is consensual. To this end, the classification proposed by the EAE/ASE, based on the E/E' ratio and other parameters [25], may be useful for the therapeutic decision of these patients and is cited by several review articles [8,9].

Intraoperative management

The benefit of neuraxial versus general anesthesia is much debated in the literature. Although there are no evidence-based data to recommend which anesthetic procedure (regional, general or combined anesthesia) should be used preferentially in patients with HF, generally studies show a preference for regional anesthesia over general anesthesia in elective surgical procedures [12,28,29].

If a neuraxial procedure is used, it is important to remember that a reduction in systemic resistance with hypotension may be caused by sympatholysis. Therefore, adequate monitoring and slow titration of continuously administered anesthesia to control the extent of the drug's distribution are recommended. Moreover, is important to ensure adequate ventilation and oxygenation to prevent increases in pulmonary vascular resistance [28].

However, in patients with ADHF, requiring emergency surgery, if tracheal intubation and positive pressure ventilation are needed to manage pulmonary oedema, then there is little reason to select a regional anesthesia technique. Hence, general anesthesia is still the method of choice, allowing ventilation to be controlled, with the majority of authors recommending a balanced technique with higher opioid doses and low-dosed volatile anesthetics. When feasible (this will be rare, because these patients often cannot lie flat on the operating table), peripheral nerve block techniques, rather than general anesthesia or neuroaxial block techniques, may avoid intraoperative crystalloid infusions [28].

Summing up, the choice of anesthesia approach should be driven by several factors, like the type of surgery and patients' comorbidities and preferences, in order to determine risk-benefits [11,29].

The clinical signs of CHF cannot be easily monitored in patients during anesthesia, therefore the use of adequate monitoring represents a cornerstone in the intra and postoperative detection of exacerbation of CHF. The degree of monitoring depends on the surgical procedure and the degree of HF. Effectively, simple procedures with minimal blood loss may only require standard ASA monitoring. Nonetheless, widespread use of invasive blood pressure monitoring, also in patients undergoing minor procedures, is commonly accepted [1,9].

Routine PAC and right heart monitoring are not recommended in patients with HF during non-cardiac surgery [11,12]. Currently, several authors agree that neither PVC (which is equivalent to right atrial pressure) nor PAOP (which helps in the diagnosis of pulmonary oedema and PH) can be used as good targets (i.e. pre-load indicators) of volume responsiveness. Contrary, it is unanimous that continuous CO monitoring is the best option for monitoring the response to a fluid challenge [33].

Thus, although the method of thermodilution using PAC is, to date, considered the gold standard method for measuring CO, complications associated with PAC have led to the development of newer methods that are minimally or non-invasively [33].

The use of other non-invasive perioperative CO monitoring techniques (including TEE with Doppler monitoring) to optimize CO and fluid therapy in high-risk patients for ADHF undergoing non-cardiac surgery seems to be associated with reduced length of stay and complications, yet convincing data on hard end-points is still lacking. Nonetheless, the use of TEE as a gold-standard for intra and postoperative monitoring is consensual and it has now been a widely used monitor in perioperative setting [11,12].

Systolic dysfunction

During surgery, management strategies for the patient with low EF, include:

- Maintaining forward flow to mitigate coronary ischemia, PH and acute/chronic end-organ dysfunction, because of hypoperfusion;
- Promoting inotropic without inducing/worsening ischemia [2].

Seeing the latest guidelines and the various articles analysed, a strategy aimed at maintaining MAP > 65 - 70 mmHg is required [7,35,66]. Interestingly, contrary to the theory that hypertensive patients need higher-than-normal pressures to maintain organ perfusion, Salmasi., *et al.* [66] in 2017, pointed that preoperative pressure had no important effect on the relationship between intraoperative hypotension and myocardial and kidney injury.

