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Perioperative Management of Patients With Heart Failure: A Review

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RESUMO

Introdução: A insuficiência cardíaca é uma síndrome clínica que representa a fase terminal de uma ampla variedade de condições cardíacas subjacentes. Estes doentes continuam a registar uma taxa de morbimortalidade inaceitavelmente elevada quando submetidos a procedimentos cirúrgicos, sejam eles cirurgias cardíacas ou não. Por conseguinte, são necessários cuidados especiais durante o pré, intra e pós-operatórios, de forma a maximizar a segurança dos doentes.

A presente revisão literária visa concretizar uma revisão sistemática das estratégias utilizadas na abordagem dos doentes com insuficiência cardíaca e fornecer ao leitor uma nova perspetiva sobre o diagnóstico e tratamento desta síndrome.

Métodos: Esta dissertação foi elaborada a partir de artigos científicos publicados entre 2005 e 2018, disponíveis no PubMed e Google.

Resultados: Visando a prevenção de complicações perioperatórias, várias práticas são sugeridas.

Pré-operatório: o recurso ao ecocardiograma para o diagnóstico de insuficiência cardíaca está bem estabelecido e é superior às escalas de avaliação de risco e aos biomarcadores no que respeita à estratificação do risco cirúrgico; a otimização terapêutica com beta-bloqueadores, IECAs/ARAs e diuréticos é indispensável; as cirurgias devem ser proteladas nos casos em que o tratamento médico adequado não foi estabelecido ou em que se verifique a presença de insuficiência cardíaca aguda no pré-operatório.

Intra-operatório: o ecocardiograma transesofágico é o exame de eleição para a monitorização; os agentes inotrópicos e vasopressores, apesar de recomendados e utilizados desde há vários anos em doentes com insuficiência cardíaca aguda hipotensiva, continuam a ser controversos; os vasodilatadores, mais comumente a nitroglicerina, deverão constituir o tratamento predominante nos doentes com insuficiência cardíaca aguda hipertensiva; doentes normotensos geralmente requerem doses significativas de diuréticos de ansa intravenosos.

Pós-operatório: procurar alcançar os níveis pré-operatórios dos doentes; a monitorização eco e eletrocardiográficas devem ser mantidas; evitar fatores precipitantes da insuficiência cardíaca aguda.

Conclusão: Foram alcançados recentes desenvolvimentos na área da anestesiologia cardiovascular, contudo há ainda diferenças na abordagem dos doentes durante o período perioperatório e, até mesmo falta de concordância em alguns tópicos, o que evidencia a necessidade de ensaios clínicos maiores.

Palavras-chave: insuficiência cardíaca, disfunção sistólica, disfunção diastólica, anestesia, abordagem perioperatória.

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.

Key words: 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 Balloom Pump
CCB - Calcium Channel Blockers
DBP - Diastolic Blood Pressure
HMOD - Hypertension-Mediated Organ Damage
LA - Left Atrial
PACU - Postanesthetic Care Unit

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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. End-organ dysfunction can manifest as chronic renal failure with an elevated creatinine and BUN, hepatic failure leading to elevated liver transaminases and neurologic dysfunction including syncopal episodes. 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 sympathetic nervous system increases the amount of circulating catecholamines to increase CO by increasing contractility and HR. In addition, this causes arteriolar vasoconstriction which stimulates the secretion of renin. Activation of the renin–angiotensin-aldosterone system is responsible for salt and water retention. Furthermore, the hypothalamus releases vasopressin which also causes renal water reabsorption. As the LV may no longer be able to deal with this amount of fluid secondary to its diseased state. The pulmonary system becomes congested and oxygen exchange across the pulmonary vasculature does not occur with efficiency[2].The perpetuation of these mechanisms causes a vicious circle that leads to a progressive worsening of the cardiac function.

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[3].

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.[4] 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, this 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[5].

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[6,7].

In 2007 the ACC/AHA perioperative guidelines identify three categories of surgery-specific risk: high, intermediate and low cardiac risk (<1%, 1–5%, and >5% of cardiac morbidity rates, respectively)[8,9].

- High risk refers to vascular surgery – e.g: aortic and other major vascular surgery, as well as peripheral vascular surgery;
- Intermediate risk – e.g: intraperitoneal and intrathoracic procedures, orthopaedic, prostate, head and neck surgeries.
- Low risk - e.g: endoscopic and superficial procedures, cataract, breast and ambulatory surgeries[8,9].

