Diastolic heart failure in anaesthesia and critical care

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Diastolic heart failure is an underestimated pathology with a high risk of acute decompensation during the perioperative period. This article reviews the epidemiology, risk factors, pathophysiology, and treatment of diastolic heart failure. Although frequently underestimated, diastolic heart failure is a common pathology. Diastolic heart failure involves heart failure with preserved left ventricular (LV) function, and LV diastolic dysfunction may account for acute heart failure occurring in critical care situations. Hypertensive crisis, sepsis, and myocardial ischaemia are frequently associated with acute diastolic heart failure. Symptomatic treatment focuses on the reduction in pulmonary congestion and the improvement in LV filling. Specific treatment is actually lacking, but encouraging data are emerging concerning the use of renin–angiotensin–aldosterone axis blockers, nitric oxide donors, or; very recently, new agents specifically targeting actin–myosin cross-bridges.

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Left ventricular (LV) diastolic dysfunction refers to abnormalities of diastolic distensibility, filling, or relaxation, regardless of whether LV ejection fraction (LVEF) is normal or abnormal and whether the patient is symptomatic or not.⁸ If signs and symptoms of congestive heart failure (effort intolerance, dyspnoea, and pulmonary oedema) develop in a patient with normal or near normal systolic function, it is appropriate to classify this situation as diastolic heart failure. Chronic diastolic heart failure and decompensated diastolic heart failure are common entities, but their frequency is widely underestimated. Underestimation of diastolic heart failure might be related in part to the difficulties in obtaining the criteria defined by AHA-ACC guidelines,⁵² requiring objective evidence using echocardiography. In addition, the poor sensitivity and specificity of echocardiography to recognize diastolic heart failure may aggravate this underestimation. There is increasing evidence that clinicians should differentiate systolic from diastolic heart failure since pathophysiology and management may differ greatly between the two entities.¹¹⁰

Since patients with diastolic heart failure are at high risk of decompensation in the perioperative period or during an ICU stay,⁸⁴ anaesthetists should be familiar with the pathophysiology of diastolic heart failure.

Epidemiology of diastolic heart failure

Between 30% and 50% of patients with chronic heart failure have preserved LVEF.¹⁴ ⁷³ ⁸¹ ¹¹⁰ Two recent cohorts of patients hospitalized with decompensated heart failure showed that 35% had a preserved LVEF,⁶⁶ and that patients with preserved LVEF were 2–4 yr older than those with impaired ejection fraction and were mainly women (≥70%). Diastolic heart failure represents <15% of chronic heart failure in patients younger than 50 yr, and the proportion raises to 33% in 50–70 yr olds and to 70% in those aged >70 yr.¹²⁰ This prevalence in elderly subjects is related to alterations in the cardiovascular system frequently associated with ageing, namely, coronary artery disease, systemic hypertension, hypertrophic, and infiltrative cardiomyopathies that cause structural changes of the LV leading to chronic deterioration of LV diastolic properties.³

Diastolic heart failure is a condition that greatly affects patient outcome. Several authors have shown that the readmission rate and mortality rate were high in diastolic heart failure patients and might be similar to those observed in systolic heart failure.¹⁴ ⁵⁸ ⁹³ Recent studies reported that 16–30% of patients with diastolic heart failure had to be readmitted within 6 months after hospital discharge for
chronic heart failure symptoms, a figure that is comparable with the 22% observed in patients with impaired LVEF. Mortality rates in diastolic heart failure patients at 1 and 3 yr seem slightly lower than or comparable with those in systolic heart failure.

Pathophysiology of LV diastolic dysfunction

LV diastolic dysfunction can be defined as the inability of the LV chamber to fill up at low atrial pressures. This dysfunction can result either from an impairment in LV compliance (passive mechanism) or from an alteration in LV relaxation (active process). Relaxation is usually the first to alter in LV diastolic dysfunction and relaxation abnormalities can occur abruptly, especially in the context of anaesthesia or critical care.

Physiology and pathophysiology of LV relaxation

Zile and Brutsaert defined relaxation as ‘the time period during which the myocardium loses its ability to generate force and shorten and returns to an unstressed length and force’. From a mechanical point of view, the transition between systole and diastole was described as the time of aortic valve closure. However, the transition between contraction and relaxation corresponds to the dissociation of actin–myosin cross-bridges that begins during the early phase of LV ejection, before aortic valve closure.

The dissociation of actin–myosin cross-bridges follows the lowering of the intracellular calcium concentration (Fig. 1).

Myocyte energy imbalance

Since relaxation is an energy-consuming process, it is adversely affected by myocardial ischaemia. Ischaemia precludes optimal calcium exchanges between the cytosole and sarcoplasmic reticulum, and is rapidly associated with impairment in LV relaxation. Sepsis is also likely to alter myocytes energetic balance and, thus, to alter LV relaxation.

Contraction–relaxation coupling

As described earlier, relaxation begins early during systole indicating that relaxation and contraction are

![Diagram of calcium-induced calcium release in cardiac myocytes](https://example.com/diagram.png)

Fig 1 Calcium-induced calcium release in cardiac myocytes. After electrical stimulation, calcium influx through the calcium channels (I_{Ca}) stimulates ryanodin receptors (RyR) to release more calcium from the sarcoplasmic reticulum (SR) into the cytosol. Calcium concentration falls (i) by reuptake in the SR via phospholamban (PLB) stimulation and (ii) by calcium efflux by Na^+/Ca^{2+} exchange (NCX). The inset summarizes the time course: action potential precedes calcium influx and the peak of myocyte contraction is seen while intracellular calcium concentration falls. From Bers and Despa with permission.
LV pressure decline. As a consequence, LV relaxation is greatly affected by the lack of homogeneity in LV contraction. Both LV segmental coordination and atrio-ventricular synchronization are essential to guarantee an efficient relaxation.\(^1\) The loss of atrial contraction associated with atrial fibrillation not only alters LV filling but also results in a slowing of myocardial relaxation. Several other factors known to alter contractile function, including changes in afterload and the use of inotropes, markedly affect relaxation. However, the effect of preload variations on relaxation is not clear.

**Impact of afterload conditions on relaxation**

**Afterload dependency**

In failing hearts, an increase in afterload induces a delay in the onset of relaxation and an increase in the time-constant of isovolumetric relaxation (\(\tau\), ms).\(^1\) The afterload-dependence of \(\tau\) has also been shown to be influenced by the inotropic state. Facing an increased afterload, beta-adrenoreceptor agonists help to keep \(\tau\) constant, whereas antagonists (beta-blockers) markedly increased it.\(^1\)

To describe better the relationship between load, contractility, and relaxation, the concept of relative load was defined experimentally as the ratio of peak systolic LV pressure to peak isovolumetric pressure.\(^3\) The higher the relative load, the lower the contractile reserve (Fig. 2A). The contractile reserve quantifies the percentage force developed by the LV with respect to its maximum value. The consequences on relaxation of an elevation in LV afterload can range from a moderate acceleration to a marked deceleration, depending on the relative load. Up to a relative load of around 80\%, the diastolic decline in LV pressure accelerates, but above this, LV pressure decline decelerates. Acceleration of the LV pressure decrease in response to a load elevation is observed in the normal heart, whereas slowing of the LV pressure decline is associated with impaired cardiac function.\(^3\) This introduced the concept of afterload reserve which relates to the capacity of the normal LV to respond to elevation of afterload without changes in LV end-systolic volume and LV pressure decline.\(^3\)

Ventricles with altered contractile function consistently show a decreased ‘afterload reserve’,\(^2\) In such ventricles, even a small afterload elevation will cause a marked deterioration in LV relaxation and increase LV systolic and diastolic volumes.

An alternative concept: end-systolic volume dependency

Chemla and colleagues\(^1\) recently proposed an alternative approach based on the suggestion that, at constant heart rate, relaxation might depend more on LV end-systolic volume than on afterload, namely LV systolic pressure. Indeed, recoiling forces are generated when the LV contracts below its equilibrium volume (usually slightly higher than LV end-systolic volume) and therefore recoiling forces act during early diastole. Thus, since a healthy heart is able to respond to increased afterload without any change in its LV end-systolic volume, relaxation remains unaffected. However, in failing dilated ventricles, LV end-systolic volume might exceed the equilibrium volume, which deprives the LV of recoiling forces and impairs the rate of isovolumetric relaxation.

**Impact of preload conditions**

Myocardial relaxation was initially considered not to be affected by preload conditions.\(^3\) However, it has been suggested that marked preload variation can modify actin–myosin cross-bridge kinetics.\(^4\) Indeed, in a patient with LV diastolic dysfunction, a leg elevation manoeuvre can result in a substantial increase in end-diastolic pressure (Fig. 2a). This case report suggests that LV diastolic dysfunction can be undetected in normo- or hypovolaemic patient. In contrast, any excess in fluid can induce a dramatic increase in LV end-diastolic pressure (LVEDP). Thus, preload reserve is reduced in patients with altered LV diastolic properties.

**Analysis of diastole by cardiac catheterization**

Diastolic heart failure is characterized by an elevated LVEDP (16–26 mm Hg) in 92\% of patients,\(^10\) whereas control patients had an average of 10 mm Hg. Using micromanometer catheters, it is possible to acquire high-fidelity instantaneous LV pressure curves. Such tools are used to plot pressure/volume loops and to assess the rate of LV pressure decline (\(dP/dt_{\text{max}}\)) and the time constant of isovolumetric relaxation (\(\tau\)).

**Pressure/volume loops**

Systolic and diastolic functions are best described using the LV pressure/volume relationship, represented graphically as P/V loops (Fig. 3). In animals, a series of pressure/volume loops can be measured at baseline and after changes in preload (by inferior vena cava occlusion). The latter allow measurements of preload-independent variables as the end-systolic pressure/volume relationship and end-diastolic pressure/volume relationship.

In humans, pressure/volume tracings are usually performed only at baseline. In one study,\(^5\) pressure/volume loops were performed at baseline and during a sustained handgrip manoeuvre (Fig. 4).

Using this mechanical approach, diastole begins at the closure of the aortic valve and lasts until the closure of the mitral valve. Diastole can be divided into two phases. The first corresponds to the LV pressure decline at constant volume, isovolumetric relaxation, which lasts from closure of the aortic valve to opening of the mitral valve. The second, auxotonic relaxation, corresponds to LV chamber filling and lasts until the closure of the mitral valve. LV filling mainly depends on the pressure gradient between the left atrium (LA) and LV, which is mainly...
influenced by passive chamber properties (compliance), active relaxation, and, at end-diastole, by atrial contraction. Thus, impairment of LV compliance (decreased LA–LV pressure gradient), or the loss of atrial contraction, directly impair diastolic filling. Structural modifications (i.e. myocardial hypertrophy, fibrosis) mainly affect the passive, late phase of diastole and are more likely to develop chronically, whereas functional factors (i.e. ischaemia, sepsis) adversely affect active relaxation during early diastole. In LV diastolic dysfunction, the diastolic portion of the pressure/volume loop (compliance curve) is shifted to the left and upward (Fig. 3). Consequently, for a given LV end-diastolic volume (LVEDV), LVEDP is increased and may result in pulmonary congestion.

Systolic dysfunction also affects the pressure/volume loop: the end-systolic pressure/volume slope is shifted
downward and to the right, indicating a reduction in contractility, whereas end-systolic and end-diastolic LV volumes are increased, which may also lead to upstream congestion. Patients with heart failure can have combined systolic and diastolic dysfunction. In such cases, modest increases in LVEDV may result in large increases in LVEDP. Kawaguchi and colleagues recently demonstrated that, in patients admitted with heart failure but with preserved LVEF, the diastolic portion of the pressure/volume loops, although apparently normal at rest, altered on exertion. Indeed, manoeuvres such as sustained isometric handgrip markedly impaired LV diastolic properties, increased LVEDP, and could reveal diastolic heart failure (Fig. 4).

**Pressure decline analysis**

In diastolic heart failure patients, LV pressure decline analysis reveals a significant increase in the time constant of isovolumetric relaxation, \( \tau \).

A recent multicentre, prospective study, using cardiac catheterization and echocardiography to assess LV diastolic properties in 47 patients with diastolic heart failure and 10 normal controls, demonstrated that insight into the respective roles of active relaxation and compliance could be gained using a detailed analysis of the LV diastolic pressure curve. The following measurements are of particular interest:

(i) \( \tau \), the time constant of the isovolumetric relaxation;
(ii) \( P_{\min} \), LV minimal pressure after the opening of the mitral valve;
(iii) \( P_{\text{Pre-A}} \), LV pressure just before atrial contraction;
(iv) LVEDP, LV end-diastolic pressure, just after atrial contraction.

This study showed that in patients with diastolic heart failure, in contrast to the control subjects, isovolumetric relaxation was incomplete at the time of \( P_{\min} \). Thus, \( \tau \) was prolonged and \( P_{\min} \) increased, resulting in a positive correlation between \( \tau \) and \( P_{\min} \). Incomplete relaxation accounted for 7 (1) mm Hg of the measured increase in \( P_{\min} \). In these patients, LV compliance was also significantly altered with an increase in LVEDP, despite a reduced LVEDV.

**Assessment of LV diastolic function in clinical practice**

There are differences between heart failure with reduced and preserved ejection fraction with regards to symptoms, physical examination, echocardiographic and ECG abnormalities, and X-ray findings (Table 1).

**Echocardiography**

The combination of several ultrasound modalities is useful in the assessment of diastolic function in patients with possible diastolic heart failure. These modalities include: 2-D echo, pulsed-wave Doppler, M-mode colour Doppler, and tissue Doppler imaging. In the presence of acute pulmonary oedema, echocardiography is suggestive of diastolic heart failure, if preserved LV systolic function is associated with indirect signs of elevated LA pressure.
Table 1 Characteristics of heart failure with preserved or reduced LVEF

<table>
<thead>
<tr>
<th></th>
<th>Altered ejection fraction</th>
<th>Preserved ejection fraction</th>
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<tbody>
<tr>
<td>Dyspnoea</td>
<td>Chronic</td>
<td>Transient mainly</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>Present</td>
<td>Rare</td>
</tr>
<tr>
<td>SS/S4 gallop</td>
<td>S3 &gt; S4</td>
<td>S4 mainly</td>
</tr>
<tr>
<td>Pales</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>Present</td>
<td>Rare</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>Constant</td>
<td>Inconstant</td>
</tr>
<tr>
<td>LV dilatation</td>
<td>Nearly constant</td>
<td>Absent</td>
</tr>
<tr>
<td>ECG abnormal</td>
<td>Constant</td>
<td>Inconstant</td>
</tr>
<tr>
<td>BNP</td>
<td>Markedly increased</td>
<td>Often mildly increased</td>
</tr>
</tbody>
</table>

LV systolic function can be assessed by 2-D echo and global performance estimated qualitatively ('eye-balling') and, if possible, quantitatively (measurement of ejection fraction). These measurements should be performed as soon as possible after the onset of symptoms, as a low ejection fraction can return to normal within 24–48 h after treatment of decompensated heart failure. Ejection fraction values ranging between 0.4 and 0.5 are not strictly ‘normal’, but cannot explain per se the occurrence of acute pulmonary oedema. Therefore, the criterion generally required to define ‘preserved LVEF’ is a value >0.5. However, Petrie and colleagues showed that ‘heart failure with preserved LVEF’ could be associated with subtle LV systolic dysfunction, yet recognizable using new measures of LV systolic function (measurement of LV systolic atrio-ventricular plane displacement). Another study, however, concluded that even if ‘subtle abnormalities in regional systolic function’ might exist in diastolic heart failure, they are ‘unlikely to be responsible for clinical signs of heart failure’.

LA pressure cannot be directly measured using echocardiography. Pulsed-wave Doppler measures the velocity of blood at a precise location: the Doppler ‘window’. This velocity is proportional to the pressure gradient. Thus, if the Doppler window is placed at the tip of the mitral valve, the diastolic flow velocity profile will reflect the pressure gradient between the LA and the LV. The mitral blood flow is composed of an E (early) wave for passive diastolic filling followed by an A (auricular) wave for atrial systole. Mitral blood flow profile is affected by LV relaxation, LV compliance, and LA pressure. Normal diastole is characterized by a predominant E wave (peak and area under the curve), implying that most of the LV filling is occurring during the early phase of diastole. Mitral blood flow abnormalities are of three types:

(i) in mild diastolic dysfunction, only relaxation is impaired and atrial contraction contributes relatively more to ventricular filling; thus, peak of A wave >peak of E wave, with prolonged E wave deceleration time (usually >240 ms);
(ii) in moderate diastolic dysfunction, relaxation is impaired, LV compliance is decreased, and atrial pressure increased; a pseudo-normal pattern with a predominant E wave is observed, but the E wave deceleration time is shortened;
(iii) in severe diastolic dysfunction, LV compliance is extremely low; a restrictive pattern is observed with a high peak E wave velocity, usually more than twice the peak A wave velocity.

However, Zile and colleagues reported a lack of sensitivity of the mitral blood flow analysis for the diagnosis of diastolic heart failure. In their study, the E/A ratio was abnormal in only 48% of the patients presenting signs of heart failure with a normal ejection fraction. The E wave deceleration time was found to be more sensitive (abnormal in 64% of the patients).

If the Doppler window is located within a pulmonary vein, the flow velocity will reflect the pressure gradient between the vein and the LA throughout the cardiac cycle. A markedly increased LA pressure (>18 mm Hg) will generate characteristic alterations in the velocity profiles. Pulmonary vein flow is composed of two waves, one systolic and one diastolic. The elevation of the LA pressure impairs atrial filling, and the pulmonary vein diastolic wave becomes predominant. Nevertheless, pulmonary vein flow abnormalities cannot discriminate between systolic and diastolic heart failure.

Tissue Doppler Imaging directly measures myocardial velocity and allows wall movements to be directly analysed. Tissue Doppler has been validated for the evaluation of cardiac function. Although influenced by LVEF, E/Ea measurement performed on the lateral mitral annulus can reliably be used to evaluate filling pressures in patients presenting with a preserved ejection fraction. The E (early mitral inflow velocity)/Ea ratio is considered a useful indicator of LV filling pressures. Although influenced by LVEF, E/Ea ratio is often mildly increased in patients with diastolic heart failure.

None of these Doppler indices is 100% sensitive or specific and a combination of indices is usually required to ascertain high LA pressure.

**Natriuretic peptides**

Brain natriuretic peptide (BNP) is recognized as a specific marker of heart failure in patients presenting with acute dyspnoea. Maisel and colleagues measured BNP in 1586 patients presenting with acute dyspnoea. Of the 452 patients with a final diagnosis of heart failure, 165...
Diastolic heart failure in clinical practice

Many factors including uncontrolled hypertension, atrial fibrillation, myocardial ischaemia, anaemia, renal insufficiency, and non-compliance with treatment may precipitate overt systolic and diastolic heart failure. However, uncontrolled hypertension is involved in more than 50% of the cases of acute (decompensated) diastolic heart failure. Anaesthetists may have to deal with acute hypertensive pulmonary oedema in patients with preserved LV systolic function.

Perioperative setting

The perioperative period carries a risk of decompensation of chronic diastolic heart failure or induction of acute diastolic dysfunction. Therefore, it is important to identify high-risk patients and situations and drugs likely to adversely affect LV diastolic function and be able to prevent and treat acute decompensations.

Preoperative screening should focus on the detection of:

(i) history of diastolic heart failure or structural factors potentially associated with an impaired LV diastolic function: LV hypertrophy (except in young athletes) and atrial arrhythmia affecting LV ‘active filling’;

(ii) factors carrying a higher risk of diastolic heart failure: female, age more than 70 yr old, history of untreated hypertension, ischaemic heart disease, or diabetes mellitus;

(iii) clinical signs of heart failure, especially dyspnoea on exertion;

(iv) specific measures from echocardiography: LV hypertrophy, impairment of diastolic function, preserved LVEF.

Different guidelines have been published in order to clarify the definition and the diagnosis of diastolic heart failure. Vasan and Levy produced pragmatic criteria that are widely used in the cardiology. They separated the diagnostic procedure into three sequential steps: (1) diagnosis of heart failure, (2) preserved systolic LV function (LVEF >0.5), and (3) documentation of LV diastolic dysfunction if feasible (Table 2).