Yet, it is important to note that patients with advanced HF may present with alarmingly low SBP. This may, in fact, reflect their baseline SBP. Even when resuscitating shock, a common mistake is attempting to normalize SBP and HR to values seen in those with baseline normal cardiac structure and function. However, for patients with severely reduced EF, a 'normal' SBP may be unattainable and tachycardia may be the main contributor to CO [36].

For patients with low SBP, administering a fluid bolus is nearly a reflexive action. But, in the setting of hypoperfusion, secondary to HF rather than hypovolemia, this may worsening pulmonary oedema. Therefore, optimizing volume status through diuresis and vasodilation may lead to significant clinical improvement in the hypotensive AHF patient. Still, in some refractory cases, inotropics and vasopressors are required to increase CO and blood pressure [36].

Effectively, even though inotropics and vasopressors improve hemodynamics, to date, none are associated with better clinical outcomes [57]. However, in the absence of alternatives, the inotropic and vasopressor agents remain essential in the management of patients in CS and that is why, the ESC/ESA and ACC/AHA guidelines state that inotropics and vasopressors may be considered (Class 2b) or are recommended (class 1), respectively [7,34].

As a consequence of all mentioned above, the authors believe that, in the light of current knowledge, the use of inotropic drugs and vasopressors in the minimum doses and only during the strictly necessary period of time will be recommended [67].

After data from the SOAP II study, noradrenaline should be the drug of choice in patients with CS, hypotensive and with vasoplegia and may be associated with an inotropic agent [38]. Furthermore, as stated by Amado., *et al.* [67] the association of vasopressin should be considered in those in need of high doses of noradrenaline or in cardiac rhythm unstable patients in whom it is unsafe to increase the dose of noradrenaline. However, to date, there are no RCTs in patients with CS treated with vasopressin.

Additionally, dopamine appears to be the drug with the most adverse effects and with no apparent benefits, therefore, deserves to play a limited role in the treatment of patients in shock [38,68].

Regarding inotropic agents, in the largest study to date involving milrinone, OPTIME-CHF, patients in shock were excluded. However, this study was important in elucidating the bidirectional effect of milrinone based on the etiology of ADHF. Effectively, although milrinone has many advantageous properties in the management of HFrEF, it may be deleterious in ischemic HF [39].

Levosimendan is the latest inotropic available for the treatment of AHF. Considering the available literature, levosimendan should be considered more often as a preferable alternative to conventional adrenergic inotropics, based on the assessment of the drug's haemodynamic effects and its highly reassuring safety profile in clinically unstable patients [44]. The question of benefit in long-term mortality remains contentious, but the striking lack of any increase in mortality with levosimendan in the ALARM-HF registry [39], along with direct comparison with dobutamine in RCTs and in meta-analysis, suggest that, among available inotropics, levosimendan is less likely to worsen prognosis [42,46].

Gathering the analyzed information, levosimendan is the most relevant option in AHF patients undergoing β-blocker therapy, since it acts independently of β-adrenergic receptors. Furthermore, although levosimendan alone is not suitable for the treatment of patients with hypotension due to its vasodilator properties, the authors seem to currently agree that this drug may be preferred in patients with CS when combined with noradrenaline or other vasopressors [7,44,68].

In patients with ADHF and low EF if SBP > 90 mmHg, but mainly if absence of hypotension, diuretics and vasodilators are useful. In fact, intravenous loop diuretics are the cornerstone of acute therapy for AHF patients and studies suggest that it is used in almost 90% of patients hospitalized with AHF with no difference between administration of bolus diuretics or continuous infusion [36,47]. Regarding vasodilators, they have dual benefit by decreasing venous tone (to optimize preload) and arterial tone (decrease afterload), which, consequently, may also increase SV. However, according to guidelines, dosing these drugs should be carefully controlled to avoid excessive reductions in blood pressure, which is related to poor results [7,35,36].