More than 20% of patients are expected to have acute cardiovascular dysfunction in the perioperative period of cardiac surgery. AHF is defined as a rapid onset of symptoms secondary to abnormal cardiac function resulting in an inability to pump sufficient blood at normal end-diastolic pressures. Clinically, it presents as CS, pulmonary oedema, or left/right/biventricular congestive HF, sometimes in conjunction with high blood pressure (hypertensive HF) or high CO[10]. 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[11].

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[12]. And, despite advances in perioperative care during the last years, patients with HF undergoing non-cardiac surgery still have an unacceptable high morbidity and mortality[11].

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. 2946 articles resulted from this research.

Thereafter, the selection of the articles was performed by reading their abstracts and, subsequently, by a complete reading. At this stage, were excluded, in the following order: case reports; case series including less than 30 patients; studies regarding other syndromes/diseases than HF; studies related to specific features in HF, but not focusing on this pathology; specific surgical details; specificities of diagnosis and treatment of abnormalities existing in HF.

Applying these inclusion and exclusion criteria, 120 publications were selected to this revision.

Lastly, other articles were analysed, by consulting bibliographic references of the initially selected articles, where the year of their publication was not taken into account, ending up with 139 publications being analysed for this review (Figure 1).

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[13].

Population-based studies have shown that approximately half of the patients with HF have a normal LVEF[1,13-15]. 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[15].

Differentiation of patients with HF based on LVEF is important due to different underlying aetiologies, demographics, co-morbidities and response to therapies[13].

Coronary artery disease, with or without history of MI, is the major risk factor for developing HFrEF[1,14]. Myocardial injury leads to remodelling of the extracellular matrix through fibroblast proliferation, which results in ventricular thinning. As a consequence, patients with HFrEF typically present with dilated left ventricular cavity and impairment of systolic function[16].

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[1,14,17]. The ventricular remodelling also occurs in patients with HFpEF - with aging, the myocyte number decreases because of cell necrosis and apoptosis. There are fibroblast proliferation that produce collagen and interstitial fibrosis occurs. As result, the heart becomes stiffer and less compliant. The stiffer and less compliant ventricle affects diastolic relaxation as well as systolic contraction. Chronically elevated afterload from stiff vasculature leads to LVH and prolongation in systolic contraction time. Prolonged systolic contraction, in turn, impinges on early diastole[18].

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[13].

Indeed, as stated by Desai et al.[19], it is still unclear whether HFpEF patients will develop progressive worsening of EF in the long term as the disease progresses in association with subsequent events, although there is some evidence to suggest that patients with HFpEF can only develop progressive LV remodelling if inter-current MI occurs. Thus, for some patients, clinical outcomes may be influenced by progressive LV remodelling and in others, they may be influenced by vascular effects or other effects[20]. There is still much to be knowledgeable about why some patients with similar co-morbid conditions develop progressive remodelling while others aggravate diastolic function[20].

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[20]. Irrespective of this recent finding, several studies have shown that mortality associated with HFpEF is unacceptably high[21].

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[14,15].

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[22].

A retrospective study conducted between 2004 and 2011, which included 16,827 patients with HF undergoing non-cardiac surgery, established a 30-day mortality risk score. This index is composed of 7 variables: gender, age, body mass index category (kg/m2), renal disease, cerebrovascular disease, use of insulin, acute surgery and high-risk surgery[23].

This risk score differs from RCRI of Lee et al.[24], since it excludes IHD, which was not significant, and also includes other variables, namely, age, sex, body mass index and acute surgery.

In 2010, a systematic review was carried out to evaluate the ability of the RCRI to predict cardiac complications and death after non-cardiac surgery. This meta-analysis concluded that the RCRI discriminated moderately well between patients at low versus high risk for cardiac events after mixed non-cardiac surgery. However, it did not perform well at predicting cardiac events after vascular non-cardiac surgery or at predicting death[25].

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[26].

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[27]. (superior to RCRI, which showed only a sensitivity of 64 % and specificity 70%)[25].

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[28].

According to PROBE-HF study, BNP cut-off value is likely around 20-30 pg / mL and NT-proBNP cut-off value is likely around 125 pg / mL for preoperative screening purposes in patients with moderate to high risk of HF[29].

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[30].

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[3,5,31]. Looking at the results by Andersson et al.[32], 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 (Class 1, Level B)[26,33].