Table 2: Definition of definite, probable, and possible DHF. SAP, systolic arterial pressure; DAP, diastolic arterial pressure; BP, blood pressure

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria</th>
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<tr>
<td>Definite</td>
<td>Clinical evidence of heart failure</td>
</tr>
<tr>
<td></td>
<td>Preserved LVEF within 72 h of the heart failure events + documented diastolic dysfunction</td>
</tr>
<tr>
<td>Probable</td>
<td>Clinical evidence of heart failure</td>
</tr>
<tr>
<td></td>
<td>Preserved LVEF within 72 h of the heart failure events but no documentation of diastolic dysfunction</td>
</tr>
<tr>
<td>Possible</td>
<td>Clinical evidence of heart failure</td>
</tr>
<tr>
<td></td>
<td>Preserved LVEF but not at the time of the heart failure events without documentation of diastolic dysfunction</td>
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Upgrade from possible to probable diastolic heart failure

SAP >160 mm Hg or DAP >100 mm Hg during the episode of heart failure, which may include the following:

- tachyarrhythmia
- precipitation of event by the infusion of a small amount of i.v. fluid
- clinical improvement in response to therapy directed at the cause of diastolic dysfunction
- (such as lowering BP, reducing heart rate, or restoring the atrial booster mechanism)

On the basis of this, and using the criteria proposed by Vasan and Levy, a specific algorithm can be proposed for the preoperative risk stratification of LV diastolic function impairment (Fig. 5). Particular attention should be paid in patients with potential LV diastolic dysfunction to avoid a further deterioration of diastolic function, especially hypovolaemia, tachycardia, and rhythms other than sinus. For elective surgery, patients with definite diastolic heart failure group would benefit from a cardiologist opinion and their treatment checked to optimize diastolic function before surgery.

Perioperative period

During the perioperative period, haemodynamic changes and anaesthetic agents can adversely affect LV diastolic function.

(36.5%) had preserved LV function on echocardiography, whereas 287 (63.5%) had systolic dysfunction. Patients with non-systolic heart failure had significantly lower BNP concentrations than those with systolic heart failure (413 vs 821 pg ml⁻¹, P<0.001). When comparing patients with acute diastolic dysfunction with those with non-cardiogenic dyspnoea, a BNP concentration ≥100 pg ml⁻¹ had a sensitivity of 86%, a negative predictive value of 96%, and an accuracy of 75% for detecting abnormal diastolic dysfunction. Mildly elevated values of BNP may not differentiate between systolic and diastolic heart failure and BNP may be normal in some cases of acute hypertensive pulmonary oedema in patients with preserved LV systolic function.
Haemodynamic changes affecting diastolic time, such as arrhythmia and myocardial ischaemia, are likely to decompensate further pre-existing diastolic dysfunction. Tachycardia shortens diastole and is likely to impair LV filling. Rhythm disturbances can be precipitated by hypo- or hyper-kalaemia, anaemia, or hypovolaemia. Treatment with beta-blockers or non-dihydropyridine calcium-channel blockers has been proposed to prevent tachycardia and improve LV filling. 6 94 Myocardial ischaemia or acute increases in cardiac loading (volume loading or changes in position) (Fig. 2a) may result in a significant slowing of myocardial relaxation. Myocardial ischaemia may also induce rhythm disturbances that will further aggravate LV diastolic dysfunction. Thus, prevention of ischaemic episodes should remain a major objective for anaesthesiologists dealing with suspected diastolic heart failure. Beta-blockers still remain the best drug to achieve a safe reduction in myocardial oxygen consumption. Indeed, periprocedural use of beta-blockers has been shown to reduce overall mortality due to cardiac events. 64 113 Whether this strategy is still applicable to diastolic heart failure remains to be determined. Finally, the use of regional or general anaesthesia is still debated, but no study has found benefit of one technique over the other.

The effect of anaesthetic agents on LV diastolic properties has been extensively studied for volatile agents, but less for i.v. agents (Table 3). The volatile agents, sevoflurane and desflurane, as well as opioids and muscle relaxants do not appear to affect LV diastolic properties.

In high-risk diastolic heart failure patients, anaesthesiologists should pay particular attention to the choice of monitoring and to avoiding acute perioperative changes in load conditions, heart rate, and myocardial oxygen balance.

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**Fig 5** Algorithm for preoperative risk stratification of patients with suspected diastolic heart failure.
There are no good clinical data on the action of anaesthetic drugs in LV diastolic dysfunction.

### Recovery room, ICU, and emergency room

#### Hypertensive crisis

Gandhi and colleagues\(^{36}\) compared the echocardiographic findings on admission and after 2–3 days of treatment in patients presenting with acute pulmonary oedema as a consequence of severe arterial hypertension. Although transient LV systolic dysfunction due to the hypertensive crisis was expected, no difference in LVEF and regional wall motion was found between the acute episode and after 24 and 72 h of treatment. Around 50% of the patients admitted with an acute pulmonary oedema had preserved ejection fraction and 89% of the patients who had a preserved ejection fraction after treatment also had no sign of systolic dysfunction during the acute episode. Similarly, in patients with an impaired ejection fraction, no differences were found within the first 72 h, suggesting that acute diastolic failure might also be the major mechanism of decompensation in patients with baseline systolic dysfunction. Acute diastolic dysfunction during hypertensive crisis remains poorly understood. In diastolic heart failure at rest, it is understandable that a small increase in LVEDV will lead to a marked elevation in LVEDP. However, this is less clear in patients without diastolic dysfunction at rest. It has been proposed that a hypertensive crisis leads to a marked increase in coronary perfusion pressure and thus in coronary turgor.\(^{114}\) Nevertheless, it is unlikely that an increase in coronary blood volume can cause a significant increase in wall thickness.

#### Myocardial ischaemia

Myocardial ischaemia is one of the main mechanisms of LV diastolic dysfunction in the early postoperative period, and several factors, including pain-induced sympathetic activation (tachycardia, hypertension), shivering, anaemia, hypovolaemia, and hypoxia, may alter myocardial oxygen balance.

In a rabbit model,\(^{80}\) the early and late haemodynamic consequences of a circumflex artery ligation were analysed by echocardiography and Doppler. One hour after experimental infarct, the rabbits exhibited a significant alteration of the LV filling pattern; decrease in E and A waves, A wave reversal velocities and increase in the mean pulmonary venous systolic-to-diastolic ratio. Three weeks after coronary ligation, the rabbits still exhibited significant abnormalities in filling pattern. Stugaard and colleagues\(^{100}\) assessed LV diastolic function in 20 patients during coronary angioplasty and in eight anaesthetized dogs during experimental coronary occlusion. Diastolic function was explored using M-mode Doppler, which determines the time difference between the peak velocity in the apical region and in the mitral tip. The authors reported a significant increase in time difference in both patients and dogs, and the time difference evolution correlated significantly with the variation in the time constant of isovolumetric relaxation. Pacing tachycardia, volume loading, and vena cava restriction did not significantly alter the time difference.

Nitric oxide (NO) metabolism seems to play a controversial role in acute diastolic dysfunction following episodes of ischaemia–reperfusion. A beneficial role for NO has been suggested since pre-treatment with cGMP donors or with NO donors protects myocytes from relaxation failure in experimental models of hypoxia-reoxygenation.\(^{30,92}\) However, excessive NO production during reperfusion appears to alter diastolic function due to an excess of peroxynitrite formation.\(^{115}\)

#### Sepsis

Increasing evidence suggests that both systolic and diastolic functions are affected in severe sepsis and septic shock.\(^{85}\) We recently showed, using pressure/volume tracings in anaesthetized endotoxaemic rabbits, that LV diastolic properties are altered; prolonged relaxation, decreased LV compliance leading to increased end-diastolic pressure.

In a transmitral Doppler analysis of 13 patients in septic shock,\(^{54}\) 10 in sepsis without shock, and 33 controls with septic shock and sepsis without shock had a
The management of diastolic heart failure

**Initial management of acute decompensated diastolic heart failure**

The management of acute decompensated diastolic heart failure is based on a reduction in pulmonary congestion and a correction of the precipitating factors, such as a hypertensive crisis, myocardial ischaemia, acute rhythm disturbances, and sepsis. Specific treatment of precipitating factors should always be considered: vasodilators for hypertensive crisis, coronary revascularization, restoration of sinus rhythm, and haemodynamic optimization in septic shock.

A hypertensive crisis can be managed by i.v. calcium-antagonists such as nicardipine or nifedipine (sublingual nifedipine is not recommended). High-dose nitrates i.v. can decrease both preload and afterload. Sodium nitroprusside can also produce balanced vasodilatation, but may result in severe unloading or hypotension in these nondilated ventricles. Angiotensin converting enzyme inhibitors are not useful in the acute phase because of their slower onset of action. Beta-adrenergic blockers or diltiazem may be used in acute heart failure related to rapid atrial fibrillation or severe myocardial ischaemia.

Pulmonary congestion can be reduced by controlling blood volume or improving LV filling. Because of the steepness of the LV diastolic pressure/volume relationship, a small decrease in LVEDV can lead to a marked decrease in LVEDP. The reduction in the blood volume can be achieved either by nitrates or by diuretics, in order to reduce venous return and decrease LVEDV. Nevertheless, diuretics should be carefully considered in the context of acute hypertensive crisis, as blood volume is often already decreased by chronic hypertension or the long-term use of diuretics. As contractile function is preserved, the role of sympathomimetic inotropes is limited. Digoxin is useful only to slow the heart rate in rapid atrial fibrillation.

Continuous positive airway pressure seems to be effective in the treatment of diastolic dysfunction.11

**Future treatments for acute diastolic heart failure**

Future approaches will probably focus on the optimization of LV relative load at the cardiac level and cardiac myocytes calcium homeostasis at the cellular level.

As mentioned earlier, drugs that may decrease LV relative load are of interest. The decrease in the relative load can be obtained either by decreasing cardiac load or by improving systolic function, or by the combination of both. Thus, levosimendan may be a candidate for acute diastolic heart failure treatment as it combines a vasodilator effect, by opening ATP-sensitive K+ channels, and a positive inotropic effect, by modulating the interaction between troponin and calcium.105 Despite a ‘calcium sensitizer’ effect that is expected to worsen diastolic properties of the heart, levosimendan has been recently shown to improve LV diastolic properties.77 99

The effect of NO donors on LV diastolic function has been studied in animals and humans.78 They have been shown to induce an early relaxation and a decrease in basal tone both related to a reduction in cardiac myofilament
responsiveness to Ca\(^{2+}\), within seconds of administration in vitro. Similarly, intracoronary injections of the NO donor, sodium nitroprusside, in normal hearts caused an earlier onset of LV relaxation, a decline in LV minimum and end-diastolic pressures, an increase in LVEDV, and a down and rightward shift of the LV diastolic pressure/volume relationship, within minutes of administration.79 These results are consistent with a direct NO-induced improvement in diastolic function. A direct beneficial effect of NO donors on diastolic dysfunction has not been shown in patients in the acute/early phase of acute diastolic heart failure. Of note, two other vasodilators, urapidil and nicardipine, seem to have no effect on relative load or directly on the diastolic properties of the LV.25 In addition, another endogenous cardiovascular mediator, endothelin, has no effects on diastolic properties in normal or chronic heart failure patients.51

**Long-term management of chronic LV diastolic dysfunction**

Myocardial remodelling over months or years is essential to restore adequate LV filling conditions. Several approaches have been proposed to control LV structural abnormalities. Because the renin–angiotensin–aldosterone system plays an important role in the development of diastolic heart failure and particularly in myocardial remodelling and fluid retention, angiotensin-converting enzyme inhibitors, angiotensin receptors antagonists, and aldosterone antagonists have been proposed in the treatment of diastolic heart failure.19 Spironolactone has recently been shown to limit the evolution of cardiac muscle fibrosis.53 91 A study of enalapril on diastolic heart failure in elderly patients with prior myocardial infarction7 reported a benefit in terms of exercise capacity. The CHARM-preserved study is a multicentre, randomized, double-blinded study comparing in diastolic heart failure the effects of a selective angiotensin-receptors blocker (candesartan) and placebo.117 This showed a significant reduction in hospitalization rate after 36 months follow-up in the candesartan group. Losartan has been shown to improve echocardiography and exercise tolerance.5

Of note, cardiac resynchronization therapy affects LV loading conditions and has recently been shown to improve LV filling.1

**Conclusion**

Although frequently underestimated, diastolic heart failure is a common pathology. Diastolic heart failure is recognized as the mechanism involved in heart failure with a preserved LV function, and LV diastolic dysfunction can also account for acute heart failure occurring in critical care situations. Hypertensive crisis, sepsis, and myocardial ischaemia are frequently associated with acute diastolic heart failure. Symptomatic treatment focuses on the reduction in pulmonary congestion and the improvement in LV filling. Specific treatment is actually lacking, but encouraging data are emerging concerning the use of renin–angiotensin–aldosterone axis blockers, NO donors or very recently new agents specifically targeting actin–myosin cross-bridges.

**Acknowledgement**

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Is a rethink of our approach to hypertension necessary?

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Introduction
The risks and management of hypertensive patients for elective anaesthesia are often debated. There is a perception that patients with untreated or ineffectively treated hypertension are at risk, in particular for cardiac and cerebrovascular events.

The change in internal to external diameter of the vasculature results in an altered vascular pressure-flow relationship in the hypertensive patient. This gives rise to the exaggerated hypertensive and hypotensive response seen. The hypotensive tendency is aggravated by the diastolic dysfunction often present. In addition, autoregulation is right shifted, impacting on the lower limit of autoregulation.

Treating patients for their hypertension requires months to years to restore the autoregulation towards normal, even though the blood pressure may have been normalized. Except for patients with significant end-organ dysfunction (such as cardiac failure), application of our knowledge of the pathophysiology of hypertension, combined with skill, should allow the anaesthetist to reconsider some of the current dogma in the management of the hypertensive patient.

Anaesthetists have differing approaches to the patient with hypertension scheduled for elective surgery. On many occasions, this leads to surgery being cancelled because the practitioner is of the opinion that the hypertension is uncontrolled. In this paper, the position projected by the authors, is that if the pathophysiology of hypertension is clearly understood, the majority of hypertensive patients can be accepted for anaesthesia, whether blood pressure control is deemed adequate or not. Nonetheless, it is also important that the anaesthetist appreciates the exceptions, and the reasons for these exceptions.

It must be made clear at the outset that this paper is written with the intent to provoke debate and discussion on this topic. Furthermore, the opinion stated in this article does not question existing wisdom that long-term advantages can be gained from the effective treatment of chronic hypertension. The discussion that follows therefore applies only to the perioperative period.

Anaesthetic problems associated with the hypertensive patient
The hypertensive patient presents the anaesthetist with three main problems:
1. Episodes of hypertension;
2. Periods of hypotension;
3. Concerns regarding (pre-existing or consequent) end-organ damage, especially the brain, heart, vasculature and kidneys.

The first two are well known occurrences in patients with hypertension subject to anaesthesia and surgery. In our view, understanding the pathophysiology should enable the anaesthetist to prevent these problems. We will also argue that concerns regarding end-organ damage are speculative and or can be effectively managed.

The essential pathophysiology of hypertension
Vascular pathophysiology and blood pressure lability
Changes occur both in:
• The structure of the peripheral arteries;
• Intravascular blood volume.

These pathophysiological changes are of practical significance as they are central to the understanding of the variations in blood pressure that anaesthetist has to deal with.

There are a number of well described changes that occur in the large, medium and small arteries and arterioles. Cumulatively this is referred to as medial hypertrophy.1 Medial hypertrophy results in the normal vascular lumen to wall ratio of 1:5.2 decreasing to 1.3 to 4.7 in the hypertensive patient.2

The importance of this smaller than normal lumen to wall ratio was summarized in experimental work by
Folkow. In his studies, controlled perfusion of the vasculature of normotensive and hypertensive rats resulted in the flow – pressure relationships depicted in Figure 1. From the flow – pressure quotient, which is the inverse of resistance, one can deduce from the graph that normotensive rats have a lower vascular resistance when compared to the hypertensive rat.

When Folkow subjected the vasculature to catecholamine stimulation, (Figure 2), the threshold for a response was the same in the normal and hypertensive rats. However, once a response was obtained, the slope of the dose-resistance relationship was steeper for the hypertensive rats compared with the normotensive ones.

The following conclusions can be drawn from these experiments:

- The threshold for obtaining a pressure response appears to be similar for the hypertensive and normotensive rat. Therefore, the problem is not that the vasculature of hypertensive rats is inherently more sensitive to stimuli.
- However, the problem is that once a response is obtained, the extent of this response is more pronounced in the hypertensive compared with the normotensive rats.

The interpretation of these results is that there is no difference in autonomic control of the vasculature in hypertensive and normotensive subjects. However, the pathophysiological problem is that resistance to flow is higher in hypertensive subjects because of the smaller internal lumen of the vasculature. These conclusions apply equally to hypertensive human subjects.

Blood pressure changes in lieu of the vascular changes

From the above results, Folkow and colleagues compiled the instructive vascular response curves for both normotensive and hypertensive subjects (Figure 3). The authors used % shortening of the circumferential arterial muscles and resistance on the x and y-axes respectively. For the purpose of clinical applicability and clarity, the x and y-axes may be relabeled “vasoconstriction” and “blood pressure” respectively. These extrapolations are justified because of the relationship between the circumference of a vessel and its radius (circumference = 2πr) and the relationship between pressure, flow and radius described in Pouseuille’s equation.

Consider, on the one hand, what would happen if vasoconstriction occurred and the vessel diameter in Fig 4 decreased from a1 to a2. The resulting increase in blood pressure would be significantly greater in the hypertensive patient, compared with the normotensive one.

On the other hand, if the stress is removed, autonomic mediated vasoconstriction will decrease and the internal radius of the vessel will increase. For similar decreases in vessel radius (from c1 to c2 on the y axis of Fig. 5), the resultant fall in blood pressure is represented by decreases from d1 to d2, and from e1 to e2, for the normotensive and hypertensive patients respectively. Figure 5 therefore illustrates that the extent of the fall in blood pressure, after similar percentage increases in

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<th>Fig 1: Flow and pressure relationship in normo (N) and hypertensive (H) rat vasculature. The resistance is higher in the H rat.</th>
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<th>Fig 4: For any particular increase in vasoconstriction (a1 to a2), the resultant increase in blood pressure will be significantly more in the H (c1 to c2) compared to the normotensive (N) (form b1 to b2). This graph explains the excessive pressor response seen in the uncontrolled hypertensive patient.</th>
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vessel diameter, will be much greater in hypertensive than normotensive patients.

On studying Figures 4 and 5, it is easy to appreciate both the excessive hypertension following a vasoconstrictory stimulus (for example laryngoscopy and intubation) and also the exaggerated fall in pressure that follows even small amounts of vasodilation (for example when the appropriate anaesthetic level for surgery has been achieved).

On studying Figures 4 and 5, it is also noteworthy that, when the point of maximal vasodilatation is approached, the Folkow relationships for both hypertensive and normotensive patients approximate each other and are located on the less steep part of the vessel radius - pressure curve. Therefore, albeit the resting vessel resistance remains increased in hypertensive patients, the percent blood pressure change which occurs when the vessel diameter changes, is less when the patient is operating on the left side of the Folkow curve.

Another important pathophysiological principle is that uncontrolled hypertensive patients have a contracted intravascular blood volume. The effect of this will be aggravated by the well documented diastolic dysfunction often seen in the hypertensive patient. The single most important defense against a fall in blood pressure, when the stress stimulus is withdrawn, is the status of the intravascular volume.

Hence, the hypertensive patient is not only penalized by virtue of the vessel diameter dynamics, but preload, the main physiological buffer protecting against hypotension, is less efficient. Notwithstanding this problem, the opinion has often been expressed that, because a patient is hypertensive, fluid loading should be on the conservative side. Such an approach (partially) explains the subsequent hypotension the anaesthetist has achieved.

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**Autoregulation**

Autoregulation is defined as the “intrinsic tendency of an organ or tissue to maintain constant blood flow despite changes in arterial pressure”. The salient feature illustrated in a characteristic normal autoregulation curve is that between certain limits of blood pressure (marked by points a and b in Figure 6), organ blood flow is constant. If blood pressure decreases below point a, termed the lower limit for autoregulation (LLA), or above point b, the upper limit for autoregulation, flow becomes pressure dependant. Pressure dependant flow has particular physiological implications for the anaesthetist. To illustrate these implications, one can apply the autoregulation concept to the brain. Normal brain blood flow averages 50 ml/min/100g tissue. Below the lower limit of autoregulation, brain blood flow progressively decreases. When brain blood flow decreases to 20 - 25 ml/100g/min, electrical activity of the brain ceases. Cessation or a decrease of organ function with reductions in their blood flow and nutrient supply is termed hibernation, a term more often used in cardiac pathophysiology. Hibernation represents a method whereby organs protect themselves against low oxygen supply scenarios and does not necessarily equate to tissue damage. Once nutrient flow is improved, function will be restored. Only when blood flow decreases to 6 - 15 ml/min/100g brain tissue, will membrane dysfunction and neuronal death occur.

The important question that has to be addressed is what is the mean arterial pressure (MAP) at which organ blood flow decreases to potentially dangerous levels? Strangaard and colleagues studied the effects of decreasing blood pressure on cerebral blood flow in awake patients. The 3 groups they studied comprised normotensive (mean arterial pressure [MAP] 98 ± 10 mm Hg), treated hypertensive (MAP 116 ± 18 mm Hg) and untreated hypertensive subjects (MAP 145 ± 17 mm Hg). The initial part of their study comprised lowering blood pressure and noting the point where flow becomes pressure dependant (LLA). Thereafter, they continued lowering blood pressure to the level where the patients demonstrated signs of cerebral ischaemia (ischaemic threshold, IT).