Diastolic dysfunction

During surgery, management strategies for the patient with preserved EF, include:

- Maintaining the preoperative parameters as close as possible, once any minor deviation from the "normal parameters" can lead to hypotension and low CO or pulmonary venous congestion;
- Maintaining operating volume, since the LV with HFpEF operates at 'just adequate' volume [8].

In general, HFpEF patients with AHF have higher SBP than HFrEF patients and develop PH due to chronic pulmonary venous and variable reactive pulmonary arterial hypertension. Thus, pulmonary oedema in these patients is more likely to be caused by vascular redistribution than by hypervolemia. Therefore, vasodilators are the mainstay of treatment [36].

In fact, several authors recommend, along with diuretics, vasodilators as first-line agents [36,51]. This is support by other studies which reported that intravenous nitroglycerin at high doses can rapidly achieve pulmonary decongestion and reduce downstream critical care needs in these patients [49,53]. Intravenous nitroglycerin bolus in doses up to 2 - 3 mg were used in these studies and, as stated by Hunter., *et al.* [36], it is well tolerated and effective, although many clinicians are reluctant to administer such large doses.

Nesiritide, despite initially promising data and inclusion in earlier guidelines, was not superior to placebo in the ASCEND-HF trial. Thus, since nesiritide and all new vasodilators have not shown to be as effective as either nitroglycerin or nitroprusside, it seems reasonable that these two drugs remain first-line vasodilators for use in hypertensive AHF [55].

Postoperative

The ESC/ESA and ACC/AHA guidelines and several review studies considered that the measurement of BNP/NTpro-BNP is also useful for additional risk assessment in the postoperative period, since the high levels are correlated with the risk of mortality and cardiac complications and therefore should be included in the postoperative evaluation of patients [1,57,61].

Both BNP and NT-proBNP perform well to rule out, but less well to rule in, the diagnosis of AHF. In addition, the authors caution that the specificity of these biomarkers, above the proposed cut-off points, is limited by a wide variety of causes [7,35,36]. In this way, and as stated by Hill., *et al.* [68], it is possible infer that these tests are especially useful when the clinical diagnosis is equivocal or access to advanced diagnostic tools, such as echocardiography, is not readily available.

In fact, it is unanimous that monitoring with echocardiography (TTE or TEE) should be maintained during the PACU and the first postoperative days in patients with or at risk of HF who underwent intermediate or high-risk non-cardiac surgery [11,12]. Particularly, in patients with a relevant risk of volume shifting (blood loss) and/or rapid changes of systemic vascular resistance, the use of TEE is strongly recommended [1]. As stated by Soussi., *et al.* [57], continuous monitoring in the postoperative period can be obtained by a single-use miniaturized TEE probe that can be left in place 72 hours in ventilated patients.

To date, there are no studies available which demonstrate an outcome benefit of invasive filling pressure monitoring. Two potential exceptions are the patient with severe PH and at risk for acute exacerbation of right ventricular dysfunction and patients with CS who do not respond to initial treatment, in whom PAC should be considered [58].

Besides echocardiography, electrocardiogram monitoring should be maintained postoperatively for all patients, as both guidelines strongly recommend [11,12].

In what concerns to postoperative pain management, it is advisable to consider epidural analgesia. Yet, general evidence-based consensus is needed [11,12,59].

In addition, it has now become obvious that all non-selective NSAIDs, as well as COX-2 inhibitors, carry an increased risk of MACE [5]. So, the ESC/ESA guidelines stated that these drugs should be avoided in cases of renal and heart failure, or in patients who are elderly, on diuretics, or those with unstable haemodynamic [12].

Systolic dysfunction

Reviewing the available studies, the authors share the view that medication for HF, if discontinued preoperatively, should be resumed as soon as clinically feasible [11,12].