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[3,31,34]. About that, the remaining recommendations offered by current guidelines remain weak[26,33].

In 2005, Lindenauer et al. reported that perioperative β-blocker therapy is associated with a reduced risk of in-hospital death in high-risk patients (RCRI score ≥2), but not in low-risk ones (RCRI 0 or 1), in which it may even present possible harm[35,36].

In 2008, the POISE study also investigated this issue and was the first large-scale trial to randomize 8,351 patients to metoprolol or placebo (100 mg of metoprolol extended release prior to surgery followed by 200 mg per day for up to 30 days). The study determined a decrease in the rate of perioperative MI in at-risk patients who started β-blocker therapy in the perioperative period. However, these patients had higher all-cause mortality and higher rate of perioperative stroke[37]. The results of the POISE study were called into question, mainly, by the choice of metoprolol dose, which is much higher

than that used in previous studies, which could explain the occurrence of hypotension and bradycardia[3,31,38].

In 2013, a retrospective cohort analysis conducted by London et al.[39] stated that, in patients undergoing non-cardiac and non-vascular surgery, perioperative β-blocker exposure was associated with lower rates of 30-day all-cause mortality in patients with 2 or more RCRI factors. Furthermore, it was also associated with lower rates of MI and cardiac arrest in patients undergoing non-vascular surgery. Hearteningly, the authors noted no associations between perioperative β-blockade and the risk of postoperative stroke.

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[26,31].

Regarding the use of ACEIs or ARBs, there is still more controversy. The different guidelines vary in the recommendations and the evidence is limited[26,33,40,41].

Several studies have shown that continuing therapy with ACEIs and ARBs in chronic users before non-cardiac surgery is associated with a clear increase in the incidence of intraoperative hypotension[26,33,40-42]. 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)[42].

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[41].

Conversely, some studies have shown that the preoperative administration of ACEIs may also protect the kidney in vascular surgical patients[40,43]. 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[44].

Diuretics are recommended to reduce the signs and symptoms of congestion in patients with HFrEF. On the subject of diuretics, the ESC/ESA guidelines support their maintenance until the day of surgery, but these drugs are not addressed in the ACC/AHA guidelines[26,33].

As stated by Groban et al.[40], although it is not clear that doses of potassium-sparing diuretics used to treat HF contribute to anesthesia-induced hypotension, there is no doubt that these drugs can cause life-threatening hyperkalemia. The increased risk of hyperkalemia associated with taking this class of diuretics, namely eplerenone and spironolactone, is documented in several studies[40,45-47].

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)[26].

In 2013, Harrison et al.[48] conducted a meta-analysis of RCTs and reported that, the perioperative administration of levosimendan in patients with low EF (<40%) undergoing cardiac surgery, was associated with reduced 30-day mortality (less than 7% when compared to the control group; 95% CI) and other adverse outcomes (myocardial injury, need for dialysis and postoperative AF).

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[26].

According to Flu et al.[49], 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 this patients who underwent low or intermediate-risk non-cardiac surgery[50].

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)[51].

Hence, as stated by Nicoara et al.[15] and Gelzinis[17], patients with grade I and II are preload tolerant, require a longer period of diastole, and are dependent on atrial contraction for adequate LV filling. Therefore, these patients may benefit from β-blockers and rate-slowing agents or require, during anesthetic management, fluid administration to increase LA pressure, avoiding tachycardia, and to allow adequate diastolic filling and maintenance of sinus rhythm. In contrast, patients with grade III have a fixed SV, so empirically lowering their HR may result in decreased CO and worsening of symptoms. Thus, the administration of diuretics may have a salutary effect by reducing intravascular volume and the risk of pulmonary oedema. 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 [52]. However, as noticed by Zannad et al.[53], uncontrolled hypertension is involved in more than 50% of the cases of acute (decompensated) diastolic HF.

INTRAOPERATIVE MANAGEMENT

Most anesthetic techniques reduce sympathetic tone, leading to a decrease in venous return due to increased venous system compliance, vasodilatation and, finally, decreased blood pressure. Thus, anesthetic management must ensure the proper maintenance of organ flow and perfusion pressure[1,26].

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[54].

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[55].