A particularly instructive aspect of the Strangaard study is that, if the LLA is described as a percentage of the pre-test MAP, the LLA occurred at approximately 75% of the baseline MAP. This study also demonstrated that a significant linear relationship between the MAP and LLA (and IT) existed. The
Strangaard study is valuable in that it provides the anaesthetist with a rough guide as to how much reduction of the awake preoperative blood pressure can be tolerated intraoperatively. The important guideline that is created is that a reduction of blood pressure in excess of 20% of baseline should not be tolerated.

Albeit the above guideline is useful, cognizance should be taken of the wide variation in LLA that occurs. Drummond, in a letter to the editor of Anesthesiology, pointed out that mean LLA values range between 73 to 91 mm Hg in awake normotensive patients; however LLA values for individuals varied between 41 to 113 mm Hg. This wide variation in LLA represents perhaps one of the limiting factors when dealing with the concept of autoregulation i.e. the anaesthetist does not know the exact limits for any particular patient.

In the hypertensive patient it has been confirmed that the positions of the coronary and cerebral autoregulation curve are shifted to the right."

The problem that the anaesthetist is therefore presented with is that the position of the LLA and slope of the pressure dependant portion of the autoregulation is unknown for individual patients. In other words, it is not known at what blood pressure organ blood flow will decrease sufficiently to result in tissue damage. Hence it is prudent that anaesthetists elect not to approach the LLA too closely and remain on the flow independent part of the autoregulation curve.

Changes in pathophysiology with treatment
Rat studies indicate that antihypertensive drug therapy effectively reduces blood pressure. However, from the anaesthetist’s perspective, the reduction of blood pressure is not the final aim of antihypertensive treatment. What is of importance to the anaesthetist is preservation of organ blood flow. It is therefore of some significance to note that only if this therapy is effective in reducing blood pressure and is administered for sufficient time, will remodeling of the vasculature occur. Chronic antihypertensive treatment (over an extensive period) represents a method of normalizing autoregulation and lessening the risk of organ underperfusion during anaesthesia.

Two studies are instructive in this regard. In the one study, Hoffman subjected both spontaneous hypertensive (SHR) and normotensive rats to antihypertensive therapy. In the SHR group that was treated with antihypertensive drugs, blood pressure was effectively reduced to that of the control group after 2 weeks of therapy. At this point, they subjected both the treated and untreated animals to hypertensive episodes. There was no difference between cerebral blood flow and oxygen consumption in the treated and untreated SHR groups. The lesson learned from this study is that normalization of blood pressure is not synonymous with normalization of autoregulation.

It is also noteworthy that in the Hoffman study, autoregulation was not restored by 10 weeks of antihypertensive therapy. If it is considered that a single rat month approximates 37 human months, and if we are allowed the liberty of a direct extrapolation of these time periods, it implies that blood pressure must be effectively controlled for years in humans before the anesthetist can rely on a normal autoregulation curve.

Another study demonstrated similar results to the Hoffman study. In this study, a renal artery clip hypertensive rat model was studied. After release of the clip, blood pressure decreased to normal values within 1 week. However, the exaggerated pressor response seen in hypertensives only normalized 19 weeks after removal of the clip.

This perspective presents anaesthesiologists with the following dilemma. Even if the patient is on treatment for hypertension, we cannot assume that autoregulation is normalized until months or years have passed after the therapy was initiated. Therefore, when we are presented with patients that have hypertension who have relatively recently started treatment, we do not know which intraoperative blood pressure should be regarded as “safe” in order to maintain organ blood flow?

Risk to organs
Long standing uncontrolled hypertension is a proven threat to the brain, heart, vasculature, kidneys and eyes. However, in the anaesthetist’s peroperative management, the two organs that are paramount are the brain and heart. This does not imply that the other organs can be managed with a casual attitude, but that these two organs present a greater potential to cause acute life threatening crises.

Cardiac risk
The question arises whether hypertension results in an increased cardiovascular risk? It is interesting that the Goldman cardiac risk index, one of the earliest and best known scoring systems developed to determine perioperative cardiovascular risk, did not include hypertension as one of its parameters. Furthermore, a large study published in 1990 also did not consider hypertension as an independent risk factor in patient undergoing non-cardiac surgery. However, Howell and colleagues did report an association between the history of hypertension and perioperative cardiovascular death. A meta-analysis could not confirm a significant increase in the odds ratio for perioperative cardiac outcome and hypertensive disease (OR 1.35 (1.17 – 1.56)).

At a minimum there is significant doubt whether a clear link has been established between hypertension and perioperative cardiovascular risk with the proviso that certain aspects of the cardiac risk be managed in an effective manner as is explained below.

The earliest studies from the Oxford Group, lead by Pryse-Roberts, warned that the untreated or ineffectively treated hypertensive patient is at risk of both excessive pressor response and myocardial ischaemia. They also reported that, in these hypertensive patients, the peroperative use of β adrenergic receptor blockers reduced the incidence of myocardial ischaemia. In the non β-blocked patients, the incidence of myocardial ischaemia was 38% compared to 4% in those who received practolol. The Oxford Group’s studies were conducted in a small group of patients, but were reconfirmed in a larger and more recent study. Stone and colleagues (comparing oxprenolol, acebutolol and labetolol with no treatment in hypertensives) showed that use of β adrenergic blockers in the perioperative period,
reduced the incidence of myocardial ischaemia to much the same figures as reported in the earlier Prys Roberts study. On closer inspection of the Stone data, it is evident that the peak blood pressures recorded during intubation and extubation were within reasonable clinical proximity of each other (except for a group who received labetolol). The untreated patients had mean blood pressures of $125\pm4$ and $127\pm3$ mmHg on intubation and extubation respectively. This compares favorably with the $118\pm4$ and $119\pm3$ mmHg recorded in the patients treated with oxprenolol. However, more consistent differences in heart rate were observed in the Stone study. Data demonstrated that the group who received β adrenergic blockade had lower heart rates during periods of stress compared with non-treated patients. It is reasonable to suggest that the differences in the incidence of myocardial ischaemia between the groups were most probably the result of the slower heart rate associated with β adrenergic blockade and not the insignificant differences in blood pressure per se.

Why is it that the myocardial ischaemia seen during or after laryngoscopy and intubation as well as other periods of stress, appears to be related to increases in heart rate rather than increases in blood pressure? The answers may lie, on the one hand, with the observation that coronary blood flow varies directly with the perfusion pressure in the presence of stress, appears to be related to increases in heart rate rather than increases in blood pressure? The answers may lie, on the one hand, with the observation that coronary blood flow varies directly with the perfusion pressure in the presence of a critical coronary artery stenosis.\(^ {25}\) This means that small increases in blood pressure will increase or maintain coronary blood flow. On the other hand, the myocardial ischemia associated with periods of stress is most likely the result of an oxygen delivery problem associated with the decrease in diastolic time that accompanies an increase in heart rate.\(^ {26}\)

According to this interpretation of the data, the main cardiac risk for the hypertensive patient is an ischaemic insult. This risk is more closely related to diastolic coronary perfusion time and not the blood pressure. In the hypertensive patient, provided that the pressor response is not so great that it causes the left ventricle (LV) to fail, the logical conclusion is that the major acute perioperative cardiac risk (i.e. myocardial ischaemia) can be managed with β adrenergic blockers. Therefore, the perceived cardiac risks should not deter the anaesthetist from subjecting the hypertensive patient to anaesthesia and surgery, whether the hypertension is controlled or not.

In fact, the popular practice of using β blockers as an adjuvant to reduce cardiovascular stress, acknowledges the above logic. Vascular tone is the result of a balance between β₁ and α adrenergic stimuli. If the β₁ and β₂ receptors are blocked with an appropriate drug, the alpha-receptors are left, so to speak, relatively unopposed. This explains why in many patients there may well be a further small increase in blood pressure when α adrenergic blockers are initiated. Hence, treatment of the expected hypertensive pressor response with a β adrenergic blocker alone defies logic, but in most instances, serendipitously brings the ischemic risk under control by containing the heart rate.

There are 3 other caveats regarding the cardiovascular system and anaesthesia in hypertensive patients.

1. Assidao and Donegan\(^ {27}\) have shown that uncontrolled preoperative hypertension is associated with an increased risk for transient ischemic attacks (TIA) in patients undergoing carotid endarterectomy. This represents one of the few studies and scenarios in which the hypertensive patient has unequivocally been shown to have an increased perioperative risk.

2. It is important to appreciate that, if left ventricular (LV) afterload is high enough to prevent the LV ejecting effectively, the blood pressure requires effective treatment before embarking on anaesthesia. This caveat especially applies to patients with marginal or poor LV performance.

3. There is also the fear that the hypotensive episodes will result in trespassing into the region below the LLM. This hypotensive risk can be managed in the following ways:
   a. Careful fluid preloading, taking cognizance of the 15-200% intravascular fluid deficit,
   b. The use of the synergistic relationship that exists for example between opioids and anaesthesia agents. This synergistic relationship applies to both the reduction in the dose of induction agents needed to produce sleep, as well as the reduction in the MAC of inhalation agents.
   c. Frequent measurements of blood pressure.
   d. The availability of pressor agents to maintain blood pressure if required.

In summary, there is no final and or convincing proof that blood pressure per se represents the major risk in the hypertensive patients when viewed from a cardiac perspective. The real risk appears to be that of an increase in heart rate and myocardial ischaemia; we have drugs that can effectively manage this potential problem. Furthermore, the caveats mentioned emphasize that the approach to the hypertensive patient must be individualized and end-organ function examined before a decision can be made whether or not to accept the current blood pressure for the purpose of anaesthesia.

The Brain

Another organ that is of great concern to the anaesthetist when the topic of hypertension is discussed, is the brain. The concern is that because perioperative blood pressure can vary significantly in hypertensive patients, this may lead to cerebral injury. Because of the position of the autoregulation curve, hypotension would cause hypoperfusion of the brain, whereas high blood pressures would rupture the vessels and cause cerebral bleeding.\(^ {28}\)

Any brain injury (which was caused by excessive pressure and flow variation during anaesthesia) is likely to be evident shortly (hours rather than days) after surgery.

A review by Kam and Calcroft\(^ {29}\) estimates the incidence of perioperative stroke during general surgery at 0.2 – 0.7%. Nonetheless, this incidence of perioperative stroke is modified by several factors. Both Kam and Calcroft\(^ {27}\) and Wong\(^ {29}\) emphasize that the incidence of stroke varies with age. The risk of perioperative stroke in males is 0.38% for subjects over 50, 0.5% over 70, 3.54% over 80 and 3.2% over the age of 90. The stroke usually occurred well into the postoperative period, happening on average on the 7th postoperative day.

Moreover, a prior history of cerebrovascular pathology has
been shown to be associated with a 10 fold increase in the incidence of perioperative stroke.\(^{21}\)

The association between hypertension and postoperative stroke has been examined by a limited number of studies. A study often referred to is that of Parikh and Cohen.\(^{32}\) This retrospective study with matched controls studied 24641 patients and reported a perioperative stroke rate of 0.08\%. On close inspection of the paper, issues are raised which belie the conclusions the authors made i.e. hypertension is a risk for perioperative stroke. Firstly, 6 of their 20 patients that suffered a stroke had atrial fibrillation (AF), a major risk factor in itself for perioperative stroke. Secondly, one patient had an episode of significant hypertension in the postoperative period. A subsequent CT scan revealed the patient had suffered a cerebral bleed. This begs the question as to whether the bleed or the hypertension occurred first. Lastly, if both the published stroke rate for the 67 year average age in this study and also the atrial fibrillation group is taken into account, it becomes clear that the conclusions of this study, that hypertension is a risk for perioperative stroke, were indeed speculative.

Data studying the association of perioperative stroke and hypertension suffers from a problem with the definition of what is meant by the term “perioperative”? It is the opinion of the authors that if blood pressure fluctuations, be it hyper- or hypotension, are indeed the cause for cerebral injury, it should be present immediately or very soon after the anaesthetic. We are critical of studies that employ, for instance, a 30-day postoperative evaluation period as a reflection of the effects of blood pressure fluctuations during anesthesia on brain tissue. While it may be acceptable to term this period “perioperative”, it is probably not acceptable and speculative to attribute a stroke to blood pressure variation occurring during the procedure.

It is relevant to this discussion that the data from a study conducted by Hart and Hindman\(^{33}\) be considered. This study showed that stroke was associated with hypertension that occurred in the postoperative recovery period. There was no association between stroke and intraoperative events and this study emphasizes the necessity for close control of blood pressure into the post operative period.

The role of AF is repeatedly stressed as one of the major causes of postoperative stroke. The data from Hart and Hindman\(^{33}\) reveals that in 42\% of their cases, stroke was cardiogenic in origin with AF being the most important single factor.

Larsen\(^{34}\) found 9 postoperative strokes in 2463 surgical patients. However, on close examination of this data, the majority of the strokes occurred after the 5th postoperative day. In addition, 3 patients had AF and only 4 had hypertension. Of those 4 patients with hypertension, 2 had AF. Furthermore, only two patients did not have other known risk factors such as previous cerebral incidents and dementia. If the 2 patients with AF in the hypertensive group are discounted, only two patients who suffered a stroke postoperatively (from day 5 onwards) had hypertension. Also, it is reasonable to ask why the authors considered that stroke on or after the 5th postoperative day was related to anaesthesia. This interpretation gives a different perspective of the data as presented by the authors.

In summary, studies looking at the association between perioperative stroke and hypertension suffer from many limitations, and are difficult to interpret. While logic suggests that tight blood pressure control is to be advocated perioperatively, at least one study disputes the contention that intraoperative hemodynamic instability increases perioperative stroke. Furthermore, there is clear evidence that factors other than perioperative blood pressure fluctuations such as AF, increasing age, postoperative hypotension, uncontrolled hypertension in patients scheduled for carotid endarterectomy, and prior cerebrovascular incidents increase the risk of perioperative stroke.

A time for change?

Decisions to accept hypertensive patients for elective surgery are frequently non-scientific and based on “gut feeling” driven opinions. The available guidelines also reflect personal preference and the uncertainty.\(^{35}\) In developing a new approach, the following should be considered:

1. The anaesthetist must understand the pathophysiology of the variation in blood pressure that is so often seen in these patients. The initiation of antihypertensive treatment will result in rapid reductions in blood pressure. However, the anaesthetist may be misled to accept the new lower pressure as a reference point. It must be remembered that vascular remodeling is still taking place and both the pressor response and autoregulation are still that of the hypertensive patient. It probably requires many months or even years of effective treatment before it is reasonable to accept that vascular remodeling has normalized. One must not be misled by the dangerous practice of colleagues who start treatment in their rooms and admit the patient one week later with a normal blood pressure.

2. Our (extrapolated) knowledge about the change in the autoregulation curve must be meticulously applied. This means that variations of more than 20\% in the preoperative mean arterial pressure should not be allowed.

3. Contingency plans should be made to measure, prevent and treat hypotension by restoration of the intravascular volume and use of \(\alpha\) adrenergic agonists. Hypertensive episodes can easily be managed firstly by ensuring a proper surgical level of anaesthesia and secondly, with the use of intravenous vasodilators.

4. It appears that the cardiac risk, is primarily that of myocardial ischaemia. To a large extent, heart rate control will contain this problem. However, it must also be understood that \(\beta\) adrenergic blockers will not contain the pressor response to stressful stimuli. As mentioned, administration of an intravenous vasodilator may be required to control pressure surges.

5. Literature seems to suggest an increased perioperative risk of stroke in hypertensive subjects. However, rigorous interrogation of the published data indicates that the real risk of stroke appears to be a very uncertain issue.

a. Nonetheless, cognizance must be taken of the fact...
that patients with prior cerebral incidents appear to be at a higher risk of sustaining postoperative cerebral events.

b. Furthermore, carotid artery surgery results in a higher incidence of cerebral events in patients who have elevated blood pressure preoperatively. In this subgroup of patients, the available data suggests that preoperative blood pressure control is indeed wise.

6. The blood pressure that the anesthetist should accept must be individualized. For instance, patients with a raised blood pressure who is either in congestive heart failure, or is scheduled for carotid endarterectomy, have specific and understood reasons why the blood pressure needs to be controlled before embarking on elective surgery.

In the light of better knowledge of the pathophysiology, appreciation of the above proviso’s, combined with anaesthetic skills and the judicious use of the appropriate drugs, the often quoted views on hypertension in the perioperative period need to be reconsidered.

References
Hypertension, hypertensive heart disease and perioperative cardiac risk

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The evidence for an association between hypertensive disease, elevated admission arterial pressure, and perioperative cardiac outcome is reviewed. A systematic review and meta-analysis of 30 observational studies demonstrated an odds ratio for the association between hypertensive disease and perioperative cardiac outcomes of 1.35 (1.17–1.56). This association is statistically but not clinically significant. There is little evidence for an association between admission arterial pressures of less than 180 mm Hg systolic or 110 mm Hg diastolic and perioperative complications. The position is less clear in patients with admission arterial pressures above this level. Such patients are more prone to perioperative ischaemia, arrhythmias, and cardiovascular lability, but there is no clear evidence that deferring anaesthesia and surgery in such patients reduces perioperative risk. We recommend that anaesthesia and surgery should not be cancelled on the grounds of elevated preoperative arterial pressure. The intraoperative arterial pressure should be maintained within 20% of the best estimate of preoperative arterial pressure, especially in patients with markedly elevated preoperative pressures. As a result, attention should be paid to the presence of target organ damage, such as coronary artery disease, and this should be taken into account in preoperative risk evaluation. The anaesthetist should be aware of the potential errors in arterial pressure measurements and the impact of white coat hypertension on them. A number of measurements of arterial pressure, obtained by competent staff (ideally nursing staff), may be required to obtain an estimate of the 'true' preoperative arterial pressure.

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The importance of hypertension

The association between elevated arterial pressure and cardiovascular disease is unequivocally established and well known to doctors and the general public. The risk of cardiovascular events in the general population increases steadily with increases in arterial pressure. The individuals at greatest risk of suffering a cardiovascular event because of hypertension are those with the highest arterial pressures. However, mild to moderate hypertension is more common than severe hypertension, and much of the population burden of disease because of hypertension may be attributed to moderate rather than severe hypertension. This is illustrated in Figure 1, which documents the association between systolic hypertension and deaths as a result of coronary artery disease.⁷⁴ The highest risk of death is seen in patients with systolic arterial pressures of greater than 180 mm Hg. However, the greatest number of excess deaths (calculated as the difference between the number of deaths that would be expected from coronary artery disease on the basis of the rate in the group with a systolic arterial pressure of less than 110 mm Hg and the number of deaths actually recorded) is seen in the largest group of subjects. That is, those with systolic arterial pressures of between 140 and 149 mm Hg. Hence, medical guidelines for the treatment of hypertension emphasize the treatment of mild to moderate hypertension. The British Hypertension Society Guidelines on the management of hypertension use a threshold of 140/90 mm Hg for the initiation of treatment.⁶³ This review will

⁷This article is accompanied by Editorial II.
The introduction of antihypertensive drugs led to concerns that patients on such drugs might be at increased risk of perioperative cardiac lability. In 1966, Dingle recommended that patients presenting for anaesthesia and surgery should, if possible, undergo autonomic testing before their operation. This would give some indication of their risk of cardiac lability and whether or not their antihypertensive therapy should be continued. These recommendations were overtaken by the work of Prys-Roberts and colleagues, who published a series of studies on the interaction between hypertension and anaesthesia and elective surgery. Fifteen of the patients were classified as normotensive, although by current standards all of their control patients would now be considered hypertensive. The remainder of the patients were classified as treated or untreated hypertensives. By current standards, these patients would probably be considered to have severe hypertension as several were reported as having systolic arterial pressures of 220–230 mm Hg. The patients underwent intensive haemodynamic monitoring. The authors reported that the untreated hypertensive patients had a greater decrease in arterial pressure at induction of anaesthesia and that they were more prone to intraoperative myocardial ischaemia. There were no adverse events reported in either the control or hypertensive groups.

On the basis of these findings the authors recommended that, where possible, hypertensive patients should have anaesthesia and surgery deferred to allow their hypertension to be treated. This recommendation led to a major change in anaesthetic practice, and to the modern perception that where possible untreated hypertensives should not be subjected to elective anaesthesia and surgery without first treating their arterial pressure. However, these recommendations should be applied with some caution. The perception of what constitutes hypertension has changed considerably since these studies were undertaken. Arterial pressures that in the early 1970s would have been considered acceptable are today consistent with levels of hypertension where treatment is obligatory. As already stated, all of the control patients in the study by Prys-Roberts and colleagues would now be considered to be hypertensive. The recommendations of Prys-Roberts and colleagues therefore need to be reconsidered in the light of the modern views of hypertension and its management.

