Perioperative Management of Cardiac Failure

S Goga

Commentator: T Chetty   Moderator: I Osborn

UNIVERSITY OF KWAZULU-NATAL

Department of Anaesthetics

CONTENTS

11. Cleland JG, Freemantle N, Coletta AP, et al. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. Eur J Heart Fail 2006; 8:105–110.
12. McMurray JJ, Teerlink JR. Late-breaking clinical trials session: Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studies (VERITAS). JAMA. 2007 Nov 7;298(17):2009-19.
13. Wolfgang G, Toller et al. Acute perioperative heart failure. Current opinion in anaesthesiology 2005, 18:129-135.
14. Tavares M, Rezlan E et al. New pharmacologic therapies for acute heart failure. Crit Care Med. 2008 Jan; 36(1 Suppl):S112-20. Review.
15. Petersen JW, Felker GM. Inotropes in the management of acute heart failure. Crit Care Med. 2008 Jan; 36(1 Suppl):S106-11. Review.
16. Helmut R, Motsch J et al. Newer approaches to the pharmacological management of heart failure. Current opinion in anaesthesiology 2006, 19:75-81.
17. Groban L, Butterworth J. Perioperative management of chronic heart failure. Anesth Analgesia 2006, 103:557-75.
18. Houser SR, Margulies KB. Is depressed myocyte contractility centrally involved in heart failure? Circulation research 2003;92:350-8.
19. Magner JJ, Royston D. Heart failure. Br J Anaesth 2004; 93:74-85.
20. Elkayam U, Janmohamed M et al. Vasodilators in the management of acute heart failure. Crit Care Med 2008; 36, No1 (suppl.) S95-S105.
21. E Catina, F Milazzo. Ecchocardiography and cardiac assist devices. Minerva Cardioangiol 2007, 55: 247-65.

REFERENCES

1. Hunt SA et alHunt SA. American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2005;46:e1–82.
2. Flood C, Fleischer LA. Preparation of the Cardiac Patient for Noncardiac Surgery. American Family Physician 2007;75:656-65.
3. Hernandez et al. Outcomes in Heart Failure Patients After Major Noncardiac Surgery. Journal of the American College of Cardiology 2004; 44:1446-53.
4. Rodseth RN. B type natriuretic peptide – a diagnostic breakthrough in peri-operative cardiac risk assessment? Anaesthesia 2009; 64(2):165-78.
5. Velagaleti RS et al. Relations of biomarkers represnting distinct biological pathways to left ventricular geometry. Circulation 2008; 118:2252-2258.
6. Ryckwaert F, Colson P. Hemodynamic effects of anesthesia in patients with ischemic heart failure chronically treated with angiotensin-converting enzyme inhibitors. Anesth Analg 1997; 84:945–9.
7. Licker M, Bednarkiewicz M, Neidhart P, et al. Preoperative inhibition of angiotensin-converting enzyme improves systemic and renal haemodynamic changes during aortic abdominal surgery. British J Anaesthesia 1996;76:632–9.
8. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Carvedilol or Metoprolol Eur Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol Eur Trial (COMET): randomised controlled trial. Lancet 2003;362:7–13.
9. POISE Study Group, Devereaux PJ et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet. 2008 May 31;371(9627):1839-47.
10. The digitalis investigation group et al. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525–33.

WHAT IS CARDIAC FAILURE?

The AHA/ACC defines heart failure as: 'a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood'.[1] The clinical syndrome of HF may result from disorders of the pericardium, myocardium, endocardium, or great vessels, but the majority of patients with HF have symptoms due to an impaired LV myocardial function.

Heart failure may be associated with a wide spectrum of LV functional abnormalities, ranging from normal LV size and preserved EF to severe LV dilatation and/or markedly reduced EF. In most patients, abnormalities of systolic and diastolic dysfunction coexist.

WHY IS CARDIAC FAILURE IN THE PERIOP PERIOD IMPORTANT?

In the perioperative period there may be triggers of acute cardiac failure; i.e. hypertension, inadequate volume management, anaemia, tachyarrhythmia's, the withdrawal of heart failure drugs, hypercoagulability and myocardial ischaemia.

Previous studies have demonstrated that heart failure is an important risk factor, but the magnitude of its impact in the perioperative period may be underappreciated. Heart failure is appreciated as one of the major predictors of adverse perioperative outcome as used commonly in the Lee's revised cardiac index scoring system[2].

However here it is weighted equally to CAD. In a recent study by Hernandes et al[3] there was a statistically significant increase in: death before discharge or within 30 days of surgery; in patients who had a history of cardiac failure vs. patients with CAD (11.7% after risk adjustment in the HF cohort compared with 6.6% in the CAD cohort and 6.2% in the control cohort - HF vs. CAD, p < 0.001; CAD vs. Control, p = 0.518).