In what concerns to anesthetic agent choice, studies are limited and there is conflicting evidence[1,26,33,40]. A meta-analysis published in 2013, involving 38 RCTs concluded that, in patients undergoing cardiac surgery, inhalation anesthesia (especially when sevoflurane or desflurane are used), as opposed to total venous anesthesia, was associated with a 50% reduction in mortality (OR 0.51; 95% CI, 0.33-0.81; P=0.004)[56].

Comparable data relating to non-cardiac surgery are even scarcer. For instance, one small study observed a lower incidence of MACE in vascular surgery patients anesthetized with a volatile agent than with an intravenous anesthetic[57], but two other studies in non-cardiac surgery patients observed no difference in outcome[58,59].

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[1,15,16,40,60].

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[61].

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[62].

CVP has been used to guide fluid challenges for over 40 years[63]. 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[64-66].

A recent meta-analysis of 43 studies, with a total of 803 patients, demonstrated the inadequate agreement of CVP with the volume status. Of these, 22 studies involved patients in ICU, 20 studies analysed the use of CVP within the operative monitoring and 1 study was conducted in healthy controls. Overall, 57 ± 13% of patients were volume-responsive and the average CVP initially measured was 8.2 ± 2.3 mmHg in the volume-responsive group and 9.5 ± 2.2 mmHg in nonvolume-responsive patients. The AUC

value for the ROC curve was 0.56 (95% CI, 0.54-0.58). There was no difference between patients in the ICU and in the operating room. The same results were also obtained for cardiac and non-cardiac surgery patients. In all groups, correlation of the initial CVP measurement with the change in cardiac index and SV was poor[66].

Furthermore, a retrospective study reported positive predictive values of only 51% and 54% for CPV<8 mmHg and PAOP<11 mmHg, respectively, to predict a haemodynamic response to volume. The combination of CVP and PAOP did not improve prediction (sensitivity of 35% and specificity of 71%). Even in patients with reduced LVEF (<30%) the predictive power of CVP and PAOP remained inadequate[67].

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[68]. Though, it is important to remember that significant increases in CO with fluid can occur in patients with CVP>15 mmHg and many patients with a low CVP fail to respond to a fluid challenge[69].

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[70-73]. 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[71].

If the main target of a fluid challenge is an increase in SV, the primary safety limit is the failure to increase the SV[71]. Regarding the study by Monnet et al.[74], 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.

Acute hypovolemia may occur, especially in high-risk surgeries, which may cause a decrease in CO and requires volume replacement to prevent tissues' oxygen decrease. Strunden et al.[70] proposed a possible algorithm to manage the perioperative administration of fluids to treat hypovolamia following acute blood loss. Patients with undesirable hypotension and SV variation >15% should receive crystalloid infusion, at a ratio of 4:1, to measured loss if they have renal failure or sepsis; or HES 6% 130/0.4, at a ratio of 1:1, to measured loss in the absence of renal failure or sepsis. If therapy is effective, then basic infusion of crystalloids of 1 ml/kg/h is recommended. In contrast, if hypoperfusion does not reverse inotropics are recommended.

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[75-77].

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)[13,78].

In fact, the available inotropics have been associated with harm, though the evidence base is small and inconsistent[79]. In this context, in a study by Mebazaa et al.[80], 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[79]. 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)[81].

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)[82].

Four major studies have reported the use of levosimendan in AHF: LIDO[83], RUSSLAN[84], REVIVE-II[85] and SURVIVE[86]. 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[87].

Re-analysis of the REVIVE-II mortality data, identified low blood pressure at baseline (SBP <100mmHg or DBP <60mmHg) as a factor associated with increased mortality risk with the use of levosimendan[87].

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[88].

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[89].

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[13,79].

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[13,78].

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[13,78]. 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[90].

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[91].

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 [92]. Therefore, to achieve the desired effect, higher doses or an increased frequency of treatment with furosemide are required[79,93].

Another strategy to investigate optimal diuretic therapy is to evaluate its combination with other agents. Cotter et al.[94] 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).

In the ROSE-AHF trial, the investigators explored the hypothesis that low-dose dopamine or low-dose nesiritide in addition to loop diuretic therapy would enhance decongestion while preserving renal function. However, there were no differences between the two groups when compared to placebo for the endpoints of enhanced diuresis (P=0.59 and P=0.49 for dopamine and nesiritide, respectively) or preservation of renal function at 72 hours (P=0.72 and P=0.36 for dopamine and nesiritide, respectively)[95].