### The classification of hypertension

It has been indicated above that raised arterial pressure is associated with a continuum of risk, with greatest risk associated with the highest arterial pressures. For the purposes of analysis, discussion and treatment recommendations, it is necessary to grade and classify raised arterial pressure in some way or another. This may be done implicitly by defining treatment thresholds, as in the British Hypertension Society guidelines, or explicitly, by dividing arterial pressure into bands of increasingly severe hypertension, as in the classification of the Sixth Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure (JNC VI). However, it has been pointed out that the differences between classifications can have major implications for estimating the prevalence of hypertension and the number of people in a population who may require treatment. The World Hypertension Society/International Society of Hypertension (WHO/ISH) guidelines set lower thresholds than those advocated by either the British Hypertension Society or JNC VI. Acceptance of the WHO/ISH thresholds results in 45% of the population as a whole and 60% of the adult population being classified as hypertensive. It is important to remember the ultimate goals in the treatment of hypertension. These are the reduction of the risk of cardiovascular events for the individual patient and in the population as a whole. Hypertension is only one of a number of risk factors for cardiovascular disease and a number of guidelines, including those issued by the British Hypertension Society, advocate treatment not on the basis of arterial pressure alone but according to the overall estimate of cardiovascular risk (Fig. 2).
For the purposes of this review, the classification of hypertension described in JNC VI will be followed (Table 1). This classification is based solely on arterial pressure readings and does not take into account other risk factors, although the importance of taking these into account when deciding on treatment is highlighted. It defines bands for both systolic and diastolic pressure. Where a patient’s systolic and diastolic arterial pressures fall into two different categories, the higher category is selected. It offers a graded classification with six bands of arterial pressure and acknowledges that levels of arterial pressure above optimal pressures of less than 120/80 mm Hg carry some increased risk, while not leading us to classify a large proportion of the population as hypertensive. The anaesthetist is often called upon to take a view on whether or not a given level of arterial pressure is clinically important. The JNC VI classification allows us to identify the place of an individual patient’s arterial pressure on a scale of increasing severity. It does, however, have some limitations when applied to the patient presenting for surgery. The most important is that the classification of hypertension is based on the average of two or more readings of arterial pressure taken at two or more visits after initial screening. However, in current British
practice, it is uncommon for the anaesthetist to have the benefit of arterial pressure readings taken on a number of recent occasions.

**Defining the questions**

The perioperative management of hypertensive patients is a complex issue that can be divided into a number of different questions.

1. Is having a diagnosis of hypertension of itself associated with increased perioperative risk, regardless of the arterial pressure at the time of admission to hospital for surgery?

2. Is elevated arterial pressure at the time of admission for surgery associated with increased perioperative cardiac risk?

3. What is the importance, if any, of poorly controlled hypertension in the perioperative setting? Is there any interaction between elevated admission arterial pressure and being diagnosed with hypertensive disease previously such that this increases perioperative risk?

4. Does the treatment of elevated admission arterial pressure before surgery reduce perioperative cardiac risk?

For the purposes of this review the term ‘hypertensive patient’ refers to anyone who has been labelled a hypertensive: that is, someone for whom interventions to lower persistently raised arterial pressure would be appropriate, or someone who is already on treatment for hypertension. Raised arterial pressure will be described as such.

The core of this review will be an examination of the available observational studies that address the first three questions and a discussion of the issues surrounding the interpretation of these studies. Related issues including arterial pressure measurement, white coat hypertension, the use of ambulatory arterial pressure monitoring, and perioperative arterial pressure lability will also be discussed. Recommendations will be offered for the perioperative management of hypertensive patients, although these are based only on observational data. It should be stated at the outset that the authors know of no randomized controlled trial that addresses the final question. The practice of deferring elective surgery to allow poorly controlled arterial pressure to be treated is solely based on the perception that such elevated pressure is associated with increased perioperative risk, and therefore reducing the arterial pressure must be a good thing to do. There is no level one evidence to support this approach.⁷⁶

**Hypertensive disease and anaesthesia**

This section presents a meta-analysis of observational studies examining the association between hypertension and perioperative cardiac risk in patients undergoing non-cardiac surgery. Papers were identified as relevant to the association between hypertension and perioperative cardiovascular outcome if published between 1971 and the end of 2001. The former date was chosen as the lower cut-off year, because this was the year in which the paper ‘Studies of anaesthesia in relation to hypertension. I. Cardiovascular responses of treated and untreated patients’ was published.⁶² The MEDLINE database was interrogated using the following combinations of search terms: {anaesthesia OR anesthesia} AND cardiac risk; {anaesthesia OR anesthesia} AND cardiovascular risk; hypertension AND postoperative complication AND adult NOT animal; hypertension AND intraoperative complication AND adult NOT animal; arterial pressure AND postoperative complication AND adult NOT animal; arterial pressure AND intraoperative complication AND adult NOT animal; preoperative risk stratification.

All searches were limited to articles in English. The abstracts of the papers identified were scanned ‘on-line’ to identify relevant papers. The reference lists of those papers that were identified for inclusion in the meta-analysis were also scanned to identify further relevant studies.

The papers identified from these searches were read in full. Those that included data concerning the association between hypertensive disease and perioperative cardiovascular complications were identified. Reports were included if they examined outcomes considered to be major cardiovascular complications occurring up to 30 days after anaesthesia and surgery. Major cardiovascular complications were considered to be cardiovascular death, myocardial infarction, new or more severe angina, heart failure, life-threatening arrhythmias, and cerebrovascular accident. Several studies examined ‘minor’ complications such as perioperative bradycardia and tachycardia, and perioperative hypotension and hypertension, and more serious complications. Where it was impossible to separate information on major complications from data on all complications, both major and minor, the study was excluded. Studies that reported the association between hypertension and perioperative myocardial ischaemia detected on Holter monitoring but did not contain data on the association between hypertension and clinically evident events were excluded.

For a study to be included, it had to be possible to derive from the report the crude odds ratio for the association between hypertension and perioperative cardiovascular complications, together with the variance of that odds ratio. The ideal would have been to include the adjusted odds ratios in which allowance had been made for the effect of other confounding variables. In most instances, this was not available.

A number of relevant studies were not primarily designed to examine hypertension or other perioperative cardiovascular risk factors, but were studies of diagnostic tests for preoperative cardiovascular assessment or (in one case) of the value of actively warming the patient during surgery. We have included those studies where the report of the study...
included relevant data on the association between hypertension and perioperative cardiovascular complications.

A number of studies examining stroke after carotid endarterectomy have been excluded, as it is argued that these studies examined a particular complication in an exceptional population, and the findings from such studies may not generalize to patients undergoing other types of surgery.

The main focus of this meta-analysis was the association between hypertensive disease and perioperative complications, rather than any association between admission arterial pressure and such complications. Consequently, studies that defined hypertension solely in terms of the level of admission arterial pressure were excluded. Studies were included where the definition of hypertension was not given. For example, in the ‘Multi-Center Study of General Anaesthesia’, the anaesthetist was asked to indicate if the patient was hypertensive or not, but the definition of hypertension used is not given.20

A total of 4691 citations were identified from the MEDLINE database. From these, 128 potentially relevant studies were identified from 126 reports. (The full list of 126 citations can be viewed in the version of this review published on the British Journal of Anaesthesia website at http://bja.oupjournals.org/.) For these 128 studies, the full reports were obtained and read in detail. Ninety-eight studies described in 97 reports were excluded from further analysis.

In 80 studies, including the two studies described in a single paper, an effect estimate for the association between hypertension and cardiac complications was not given and could not be derived from the publication. Three studies were excluded because they appeared to include patients who had been examined in another study already included in the meta-analysis. In each case, only one of the pair of papers concerned was included in the meta-analysis.39 41 58 In six of the excluded studies, hypertension was defined in terms of the arterial pressure alone with no reference to hypertensive disease. In two studies, hypertension was defined as either an elevated admission arterial pressure or a history of treatment with antihypertensive medications and no indication was given of which patients fell into each category. One study was excluded because preoperative coronary artery by-pass grafting and perioperative cardiac complications were

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grouped together as one outcome. Separate information was not given on the association between hypertension and perioperative complications. One study included data on 676 operations in 617 patients. No information was given on which patients underwent more than one procedure. It was felt that using data from this study could lead to an underestimate of the variance of the odds ratio for hypertension and the study was excluded from the meta-analysis. (The full list of excluded studies can be viewed in the electronic version of this paper.)

Initially, it was planned to restrict this review and meta-analysis to patients undergoing general anaesthesia. It rapidly became clear that this was not practical. In those papers containing useful data that also gave information on the type of anaesthesia used a significant proportion of patients received regional or local anaesthesia.3 5 26 53 64 67 69 75 78 81 Many papers, that did not indicate the type of anaesthesia used, included patients some of whom were likely to have been managed with local regional anaesthesia, for example those undergoing carotid endarterectomy or lower limb revascularization.

Thirty studies were included in the final meta-analysis (Table 2).3–6 16 18 21 22 26 30 33 34 39–41 43 44 53 54 58 64 67 69 70 72 75 77 78 81 These studies were published between 1978 and 2001 and include 12 995 patients. The analysis included two separate studies by Rao and colleagues, both described in the same paper.54 One was a retrospective study of 364 patients anaesthetized between June 1973 and June 1976, and the other a prospective study of 733 patients anaesthetized between July 1977 and June 1982.

A fixed effects meta-analysis of the crude odds ratios from these studies for the association between hypertension and cardiovascular complications was performed using the ‘meta’ command of Stata v7.0. The Forrest plot of the data is shown in Figure 3. The pooled odds ratio from this analysis was 1.35 (1.17–1.56) P<0.001. However, the test for heterogeneity also achieved statistical significance (Q=44.76, 29 df, P=0.031). (Heterogeneity represents the extent or magnitude of differences in treatment or exposure effects between different studies.)52 The source of this heterogeneity was sought through a number of sensitivity analyses grouping the data by year of study (for example 1978–1990 and 1991–2001), and by type of surgery. These analyses yielded little impact on the odds ratio and there remained considerable heterogeneity within the subgroups studied. Thus, the odds ratio of 1.31, while statistically significant, is small and must be interpreted with considerable caution in this meta-analysis of heterogeneous observational studies, with no correction for confounding. In the context of a low perioperative event rate, this small odds ratio probably represents a clinically insignificant association between pre-existing hypertension and perioperative cardiac risk.

Pre-existing hypertension and target organ damage

The association between hypertension and end or target organ damage is well established. Hypertension is inextricably linked to ischaemic heart disease and heart failure, to
anaesthetist a licence to ignore the target organ damage may be of limited importance, but this does not grant the  

Section: Cardiovascular complications, pre-existing hypertension  

Section: The meta-analysis of observational studies described above suggested an association between a diagnosis of hypertension and increased perioperative cardiac risk. However, the odds ratio was small and the conclusion must be treated with some circumspection in the light of heterogeneity of the studies examined. This is not to dismiss the role of clinically evident target organ damage in increasing perioperative risk. A recent study by Lee and colleagues identified ischaemic heart disease, heart failure, and renal failure as risk factors for perioperative cardiac complications.42 In assessing perioperative risk of major cardiovascular complications, pre-existing hypertension per se may be of limited importance, but this does not grant the anaesthetist a licence to ignore the target organ damage caused by hypertension. Such damage may carry significant risk and its importance should be assessed using guidelines such as those referenced above.9,15  

Admission arterial pressure and perioperative cardiac risk  

The best-designed study in this area is that of Goldman and Caldera.57 This examined a sub-population of patients who were studied in the production of the Goldman Risk Index. Patients were divided into five groups. These were: normotensive patients, patients treated with diuretics, treated hypertensives whose arterial pressure was controlled, patients who were hypertensive despite treatment, and untreated hypertensives. No significant differences in perioperative cardiac risk were found between the hypertensive patients and the remaining groups. However, although extremely well designed, this study lacked the statistical power to either confirm or refute an association between hypertensive heart disease and perioperative cardiac risk. Other studies, such as those by Cooperman, Eerola, and Steen examined admission arterial pressure as one of a number of variables that may contribute to perioperative cardiac risk. However, these studies either lacked the statistical power to effectively examine hypertension as a risk factor, or gave only limited information on the impact of hypertension in the final report of the study.13 17 75  

None of the studies described above examined admission arterial pressure as a continuous variable. All have taken a specific cut-off for arterial pressure. The only studies of which the authors are aware that have examined arterial pressure as a continuous variable are those by Howell and colleagues.33 34 The first was a retrospective case controlled study which examined patients who died of a cardiac cause within 30 days of anaesthesia and elective surgery and a matched controlled population who underwent the same operations but who did not die.34 There were no significant differences between admission systolic and diastolic arterial pressures between the cases and the controls (Fig. 4). The second was a similar study of emergency surgery; again there were no significant differences between the arterial pressures of the cases and the controls, although in this case there was a tendency for the survivors to have higher admission arterial pressure than those patients who died.33 While both of these studies suggest that there is no association between admission arterial pressure and perioperative cardiac risk, they are both limited by the fact that most of the patients studied had Stage 1 or Stage 2 hypertension. Few patients with Stage 3 hypertension were studied.  

There is very little evidence on which to base the perioperative management of patients who present for surgery with admission arterial pressures consistent with Stage 3 hypertension. Perhaps the best data come from the original study by Prys-Roberts and colleagues.62 In this
study most, if not all, of the hypertensive patients had arterial pressures consistent with Stage 3 hypertension. As already discussed, this study demonstrated increased cardiovascular lability and an increased risk of perioperative myocardial ischaemia in patients with poorly controlled hypertension. It was too small to determine if there was an increased incidence of cardiac events in this population.

The evidence from medical studies suggests that patients with Stage 3 hypertension are at significantly increased risk of target organ damage, whether or not this is clinically evident. For example, Stamler and colleagues, and Liao and colleagues demonstrated a steadily increasing incidence of ECG abnormalities in this population. There is certainly evidence to support a steadily increasing incidence of postoperative myocardial ischaemia with increasing admission systolic arterial pressure. Many patients with admission arterial pressures consistent with Stage 3 hypertension will have isolated systolic hypertension. There is evidence from the Framingham population of significantly increased cardiovascular risk in this population. Recent analyses suggest that systolic pressure and pulse pressure are more reliable indicators of cardiovascular risk than diastolic pressure. On the basis of these data, we suggest that it is appropriate to defer anaesthesia and surgery where possible in patients with admission arterial pressures consistent with Stage 3 hypertension, especially if there is evidence of target organ damage. However, it must be borne in mind that this recommendation is made on the basis of evidence of risk in medical patients rather than data on perioperative risk. Studies of perioperative risk in patients with Stage 3 hypertension are required.

**Isolated systolic hypertension**

The steady increase in arterial pressure with age in the Western population is well known. An analysis of data from the Framingham population by Franklin and colleagues has added detail to this picture. They describe a steady increase in systolic arterial pressure starting in childhood and continuing throughout adult life. In contrast, diastolic pressure rises in early adult life and then stabilizes or declines in the fifth and sixth decade of life. There is a steady rise in pulse pressure throughout adult life and the rate of rise increases after the age of 50 yr. It is against this background that the phenomenon of isolated systolic hypertension has been recognized; that is the situation in which the diastolic arterial pressure is normal, but the systolic arterial pressure is elevated. As might be expected, isolated systolic hypertension accounts for the majority of hypertension in patients over 50 yr old. In the NHANES III data, Franklin and colleagues found that 80% of the subjects aged over 50 yr who had hypertension had isolated systolic hypertension. As a corollary of this, pulse pressure had been found to be strongly associated with cardiovascular risk. The benefits of treating isolated systolic hypertension are now clearly established.

While the studies of hypertension undertaken by Prys-Roberts and colleagues used the then standard definition of hypertension of a diastolic arterial pressure of greater than 95 mm Hg, it is clear from their publications that many of their patients had severe systolic hypertension. Most later studies that have included an examination of the association between admission arterial pressure and perioperative complications have focused on older patients: for example, in the study by Cooperman and colleagues the average age of the patients was 61 yr; in the study by Eerola and colleagues, 69 of the 111 patients studied were over 60 yr old; and in the study of myocardial re-infarction by Steen and colleagues, 361 of the 466 patients studied were aged 60 yr or over. It is likely that the majority of poorly controlled hypertensives in these studies had isolated systolic hypertension.

A recent study by Aronson and colleagues examined the association between isolated systolic hypertension and cardiovascular complications in patients undergoing cardiac surgery and these data are worth rehearsing here. This was a prospective study of over 2000 patients in 24 centres undergoing elective cardiac surgery. Patients were classified as having normal preoperative arterial pressure, isolated systolic hypertension (systolic arterial pressure greater than 140 mm Hg), diastolic hypertension (diastolic arterial pressure greater than 90 mm Hg) or a combination of these. After adjusting for other risk factors, isolated systolic hypertension was associated with a small but statistically significant increase in the likelihood of perioperative morbidity (odds ratio 1.3, 95% confidence interval 1.1–1.6). The mean systolic arterial pressure of the patients with isolated systolic hypertension is not given, although as the average age of the patients was 65 yr, it is tempting to speculate that it was considerably greater than 140 mm Hg.

It is clear that many of the patients who present for surgery and have arterial pressures consistent with Stage 3 hypertension will be elderly patients with isolated systolic hypertension. There are few if any studies that explicitly examine the impact of isolated systolic hypertension on outcome from non-cardiac surgery and, as with Stage 3 hypertension, work in this area is required. However, the findings of the study by Aronson and colleagues and the work of Franklin and colleagues on the Framingham population do little to reassure the anaesthetist.

**White coat hypertension**

So-called white coat hypertension is directly relevant to anaesthetic practice. It is formally defined as a persistently elevated clinic arterial pressure in combination with a normal ambulatory arterial pressure. Various different arterial pressure thresholds have been used to define white coat hypertension in different studies, leading to conflicting data as to the prognosis of this condition. Recently, criteria have been agreed and are now widely accepted. These define white coat hypertension as an office arterial pressure
hypertension. Kaplan identifies four prospective studies of the data indicate a benign prognosis for white coat different studies in this area, but suggest that the majority and colleagues highlight the difficulties in comparing cardiovascular complications than patients with sustained levels consistent with normotension may be at less risk of consistent with Stage 3 hypertension that then settle to for elective surgery with admission arterial pressures hypertension. However, extrapolating from data derived from a long-term study conducted in the medical setting to draw conclusions about patients undergoing surgery is a leap, and any conclusions drawn have to be treated with some caution.

The various guidelines on the management of hypertension all indicate that the arterial pressure should be measured on a number of occasions over a period of weeks before the diagnosis of hypertension is confirmed. It is rare for the anaesthetist to have this luxury and often a decision has to be made on perioperative management on the basis of two or three readings taken over a period of hours.

Both doctors and nurses may produce an initial elevation in arterial pressure when they visit a patient, but the effect is greater for doctors than for nurses. This is impressively illustrated by data from Mancia and colleagues. They studied 30 subjects who underwent a 24-h intra-arterial recording after 5–7 days in hospital. During the intra-arterial recording period the arterial pressure was additionally measured at different times using a sphygmomanometer by a male doctor and a female nurse, half of the subjects being randomized to see the doctor first, and the other half the nurse. When the doctor took the first reading, the arterial pressure rose by an average of 22/14 mm Hg. The rises when the first arterial pressure was taken by a nurse were only half as great. The arterial pressure usually returned to near baseline after 10 min when the reading was taken by a nurse, but this was not the case when the pressure was taken by a doctor (Fig. 5). It is clear from their data that, in many surgical patients, the admission arterial pressure will not equate to the patient’s usual arterial pressure. If a member of the medical staff finds the patient’s arterial pressure to be elevated, this should be confirmed by a nurse with appropriate training.

Cardiovascular lability
Patients diagnosed as ‘hypertensive’ have a reputation for displaying increased cardiovascular lability during anaesthesia. There is certainly a pathophysiological basis for such behaviour. Established hypertension is associated with an increased systemic vascular resistance. The systemic vasodilation associated with anaesthesia might well be expected to have profound effects on arterial pressure in such patients. Prys-Roberts and colleagues, and Goldman and Caldera both demonstrated that induction of anaesthesia is associated with a decrease in arterial pressure to a similar nadir in both hypertensive and normotensive patients. However, because hypertensive patients in these studies generally had a higher pre-induction arterial pressure, absolute decrease in arterial pressure in these patients was greater. For many anaesthetists, however, cardiovascular lability implies something more than the decrease in arterial pressure seen at induction of anaesthesia. It suggests swings in arterial pressure over a wide range of values, graphically described by Longnecker as ‘Alpine Anesthesia’.
Robert and colleagues established that poorly controlled hypertensive patients have a more vigorous cardiovascular response to laryngoscopy and intubation than do normotensive or well-controlled hypertensives. Studies by Charleson and colleagues documented swings in arterial pressure in hypertensive and diabetic patients. However, their work makes no comparison between hypertensive and normotensive patients in respect to their cardiovascular behaviour, and neither confirms nor refutes the suggestion that hypertensives are particularly prone to cardiovascular instability. Chung and colleagues examined the association between pre-existing medical conditions and adverse events in 17,638 patients undergoing day-case surgery. They identified an association between pre-existing hypertension and intraoperative cardiovascular events. No major complications, such as death or perioperative infarction, are reported and the majority of these cardiovascular events were episodes of hypertension, although there were also instances of hypotension and arrhythmia. In the large ‘Multicenter Study of General Anesthesia’, it was noted that hypertensive patients were more likely to require interventions for perioperative hypertension. However, the definition of hypertension used in this study was not given in the report. Taken together, the weight of the evidence is that patients with hypertension may be expected to suffer a greater decrease in arterial pressure at induction of anaesthesia than normotensive patients, although the arterial pressure probably decreases to a similar nadir in both patient groups. The work of Prys-Roberts and colleagues supports a more vigorous response to noxious stimuli in these patients. The findings of Chung and colleagues indicate that patients with pre-existing hypertension frequently have high arterial pressures during the intraoperative period.