Despite improvements in surgical technique and myocardial protection, LCOS is still common during the postoperative period [62]. Although haemodynamic criteria for defining LCOS vary, clinically speaking, the condition presents with hypotension and end-organ hypoperfusion. Meanwhile, in CS, the low system oxygen delivery, along with low CO, is complicated by multi-organ dysfunction. Thus, there is a continuum from LCOS to CS and the severity may hardly be perceived by the clinical variables [44].

In the light of current knowledge, the use of a drug such as levosimendan, which acts both in the increase of CO and venodilatation, may have a more favourable impact on patients with LCOS than an agent that acts only as a cardiac stimulant [44].

The need to intervene in the early stages is pointed out by several authors, particularly because in the following stages, therapeutic approaches are mainly based on positive inotropics, which effectively enhance myocardial performance and so that, their potential benefit needs to be judged against the side-effect of raised myocardial oxygen consumption, especially in context of infarct-related LCOS/CS [44,61].

Still, given the limited evidence currently available, the strong need for large, well-designed RCTs on this topic is unanimous. Additionally, future research focussing on the early, goal-directed treatment concept should be defined and validated in future trials [44].

Diastolic dysfunction

Pulmonary oedema and AF are common postoperative complications in patients with non-compliant heart. Therefore, the low dose infusion of nitroglycerin (25 μg/min) should be maintained in patients with known diastolic dysfunction, as advocated by several authors [8].

Concerning the acute HR control in patients with AF, treatment with β-blockers, CCB, or digoxin are effective, taking into account the strong ESC/ESA and ACC/AHA guidelines recommendations. Additionally, several review studies mention the efficacy of these drugs in patients with HFpEF [8].

Another well-established risk factor for HFpEF is systolic hypertension, so it should be monitored postoperatively in all patients, especially those with or at risk of diastolic dysfunction, thus reducing the risk of pulmonary oedema and hypertensive AHF [8,51]. Furthermore, adequate postoperative analgesia and prevention of postoperative shivering by controlling body temperature during the operation are also important to avoid a hypertensive crisis [8].

Given the available literature for the treatment of hypertensive emergency, this should include intravenous vasodilators in combination with loop diuretics. Regarding vasodilators, taking into consideration the recommendations of the guidelines for the management of hypertension [64,65] and the greater number of concordant studies, nitroglycerin appears to be the first choice in the treatment of hypertensive emergencies in patients with HF [36,49,53,54].

Key Learning Points

Preoperative management

1. HF is a complex clinical syndrome that comprises a wide range of patients, who are defined based on their LVEF: HFpEF, HFmrEF, HFrEF. There is no doubt that HF increases perioperative morbidity and mortality among patients undergoing surgery, regardless of the predominant dysfunction: systolic/diastolic.
2. Preoperative cardiac evaluation depends on surgical risk of the patient, which is based on four categories: urgency of surgery, complexity of procedures involved, extent of medical comorbidities, and severity of underlying heart disease.
3. All patients with suspected or already diagnosed HF and who are scheduled for intermediate or high-risk surgery should previously perform a TTE.
4. Therapeutic optimization using β-blockers, ACEIs/ARBs and diuretics is indispensable in all patients with HF undergoing intermediate or high-risk surgery.

Systolic dysfunction

1. β-blockers should be maintained in the perioperative in patients with HF and initiated in those at high-risk with severe comorbidities. Meanwhile, in low-risk patients, such as patients with uncomplicated hypertension, these drugs should be withdrawn.
2. Although controversial findings, ACEIs/ARBs should be continued in perioperative, under close monitoring, and, in individual cases, may be discontinued at the morning of surgery to avoid severe intraoperative hypotension.
3. Diuretics should also be maintained until the day of surgery, under electrolytic monitoring.
4. Levosimendan infusion for 24 hours prior to cardiac surgery is advantageous, especially in patients with HFrEF.

Diastolic dysfunction

1. The E/E' ratio should be assessed using a TTE in all patients with suspected or already diagnosed HFpEF undergoing intermediate or high-risk surgery.