The authors concluded, "Although previous strategies for preoperative risk stratification emphasized the identification of coronary disease, the importance of HF is clear from this study".

Table 1 – Outcomes CAD vs HF vs Control

Table 5. Outcomes

	HF (n = 1,532)	CAD (n = 1,757)	Control (n = 44,512)	p Value*
Primary outcome: 30-day mortality (95% CI)				
Observed (%)	15.4 (13.6–17.3)	6.6 (5.5–7.8)	6.1 (5.9–6.3)	
Risk-adjusted (%)	11.7 (10.2–13.1)	6.6 (5.4–7.8)	6.2 (6.0–6.4)	<0.001
Mortality during surgery admission (95% CI)				
Observed (%)	10.7 (9.2–12.0)	5.0 (4.0–6.1)	4.1 (3.9–4.2)	
Risk-adjusted (%)	7.9 (6.8–9.0)	4.6 (3.6–5.5)	4.1 (3.9–4.3)	<0.001
30-day mortality in discharged patients (95% CI)				
Observed (%)	8.4 (6.9–9.9)	2.9 (2.1–3.7)	3.3 (3.1–3.5)	
Risk-adjusted (%)	6.5 (5.4–7.6)	3.3 (2.4–4.3)	3.2 (3.0–3.4)	<0.001
Readmission rate within 30 days (95% CI)				
Observed (%)	23.6 (21.5–25.8)	15.5 (13.8–17.2)	10.9 (10.6–11.2)	
Risk-adjusted (%)	20.0 (18.3–21.8)	14.2 (12.5–15.8)	11.0 (10.7–11.3)	<0.001
Mean length of stay (days ± SD)	11.0 ± 10.6	9.3 ± 10.5	8.9 ± 11.1	
Mean length of ICU stay (days ± SD)	4.9 ± 6.0	4.2 ± 5.2	4.1 ± 5.6	0.015
Patients with an ICU stay (%)	44.7	48.2	28.0	0.053
Mean time to readmission (days ± SD)	13.0 ± 8.5	13.3 ± 8.5	13.2 ± 8.4	0.709

*p value for difference between HF and CAD groups; p value for difference between CAD and control group is >0.05 except for readmission rate (<0.001) and % ICU stay (<0.001).

Abbreviations as in Tables 1 and 3.

CLASSIFICATION OF CARDIAC FAILURE

Causes of heart failure are many but for the purposes of the discussion 'the cardiac patient for non-cardiac surgery' causes are more often related to ischaemic heart disease, hypertension, diabetes and age.

The AHA/ ACC have recently developed a new classification for patients with heart failure, which takes cognisance of the progressive nature of the disease[1]. Identifying the 'at risk' patient and instituting timely therapy is crucial in halting the progression of the disease.

Transplantation

Cardiac transplantation is the most effective treatment for patients with cardiac failure refractory to medical or other surgical therapy. However this resource is limited due to the limited number of donor organs available and limited by the resources and expertise to carry out the procedure.

CONCLUSION

Many patients present to us in the perioperative period with either acute or chronic heart failure. These patients have a higher risk of adverse perioperative outcome and it is incumbent on us as perioperative physicians to have a good knowledge of the pathophysiology of this disease process and of the non/pharmacologic options available to us to optimally manage these patients.

may soon be headed in the direction of ambulatory, longer term use. It is effective in the treatment of intractable angina and cardiogenic shock and has been shown to have considerable benefit in cases of acute MI in combination with either percutaneous transluminal coronary angioplasty or thrombolysis. For perioperative protection, it is clear that the effectiveness of IABP is greatest when introduced before surgery.

Other modalities of protection (pharmacological and metabolic modulation) should always accompany IABP use. Complications include limb ischaemia and bleeding (3±5%), and risk must be balanced against benefits.

Left ventricular assist devices (LVAD)

LV assist devices (LVAD) are being used increasingly in the setting of end-stage heart failure, primarily because of the shortage of organs available for transplantation but also because evidence shows that patients implanted with these devices show a greater reduction in risk of death than those on optimal medical therapy. (The survival rate at 1 yr was 52% in the device group and 25% in the medical-therapy group, and at 2 yr was 23% and 8%, respectively)*

The frequency of serious adverse events (infection, bleeding and malfunction of the device) in the device group though was 2.35 times that in the medical-therapy group.

Factors that have an impact on the effectiveness of LVAD include required ventilatory support, a coagulopathy, right heart function, infection and renal function. Most patients with heart failure have mild pulmonary hypertension, which resolves over time with the placement of a LVAD and unloading of the left heart. However, the right heart may not be able to tolerate this reactive pulmonary hypertension and may need support for a few days.

Right heart failure can be catastrophic and support can be provided with inotropic drugs most commonly PDIs. A right VAD can be inserted. The simplest protection is to ensure that the patient's cardiac index is not raised precipitously following LVAD placement, which might cause the right ventricle to fail.