The clinical impact of wide variations in arterial pressure is difficult to quantify, not least because most anaesthetists would not be prepared to leave large changes in arterial pressure untreated for more than a short period of time. Charleson and colleagues reported that, within a high-risk group of hypertensive patients and diabetic patients undergoing elective non-cardiac surgery, those with more than 1 h of a decrease in mean arterial pressure of greater than/equal to 20 mm Hg and those with less than 1 h of a decrease in arterial pressure of greater than/equal to 20 mm Hg and more than 15 min of an increase in arterial pressure of greater than/equal to 20 mm Hg were at greatest risk of complications. In so far as we can tell, the use of vasoactive drugs was allowed in the perioperative period. One has to ask if, in the patients who had wide excursions of arterial pressure, a decision was made not to treat these changes in arterial pressure or if the changes in arterial pressure were refractory to treatment because of ongoing perioperative cardiovascular complications. The association between intraoperative myocardial ischaemia and haemodynamic changes is certainly not clear-cut. In a study of 100 patients who either had, or were at risk for, coronary artery disease, intraoperative ischaemic episodes were preceded by acute increases in arterial pressure in only 15% of episodes and by acute decreases in only 8% of episodes. A recent paper by Reich and colleagues has described an association between intraoperative hypertension and tachycardia and adverse outcome in protracted surgery. It was by no means clear, however, that this was a causal association.

**Perioperative management of patients with hypertension or raised arterial pressure**

The meta-analysis presented above suggests association between a diagnosis of hypertension and increased perioperative cardiac risk. However, the odds ratio for the effect of hypertension was small and the conclusion must be treated with some circumspection in the light of heterogeneity of the studies examined. There is evidence from many studies that conditions that may represent target organ damage as a result of hypertension contribute to perioperative cardiac risk. A study by Lee and colleagues identified ischaemic heart disease, heart failure, and renal failure as risk factors for perioperative cardiac complications. It would seem sensible to suggest that anaesthetists should pay more heed to the presence of significant target organ damage than to a diagnosis of hypertension per se.

With regard to the management of surgical patients with elevated admission arterial pressure, there are few substantive guidelines over which patients should be cancelled to allow treatment before surgery or the duration of such treatment before proceeding with surgery. The American Heart Association/American College of Cardiology (ACC/AHA) guidelines comment that hypertension (Stages 1 and 2) is not an independent risk factor for perioperative cardiovascular complications. However, they suggest that Stage 3 hypertension (SAP $\geq 180$ mm Hg and/or DAP $\geq 110$ mm Hg) should be controlled before surgery. To quote the guidelines:

‘In many instances establishment of an effective treatment regimen can be achieved over several days to weeks of preoperative outpatient management. If surgery is more urgent, rapid acting agents can be administered to allow effective control in a matter of minutes or hours. Beta-blockers appear to be particularly attractive agents. Continuation of preoperative antihypertensive treatment through the perioperative period is critical.’

The observational data presented in this review support the recommendations for Stages 1 and 2 hypertension. The AHA/ACC recommendations for Stage 3 hypertension are not supported by substantial data relating exclusively to patients with arterial pressures greater than 180/110 mm Hg. The best perioperative management of these patients remains unclear. The options available to the anaesthetist are: to ignore the elevated arterial pressure and to continue with anaesthesia and surgery; to institute acute treatment to control the arterial pressure; or to defer surgery for a period of weeks to allow the arterial pressure to be controlled.
High arterial pressures are associated with high levels of afterload and cardiac work. This may predispose to myocardial ischaemia and infarction, especially in the presence of coronary artery disease and left ventricular hypertrophy, and therefore simply ignoring markedly elevated arterial pressure may not be appropriate. However, there is evidence that very rapid control of arterial pressure with drugs such as sublingual nifedipine is associated with increased morbidity and mortality. Taken together, these concerns pose the dilemma that markedly raised arterial pressures and wide excursions of arterial pressure should be avoided in the perioperative period, but that dramatic acute reductions in arterial pressure may also be fraught with risk.

Observational data lend weight to these concerns. The work of Charlestone and colleagues suggests that excursions in mean arterial pressure of greater than 20% in patients with hypertension and or diabetes are associated with perioperative complications. The work of Gould and colleagues indicates that marked perioperative reductions in arterial pressure may be associated with reduced splanchnic blood flow even in the ‘well filled’ patient. The best course of action for the anaesthetist would seem to be to defer surgery to allow the arterial pressure to be treated. However, there are no trial data to suggest that this strategy reduces perioperative risk and this advice takes no account of the many issues and problems associated with cancelling an operation within 24 h of surgery. Also, if surgery is deferred to allow the arterial pressure to be treated, it is unclear for how long treatment should be given before the patient returns to have his or her operation.

Weksler and colleagues reported recently the results of a clinical trial in which patients were brought to a waiting room in the operating theatre suite, sedated with midazolam, and had their diastolic pressures measured whilst awaiting surgery. 989 patients whose diastolic arterial pressure was between 110 and 130 mm Hg immediately before surgery were entered into the trial. 589 patients were randomized to receive nifedipine 10 mg administered intranasally, while 400 patients were randomized to have their surgery postponed. Those patients in whom surgery was deferred remained in hospital until the diastolic arterial pressure was below 110 mm Hg for at least 3 consecutive days. The frequency of perioperative hypotension and hypertension was similar in the two groups, as was the incidence of tachyarrhythmias and bradyarrhythmias. There were no neurological or cardiovascular complications in either group. This study has a number of weaknesses. It was not blinded, it ran over a 9-yr period, during which many other aspects of patient management could have changed, and systolic hypertension was not studied. However, it offers no support for deferring anaesthesia and surgery to allow the arterial pressure to be treated.

We suggest that, if the patient is considered fit for surgery in other respects, their operation should not be deferred simply on account of an elevated admission arterial pressure. If the arterial pressure is consistently elevated to levels of 180 mm Hg systolic or greater or 110 mm Hg diastolic or greater, surgery may proceed, but care should be taken to ensure perioperative cardiovascular stability. Invasive arterial pressure monitoring is indicated for major procedures, and the arterial pressure should be actively managed to prevent excursions of the mean arterial pressure of greater than 20% from baseline. Monitoring should continue into the postoperative period until it is clear that the patient is cardiovascularly stable. It may be appropriate to manage the patient in a high dependency area in the immediate postoperative period. In those patients in whom there is no contraindication, perioperative beta-adrenergic block may be of value. These drugs are known to reduce perioperative myocardial ischaemia and cardiovascular complications in high-risk patients. They carry the additional merit of not producing marked arterial pressure reductions in normotensive subjects. It should be pointed out that Boersma and colleagues have produced observational data that support the widespread use of perioperative beta-adrenergic blockade, but that the available data from randomized controlled trials only provide clear support for their use in high-risk patients with demonstrable new wall motion abnormalities on dobutamine stress echocardiography.

Clinical trial data to support the use of perioperative beta-adrenergic block in other patients with cardiac disease are awaited. There may be a place for other sympatholytic therapies such as alpha-2 agonists or thoracic epidural block. The pharmacology and use of the alpha-2 agonists has been reviewed by Khan and colleagues. A meta-analysis by Rogers and colleagues suggested that neuroaxial block does offer protection from perioperative myocardial injury. The validity of this finding has been challenged and the current position remains unclear. Although Weksler and colleagues reported no problems with intranasal nifedipine administered to 589 patients immediately before surgery, we are unable to recommend its use because of the concerns expressed by Varon and colleagues.

In making clinical judgements about perioperative management, white coat hypertension is an ever-present problem. If the preoperative arterial pressure is giving cause for concern, several further readings should be obtained by someone who is competent to do so. It seems indefensible to defer planned surgery on the basis of a single arterial pressure reading. In view of the vigorous alerting reaction that can be produced by a visit from a doctor, readings obtained by an experienced nurse may be invaluable. If at all possible, the patient’s family doctor should be contacted and enquiry made about arterial pressure readings obtained in the family practitioner’s office. It must be a source of irritation for the patient and family doctor for surgery to be deferred and the patient be sent back for treatment of their arterial pressure when they have been on carefully monitored treatment for months or years and the arterial pressure is known to be well controlled.
**Addendum**

During the preparation of this review, there has been published the Seventh Report of the Joint National Committee on prevention, detection, evaluation and treatment of high arterial pressure (2003). This recognizes that the risk of cardiovascular disease begins at a pressure of 115/75 mm Hg and doubles with each increment of 20/10 mm Hg. Individuals with a systolic arterial pressure of 120–139 mm Hg or diastolic arterial pressure of 80–89 mm Hg should be considered as pre-hypertensive. The JNC VII classifies arterial pressure in adults as: normal: systolic arterial pressure greater than 120 mm Hg and diastolic arterial pressure less than 80 mm Hg; pre-hypertension: systolic arterial pressure 120–139 mm Hg or diastolic arterial pressure 80–89 mm Hg; Stage I hypertension: systolic arterial pressure 140–159 mm Hg or diastolic arterial pressure 90–99 mm Hg; Stage II hypertension: systolic arterial pressure greater than 160 mm Hg or diastolic arterial pressure greater than 100 mm Hg.

As in previous publications from the JNC, there are no recommendations or guidelines for the perioperative care of the hypertensive patient.10

**Longer version of this paper**

A longer version of this paper can be found in *British Journal of Anaesthesia* on-line as supplementary data.

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Hypertension affects > 65 million people in the United States and is one of the leading causes of death. One to two percent of patients with hypertension have acute elevations of BP that require urgent medical treatment. Depending on the degree of BP elevation and presence of end-organ damage, severe hypertension can be defined as either a hypertensive emergency or a hypertensive urgency. A hypertensive emergency is associated with acute end-organ damage and requires immediate treatment with a titratable short-acting IV antihypertensive agent. Severe hypertension without acute end-organ damage is referred to as a hypertensive urgency and is usually treated with oral antihypertensive agents. This article reviews definitions, current concepts, common misconceptions, and pitfalls in the diagnosis and management of patients with acutely elevated BP as well as special clinical situations in which BP must be controlled.

Key words: aortic dissection; β-blockers; calcium-channel blockers; clevidipine; eclampsia; fenoldopam; hypertension; hypertensive crises; hypertensive encephalopathy; labetalol; nicardipine; nitroprusside; pre-eclampsia; pregnancy

Abbreviations: ACE = angiotensin-converting enzyme; APH = acute postoperative hypertension; DBP = diastolic BP; FDA = Food and Drug Administration; JNC = Joint National Committee; MAP = mean arterial pressure; SBP = systolic BP

Hypertension is one of the most common chronic medical conditions in the United States, affecting close to 30% of the population > 20 years old. While chronic hypertension is an established risk factor for cardiovascular, cerebrovascular, and renal disease, acute elevations in BP can result in acute end-organ damage with significant morbidity. Hypertensive emergencies and hypertensive urgencies (see definitions below) are commonly encountered by a wide variety of clinicians. Prompt recognition, evaluation, and appropriate treatment of these conditions are crucial to prevent permanent end-organ damage. This article reviews our current understanding of hypertensive crises, the common misconceptions and pitfalls in its diagnosis and management, as well as pharmacotherapy and special situations that clinicians may encounter.

Definitions

The classification and approach to hypertension undergoes periodic review by the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, with the most recent report (JNC 7) having been released in 2003 (Table 1). Although not specifically addressed in the JNC 7 report, patients with a systolic BP (SBP) > 179 mm Hg or a diastolic BP (DBP) > 109 mm Hg are usually considered to be having a “hypertensive crisis.” The 1993 report of the JNC proposed an operational classification of hypertensive crisis as either “hypertensive emergencies” or “hypertensive urgencies.” This classification remains useful today. Severe elevations in BP were classified...
as hypertensive emergencies in the presence of acute end-organ damage, or as hypertensive urgencies in the absence of acute target-organ involvement. Distinguishing hypertensive urgencies from emergencies is important in formulating a therapeutic plan. Patients with hypertensive urgency should have their BP reduced within 24 to 48 h, whereas patients with hypertensive emergency should have their BP lowered immediately, although not to “normal” levels. The term malignant hypertension has been used to describe a syndrome characterized by elevated BP accompanied by encephalopathy or acute nephropathy.4 This term, however, has been removed from National and International Blood Pressure Control guidelines and is best referred to as a hypertensive emergency.

Epidemiology

Hypertensive emergencies were first described by Volhard and Fahr5 in 1914, who saw patients with severe hypertension accompanied by signs of vascular injury to the heart, brain, retina, and kidney. This syndrome had a rapidly fatal course, ending in heart attack, renal failure, or stroke. It was not, however, until 1939 when the first large study6 of the natural history of hypertensive emergencies was published. The results of this seminal article by Keith and colleagues6 revealed that untreated hypertensive emergencies had a 1-year mortality rate of 79%, with a median survival of 10.5 months. Prior to the introduction of antihypertensive medications, approximately 7% of hypertensive patients had a hypertensive emergency.7 Currently, it is estimated that 1 to 2% of patients with hypertension will have a hypertensive emergency at some time in their life.8,9

In the United States, hypertensive emergencies continue to be quite common, and the epidemiology of this disorder parallels the distribution of essential hypertension, being higher among the elderly and African Americans, with men being affected two times more frequently than women.10,11 Despite the development of increasingly effective antihypertensive treatments over the past 4 decades, the incidence of hypertensive emergencies has increased.12

The vast majority of patients presenting with a hypertensive emergency to an emergency department have a previous diagnosis of hypertension and have been prescribed antihypertensive agents.10,13 However, in many of these patients BP control prior to presentation was inadequate.13 The lack of a primary care physician, as well as the failure to adhere to prescribed antihypertensive regimens have been associated with the development of a hypertensive emergency.14,15 In some studies,15 > 50% of patients presenting to an emergency department with a hypertensive emergency were not adherent with their antihypertensive medication regimen in the preceding week. In both major metropolitan areas and smaller communities, illicit drug use has been reported14 to be a major risk factor for the development of hypertensive emergency.

Pathophysiology

Acute severe hypertension can develop de novo or can complicate underlying essential or secondary hypertension. The factors leading to the severe and rapid elevation of BP in patients with hypertensive crises are poorly understood. The rapidity of onset suggests a triggering factor superimposed on preexisting hypertension. Hypertensive crisis is thought to be initiated by an abrupt increase in systemic vascular resistance likely related to humoral vasoconstrictors.16,17 The subsequent increase in BP generates mechanical stress and endothelial injury leading to increased permeability, activation of the coagulation cascade and platelets, and deposition of fibrin. With severe elevations of BP, endothelial injury and fibrinoid necrosis of the arterioles ensue.16,17 This process results in ischemia and the release of additional vasoactive mediators generating a vicious cycle of ongoing injury. The renin-angiotensin system is often activated, leading to further vasoconstriction and the production of proinflammatory cytokines such as interleukin-6.18,19 The volume depletion that results from pressure natriuresis further simulates the release of vasoconstrictor substances from the kidney. These collective mechanisms can culminate in end-organ hypoperfusion, ischemia and dysfunction that manifests as a hypertensive emergency.

Clinical Presentation

Most patients have persistent BP elevation for years before they manifest a hypertensive emergency. The clinical manifestations of hypertensive emergency are directly related to the particular end-organ dysfunction that has occurred (Table 2).
The signs and symptoms therefore vary from patient to patient. Zampaglione and colleagues\textsuperscript{20} reported that the most frequent presenting signs in patients with hypertensive emergencies were chest pain (27%), dyspnea (22%), and neurologic deficits (21%). No particular BP threshold has been associated with the development of a hypertensive emergency. However, organ dysfunction is uncommon with a DBP < 130 mm Hg (except in children and pregnancy).\textsuperscript{21} The absolute level of BP may not be as important as the rate of increase. For example, in patients with long-standing hypertension, a SBP of 200 mm Hg or a DBP up to 150 mm Hg may be well tolerated without the development of hypertensive encephalopathy; whereas in children and pregnant women, encephalopathy may develop with a DBP of only 100 mm Hg.\textsuperscript{22}

Initial Evaluation

Patients with hypertensive emergency usually present for evaluation as a result of a new symptom complex related to their elevated BP. Patient triage and physician evaluation should proceed expeditiously to prevent ongoing end-organ damage. A focused medical history that includes the use of any prescribed or over-the-counter medications should be obtained. If the patient is known to have hypertension, their hypertensive history, previous control, current antihypertensive medications with dosing, adherence with their medication regimen, and the time from last dose are important facts to acquire prior to initiating treatment. Inquiry into the use of recreational drugs (amphetamines, cocaine, phenylcyclidine) or monoamine oxidase inhibitors should be made. Confirmation of the BP should be obtained by a physician in both arms using an appropriate-size BP cuff. The appropriate-size cuff is particularly important because the use of a cuff too small for the arm has been shown to artificially elevate BP readings in obese patients.\textsuperscript{23,24}

The physical examination should attempt to identify evidence of end-organ damage by assessing pulses in all extremities, auscultating the lungs for evidence of pulmonary edema, the heart for murmurs or gallops, the renal arteries for bruits, and performing a focused neurologic and funduscopic examination. Headache and altered level of consciousness are the usual manifestations of hypertensive encephalopathy.\textsuperscript{25,26} Focal neurologic findings, especially lateralizing signs, are uncommon in hypertensive encephalopathy, being more suggestive of a cerebrovascular accident. Subarachnoid hemorrhage should be considered in patients with a sudden onset of a severe headache. The ocular examination may show evidence of advanced retinopathy with arteriolar changes, exudates, hemorrhages, or papilledema assisting in the identification of hypertensive encephalopathy. Cardiac evaluation should aim to identify angina or myocardial infarction with the focus on clarifying any atypical symptoms such as dyspnea, cough, or fatigue that may be overlooked.\textsuperscript{10,27} On the basis of this evaluation, the clinician should be able to distinguish between a hypertensive emergency or an urgency and to formulate the subsequent plan for further diagnostic tests and treatment.

If the clinical picture is consistent with aortic dissection (severe chest pain, unequal pulses, widened mediastinum), a contrast CT scan or MRI of the chest should be obtained promptly to rule out aortic dissection. Although transesophageal echocardiography has excellent sensitivity and specificity for aortic dissection, this study should not be performed until adequate blood control has been achieved. In patients presenting with pulmonary edema, it is important to obtain an echocardiogram to distinguish between diastolic dysfunction, transient systolic dysfunction, or mitral regurgitation.\textsuperscript{28} Many patients, particularly the elderly, have a normal ejection fraction, and in such patients heart failure is due to isolated diastolic dysfunction.\textsuperscript{28} The management of these patients differs from those patients with predominant systolic dysfunction and those with transient mitral regurgitation (Table 3).

Initial Management of BP

The majority of patients in whom severe hypertension (SBP > 160 mm Hg, DBP > 110 mm Hg) is identified on initial evaluation will have no evidence of end-organ damage and thus have a hypertensive urgency. Since no acute end-organ damage is present, these patients may present for evaluation of another complaint, and the elevated BP may represent an acute recognition of chronic hypertension. In these patients, utilizing oral medications to lower the BP gradually over 24 to 48 h is the best approach to management. Rapid reduction of BP may be associated with significant morbidity in hypertensive ur-
gency due to a rightward shift in the pressure/flow autoregulatory curve in critical arterial beds (cerebral, coronary, renal). Rapid correction of severely elevated BP below the autoregulatory range of these vascular beds can result in marked reduction in perfusion causing ischemia and infarction. Therefore, although the BP must be reduced in these patients, it must be lowered in a slow and controlled fashion to prevent organ hypoperfusion.