Diastolic Dysfunction

Approximately half of the patients hospitalized with AHF present hypertension (SBP ≥140 mmHg). Therefore, avoiding acute systemic hypertension is important during surgery[79].

The most common causes of intraoperative hypertension include inadequate analgesia and superficial anesthesia for the degree of surgical manipulation[55].

Schwartzenberg et al.[96] 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)[13,78].

As mentioned by Collins et al.[97], 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[98]. 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[97,98]. According to Elkayam et al.[99], 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[100].

In 2017, a retrospective observational cohort study stated that early administration of high-dose nitroglycerin by intermittent boluses (2mg 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)[101].

Nesiritide is an alternative to nitroglycerin. Although some studies have shown that intravenous infusion of nesiritide has beneficial hemodynamic effects in patients with ADHF [98,102], it failed in a 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)[103].

POSTOPERATIVE

In patients with stable CHF the key is achieving postoperative function that matches the patient's preoperative levels and avoiding the contributing and triggering factors that can lead to poor haemodynamic outcome. On the other hand, the management of patients with ADHF or new-onset AHF is even more challenge and

strategies are aimed, not only at maintaining the preoperative physiological parameters, but also at identifying and treating reversible or extrinsic causes of HF and being realistic with haemodynamic goals[60].

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[104].

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[105].

According to Hunter et al.[79], natriuretic peptides are the most useful biomarkers for excluding the diagnosis of AHF and cut-off points of 100 pg/mL and 300 pg/mL for BNP and NT-pro-BNP, respectively, substantially reduce the post-test probability of AHF. This may be relevant, since symptoms classically associated with HF, such as orthopnea and nocturnal paroxysmal dyspnea, are reported by only half of the patients with AHF and their specificity for diagnosis is <75%.

Several authors have pointed out the importance of postoperative TEE performed as early as possible in patients with suspected or already diagnosed HF[1,15,16,106]. Hunter et al.[79] 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.[107] have shown that TTE has a sensitivity of 83% and specificity of 72% for the diagnosis of PH.

The electrocardiogram is rarely normal in AHF, that is, it has a high negative predictive value (negative LR 0.64; 95% CI, 0.47-0.88). It is also helpful in identifying underlying cardiac disease and their potential precipitants (rapid AF, acute myocardial ischaemia). Indeed, myocardial ischaemia is one of the main mechanisms of LV systolic/diastolic dysfunction in the early postoperative[108].

Severe postoperative pain is reported in 5-10% of patients, which increases sympathetic drive and delays recovery[26]. 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) [109]. In accordance to this, the ESC/ESA and ACC/AHA guidelines state that postoperative epidural analgesia may be considered (Class 2b, Level B)[26,33].

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[110].

Systolic Dysfunction

Current ESC/ESA and ACC/AHA guidelines encourage the restart of HF medication in postoperative period, as soon as clinical conditions allow[26,33].

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[26,33].

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[111].

There is no consensus definition of what constitutes LCOS[112], but some authors define it as mixed venous saturations <60%, cardiac index <2.2L/min/m^2 and PAOP >18 mmHg[113,114].

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[111,113,114].

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[115].

Diastolic Dysfunction

In patients with diastolic dysfunction, hypoxemia and/or AF are the most common complications in the postoperative period, since the restored vascular sympathetic tone due to the emergency and resolution of general or regional anesthesia causes a volume displacement to the central blood volume[14,18]. For instance, Ashes et al[116] studied the association between the dynamic changes that occur in diastolic function in the perioperative period and the risk of postoperative AF after CABG surgery. They found that new or worsened grade of LV diastolic dysfunction, according to the EAE/ASE recommendations, was associated with increased risk of postoperative AF (OR 1.424; 95% CI, 1.1519-11.356; P=0.0055).

Furthermore, postoperative pain may induce tachycardia and hypertension with the potential of triggering acute (decompensated) diastolic HF[60].

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[22].

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[117,118]. 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[13,78].

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)[119].

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[120,121].

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[120,121].

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[14,52].

DISCUSSION

CHF is one of the most common diseases in the western population and its incidence has been increasing annually, with serious impact on the morbidity and mortality of these patients, especially when undergoing surgery[1,3,40]. In fact, HF is a well-recognized factor for adverse outcomes and death during the three phases of the perioperative period and it is an important predictor in several commonly used risk scores[23,24].