Patients usually have preoperative echo's to rule out contraindications to placement of these devices[21]

Table 2 – Classification of Heart Failure

Stage	Description	Examples
A	Patients at high risk for heart failure because of the presence of conditions strongly associated with the development of heart failure; no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves; no current or previous history of signs or symptoms of heart failure	Patients with systemic hypertension, coronary artery disease, diabetes mellitus, history of cardiotoxic drug therapy or alcohol abuse, history of rheumatic fever, family history of cardiomyopathy
B	Patients with structural heart disease that is strongly associated with the development of heart failure but who have no current or previous history of signs or symptoms of heart failure	Patients with left ventricular hypertrophy or fibrosis, left ventricular dilatation or hypo contractility, asymptomatic valvular heart disease, previous myocardial infarction
C	Patients who currently have or who in the past have had symptoms of heart failure associated with underlying structural heart disease	Patients with dyspnoea or fatigue due to left ventricular systolic dysfunction; asymptomatic patients undergoing treatment for prior symptoms of heart failure
D	Patients with advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy; need for specialized interventions	Patients who are frequently hospitalized for heart failure and cannot be safely discharged from the hospital; patients in hospital awaiting heart transplantation; patients at home receiving continuous intravenous support for symptom relief or support with a mechanical circulatory assist device; patients in a hospice setting for the management of heart failure

PATHOPHYSIOLOGY

In order to understand the mechanism of action of various therapies available it is important to understand the pathophysiology of the disease process.

On a global scale there are ventricular changes that take place, with ventricular enlargement, thickening and stiffness of the ventricular wall. Increased interstitial fibrosis and cross linking of collagen in the heart contribute further to wall stiffness. This progressive increase in wall stiffness leads to impaired ventricular relaxation and diastolic dysfunction in the heart.

The resultant decrease in cardiac output sets in motion a cascade of neurohumoral compensatory mechanisms. The major systems that are activated are the sympathetic nervous system and the renin-angiotensin aldosterone systems. These result in vasoconstriction and sodium and water retention, increased myocardial contractility and an increase in heart rate all in an attempt to maintain cardiac output. In addition to its vasoconstrictive properties angiotensin II acts as a growth factor and this may be the mechanism through which it contributes to cardiac remodelling in the progression of cardiac failure.

The persistently increased adrenergic activity results in decreased β1 receptor density and uncoupling of β 2 receptors from their downstream effecter molecules. This decreases the effect of sympathetic amines on Ca^{2+} regulatory target proteins and limits inotropic responsiveness. Besides decreasing cAMP production, adrenergic signalling abnormalities in the failing heart also include defects in the A-kinase anchoring proteins that help target cAMP to effecter proteins. Together, these changes reduce the ability of the failing heart to increase contractility in proportion to haemodynamic demands.

In normal muscles, with sympathetic stimulation; as the heart rate increases, the rate and magnitude of developed force increases. In the failing heart developed force decreases or remains unchanged. Therefore, rate-related contractile reserve is absent or significantly reduced in failing human myocardium and the ability of adrenergic agonists to increase the contractility of the failing heart is significantly blunted.

MECHANICAL ASSISTANCE

In some end-stage cardiac failure patients, mechanical assistance may be a modality of therapy while awaiting cardiac transplant, or as an interim measure while treating an underlying problem, or sometimes in conjunction with medical therapy.

Synchronized pacing

The current criteria suggest that disease processes showing the greatest benefit following biventricular pacing and internal cardio defibrillator implantation are systolic heart failure, non-reversible causes for failure, highly symptomatic patients on optimal medical therapy and in ventricular dysynchrony.

Sudden cardiac death due to arrhythmias is a common problem in patients with heart failure. Sinus rhythm in these patients is crucial since they rely on synchronized atrial systole for ventricular filling. Hence sinus rhythm should be restored and heart rate optimized in these patients, to a rate of about 80 beats/min.

Many patients with chronic heart failure have ECG evidence of an interventricular conduction delay, which may worsen LV systolic dysfunction, most often in the form of a left bundle branch block. This causes asynchronous ventricular contraction and occurs in up to one-third of chronic heart failure patients. Significant improvement can be shown in patients who have cardiac resynchronization through atrial-synchronized biventricular pacing.

Biventricular pacing has been shown to allow the heart to contract more efficiently to increase LV ejection fraction and cardiac output while consuming less oxygen. Other benefits include increased diastolic ventricular filling time, decreased PCWP and reduced mitral regurgitation.