2. Patients with grade I and II diastolic dysfunction may benefit from β-blockers or fluid administration during anesthetic management, whereas patients with grade III adequate diuretic treatment is crucial.

Intraoperative management

1. Several factors, such as the type of surgery and the comorbidities and preferences of the patients, should lead to the choice of anesthetic approach.
2. The degree of monitoring depends on the surgical procedure and the degree of HF. Minor procedures may only require standard ASA monitoring (pulse oximeter, electrocardiogram, non-invasive blood pressure device and temperature monitor). However, invasive blood pressure monitoring is also commonly accepted. Besides this, TEE should be included in all patients with or at risk of HF during intermediate or high-risk surgeries.
3. Routine PAC is not recommended in patients with HF and the use of TEE to optimize CO and fluid therapy should be preferred.

Systolic dysfunction

1. A MAP > 65 - 70 mmHg should be maintained to avoiding tissue hypoperfusion and consequent multiorgan dysfunction. For this, the use of inotropic drugs and vasopressors in the minimum doses and only during the strictly necessary period of time may be require.
2. In the hypotensive AHF patient the vasopressor of choice should be noradrenaline in detrimental of dopamine, however there is no consensus in the choice of inotropic. Several authors agree that dobutamine may be considered in patients with isolated left ventricular dysfunction. Meanwhile, in patients receiving β-blockers therapy or those with high pulmonary resistance and right ventricular dysfunction, milrinone or levosimendan appear to be more beneficial. Milrinone may be deleterious in ischemic HF unlike levosimendan, which may be the only one with survival improvement.
3. In the normotensive AHF patient, in the absence of signs of hypoperfusion, intravenous loop diuretics are generally require and low-dose vasodilators should also be considered.

Diastolic dysfunction

Patients with diastolic dysfunction are more likely to develop a hypertensive AHF. These patients, particularly those with markedly elevated blood pressure, should be treated aggressively with vasodilators, most commonly high doses of intravenous bolus nitroglycerin. Additional therapy with diuretics should be relegated to the treatment of overt volume overload or persistent congestion despite optimized hemodynamics.

Postoperative

1. In patients with HF who underwent intermediate or high-risk surgery echo and electrocardiography monitoring should be maintained.
2. Epidural analgesia is superior to systemic opioid analgesia in postoperative pain management and may be associated with reduced morbidity and mortality. Moreover, NSAID and COX-2 inhibitors must be avoided in these patients, since they increase the risk of MACE.

Systolic dysfunction

1. The resumption of HF medication in the postoperative period should be encouraging, as soon as clinically feasible and in the cases in which the therapy was started in the preoperative its suspension will depend on the context of the patient and the surgery.
2. LCOS is the most common postoperative complication in HFrEF and the most serious one, increasing the requirements for inotropics and vasopressors. The authors suggest that the use of drugs with vasodilatory properties, like levosimendan, in early stages and

development of early goal-directed algorithms reduce catecholamine requirements and may leading to improved clinical outcomes. However, more RCT are necessary.

Diastolic dysfunction

1. The prevalence of AF and hypertension in patients with HFpEF is high and may lead to ADHF.
2. In AF patients with HFpEF β-blockers, CCB, or digoxin are effective and should be used to control HR.
3. In patients with HF nitroprusside or nitroglycerine intravenous are the first-line treatment, along with loop diuretics, in hypertensive emergencies.

Conclusion

Indubitably, HF is a source of considerable perioperative morbidity and mortality.

Preoperatively, risk stratification, including assessment of cardiac function via echocardiography, and the pharmacological optimization of patients is paramount.

Adequate monitoring represents the intraoperative milestone and is essential to ensure the maintenance of preoperative parameters as close as possible and to early detection of ADHF or new-onset AHF.

Postoperatively, it is necessary to reach the patient's preoperative levels and to early identify the triggers that can lead to poor outcomes with increased morbidity and mortality.

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