PREOPERATIVE MANAGEMENT

In what concerns to the preoperative evaluation of the surgical risk, several risk scores were developed, being the RCRI, perhaps, the most well-known and simplest tool. Plus, it is the most validated clinical risk index and it has already been used in several large clinical centres and implemented in the design of large clinical investigations[6,25,36,39,122]. Although other risk scores may accurately predict the specific risk of surgery, none of them, except the RCRI, were externally validated[122].

In addition, although risk scores are useful in elective surgeries, several clinical variables, such as LVEF and clinical stability, are important for risk stratification[23,30,49]. 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[26,33,122].

Taking into account the various articles analysed, it is possible to infer that patients undergoing very low-risk surgery (eg, 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[7,8,22,33].

TTE is recommended in all patients with suspected or already diagnosed HF and who are scheduled for non-cardiac intermediate or high-risk surgery[26,33]. 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[6]. Although, evaluation of BNP or NT-pro-BNP is also recommended in these cases[26,33], these biomarkers have been used less frequently in the context of perioperative medicine[123].

Despite several studies have demonstrated the benefit of BNP and NT-pro-BNP in preoperative cardiac risk stratification[25,27,28], BNP-guided therapy has not been prospectively tested in perioperative medicine[124].

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[13,78,124], 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.[52] 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[1,7].

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?[1,3,35]. 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[9].

Answering the first question, several studies have documented the reduction of mortality when chronic β-blocker therapy was continued in patients with HFrEF[32,125,126]. Moreover, the results of these studies are cited and supported by several other review studies[3,5,31,35] and by the most recent guidelines[26,78]. 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[5,26,78].

Reviewing the available literature to clarify the role of β-blockers in non-cardiac surgery, four major observational trials were more frequently cited: studies by Andersson et al.[32], Jørgensen et al.[127], Lindenauer et al.[36] and London et al.[39].

According to Andersson et al.[32], 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.[127] 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.[36] and London et al.[39] 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.

Therefore, 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[26,31,33].

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[40,41,43].

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[26,33].

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[26,40,45,93]

In cardiac surgery, inotropics are used in 20–90% of patients, depending on the preoperative state, complexity of procedure, patient's response to surgery and physician attitude. The most common reason to administer inotropics in this setting is to prevent or treat postoperative LCOS, a complication that increases both morbidity and mortality[10,89]. Several RCTs compared levosimendan to dobutamine, milrinone, or placebo in patients with HFrEF, undergoing cardiac surgery. Besides a meta-analysis of Harrison et al.[48] in 2013, two other meta-analyses (Maharaj et al.[128] in 2011 and Landoni et al.[129] in 2010) suggest that the use of this novel inotropic may prove to offer more advantages, particularly when applied to the more complex patient population.

Diastolic Dysfunction

Despite being associated with adverse outcomes in patients undergoing cardiac and non-cardiac procedures, diastolic dysfunction is neglected[15].

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[15,30,51,60].

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[51], may be useful for the therapeutic decision of these patients and is cited by several review articles[14,15,17,60].

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[26,54,55].

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[130,131].

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 [130,131]. 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[40].

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[33,55].

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[1,17,40].

Routine PAC and right heart monitoring are not recommended in patients with HF during non-cardiac surgery[26,33]. 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[70-73].

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[132].

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[26,33].

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[3].

Seeing the latest guidelines and the various articles analysed, a strategy aimed at maintaining MAP >65-70 mmHg is required[13,75-78]. Interestingly, contrary to the theory that hypertensive patients need higher-than-normal pressures to maintain organ perfusion, Salmasi et al., in 2017, pointed that preoperative pressure had no important effect on the relationship between intraoperative hypotension and myocardial and kidney injury[75].

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[79].

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[79].

Effectively, even though inotropics and vasopressors improve hemodynamics, to date, none are associated with better clinical outcomes[79]. 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[13,78].

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[133].

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[81]. Furthermore, as stated by Amado et al. [134] 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[81,134].

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[82].

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[87]. 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[80], along with direct comparison with dobutamine in RCTs and in meta-analysis, suggest that, among available inotropics, levosimendan is less likely to worsen prognosis[85,89].

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[134]. 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[13,87,134].

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[79,90]. 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[13,78,79].

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[60].

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[79,135].

In fact, several authors recommend, along with diuretics, vasodilators as first-line agents[79,97,135,136]. 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[94,100]. Intravenous nitroglycerin bolus in doses up to 2-3 mg were used in these studies and, as stated by Hunter et al.[79], 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[103]. 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[136].