Intra-aortic balloon pump (IABP)

Intra-aortic balloon counterpulsation or intra-aortic balloon pump (IABP) has been the mainstay of perioperative short-term treatment of the failing heart. Although IABPs are not suitable for all critically ill patients, their use is becoming more widespread, with good outcomes. The use of balloon pump

The concept of nitric oxide synthase antagonism offers an attractive approach to treating refractory cardiogenic shock, specifically during surgery. Perioperatively, severe hypotension is often encountered; and may not be able to be treated by one of the other new options and which is marked by significant perioperative mortality.
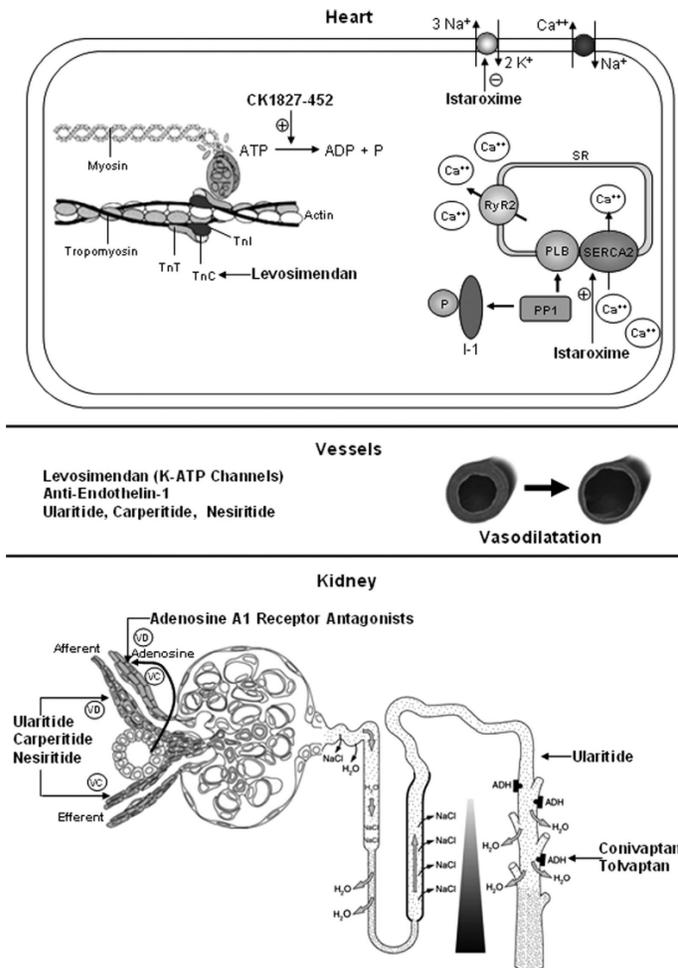

Figure 3 – Mechanisms of action of newer therapies in Heart Failure

Studies have shown that at least in the end-stage failing human heart, basal contractility is well preserved but "contractility reserve" (the ability to increase contractility with heart rate or sympathetic stimulation) is severely depressed. These changes in muscle performance and regulation explain the poor pump function, reduced exercise capacity, and tachycardia intolerance of failing myocardium.

The Ca^{2+} regulatory proteins….

In a normal cardiac myocyte, contraction is due to the activation of myofibrillar proteins by Ca^{2+} originating from sarcoplasmic reticulum (SR). Ca^{2+} release from the SR is triggered by the Ca^{2+} current (ICa^{2+}) that enters the cell through L-type Ca^{2+} channels.

The process, called Ca^{2+}-induced Ca^{2+} release, implies that the small amount of Ca^{2+} entering the cell via ICa^{2+} is "sensed" by the SR Ca^{2+} channels (also called *ryanodine receptors*). They open and release large amounts of Ca^{2+} into the cytosol activating the myofibrils.

Myocyte relaxation is due to pumping of Ca^{2+} back into the SR via a Ca^{2+} adenosine triphosphatase (ATPase) called *SERCA* (for sarcoendoplasmic reticulum Ca^{2+}-ATPase). SERCA is activated by high-cytoplasmic free Ca^{2+} concentrations and inhibited by a protein called *phospholamban* when bound to the pump.

Two major pathophysiological processes are observed in cardiac myocytes from failing hearts:

1)   A decrease in Ca^{2+} pumping capacity into the SR due to a decreased expression of SERCA and its increased inhibition by phospholamban.

2) Ca^{2+} leak out of the SR during diastole through ryanodine receptors that are likely hyperphosphorylated . Thus, Ca^{2+} not pumped by SERCA into the SR can be lost through leaky ryanodine receptors. This is associated with an increased activity/expression of the Na^+/Ca^{2+} exchanger that extrudes Ca^{2+} out of the cell during diastole in exchange for entry of Na^+.

Together with the SR Ca^{2+} leak, this process worsens SR Ca^{2+} depletion, leading to a decreased SR Ca^{2+} store and this leads to decreased activating Ca^{2+} during systole. The culmination of these processes results ultimately in systolic dysfunction.