Altered autoregulation also occurs in patients with hypertensive emergency, and since end-organ damage is present already, rapid and excessive correction of the BP can further reduce perfusion and propagate further injury. Therefore, patients with a hypertensive emergency are best managed with a continuous infusion of a short-acting, titratable antihypertensive agent. Due to unpredictable pharmacodynamics, the sublingual and IM route should be avoided. Patients with a hypertensive emergency should be managed in an ICU with close monitoring. For those patients with the most severe clinical manifestations or with the most labile BP, intraarterial BP monitoring may be prudent. There are a variety of rapid-acting IV agents that are available for use in patients with hypertensive emergency, and the agent of choice depends on the clinical presentation (Table 3). The preferred agents include labetalol, esmolol, nicardipine, and fenoldopam. Phentolamine and trimethaphan camsylate are less commonly used today; however, they may be useful in particular situations such as catecholamine-induced hypertensive crises (e.g., pheochromocytoma). Sodium nitroprusside may be used in patients with acute pulmonary edema and/or severe left ventricular dysfunction and in patients with aortic dissection. Oral and sublingual nifedipine are potentially dangerous in patients with hypertensive emergencies and are not recommend. Clonidine and angiotensin-converting enzyme (ACE) inhibitors are long acting and poorly titratable; however, these agents may be useful in the management of hypertensive urgencies. ACE inhibitors are contraindicated in pregnancy. Clevidipine is a relatively new agent under investigation for the management of postoperative hypertension and hypertensive emergencies. At this time, clevidipine is not available in the United States for use outside of clinical

### Pharmacologic Agents Used in the Treatment of Hypertensive Emergencies

A number of drugs are available for the management of hypertensive emergency. The agent of choice in any particular situation will depend on the clinical presentation (Table 3). The preferred agents include labetalol, esmolol, nicardipine, and fenoldopam. Phentolamine and trimethaphan camsylate are less commonly used today; however, they may be useful in particular situations such as catecholamine-induced hypertensive crises (e.g., pheochromocytoma). Sodium nitroprusside may be used in patients with acute pulmonary edema and/or severe left ventricular dysfunction and in patients with aortic dissection. Oral and sublingual nifedipine are potentially dangerous in patients with hypertensive emergencies and are not recommend. Clonidine and angiotensin-converting enzyme (ACE) inhibitors are long acting and poorly titratable; however, these agents may be useful in the management of hypertensive urgencies. ACE inhibitors are contraindicated in pregnancy. Clevidipine is a relatively new agent under investigation for the management of postoperative hypertension and hypertensive emergencies. At this time, clevidipine is not available in the United States for use outside of clinical
trials. The recommended IV antihypertensive agents are reviewed briefly below. Dosage and adverse effects of commonly used parenteral antihypertensive medications are listed in Table 4.

**Labetalol**

Labetalol is a combined selective α1-adrenergic and nonselective β-adrenergic receptor blocker with an α- to β-blocking ratio of 1:7.36 Labetalol is metabolized by the liver to an inactive glucuronide conjugate.37 The hypotensive effect of labetalol begins within 2 to 5 min after its IV administration, reaching a peak at 5 to 15 min following administration, and lasting for about 2 to 4 h.37,38 Due to its β-blocking effects, the heart rate is either maintained or slightly reduced. Unlike pure β-adrenergic blocking agents that decrease cardiac output, labetalol maintains cardiac output.39 Labetalol reduces the systemic vascular resistance without reducing total peripheral blood flow. In addition, the cerebral, renal, and coronary blood flow are maintained.39–42 This agent has been used in the setting of pregnancy-induced hypertensive crisis because little placental transfer occurs mainly due to the negligible lipid solubility of the drug.39

Labetalol may be administered as loading dose of 20 mg, followed by repeated incremental doses of 20 to 80 mg at 10-min intervals until the desired BP is achieved. Alternatively, after the initial loading dose, an infusion commencing at 1 to 2 mg/min and titrated up to until the desired hypotensive effect is achieved is particularly effective. Bolus injections of 1 to 2 mg/kg have been reported to produce precipitous falls in BP and should therefore be avoided.43

**Nicardipine**

Nicardipine is a second-generation dihydropyridine derivative calcium-channel blocker with high vascular selectivity and strong cerebral and coronary vasodilatory activity. The onset of action of IV nicardipine is from 5 to 15 min, with a duration of action of 4 to 6 h. IV nicardipine has been shown to reduce both cardiac and cerebral ischemia.44 The nicardipine dosage is independent of the patient’s weight, with an initial infusion rate of 5 mg/h, increasing by 2.5 mg/h every 5 min to a maximum of 15 mg/h until the desired BP reduction is achieved.21 A useful therapeutic benefit of nicardipine is that the agent has been demonstrated to increase both stroke volume and coronary blood flow with a favorable effect on myocardial oxygen balance.44–48 This property is useful in patients with coronary artery disease and systolic heart failure.

**Esmolol**

Esmolol is an ultrashort-acting cardioselective, β-adrenergic blocking agent.49–51 The onset of action of this agent is within 60 s, with a duration of action of 10 to 20 min.49–51 The metabolism of esmolol is via rapid hydrolysis of ester linkages by RBC esterases and is not dependant on renal or hepatic function. Due to its pharmacokinetic properties, some authors21 consider it an “ideal β-adrenergic blocker” for use in critically ill patients. This agent is available for IV use both as a bolus and as an infusion. Esmolol is particularly useful in severe postoperative hypertension.52–56 Esmolol is a suitable agent in situations in which cardiac output, heart rate, and BP are increased. Typically, the drug

<table>
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<tr>
<th>Agents</th>
<th>Dosage</th>
<th>Adverse Effects</th>
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<tr>
<td>Enalaprilat</td>
<td>1.25 mg over 5 min every 4 to 6 h, titrate by 1.25-mg increments at 12- to 24-h intervals to maximum of 5 mg q 6 h</td>
<td>Variable response, potential hypotension in high renin states, headache, dizziness</td>
</tr>
<tr>
<td>Esmolol</td>
<td>500 μg/kg loading dose over 1 min, infusion at 25 to 50 μg/kg/min every 10 to 20 min to maximum of 300 μg/kg/min</td>
<td>Nausea, flushing, first-degree heart block, infusion site pain</td>
</tr>
<tr>
<td>Fentolodopam</td>
<td>0.1 μg/kg/min initial dose, 0.05 to 0.1 μg/kg/min increments to maximum of 1.6 μg/kg/min</td>
<td>Nausea, headache, flushing</td>
</tr>
<tr>
<td>Labetalol</td>
<td>20-mg initial bolus, 20- to 80-mg repeat boluses or start infusion at 2 mg/min with maximum 24-h dose of 300 mg</td>
<td>Hypotension, dizziness, nausea/vomiting, paresthesias, scalp tingling, bronchospasm</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>5 mg/h, increase at 2.5 mg/h increments every 5 min to maximum of 15 mg/h</td>
<td>Headache, dizziness, flushing, nausea, edema, tachycardia</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5 μg/min, titrated by 5 μg/min every 5 to 10 min to maximum of 60 μg/min</td>
<td>Headache, dizziness, tachyphylaxis</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.5 μg/kg/min, increase to maximum of 2 μg/kg/min to avoid toxicity</td>
<td>Thiocyanate and cyanide toxicity, headache, nausea/vomiting, muscle spasm, flushing</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>1- to 5-mg boluses, maximum 15-mg dose</td>
<td>Flushing, tachycardia, dizziness, nausea/vomiting</td>
</tr>
</tbody>
</table>
is administered as a 0.5 to 1 mg/kg loading dose over 1 min, followed by an infusion starting at 50 μg/kg/min and increasing up to 300 μg/kg/min as necessary.

**Fenoldopam**

Fenoldopam is unique among the parenteral BP agents because it mediates peripheral vasodilation by acting on peripheral dopamine-1 receptors. Fenoldopam is rapidly and extensively metabolized by conjugation in the liver, without participation of cytochrome P-450 enzymes. The onset of action is within 5 min, with the maximal response being achieved by 15 min. The duration of action is from 30 to 60 min, with the pressure gradually returning to pretreatment values without rebound once the infusion is stopped. No adverse effects have been reported. An initial starting dose of 0.1 μg/kg/min is recommended. Fenoldopam improves creatinine clearance, urine flow rates, and sodium excretion in severely hypertensive patients with both normal and impaired renal function. The use of fenoldopam as a prophylactic agent to prevent contrast-induced nephropathy has been disappointing.

**Nitroprusside**

Sodium nitroprusside is an arterial and venous vasodilator that decreases both afterload and preload. Nitroprusside decreases cerebral blood flow while increasing intracranial pressure, effects that are particularly disadvantageous in patients with hypertensive encephalopathy or following a cerebrovascular accident. In patients with coronary artery disease, a significant reduction in regional blood flow (coronary steal) can occur. In a large randomized, placebo-controlled trial, nitroprusside was shown to increase mortality when infused in the early hours after acute myocardial infarction (mortality at 13 weeks, 24.2% vs 12.7%). Nitroprusside is a very potent agent, with an onset of action of seconds, a duration of action of 1 to 2 min, and a plasma half-life of 3 to 4 min. Due to its potency, rapidity of action, and the development of tachyphylaxis, we recommend intraarterial BP monitoring. In addition, sodium nitroprusside requires special handling to prevent its degradation by light. These factors limit the use of this drug.

Nitroprusside contains 44% cyanide by weight. Cyanide is released nonenzymatically from nitroprusside, the amount generated being dependent on the dose of nitroprusside administered. Cyanide is metabolized in the liver to thiocyanate. Thiocyanate is required for this reaction. Thiocyanate is 100 times less toxic than cyanide. The thiocyanate generated is excreted largely through the kidneys. Cyanide removal therefore requires adequate liver function, adequate renal function, and adequate bioavailability of thiosulfate. Nitroprusside may therefore cause cytotoxicity due to the release of cyanide with interference of cellular respiration. Cyanide toxicity has been documented to result in "unexplained cardiac arrest," coma, encephalopathy, convulsions, and irreversible focal neurologic abnormalities. The current methods of monitoring for cyanide toxicity are insensitive. Metabolic acidosis is usually a preterminal event. In addition, a rise in serum thiocyanate levels is a late event and not directly related to cyanide toxicity. RBC cyanide concentrations (although not widely available) may be a more reliable method of monitoring for cyanide toxicity. An RBC cyanide concentration > 40 nmol/mL results in detectable metabolic changes. Levels > 200 nmol/L are associated with severe clinical symptoms, and levels > 400 nmol/mL are considered lethal. Data suggest that nitroprusside infusion rates > 4 μg/kg/min, for as little as 2 to 3 h may lead to cyanide levels in the toxic range. The recommended doses of nitroprusside of up to 10 μg/kg/min results in cyanide formation at a far greater rate than human beings can detoxify. Sodium nitroprusside has also been demonstrated to cause cytotoxicity through the release of nitric oxide, with hydroxyl radical and peroxynitrite generation leading to lipid peroxidation.

Considering the potential for severe toxicity with nitroprusside, this drug should only be used when other IV antihypertensive agents are not available and then only in specific clinical circumstances and in patients with normal renal and hepatic function. The duration of treatment should be as short as possible, and the infusion rate should not be > 2 μg/kg/min. An infusion of thiosulfate should be used in patients receiving higher dosages (4 to 10 μg/kg/min) of nitroprusside.

**Clevidipine**

Clevidipine is third-generation dihydropyridine calcium-channel blocker that has been developed for use in clinical settings in which tight BP control is crucial. Clevidipine is an ultrashort-acting selective arteriolar vasodilator. Clevidipine acts by selectively inhibiting the influx of extracellular calcium through the L-type channel, relaxing smooth muscle of small arteries, and reducing peripheral vascular resistance. Similar to esmolol, it is rapidly metabolized by RBC esterases; thus, its metabolism is not affected by renal or hepatic function. Clevidipine reduces BP by a direct and selective effect on arterioles, thereby reducing afterload without affect-
ing cardiac filling pressures or causing reflex tachycardia.35 Stroke volume and cardiac output usually increase. Moreover, clevidipine has been shown to protect against ischemia/reperfusion injury in an animal model of myocardial ischemia and to maintain renal function and splanchic blood flow.87–89

Several small trials90,91 have shown clevidipine to be very effective in the control of postoperative hypertension. Although no studies have investigated the role of this drug in hypertensive emergencies, its profile makes it a potentially ideal drug for this indication. At this time, clevidipine is not available in the United States for use outside of clinical trials.

Nifedipine, nitroglycerin, and hydralazine are not recommended in the management of hypertensive emergencies. The basis of these recommendations are discussed below.

Nifedipine

Nifedipine has been widely used via oral or sublingual administration in the management of hypertensive emergencies, severe hypertension associated with chronic renal failure, postoperative hypertension, and pregnancy-induced hypertension. Although nifedipine has been administered via the sublingual route, the drug is poorly soluble and is not absorbed through the buccal mucosa. It is however rapidly absorbed from the GI tract after the capsule is broken/dissolved.92 This mode of administration has not been approved by the US Food and Drug Administration (FDA). A significant decrease in BP is usually observed 5 to 10 min after nifedipine administration, with a peak effect from 30 to 60 min, and a duration of action of approximately 6 to 8 h.93

Sudden uncontrolled and severe reductions in BP accompanying the administration of nifedipine may precipitate cerebral, renal, and myocardial ischemic events that have been associated with fatal outcomes.94 Elderly hypertensive patients with underlying organ impairment and structural vascular disease are more vulnerable to the rapid and uncontrolled reduction in arterial pressure. Given the seriousness of the reported adverse events and the lack of any clinical documentation attesting to a benefit, the use of nifedipine capsules for hypertensive emergencies and “pseudoemergencies”4 should be abandoned. The Cardiorenal Advisory Committee of the FDA has concluded that the practice of administering sublingual/oral nifedipine should be abandoned because this agent is not safe nor efficacious.95

Nitroglycerin, Hydralazine, and Diuretics

Nitroglycerin is a potent venodilator and only at high doses affects arterial tone.96 It causes hypoten-

sion and reflex tachycardia, which are exacerbated by the volume depletion characteristic of hypertensive emergencies. Nitroglycerin reduces BP by reducing preload and cardiac output; undesirable effects in patients with compromised cerebral and renal perfusion. Low-dose administration (approximately 60 mg/min) may, however, be used as an adjunct to IV antihypertensive therapy in patients with hypertensive emergencies associated with acute coronary syndromes or acute pulmonary edema.

Hydralazine is a direct-acting vasodilator. Following IM or IV administration, there is an initial latent period of 5 to 15 min followed by a progressive and often precipitous fall in BP that can last up to 12 h.97,98 Although the circulating half-life of hydralazine is only approximately 3 h, the half-time of its effect on BP is approximately 10 h.99,100 Because of the prolonged and unpredictable antihypertensive effects of hydralazine and the inability to effectively titrate its hypotensive effect, it is best avoided in the management of hypertensive crises.

Volume depletion is common in patients with hypertensive emergencies, and the administration of a diuretic together with a hypertensive agent can lead to a precipitous drop in BP. Diuretics should be avoided unless specifically indicated for volume overload, as occurs in renal parenchymal disease or coexisting pulmonary edema.

Special Conditions

Acute Aortic Dissection

Aortic dissection should be considered a likely diagnostic possibility in patients presenting to the emergency department with acute chest pain and elevated BP. Left untreated, approximately three fourths of patients with type A dissection (ascending aorta) die within 2 weeks of an acute episode, but with successful therapy the 5-year survival rate is 75%.30,101 Hence, timely recognition of this disease entity coupled with urgent and appropriate management is the key to a successful outcome in the majority of these patients. It is important to recognize that the propagation of the dissection is dependent not only on the elevation of the BP itself but also on the velocity of left ventricular ejection.30,31,101–103

A vasodilator alone is not ideal in the treatment of acute aortic dissection because this can promote reflex tachycardia, increase aortic ejection velocity, and promote dissection propagation. The combination of a β-adrenergic antagonist and vasodilator is the standard approach to treatment.30,31 Esmolol is the β-adrenergic antagonist of choice with metoprolol as a suitable alternative.104,105 Although nitroprus-
side has traditionally been used as the vasodilator of choice, nicardipine or fenoldopam are less toxic, equally effective alternatives. All patients with aortic dissection require cardiovascular surgical consultation to determine if surgical management is necessary. Unless significant medical comorbidities are present, surgery is indicated for all patients with type A dissection. Patients with type B dissections and distal aortic dissections can be managed with aggressive BP control because outcomes have been shown to be the same with either medical or surgical treatment unless complications such as leak, rupture, or impaired flow to vital organs supervene.

Cerebrovascular Accidents

The vast majority of patients with cerebral ischemia present with acutely elevated BP regardless of the subtype of infarct or preexisting hypertension. The BP elevation decreases spontaneously over time. The elevated BP is not a manifestation of a hypertensive emergency but rather a protective physiologic response to maintain cerebral perfusion pressure to the vascular territory affected by ischemia. Lowering the BP in patients with ischemic strokes may reduce cerebral blood flow, which because of impaired autoregulation, may result in further ischemic injury. The common practice of “normalizing” the BP following a cerebrovascular accident is potentially dangerous. It should be noted that the Intravenous Nimodipine West European Trial for acute stroke was stopped because of increased neurologic deterioration in the treatment group, which the investigators attributed to the effects of hypotension.

The American Stroke Association and the European Stroke Initiative guidelines recommend withholding antihypertensive therapy for acute ischemic stroke unless there is planned thrombolysis, evidence of concomitant noncerebral acute organ damage, or if the BP is excessively high, arbitrarily chosen as a SBP > 220 mm Hg or a DBP > 120 mm Hg based on the upper limit of normal autoregulation. In these patients, the aim is to reduce the pressure by not more than 10 to 15% in the first 24 h. Semplicini and colleagues demonstrated that a SBP by not more than 10 to 15% in the first 24 h. In these patients, the aim is to reduce the Hg based on the upper limit of normal autoregulation. Chosen as a SBP damage, or if the BP is excessively high, arbitrarily with the BP is currently recommended only when the SBP is > 200 mm Hg, the DBP is > 110 mm Hg or the MAP is > 130 mm Hg. A study has demonstrated that the rapid decline of BP within the first 24 h after presentation of an intracranial hemorrhage was associated with increased mortality; the rate of decline in BP was independently associated with increased mortality. Nicardipine has been demonstrated to be an effective agent for the control of BP in patients with intracerebral hemorrhage.

Preeclampsia and Eclampsia

Hypertension is one of the most common medical disorders affecting pregnancy. It complicates 12% of pregnancies and is responsible for 18% of maternal deaths in the United States. The presentation of a patient with pregnancy-induced hypertension may result in further ischemic injury. The common practice of “normalizing” the BP following a cerebrovascular accident is potentially dangerous. It should be noted that the Intravenous Nimodipine West European Trial for acute stroke was stopped because of increased neurologic deterioration in the treatment group, which the investigators attributed to the effects of hypotension.

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range from a mild to a life-threatening disease process.\textsuperscript{128} Initial therapy of preeclampsia includes volume expansion, magnesium sulfate (MgSO\textsubscript{4}) for seizure prophylaxis and BP control.\textsuperscript{129–131} Delivery is the definitive treatment for preeclampsia and eclampsia.

Magnesium sulfate is usually administered as a loading dose of 4 to 6 g in 100 mL 5\% dextrose in 1/4 normal saline solution over 15 to 20 min, followed by a constant infusion of 1 to 2 g/h of MgSO\textsubscript{4} depending on urine output and deep tendon reflexes, which are checked on an hourly basis. The next step in the management of preeclampsia is to reduce the BP to a safe range being diligent to avoid significant hypertension. The objective of treating severe hypertension is to prevent intracerebral hemorrhage and cardiac failure without compromising cerebral perfusion or jeopardizing uteroplacental blood flow, which is already reduced in many women with preeclampsia.\textsuperscript{128} Studies\textsuperscript{132–134} of women with mild preeclampsia have shown no benefit to antihypertensive therapy (labetalol or calcium-channel blockers) and suggested that antihypertensive therapy may increase the risk of intrauterine growth retardation. Antihypertensive therapy is therefore administered primarily to prevent complications in the mother. The Working Group Report on High Blood Pressure in Pregnancy\textsuperscript{135} recommends initiation of antihypertensive therapy for a DBP $\geq$ 105 mm Hg. Furthermore, most authorities and the current guidelines from the American College of Obstetricians and Gynecologists\textsuperscript{128,135–138} recommend keeping SBP from 140 to 160 mm Hg and DBP from 90 to 105 mm Hg. This recommendation is supported by a study\textsuperscript{139} that demonstrated that SBP > 160 mm Hg was the most important factor associated with a cerebrovascular accident in patients with severe preeclampsia and eclampsia. This would suggest that SBP from 155 to 160 mm Hg should be the primary trigger to initiate antihypertensive therapy in a patient with severe preeclampsia or eclampsia.\textsuperscript{139,140} It should be noted that patients with preeclampsia/eclampsia may have a very labile BP; this fact together with the narrow target BP range dictate that these patients be closely monitored in an ICU, preferably with an arterial catheter. Intracerebral hemorrhage is a devastating complication in these patients that can be avoided by scrupulous attention to BP control.

No antihypertensive medication is specifically approved by the FDA for use in pregnant women. Hydralazine has been recommended as the drug of choice to treat severe preeclampsia and eclampsia since the early 1970s.\textsuperscript{141} However, hydralazine has a number of properties that make it unsuitable for this indication. Its side effects (such as headache, nausea, and vomiting) are common and mimic symptoms of deteriorating preeclampsia. Most importantly, however, it has a delayed onset of action, an unpredictable hypotensive effect, and a prolonged duration of action. These properties may result in a precipitous hypotensive overshoot compromising both maternal cerebral blood flow and uteroplacental blood flow. Indeed, in a metaanalysis published by Magee and colleagues,\textsuperscript{142} hydralazine was associated with an increased risk of maternal hypotension that was associated with an excess of cesarean sections, placental abruptions, and low Apgar scores. Based on the available data, we suggest that hydralazine not be used as first-line treatment of severe hypertension in pregnancy. Similarly, sublingual or oral nifedipine should be avoided in this setting. Our preference is IV labetalol or nicardipine, which are easier to titrate and have a more predictable dose response than hydralazine. Both agents appear to be safe and effective in hypertensive pregnant patients.\textsuperscript{143–149} Nitroprusside and ACE inhibitors are contraindicated in pregnant patients.