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[1,106,124].

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, such as renal dysfunction, acute respiratory distress syndrome, pulmonary embolism, PH, and valvular heart disease[13,78,79]. In this way, and as stated by Hill et al.[137], 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[26,33]. 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.[106], 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[107].

Besides echocardiography, electrocardiogram monitoring should be maintained postoperatively for all patients, as both guidelines strongly recommend[26,33].

In what concerns to postoperative pain management, it is advisable to consider epidural analgesia. Yet, general evidence-based consensus is needed[26,33,109].

In addition, it has now become obvious that all non-selective NSAIDs, as well as COX-2 inhibitors, carry an increased risk of MACE[138]. 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[26].

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[26,33].

Despite improvements in surgical technique and myocardial protection, LCOS is still common during the postoperative period[111,112]. 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[87].

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[87].

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[87,111,139].

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[139].

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[14,18].

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[14,60].

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[15,40,60,97]. Furthermore, adequate postoperative analgesia and prevention of postoperative shivering by controlling body temperature during the operation are also important to avoid a hypertensive crisis[14].

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[120,121] and the greater number of concordant studies, nitroglycerin appears to be the first choice in the treatment of hypertensive emergencies in patients with HF[79,94,100,101].

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

1. 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.

APPENDIX

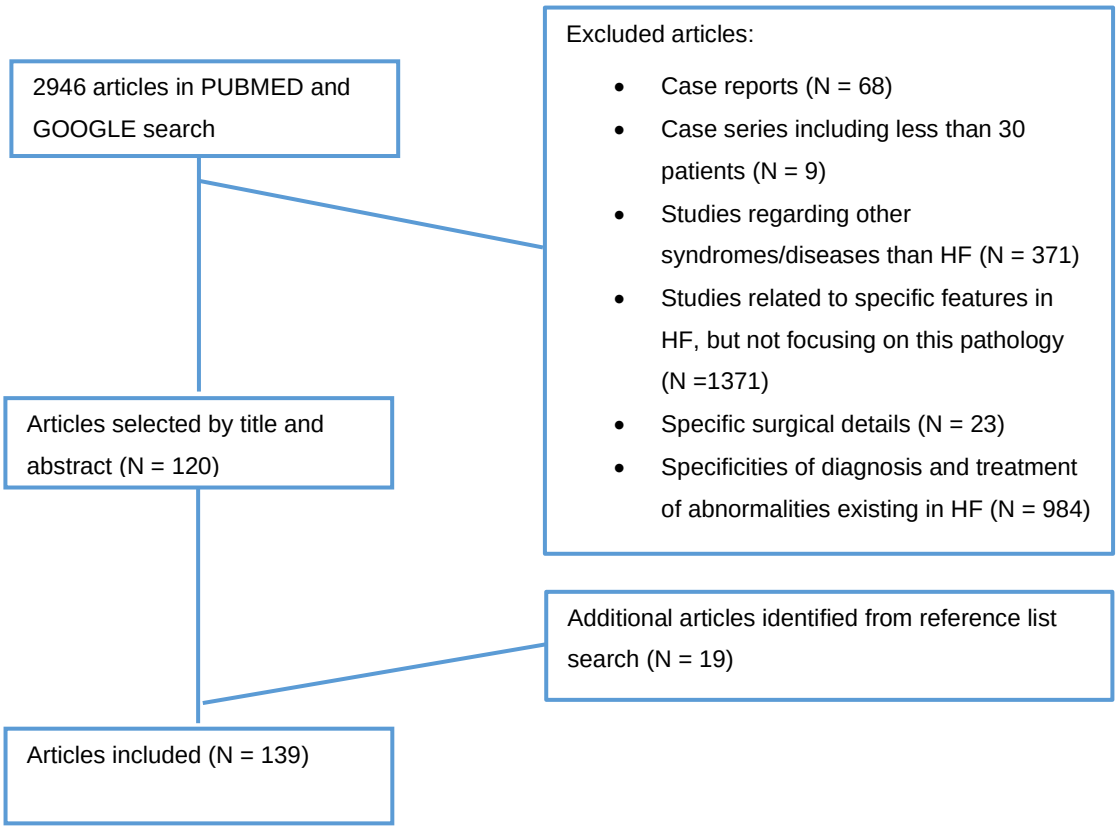

Figure 1: Article selection methodology.

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