Together with the deficient pumping function of SERCA, the ryanodine receptor leak is also responsible for an increased intracellular Ca^{2+} concentration during diastole, predisposing to incomplete diastolic relaxation that contributes to increased myocardial stiffness.

In addition, since the Na^+/Ca^{2+} exchanger extrudes 1 Ca^{2+} out of the cell in exchange for the entrance of 3 Na^+, the exchanger is creates an electric potential, thus leading to a depolarizing current during diastole, and this process contributes to the occurrence of ventricular arrhythmias.

DIAGNOSING CARDIAC FAILURE

The mainstay of diagnosis has been patient history and physical examination. We have been made aware of the inadequacies in this method of diagnosis in previous departmental presentations. In addition in the perioperative period it is often difficult to get an adequate history from a patient in cardiac failure. Other tools that may assist us in obtaining this diagnosis to guide our therapy and risk assessment for patients are:

Biomarkers

Several biomarkers have been looked at in helping us determine altered left ventricle function. We have heard exhaustively from colleagues on BNP and NT-pro-BNP[4] and that this may function as a biomarker for assisting in the diagnosis of cardiac failure as it becomes more widely available.

Another biomarker that is currently being looked into is the ARR (aldosterone- renin ratio)[5]. Higher levels of aldosterone relative to rennin maybe indicative of impaired LV geometry which may be indicative of cardiac dysfunction, preceding cardiac failure.

Echocardiograph

The AHA/ACC guidelines recommend the use of echocardiography in the diagnosis and management of heart failure[1]. Functional information that can be gained from the echocardiogram is the measurement of LV ejection fraction. Patients with an ejection fraction < 40% are generally considered to have systolic dysfunction. In addition, the echocardiogram allows for the quantitative assessment of the dimensions, geometry, thickness and

B-type natriuretic peptide: Nesiritide

It increases natriuresis and diuresis and modulates sympathetic nervous systems and the rennin–angiotensin–aldosterone systems responses to cardiac failure. Through relaxation of the smooth muscle, the preload and afterload are reduced and the cardiac index increased without increasing the heart rate or myocardial oxygen consumption.

Being an agent that has a rapid onset of action and is easy to regulate it seems that this agent is useful in the perioperative setting. However more work is needed to ascertain its usefulness in this setting.

Endothelin receptor antagonists: Bosentan/Tezosentan

Endothelin is activated in cardiac failure and is a strong vasoconstrictor. The vasodilation caused by these agents decreases afterload and potentially improves contractility and patient outcome. The VERITAS study on this drug was stopped after an interim analysis due to a low chance of reaching either of the primary end points (death or worsening heart failure at 7 days or change from baseline in dyspnoea assessment over the first 24 hrs of treatment)[12].

Vasopressin receptor antagonists

Current treatment strategies for patients with acute cardiac failure and hyponatremia consist of additional loop diuretics to remove excess fluid; and free-water restriction to correct the sodium imbalance. This approach is often inadequate as diuretic therapy produces further stimulation of vasopressin secretion and may result in maintenance or worsening of hyponatremia. The increased vasopressin levels will provide a continuing stimulus to renal water retention, maintaining or even worsening the hyponatremia. Vasopressin V2 receptor antagonism has the potential to directly improve symptoms by increasing diuresis and reducing hyponatraemia.

Nitric oxide synthase inhibition: L-NAME

A completely new approach to treatment of acute cardiac failure has been established using a nitric oxide synthase inhibition strategy. It is based on the finding that a systemic inflammatory reaction with cytokine release, which leads to an overproduction of nitric oxide in the heart and vascular system, plays an important role in the pathogenesis of cardiogenic shock. High nitric oxide concentrations have a negatively inotropic effect on the myocardium and a vasodilatory effect on the vascular system, which can contribute to circulatory collapse.

Although initial studies showed that it reduced mortality and improved worsening heart failure in patients, more recent studies show that although it improves symptoms significantly there may be a trend towards increased mortality at 90 days and a trend towards increased rates of hypotension and ventricular arrhythmias (REVIVE).[11]

Targeting Abnormal Calcium Cycling: Istaroxime

Istaroxime is a Na^+/K^+ ATPase inhibitor not related to digoxin. It also increases SERCA activity and seems to be a drug that might combine beneficial effects on both diastolic and systolic LV function. This drug is currently undergoing phase II trials.

Cardiac Myosin Activators

Cardiac myosin activators are molecules that increase myofibril ATPase activity, altering the function of myosin so that the sarcomere can increase force generation without consuming more energy in the form of ATP. Interestingly, this agent, in contrast to traditional inotropes, appears to increase systolic time rather than the rate of developed pressure.

NEW THERAPIES FOR ACUTE HEART FAILURE

Given the limitations of high-dose diuretics and vasodilators and the growing body of literature showing that inotropes, regardless of the dose used, have a detrimental effect on mortality, a variety of new agents are under investigation for the symptomatic treatment of cardiac failure and restoration of cardiac output. The new therapeutic approach is based on two goals: short-term improvement in symptoms together with long-term improvement of the organ function.