**Sympathetic Crises**

The most commonly encountered sympathetic crises are related to the recreational use of sympathomimetic drugs such as cocaine, amphetamine, or phencyclidine. Rarely, these crises may be seen with pheochromocytoma, patients receiving a monoamine oxidase inhibitor who ingest a tyramine-containing food, or patients who abruptly stop antihypertensive medications such as clonidine or $\beta$-adrenergic antagonists.

In the clinical situations characterized by sympathetic overstimulation, $\beta$-adrenergic antagonists should be avoided to prevent vascular $\beta$-receptor antagonism resulting in unopposed $\alpha$-adrenergic activity and potential increase in BP. In fact, in cocaine-induced hypertensive emergency, the use of $\beta$-adrenergic blockade can increase coronary vasoconstriction, fail to control heart rate, increase BP, and decrease survival.\textsuperscript{150–152} Interestingly, although labetalol is traditionally considered the ideal agent due to its $\alpha$- and $\beta$-adrenergic antagonism, experimental studies\textsuperscript{153–157} do not support its use in this clinical setting. BP control is best achieved with nicardipine, fenoldopam, or verapamil in combination with a benzodiazepine.\textsuperscript{152,158,159} Phentolamine is an alternative agent.\textsuperscript{160}

**Acute Postoperative Hypertension**

Acute postoperative hypertension (APH) has been defined as a significant elevation in BP during the immediate postoperative period that may lead to serious neurologic, cardiovascular, or surgical-site
Complications and that requires urgent management. Despite the widespread and long-standing recognition of APH, there is no agreement in the literature on a more precise quantitative definition. APH has an early onset, being observed within 2 h after surgery in most cases and is typically of short duration, with most patients requiring treatment for ≤ 6 h. Postoperative complications of APH may include hemorrhagic stroke, cerebral ischemia, encephalopathy, myocardial ischemia, myocardial infarction, cardiac arrhythmia, congestive cardiac failure with pulmonary edema, failure of vascular anastomoses, and bleeding at the surgical site. Although APH may occur following any major surgery, it is most commonly associated with cardiothoracic, vascular, head and neck, and neurosurgical procedures. The pathophysiologic mechanism underlying APH is uncertain and may vary with the surgical procedure and other factors. However, the final common pathway leading to hypertension appears to be activation of the sympathetic nervous system, as evidenced by elevated plasma catecholamine concentrations in patients with APH. The primary hemodynamic alteration observed in APH is an increase in afterload with an increase in SBP and DBP with or without tachycardia. There is no consensus concerning the treatment threshold for the management of noncardiac surgery patients with APH. Treatment is frequently a bedside decision by the anesthesiologist or surgeon that takes into consideration the baseline BP, concomitant disease, and the perceived risk of complications. In contrast, in cardiac surgery patients, treatment is recommended for a BP > 140/90 or a MAP of at least 105 mm Hg. Pain and anxiety are common contributors to BP elevations and should be treated before administration of antihypertensive therapy. Other potentially reversible causes of APH include hypothermia with shivering, hypoxemia, hypercarbia, and bladder distension. Short-term administration of a short-acting IV agent is recommended when there is no identifiable treatable cause of hypertension. Labetalol, esmolol, nicardipine, and clevidipine have proven effective in the management of APH.

The best clinical setting to achieve this BP control is in the ICU, with the use of titratable IV hypotensive agents. There are several antihypertensive agents available including esmolol, nicardipine, labetalol, and fenoldopam. While sodium nitroprusside is a rapid-acting and potent antihypertensive agent, it may be associated with significant toxicity and should therefore be used in select circumstances at a dose not to exceed 2 μg/kg/min. The appropriate therapeutic approach of each patient will depend on the clinical presentation of the patient. Agents such as nifedipine and hydralazine should be abandoned because these agents are associated with significant toxicities and/or side effect profile.

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Conclusions

Patients with hypertensive emergencies require the immediate reduction of the elevated BP to prevent and arrest progressive end-organ damage. The best clinical setting to achieve this BP control is in the ICU, with the use of titratable IV hypotensive agents. There are several antihypertensive agents available including esmolol, nicardipine, labetalol, and fenoldopam. While sodium nitroprusside is a rapid-acting and potent antihypertensive agent, it may be associated with significant toxicity and should therefore be used in select circumstances at a dose not to exceed 2 μg/kg/min. The appropriate therapeutic approach of each patient will depend on the clinical presentation of the patient. Agents such as nifedipine and hydralazine should be abandoned because these agents are associated with significant toxicities and/or side effect profile.


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Perioperative Management of Chronic Heart Failure

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Heart failure (HF) is one of the few cardiac conditions that is increasing. Despite a better understanding of how hormones and other signaling systems underlie the pathophysiology, and despite improved outcomes from pharmacologic therapy, many HF patients receive no effective treatment. Patients with HF commonly require medical diagnosis and management in operating rooms and critical care units; thus anesthesiologists are obliged to remain up-to-date both with advances in outpatient (chronic) medical management and with inpatient treatments for acute exacerbations of HF. Accordingly, we reviewed angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-adrenergic receptor blockers, and aldosterone antagonists because these drugs prolong life and are included in current clinical practice guidelines for treating patients with chronic HF. We also reviewed the implications of chronic HF for patients undergoing surgery and anesthesia and discuss how best to provide intensive treatment for acute exacerbations of symptoms, such as might be caused by excessive intravascular volume, inappropriate drug “holidays,” or worsening of the underlying cardiac disease.

C hronic heart failure (HF), a clinical syndrome in which abnormalities of ventricular function and neurohormonal regulation lead to pulmonary venous congestion, exercise intolerance, and decreased life expectancy, remains the one major cardiovascular (CV) disorder that has increased both in incidence and prevalence in recent years (1). Chronic HF affects nearly five million persons in the United States, where roughly 550,000 new cases are diagnosed annually. Currently, 1% of those 50–59 yr of age and 10% of those older than 80 yr have HF (2). Thus HF is primarily a disease of the elderly, and its prevalence will likely increase two- to threefold over the next decade as the median age of world populations increases (3). The increasingly prolonged survival of patients with various CV disorders that culminate in left ventricular dysfunction (e.g., acute mortality after myocardial infarction has declined) adds to the HF epidemic. Treatment of HF costs the United States an estimated $38 billion annually (4), and it contributes to approximately 250,000 deaths per year (5). Given the rapid evolution of standard therapy and the frequency with which chronic HF patients present to the operating room and intensive care unit, anesthesiologists are obliged to know contemporary “best practices” to make appropriate diagnostic and treatment choices and appropriate judgments about the need for cardiac consultations.

We review the medical management of chronic HF, focusing on the results of large-scale, randomized clinical trials and on consensus guidelines published by the American College of Cardiology (ACC), the American Heart Association (AHA), the Heart Failure Society of America, and the European Society of Cardiology (6–8). These trials and guidelines emphasize chronic HF associated with left ventricular systolic dysfunction; nevertheless, we will also discuss HF with preserved systolic function (or diastolic HF). We also review the management of acutely decompensated HF. Finally, this review does not focus on the acute HF that appears for the first time during or after cardiac surgery, as the mechanisms and treatments of this condition are quite different from chronic HF.

HF CLASSIFICATION

The updated ACC/AHA guidelines for evaluating and managing HF include a new, four-stage classification system emphasizing the progression of the disease(Fig. 1). The new guidelines include patients with “preclinical” stages of HF with the hope of slowing (and perhaps reversing) progression of disease. The staging system is meant to complement, not replace, the widely used New York Heart Association (NYHA) classification, which is organized according

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to severity of symptoms. The latter remains useful because severity of symptoms has a robust correlation with survival and quality of life (9). The ACC/AHA classification system recognizes the progressive course of HF and identifies those at risk, reinforcing the importance of neurohormonal antagonism in an attempt to arrest disease progression.

HF may result from coronary artery disease, hypertension, valvular heart disease, or any of a long list of cardiomyopathies, in which progression of the underlying disease produces symptomatic or asymptomatic left ventricular dysfunction (specifically, left ventricular systolic dysfunction for the purposes of this discussion). The neurohormonal responses to impaired cardiac performance (sympathetic stimulation, salt and water retention, and vasoconstriction) are initially adaptive but over time become maladaptive, resulting in pulmonary congestion and excessive afterload. The end result is a vicious cycle of increased and inefficient cardiac energy expenditure and worsened pump function and tissue perfusion. The renal and peripheral circulatory consequences to the neurohormonal responses in HF provided the theoretical basis for treatment with diuretics, vasodilators, and positive inotropes (10,11).

Our understanding of treatment for patients with chronic HF changed in the 1990s when clinical trials showed that angiotensin-converting enzyme (ACE) inhibitors (12,13) and angiotensin receptor blockers (ARB) (14,15), but not most other vasodilators (16), prolonged survival. Similarly, certain β-adrenergic blockers, despite negative inotropic effects, were found to improve morbidity and mortality in adequately powered, randomized, clinical trials (17–19). More recently, small doses of aldosterone antagonists added to conventional therapy for HF have reduced mortality in patients with severe HF (20,21). These accumulated outcome results support evidence from basic investigations showing that angiotensin II is a growth factor as well as a vasoconstrictor and that antagonizing this mediator accomplishes more than mere hemodynamic improvement (22). Growth factor actions of angiotensin II have been confirmed in models of inflammation, cancer, metabolic syndrome, and atherosclerosis. In a recent clinical study, increased angiotensin II receptor density was associated with increased tumor angiogenesis and poorer survival in patients with ovarian cancer (23). Overall, these data have promoted a shift in focus from renal and circulatory processes toward cardiac remodeling as the underlying mechanism of progression in HF (24). Although it is not entirely clear how the hemodynamic and neurohormonal factors interact to cause maladaptive cardiac remodeling and progression to HF, there is evidence to suggest that increased energy expenditure, increased wall stress, altered calcium regulatory function of the sarcoplasmic reticulum, altered cardiac gene expression, increased oxidative stress, myocyte necrosis, and apoptosis are involved (25) (Fig. 2).

With these underlying pathophysiologic concepts in mind, we will review the major classes of drugs that are used to treat HF, emphasizing those drugs that improve survival in chronic HF. However, even though the descriptions of each drug class are independent, clinical management of real patients will often require regimens that include multiple drugs. This will become obvious in the descriptions of recent clinical trials where “conventional therapy” will include 3 classes of drugs with the presence or absence of the “newest” drug being the only variable under study.

**INHIBITORS OF THE RENIN-ANGIOTENSIN SYSTEM**

**ACE Inhibitors**

**Mechanism(s) of Action**

ACE inhibitors inhibit the protease that cleaves the decapetide angiotensin-I to form the octapeptide angiotensin-II. Because ACE also metabolizes bradykinin, ACE inhibitors increase circulating and tissue concentrations of bradykinin, which is thought to underlie the side effects of these drugs, including cough and angioedema (Fig. 3). ACE inhibitors have several useful actions in chronic HF. They are potent vasodilators because they decrease concentrations of angiotensin-II and norepinephrine and increase concentrations of bradykinin, nitric oxide (NO), and prostacyclin (26). They reduce the secretion of aldosterone and antidiuretic hormone, thereby reducing salt and water reabsorption by the kidney, and they promote binding of angiotensin-I to receptors on nerve terminals, reducing norepinephrine release from sympathetic nerves. Within tissue, ACE inhibitors limit the production of angiotensin-II, attenuating angiotensin-II-mediated ventricular and vascular remodeling.

**Clinical Evidence**

The abundant evidence supporting the benefits from use of ACE inhibitors in chronic HF patients is summarized in Table 1. Initially, ACE inhibitors were evaluated for treatment of symptomatic HF (these clinical trials went by the acronyms of SOLVD, V-HeFT, and CONSENSUS). Patients with NYHA Class II–IV HF treated with ACE inhibitors had 16% to 31% reduced risk of mortality. In later trials, ACE inhibitors also improved outcome for asymptomatic patients with left ventricular systolic dysfunction in the following categories: patients with ejection fractions (EF)
<35% resulting from cardiomyopathy (27), patients with EF <40% 2 wk after myocardial infarction (28), and patients presenting within the first 24 h of myocardial infarction regardless of EF (29). Results from the Heart Outcomes Prevention Evaluation (HOPE) study have further expanded the indications for ACE inhibitors to include prevention of new onset HF in asymptomatic, high-risk patients (30). In this trial of patients with either diabetes or peripheral vascular disease and an additional atherosclerotic risk factor (but without HF or systolic dysfunction), ramipril (10 mg/day) reduced the new occurrence of HF by 23% over a mean 4.5-yr treatment interval.

Together, these data expand the use of ACE inhibitors as first-line preventive therapy for a broad spectrum of patients, including those with left ventricular systolic dysfunction with or without symptoms (Class B–D) and those high-risk patients with vascular disease and/or diabetes, in addition to patients with the traditional risk factors for coronary artery disease (Class A). Interestingly, retrospective data from the SOLVD and V-HeFT (Vasodilator Heart Failure trials) suggest that renin-angiotensin-aldosterone system (RAAS) inhibition, particularly with ACE inhibitors, may not be as effective in the African-American HF patient as in Caucasians. In SOLVD, there was no ethnic difference in the efficacy of enalapril for reducing mortality and preventing the development of HF, but enalapril was more effective for Caucasians in reducing hospitalizations. Moreover, in V-HeFT-II, enalapril was more effective than the combination of isosorbide dinitrate and hydralazine for Caucasians in reducing mortality but not in African-Americans. Data from the A-HeFT (African American Heart Failure Trial) showed a survival benefit in African American HF patients treated with BiDil (n = 518), a fixed-dose combination of isosorbide dinitrate (60 up to 120 mg) and hydralazine (112.5 up to 225 mg) in 3 divided doses versus placebo (n = 532), added to standard background RAS blockade (31).

Nevertheless, one should only cautiously initiate ACE inhibitor therapy in patients with low initial blood pressures (BP) (systolic blood pressures ≤80 mm Hg), marked renal dysfunction (serum creatinine levels ≥3.0 mg/dL), serum potassium concentrations ≥5.5 mMol/L, renal artery stenosis, or left ventricular outflow tract obstruction. ACE inhibitors are contraindicated in patients who are pregnant, have a history of porphyria, are in cardiogenic shock, or who have had a severe reaction (e.g., angioedema or anuric renal failure) to members of this drug class. As noted earlier (Fig. 1 and Table 1), ACE inhibitors are administered both to slow the progression of clinical HF through ACE inhibitor-mediated vasodilatory action and to inhibit the cellular mechanisms responsible for progression of HF.

**Perioperative Implications**

Anesthetic drugs, surgical procedures, patient positioning on the operating table, and blood loss influence the RAAS and the sympathetic nervous system (SNS) (32). Controversy remains whether chronic ACE inhibitor therapy should be continued or withdrawn preoperatively. Patients treated with ACE-I are prone to hypotension with induction and maintenance of general anesthesia, most likely as a result of intravascular volume deficits and the inability of angiotensin-II to counterbalance the usual anesthetic effects on the SNS (including increased venous pooling of blood, reduced cardiac output, and reduced arterial BP) (33–35). Ryckwaert and Colson (34) report a 22% incidence of severe hypotension in patients who received ACE-I until the
day of surgery. Instability of BP and heart rate after induction of anesthesia was much the same in patients receiving chronic ACE inhibitor therapy regardless of whether there was left ventricular systolic dysfunction. There are multiple case reports about hypotension in patients treated with ACE inhibitors who are also receiving general, spinal, epidural, or combined general-epidural techniques (36), and it remains unclear whether any specific anesthetic technique is more or less likely than others to show adverse interactions in patients. Long-term ACE inhibitor treatment does not exaggerate the BP decrease associated with spinal anesthesia, perhaps because vasopressin and norepinephrine concentrations remain sufficient to compensate for the inhibited RAAS (37). Although temporary withdrawal of ACE inhibitors may prevent or attenuate intraoperative hypotension and hypovolemia, the recovery of RAS control on BP may be at the expense of impaired regional circulation. Boldt et al. (38) showed, in 88 randomized cardiac surgical patients, that administration of IV enalapril after anesthetic induction until commencement of cardiopulmonary bypass (CPB) resulted in lower levels of cardiac enzyme release than clonidine, enoximone, or placebo. Perioperative ACE-I administration may also protect the

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Population</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Heart Failure SOLVD (treat)* | Enalapril             | NYHA Class II–III (EF ≤35%), Stage C            | ♥ Lower incidence of death or hospitalization for HF in enalapril group vs. placebo (48% vs. 57%)
| V-Heft II (153)        | Enalapril vs. hydralazine/isosorbide dinitrate   | NYHA II–IV, EF <45%; Stage C                        | ♥ At 2 yr, there was a decreased mortality with enalapril vs. hydralazine/isosorbide group (18% vs. 28.2%). Mortality benefit from reduction in sudden cardiac death.
| CONSENSUS†            | Enalapril             | NYHA IV, Stage D                                 | ♥ 31% decrease in mortality with enalapril vs. placebo ♥ 50% decrease in progressive HF death in enalapril vs. placebo
| Asymptomatic LV Dysfunction SOLVD (prevent)‡ | Enalapril             | NYHA I, EF ≤35%, Stage B                        | ♥ At 37 months, combined end-point of death or HF was lower in enalapril group compared with placebo (30% vs. 39%). Fewer hospitalizations for enalapril group (21% vs. 25% for placebo).
| SAVE (28)              | Captopril             | Post-MI, EF <40%, Stage B                        | ♥ 22% reduction in mortality with or without HF ♥ 25% reduction in rate of nonfatal MI ♥ 7% reduction in mortality at 30 days vs. placebo
| GISSI-3                | Lisinopril, captopril | Acute MI (with 36 h of symptoms), Stage B       |                                                                 |
| ISIS-4 (29)            |                      |                                                 |                                                                 |
| Asymptomatic High-Risk HOPE (30) | Ramipril             | History of DM, PVD, and coronary risk factors, Stage A | ♥ Significant reduction in mortality, major vascular events, and development of HF. Incidence of HF 9% vs. 11.5% (placebo). Incidence of MI, stroke, or CV-related death 14% vs. 17.8% placebo.


NYHA — New York Heart Association; EF — ejection fraction; MI — myocardial infarction; DM — diabetes mellitus; PVD — peripheral vascular disease; CV — cardiovascular.

Table 1. Selected Clinical Trials of Angiotensin-Converting Enzyme Inhibitors in Heart Failure (HF)
kidney. Aortocoronary bypass patients pretreated with captopril starting 2 days before surgery had better preserved renal plasma flow and glomerular filtration rate during CPB compared with placebo-treated patients (39). Moreover, patients undergoing aortic-abdominal surgery pretreated with a single dose of enalapril before anesthetic induction had a smaller reduction in cardiac output and glomerular filtration rate with aortic clamping and a significantly greater creatinine clearance on the first postoperative day compared with the placebo group (40). Whether the organ-protective benefits of ACE inhibitors justify their routine prophylactic administration to patients at risk requires further study.

There is overwhelming evidence of the benefit of RAS modulation in nonsurgical settings; however, the evidence supporting continuing these medications until the time of surgery is less complete and less convincing (41–43). Nevertheless, although we recognize the potential for hypotension on induction of anesthesia in patients chronically treated with an ACE inhibitor, on balance, we nevertheless suggest that anesthesiologists continue the medication. Such brief episodes of hypotension can usually be treated with modest doses of sympathomimetics (e.g., ephedrine) or α-adrenergic agonists (e.g., phenylephrine) and careful expansion of intravascular volume (39). In the rare event of hypotension refractory to these interventions either during noncardiac surgery or on weaning from CPB during cardiac surgery (44,45), the presumed ACE-I-induced decrease in catecholamine responsiveness can be managed with either small boluses (1–2 U) or an infusion of arginine vasopressin (4–6 U/h) (46). In the case of severe systemic hypotension (presumed secondary to reduced renin secretion) during spinal or epidural anesthesia, β-adrenergic stimulation with epinephrine (0.5–1 µg/min) may also be considered (47). Certainly, the problem may often be prevented by incremental administration of induction drugs and/or by selecting drugs less likely to cause hypotension (e.g., ketamine or etomidate).

Because amiodarone can increase the incidence of hypotension when combined with ACE inhibitors in anesthetized patients (48) and because ACE inhibitors combined with aprotinin may lead to a greater propensity for renal insufficiency after CPB (49)—we recognize that this may be a primary aprotinin effect (50)—hypovolemia and hypotension may pose an increased risk to these patients. If one chooses to discontinue ACE inhibitors preoperatively (e.g., for an asymptomatic HF patient without hypertension), there is no risk of rebound or other circulatory complications (51). The long-term benefits of ACE inhibitor therapy (e.g., on ventricular remodeling) will likely not be harmed by brief drug holidays. However, in cardiac surgery, Pigott et al. (52) found no reduction in the incidence of hypotension on induction of anesthesia or in the need for vasoconstrictors after CPB when ACE inhibitors were omitted before surgery.