New therapeutic strategies aim to act at the cellular level to improve vascular and myocardial function, with minimal side effects, along with improved water and sodium balance.

Natriuretic peptides play a major role in regulating Na^+ and water balance in response to neurohumoral effects of cardiac failure. Based on their abilities to restore homeostasis synthetic forms of these peptides are being investigated for use in cardiac failure.

regional motion of the ventricles and the qualitative evaluation of the atria, pericardium, valves and vascular structures.

Such a comprehensive evaluation is important, since it is not uncommon for patients to have more than one cardiac abnormality that can cause or contribute to the development of heart failure.

Diastolic LV function can also be assessed using Doppler echocardiography. The transmitral inflow velocity during diastole in the normal patient has an 'E' wave which corresponds to early passive ventricular filling. This is followed by an 'A' wave which corresponds to atrial contraction. Mild diastolic dysfunction manifests as decreased E-to-A ratio and prolonged E wave deceleration time. Severe diastolic dysfunction is seen as increased peak E-to-A ratio and decreased E wave deceleration time.
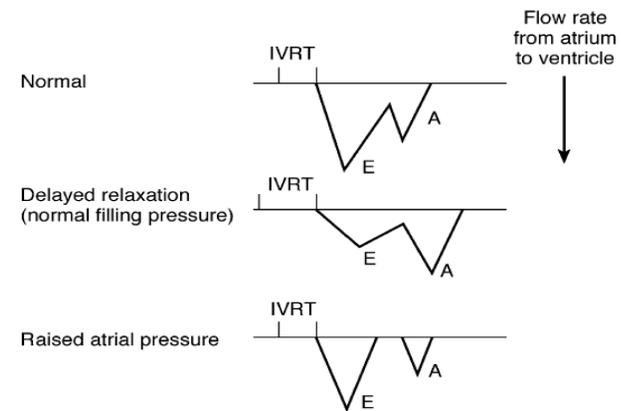

Figure 1. Doppler Echo showing Diastolic Dysfunction

Invasive Haemodynamic Monitoring

Although currently out of vogue and controversial the use of invasive haemodynamic monitoring (pulmonary artery catheters) can be useful in obtaining mixed venous oxygen saturation. If the patient presents with a low cardiac index (<2.2l/m^2/min) low systolic BP, low mixed venous sats (<60%) elevated pulmonary capillary wedge pressure (> 15 mmHg) and elevated lactate values (> 2 mg/dl), the diagnosis of cardiac failure is a likely one.

MANAGEMENT OF PERIOPERATIVE CARDIAC FAILURE

The principles in the management of these patients should be
  a) To treat the underlying cause;
  b) To remove contributing factors that can worsen heart failure, and
  c) To treat the heart failure itself

Pharmacotherapy

This will be discussed in terms of the patient with chronic heart failure on medication presenting for surgery and the patient who presents in acute (decompensated) heart failure in the perioperative period.

ACE inhibitors

As discussed previously, myocardial dysfunction results in the activation of the RAAS. While this may initially be compensatory it leads to excess strain on the heart and contributes to cardiac remodelling.

Much work has been done to show the benefit of ACE inhibitors in slowing the progression of heart failure (by inhibiting angiotensin II mediated ventricular and vascular remodelling) as well as treating symptomatic heart failure by vasodilatation and decreased Na^+ and H_2O retention.

In the perioperative setting controversy exists as to whether the ACE inhibitor therapy should be continued or withdrawn preoperatively due to the potential hypotension that patients are prone to during general anaesthesia due to RAAS inhibition. Although the some small studies have reported an incidence of severe hypotension in patients on ACE-I therapy[6] (Ryckwaert and Colson) other studies on major vascular surgical patients have shown renal benefits in patients that continued ACE-I therapy[7] (Licker et al).

Current practise seems to be to continue ACE-I therapy in the perioperative period (unless contraindicated) and episodes of hypotension can be treated with modest doses of sympathomimetics (e.g. ephedrine) or α agonists (e.g. phenylephrine) and careful expansion of intravascular volume. In the case of severe systemic hypotension (presumed secondary to reduced renin secretion) during spinal or epidural anaesthesia, β adrenergic stimulation with adrenalin (0.5–1 µg/min) may also be considered. In refractory scenarios vasopressin may also be of use.

Figure 2 – Mechanisms of action of positive inotropic drugs
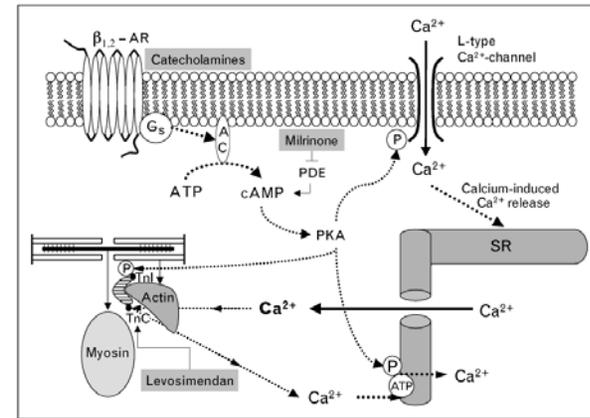
When the β-adrenoceptor (β-AR) on the surface of a myocyte is stimulated by a catecholamine, e.g. dobutamine, the signal is transferred to adenylate cyclase (AC), a membrane glycoprotein that is regulated by stimulatory guanine (G_s) nucleotide binding proteins. AC catalyses cyclic adenosine monophosphate (cAMP) synthesis from adenosine triphosphate (ATP). cAMP activates protein kinase A (PKA), and is subsequently degraded by phosphodiesterase (PDE). PKA phosphorylates (P) several intracellular proteins e.g. L-type calcium channels, Ca^{2+}-ATPase in the membrane of the sarcoplasmic reticulum (SR) and troponin I. The phosphorylation of L-type Ca^{2+} channels allows small amounts of Ca^{2+} to enter the myocytes, which subsequently induce a large Ca^{2+} release from the SR (Ca^{2+}-induced Ca^{2+} release) into the cytosol. Ca^{2+} is then bound to troponin C (TnC) and myofilament contraction is initiated. For relaxation, Ca^{2+} detaches from troponin C and is actively transferred back into the SR with the help of Ca^{2+}ATPase. Whereas the phosphorylation of Ca^{2+}ATPase accelerates relaxation (lusitropic effect), the phosphorylation of troponin I by catecholamines or phosphodiesterase inhibitors inhibits myofilament contraction. Phosphodiesterase inhibitors, such as milrinone, delay the degradation of cAMP and thereby stimulate essentially the same intracellular cascade as catecholamines. In contrast, levosimendan binds to troponin C and renders the myofilaments more sensitive to a given amount of Ca^{2+} without actively influencing the intracellular Ca^{2+} level.

NEWER INOTROPIC AGENTS

Calcium Sensitisers: Levosimendan

Levosimendin is a calcium sensitizer that stabilizes the troponin C /calcium - complex, facilitating myocardial cross-bridging and thus improving contractility. At higher doses, levosimendan also inhibits PDE, similar to other PDE inhibitors, such as milrinone.

Finally, levosimendan has vasodilator effects through its action on adenosine triphosphate-sensitive potassium channels. This results in systemic and pulmonary vasodilation, as well as direct coronary artery dilating effects, thus improving systolic function and reducing myocardial O_2 uptake.

In patients without evidence of end organ hypoperfusion and normal to elevated blood pressure, routine use of inotropic agents in these patients is not indicated. Patients who have evidence of end-organ hypoperfusion and in whom inotropic agents are indicated; represent a high-risk group and these patients have significant short-term mortality.

The inotrope should be seen as the initial phase of therapy to achieve haemodynamic stabilisation and restoration of organ perfusion. In patients in whom no reversible cause of acute deterioration exists inotropic therapy can stabilise the patient sufficiently to consider suitability of other treatments (cardiac assist devices or transplantation).

Choosing an inotrope

The most commonly used intravenous inotropes for the management of AHF are dobutamine and milrinone. Both agents increase contractility by increasing intracellular levels of cyclic AMP. Elevated levels of cAMP lead to increased calcium release from the sarcoplasmic reticulum and increased force generation by the actin-myosin apparatus, with a resulting increase in cardiac contractility. The resultant elevated levels of intracellular calcium may partially explain the side effects of these agents, especially those of arrhythmogenesis.

Dobutamine increases cAMP production by β adrenergic- mediated stimulation of adenylate cyclase, which leads to cAMP production. Phosphodiesterase (PDE) inhibitors, such as milrinone, increase cAMP levels by blocking the enzyme that breaks down cAMP.

In our setting choice of agent between milrinone and dobutamine is largely determined by cost. Milrinone has a more significant vasodilatory effect than dobutamine and although tachycardia occurs with both agents, treatment with dobutamine leads to higher heart rates than that with milrinone.

Beta Adrenergic Receptor Blockers

Now that we understand the pathophysiology of CF a little better, and following on several successful trials demonstrating the beneficial effects of β blockers in CF, it is being used more widely in the perioperative setting. β blockers modify the pathophysiological process at several levels. By attenuating both the sympathetic response and the increase in HR, it decreases myocardial O_2 demand and shifts the utilisation of substrates from free fatty acids to glucose (a more efficient form of fuel).

β blockers also offset the effects of the neurohumoral activation that occurs in CF and leads to adverse cardiac remodelling. In addition they limit disturbed excitation-contraction coupling and reverse the abnormalities in Ca^{2+} regulatory proteins, which lead to impaired myocyte contractile function.

However not all β blockers are equally effective. β adrenergic blockers are classified as being first, second, or third-generation; based on specific pharmacologic properties.

First-generation drugs, such as propranolol and timolol, block both β1 and β 2 adrenoreceptors, are considered non-selective, have no ancillary properties, and are not recommended for CF patients.

Second-generation drugs, such as metoprolol, bisoprolol, and atenolol, are relatively specific for β1 adrenoreceptors but lack additional mechanisms of CV activity.

Third-generation drugs, such as bucindolol, carvedilol, and labetalol, block both β 1 and β 2 adrenoreceptors and have vasodilatory and other ancillary properties. Specifically, labetalol and carvedilol produce vasodilation by β 1 adrenoreceptor antagonism, whereas bucindolol produces mild vasodilation through a cyclic guanosine monophosphate (cGMP)-mediated mechanism.

In addition carvedilol increases insulin sensitivity and has antioxidant effects and an affinity for β 3 adrenoreceptors. β 3 adrenoreceptors are up-regulated in HF, and their activation is thought to decrease contractility through a NO and cGMP-mediated pathway.

Although it is not clear whether these ancillary properties of the third-generation β blocker, carvedilol, translate into better outcomes as compared with second generation drugs, findings from the Carvedilol or Metoprolol European Trial (COMET) suggest that carvedilol may be more

effective than other β blockers[8]. Most guidelines include β blockers for stage B-D CF patients to limit disease progression and reduce mortality.

Following the POISE[9] study the instituition of β blocker therapy in the perioperative period has become highly controversial. But there is unanimous agreement that patients on chronic β blocker therapy should not have β blockers withdrawn in the perioperative period as acute withdrawal of chronic β blocker therapy results in worse patient outcome.

Aldosterone Receptor Blockers

Two large clinical trials have demonstrated improved outcomes with aldosterone receptor antagonists in chronic HF. The RALE Study including more than 1600 symptomatic HF (e.g., Stage C, NYHA 3–4) patients, EPHESUS Study of more than 6600 patients with symptomatic HF and showed significantly reduced all cause mortality, death from CV causes, and hospitalization for CV events with aldosterone receptor antagonists in combination with standard therapy.

Data shows that aldosterone inhibition improves endothelial function, exercise tolerance, and EF and attenuates collagen formation.

As these drugs become more widely used in the treatment of cardiac failure, we will encounter them more often in the perioperative setting.

Vasodilators in Management of Decompensated Cardiac Failure

Drugs such as nitroglycerine and nitroprusside have been used in the management of patient with cardiac failure. The drugs act by vasodilatation especially venodilatation (nitroprusside). This decreases the afterload on both right and left ventricles and in so doing increases cardiac output without affecting the heart rate. It also decreases systolic and diastolic wall stress and hence myocardial O_2 consumption is generally lowered.

Improvement in renal blood flow will result in increased diuresis that further contributes to the preload reduction in these patients. Studies have demonstrated improvement in functional class of patients and improvement in survival when compared with patients on dobutamine but has also been shown to augment the effects of inotropic agents.

In addition if the underlying contributor is ischaemic heart disease nitroglycerine improves coronary blood flow by coronary vasodilatation. Side effects of these agents are however hypotension which can be associated with worsening renal function.

INOTROPIC AGENTS

Digoxin

The only oral positively 'inotropic' agent we have available and of the inotropic agents it is the only one that does not increase mortality in CF[10].The DIG trial showed that digoxin reduced the incidence of heart failure exacerbations but had no effect on survival. It inhibits the Na^+K^+ ATPase pump thereby increasing availability of intracellular Ca^{2+}. It also enhances parasympathetic activity and decreases sympathetic tone and stimulates baro/chemoreceptors, which promote vasodilatation and reduce afterload.

In the perioperative period one of the most important concerns is of digoxin toxicity. Pedisposing factors are hypomagnesemia, hypercalcemia, and hypokalemia, all of which are likely to occur during the perioperative period. Despite these concerns, discontinuing digoxin for the perioperative period is not routine management. It is more likely to be considered in the elderly patient where renal excretion may be a concern and rate and rhythm control, as well as inotropy, can be achieved with other agents with shorter half lives and less toxicity.

Acute perioperative inotropic therapy

Given the adverse outcomes seen with inotropic therapy when given to heart failure patients, good justification should exist for their use in AHF. Inotropes must be able to achieve important therapeutic goals that cannot be met by other, safer therapies.

Two short term goals of therapy can be defined in the initial management of AHF syndromes:
1. Rapid relief of symptoms (typically dyspnea) by resolution of congestion.
2. Maintenance or restoration of adequate end-organ perfusion and function.