**ARBs**

**Mechanism of Action**

Plasma concentrations of angiotensin-II and aldosterone may increase during chronic ACE inhibitor therapy because of accumulation of substrate (angiotensin I) or because of increased production through non-ACE dependent pathways such as chymase. Moreover, non-ACE-generated angiotensin-II within the myocardium contributes to left ventricular remodeling and HF progression through AT1 receptor effects. Selective AT1-blockers prevent angiotensin-II from directly causing vasoconstriction, sodium retention, and release of norepinephrine (Fig. 3). They also delay or prevent left ventricular hypertrophy and interstitial fibrosis (53). Angiotensin-type-2 receptors (AT-2) and their actions, including NO release and vasodilation, remain unaffected by AT-1 receptor blockade (Fig. 3). The putative counter-regulatory role of AT-2 receptor signaling in the heart (anti-growth and anti-fibrotic effects) and other effects that inhibit cell proliferate or promote apoptosis are of questionable clinical importance in the overall regulation of the RAS in HF (27).

**Clinical Evidence**

Outcome benefit from ARBs was first suggested in the ELITE I trial, which showed, as a secondary end-point, a significantly reduced risk of sudden death with losartan (4.8%) compared with captopril (8.7%) (54), despite there being no between-group differences in the primary end-points: renal dysfunction or hypotension. The follow-up ELITE II trial (Table 2) had greater statistical power than ELITE I, but failed to confirm that losartan was superior to captopril in reducing mortality in older patients with HF (55). Moreover, in subgroup analyses, the ELITE II trial patients receiving preexisting β-adrenergic blockers tended to have less favorable outcomes with losartan, as opposed to captopril. Two more trials, Valsartan in Heart Failure (Val-HeFT) and Candesartan in Heart Failure Assessment in Reduction of Mortality (CHARM), tested the hypothesis that ARBs plus conventional therapy (including β-adrenergic blockers, ACE inhibitors, and diuretics) for symptomatic HF would provide additional clinical benefit. The Val-HeFT study supports the use of valsartan in patients with chronic HF who are intolerant to ACE inhibitors. However, among those patients who received ACE inhibitors and β-adrenergic blockers (93% of their patient population) there was a trend toward an increased risk of death or hospitalization when valsartan was added to standard treatment (14). On the other hand, the CHARM-Added trial (56) showed safety with regard to use of candesartan in combination with ACE inhibitors and β-adrenergic blockers (15% relative risk reduction in CV-related mortality or hospitalization). In patients intolerant to ACE (Alternative group), the relative risk reduction in mortality or hospitalization was 23%. Patients with left ventricular EF >40% not receiving ACE inhibition (Preserved
group) showed no difference in CV mortality and only a small reduction in HF hospitalizations (57,58). In the CHARM-overall trial, candesartan use significantly reduced both CV-related death and hospitalizations (relative risk reduction for CV death was 16%) (15). Taken together, these studies show that ARBs are suitable alternatives to ACE inhibitors for the treatment of patients with symptomatic HF when there are side effects to ACE inhibitors (e.g., persistent coughing, angioedema, hyperkalemia, or worsening renal dysfunction) or persistent hypertension despite ACE inhibitors and/or adrenergic blockers. The available evidence is not convincing that patients with HF benefit from the addition of ARBs to standard therapy with ACE-I and/or adrenergic blockers.

Perioperative Implications

As is true with ACE inhibitors, patients chronically treated with ARBs appear more prone to hypotension with induction of anesthesia (51,59,60) and are, we presume, also more likely to require vasoconstrictors during and after separation from CPB (44) than patients receiving other antihypertensive drugs and, perhaps, even compared with patients receiving ACE inhibitors (61). Moreover, patients receiving ARBs are less responsive to conventional vasopressors such as ephedrine and phenylephrine (59), in part because of an attenuated adrenergic responsiveness (62). Omission of the ARB on the day of surgery will not likely improve CV stability because these drugs have a prolonged duration of action (63,64); however, after a drug-free interval of at least 24 h, patients will have significantly fewer episodes of hypotension than those who continue to receive their ARB therapy (65). Vasopressin and vasopressin analogs will treat intraoperative hypotension refractory to conventional drugs in ARB-treated, anesthetized patients (46,66–68). Hypotension during anesthetic induction may be accompanied by bradycardia, particularly when vagotonic drugs are used (e.g., sufentanil). Accordingly, we and others advocate administering a prophylactic dose of glycopyrrolate (0.2 mg) to elderly patients taking an ARB on a chronic basis (69).

### Table 2. Angiotensin Receptor Blocker Trial in Heart Failure (HF)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELITE II (55)</td>
<td>Losartan 50 mg every day</td>
<td>Age ≥60 yr</td>
<td>• Losartan was not better than captopril</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NYHA II-IV</td>
<td>• No difference in mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EF ≤40%</td>
<td>• Losartan was better tolerated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Losartan + beta blocker had worse outcome</td>
</tr>
<tr>
<td>Val-HeFT (14)</td>
<td>Valsartan 160 mg twice daily, or placebo</td>
<td>NYHA II-IV</td>
<td>• No difference in all-cause mortality</td>
</tr>
<tr>
<td></td>
<td>plus open label ACE-I (93%)</td>
<td>EF &lt;40%</td>
<td>• 13% significant difference in combined morbidity/mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• HF hospital decrease 27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Most benefit observed in ACE-I intolerant patients (7% of study group) with 45% reduction in combined primary end-points</td>
</tr>
<tr>
<td>CHARM</td>
<td>Candesartan 32 mg every day vs. placebo</td>
<td>NYHA II-IV</td>
<td>• 15% relative risk reduction in all-cause mortality</td>
</tr>
<tr>
<td></td>
<td>with or without open label ACE-I</td>
<td>EF ≤40%</td>
<td>• Mild reduction in HF-related hospitalizations</td>
</tr>
<tr>
<td></td>
<td>Added (56)</td>
<td></td>
<td>• 23% relative risk reduction in HF-related mortality or hospitalizations</td>
</tr>
<tr>
<td></td>
<td>Preserved (58)</td>
<td>EF &gt;40%</td>
<td>• Significant difference in all-cause mortality</td>
</tr>
<tr>
<td></td>
<td>Alternative (57)</td>
<td>EF ≤40%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall (15)</td>
<td>ACE-I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>intolerant</td>
<td></td>
</tr>
</tbody>
</table>


ACE = angiotensin-converting enzyme; NYHA = New York Heart Association; EF = ejection fraction.

### Aldosterone Receptor Antagonists

#### Mechanisms of Action

Aside from the “traditional” effects of mineralocorticoid receptor blockade (natriuresis, diuresis, and potassium retention) (70), beneficial nonrenal effects of aldosterone antagonism include decreased myocardial collagen formation (71), increased myocardial norepinephrine uptake, and decreased circulating norepinephrine levels (71), normalization of baroreceptor function, increased heart rate variability (72), reduced endothelial dysfunction, and increased basal vascular NO bioactivity (Fig. 3) (73).
Aldosterone receptor antagonists cause conservation of potassium, and hyperkalemia is a long-recognized complication (74–76).

Clinical Evidence
Two large clinical trials have demonstrated improved outcomes with aldosterone receptor antagonists in chronic HF. The Randomized Aldactone Evaluation Study (RALES) (20), including more than 1600 symptomatic HF (e.g., Stage C, NYHA 3–4) patients, showed reduced mortality with spironolactone (26 mg/day) in combination with standard therapy (ACE inhibitor, loop diuretic, and in some cases digoxin and/or β-adrenergic blocker). Regardless of age, gender, or HF etiology, the treatment group experienced a 30% reduction in all-cause mortality and in CV mortality compared with standard therapy. Because β-adrenergic blockers were used inconsistently in the RALES study (10%–20%), the relative place of aldosterone antagonists in contemporary management of HF remained unclear. Moreover, in reports subsequent to the RALES study there was a marked increase in hospital admissions and deaths related to hyperkalemia associated with spironolactone (74). Some of the concerns were addressed in the Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). Eplerenone is a new aldosterone antagonist that lacks some of spironolactone’s common side effects (most notably gynecomastia) (77). The study was conducted in more than 6600 patients with symptomatic HF 3 to 14 days post-myocardial infarction, and showed that eplerenone (25 to 50 mg/daily, in combination with ACE inhibitor, loop diuretic, and β-adrenergic blocker, significantly reduced all cause mortality, death from CV causes, and hospitalization for CV events (21). Large-scale randomized controlled trials in class A and B HF patients are lacking. Pilot data show that aldosterone inhibition improves endothelial function (73), exercise tolerance, and EF (78) and attenuates collagen formation. Laboratory studies have shown that even in the presence of ACE inhibitors and AT-1 receptor blockade, activation of aldosterone synthetase ("aldosterone escape") in the heart and vasculature leads to myocardial hypertrophy, myocardial and vascular collagen production, endothelial dysfunction, and increased sodium retention (79,80). Laboratory and clinical data suggest that aldosterone antagonists may provide organ protection (71,81). Thus, we suspect that the indications for aldosterone receptor blockers may be widened to include patients with asymptomatic systolic left ventricular dysfunction.

Perioperative Implications
Although we doubt that doses of aldosterone receptor antagonists used for HF treatment contribute to anesthetic-induced hypotension, there is no doubt that these drugs may cause life-threatening hyperkalemia. The risk of hyperkalemia is increased when aldosterone antagonists are administered in combination with other RAS blockers, preexisting renal insufficiency, diabetes, or anemia (74–76). Thus, intraoperative measurement of serum potassium would seem prudent when these conditions are present, particularly in the event of red cell transfusion.

Beta-Adrenergic Receptor Antagonists

Mechanism of Action
In chronic HF, the beneficial effects of β-adrenergic receptor blockade include improved systolic function and myocardial energetics and reversal of pathologic remodeling. A shift in substrate utilization from free fatty acids to glucose (a more efficient fuel during myocardial ischemia) may partly explain the improved energetics and mechanics (82). β-blockade also tends to offset the effects of neurohumoral activation, a central feature of both chronic HF and of major surgery with general anesthesia (83,84). Chronic neurohumoral activation leads to adverse cardiac remodeling. Heart rate, a major determinant of myocardial oxygen consumption, is reduced by β₁-receptor blockade.

Systolic dysfunction of individual myocytes is associated with up-regulation of gene expression for natriuretic peptides and fetal-like β-myosin heavy chain and increased expression of the cardiac sarcoplasmic-endoplasmic reticulum calcium uptake pump (SERCA2) and α-myosin heavy chain (the more efficient, faster, adult isoform) (85). β-blockade reverses these changes in gene expression and concurrently improves left ventricular function (86).

β-adrenergic blockade may also limit the disturbed excitation-contraction coupling and predisposition to ventricular arrhythmias associated with HF. In animal models of HF, the increases in L-type calcium currents and in cytosolic calcium concentrations that occur in response to β-adrenergic surges often result in ventricular arrhythmias and sudden death (87). These effects are likely the result of excess activation of intracellular β-adrenergic mediated pathways via cAMP and protein kinase A (PKA), ultimately leading to an “excessive phosphorylation” state.

As noted earlier, the SNS is chronically activated in the failing heart with reduced cardiac output. In this setting, excitation-contraction coupling becomes maladaptive because of “leaky” Ca²⁺ from the sarcoplasmic reticulum (SR) (Fig. 4). Protein kinase A (PKA)-hyperphosphorylated RyR2 channels cause a diastolic SR Ca²⁺ leak that, together with reduced SERCA2-mediated SR Ca²⁺ uptake (resulting from PKA-hyperphosphorylated phospholamban that inhibits SERCA2a), depletes SR Ca²⁺ and leads to contractile dysfunction of cardiac muscle (88). This depletion of SR Ca²⁺ stores may explain, in part, the reduced contractility and the predisposition to ventricular arrhythmias of
cardiac muscle in HF (89). Interestingly, studies in animal models of HF show that chronic β-blockade may reverse the PKA hyperphosphorylated state and restore normal structure and function of the RYR2 Ca\textsuperscript{2+} release channel (90). In studies after human cardiac transplantation, β-adrenergic blockade restored RYR2 function, phosphorylation, and levels of the binding proteins toward baseline, improving ventricular compliance and responses to β-adrenergic agonists (91). Besides normalizing the calcium leak, the benefit of β-adrenergic blockade in HF patients may also include a decrease in calcium-dependent apoptosis and a metabolic effect promoting improved work efficiency (92). In a dog model of HF, β-adrenergic blockade also reduced myocyte apoptosis (93). Thus, chronic β-adrenergic blockade reduces the harmful effects of excessive SNS stimulation of the heart and reverses left ventricular remodeling.

Clinical Evidence

For many years, β-adrenergic blockers were rarely given to patients with HF because of the perceived risk of decompensation from their negative inotropic effects. However, data from both human and animal studies have shown that β-adrenergic blockers improve energetics and ventricular function and reverse pathologic remodeling. Although these beneficial effects may take 3 mo or more to manifest, they have translated into improved outcomes (reduced deaths and hospitalizations) in patients with HF. This appears NOT to be a drug class effect, as not all β-adrenergic blockers improve outcomes in HF. The
available randomized trials show that metoprolol CR/XL, bisoprolol, and carvedilol (in conjunction with ACE inhibitors) reduce morbidity (hospitalizations) in symptomatic, Stage C and D (not in cardiovascular shock) HF patients (NYHA II–IV class) (Table 3) (18,19,94,95). Although β-adrenergic blocker therapy is recommended for asymptomatic HF patients (Stage A and B), there is no evidence from randomized trials to support this apparently widespread practice (96). In clinical trials, β-adrenergic blockers are initiated in small doses and increased progressively as tolerated by the patient. The goal in clinical management is to administer the doses shown to be effective for prolonging life in clinical trials, not to decrease heart rate by an arbitrary increment or to an arbitrary target value.

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 β2 adrenoceptors, are considered nonselective, have no ancillary properties, and are not recommended for HF patients. Second-generation drugs, such as metoprolol, bisoprolol, and atenolol, are relatively specific for the β1 adrenoceptor subtype but lack additional mechanisms of CV activity. Third-generation drugs, such as bucindolol, carvedilol, and labetalol, block both β1 and β2 adrenoceptors and have vasodilatory and other ancillary properties. Specifically, labetalol and carvedilol produce vasodilation by α1 adrenoceptor antagonism, whereas bucindolol produces mild vasodilation through a cyclic guanosine monophosphate (cGMP)-mediated mechanism. Carvedilol increases insulin sensitivity (97) and has antioxidant effects (98) and an affinity for β2 adrenoceptors (99,100). β2 adrenoceptors are up-regulated in HF, and their activation is thought to decrease contractility through a NO and cGMP-mediated pathway (101–104). Although it is not clear whether these ancillary properties of the third-generation β-adrenergic 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-adrenergic blockers. COMET compared carvedilol (25 mg twice daily) to metoprolol tartrate (50 mg twice daily) in symptomatic patients with EF ≤35% and demonstrated that carvedilol reduced the risk of death relative to metoprolol (all-cause mortality risk reduction: 17%; P = 0.017 and CV death risk reduction: 20%; P = 0.0004) (105). The superiority of carvedilol over metoprolol could reflect the importance of carvedilol’s ancillary effects, pharmacodynamic (e.g., half-life) differences or other, as yet unknown, differences (106). The COMET study did NOT use the long-acting metoprolol CR-XL but instead used “conventional” metoprolol. The BEST trial showed that not all β-adrenergic blockers improve outcome in HF. Bucindolol showed no benefit compared to placebo (95). Whether the selective β1-specific drugs bisoprolol and metoprolol CR/XL exert similar clinical benefits to carvedilol remains unclear. Nonetheless, based on the results of the COMET study, carvedilol is preferred to conventional metoprolol, but not metoprolol CR/XL, for HF treatment.

Most guidelines now include long-term β-adrenergic blockade for Stage B–D HF patients, except for patients with continuing decompensation (e.g., requiring IV inotropes or vasodilators), to limit disease progression and reduce mortality (Fig. 1, Table 4). Despite concerns about inhibition of hypoglycemic symptoms, β-adrenergic blockers are advocated for diabetics with HF. There is strong evidence that the benefits from triple therapy including β-adrenergic blockers, ACE-I, and aldosterone antagonists are additive (Fig. 5) (107).

### Perioperative Implications

Although there is a lack of large clinical trials of RAAS modulation in the perioperative period, such is not the case for β-adrenergic blockers. Randomized clinical trials show that these drugs should be given to prevent ischemic events and arrhythmias in high-risk cardiac patients with ischemia, arrhythmias, or hypertension or a history of these conditions and to patients with ischemia in perioperative testing submitted for noncardiac surgery (particularly vascular surgery).
Also, β-adrenergic blockers are indicated for the treatment of perioperative hypertension, ischemia, and arrhythmias identified preoperatively and previously untreated (108). Perioperative β-adrenergic blocker therapy in high-risk patients is underused (109). Nevertheless, whether β-adrenergic blockers should be newly initiated before surgery solely for management of HF remains highly speculative. Withdrawal of β-adrenergic blocker therapy from patients who have received it chronically may be particularly dangerous (108). Recent data also suggest that while initiating β-adrenergic blocker therapy may be highly advantageous for some surgical patient populations, it may be considerably less advantageous (perhaps even deleterious) for other patient populations (110).

Adjunctive Drugs

In addition to ACE inhibitors and β-adrenergic blockers, diuretics and digoxin are often prescribed for patients with left ventricular systolic dysfunction and symptomatic HF. Diuretics provide rapid symptomatic relief of HF in the acute setting, and they maximize the benefits from ACE-I and β-adrenergic blockers, which are dependent on minimization of excessive intravascular volume (16). Moreover, older hypertensive patients who use diuretics in combination with β-adrenergic blockers have lower mean pulse pressures as compared with those patients receiving β-adrenergic blockers alone (111). Widened pulse pressure is an independent predictor of adverse CV outcomes in older persons (112). Diuretics continue to have a role in the outpatient management of HF in conjunction with ACE-I, β-adrenergic blockers, and (in some cases) aldosterone antagonists even though no randomized controlled trials have demonstrated a survival benefit from diuretics in HF. Importantly, hospitalization or death from worsening HF were significantly more frequent in HF patients receiving non-potassium-sparing diuretics than those not receiving diuretics (relative risk = 1.31, 95% confidence interval, 1.09–1.57) in a large post hoc review of data from SOLVD (Studies of Left Ventricular Dysfunction) patients (113).

Digoxin continues to be useful for patients with HF and left ventricular systolic dysfunction who remain symptomatic despite receiving ACE inhibitor, β-adrenergic blocker, and diuretic. Digoxin is the only positive inotropic drug that does not increase

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### Table 4. Diastolic Heart Failure Management

<table>
<thead>
<tr>
<th>Goal</th>
<th>Management Strategy</th>
<th>Drugs/Recommended Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce the congestive state</td>
<td>Salt restriction, Diuretics (avoid reductions in CO), ACE inhibitors, Angiotensin II-receptor blockers</td>
<td>&lt;2 g of sodium/day,  Furosemide, 10–120 mg, Hydrochlorothiazide, 12.5–25 mg, Enalapril, 2.5–40 mg, Lisinopril, 10–40 mg, Candesartan, 4–32 mg, Losartan, 25–100 mg</td>
</tr>
<tr>
<td>Target underlying cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control hypertension</td>
<td>Antihypertensive drugs (&lt;130/80), Beta blockers, ACE inhibitors, AII receptor blockers according to published guidelines</td>
<td></td>
</tr>
<tr>
<td>Restore sinus rhythm</td>
<td>Cardioversion of atrial fibrillation, AV-sequential pacing</td>
<td></td>
</tr>
<tr>
<td>Prevent tachycardia</td>
<td>Beta-adrenergic blockers, calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>Prevent/treat ischemia</td>
<td>Morphine, nitrates, oxygen, aspirin angioplasty or revascularization?</td>
<td></td>
</tr>
<tr>
<td>Treat aortic stenosis</td>
<td>Aortic valve replacement</td>
<td></td>
</tr>
<tr>
<td>Target underlying mechanisms</td>
<td>(theoretical)</td>
<td></td>
</tr>
<tr>
<td>Promote regression of hypertrophy and prevent myocardial fibrosis</td>
<td>Renin-angiotensin axis blockade,</td>
<td>Enalapril, 2.5–40 mg, Lisinopril, 10–40 mg, Captopril, 25–150 mg, Candesartan, 4–32 mg, Losartan, 50–100 mg, Spironolactone, 25–75 mg, Eplerenone, 25–50 mg</td>
</tr>
</tbody>
</table>


CO = cardiac output; ACE = angiotensin-converting enzyme; AV = atrial-ventricular.
mortality in chronic HF (Fig. 4). The Digitalis Investigators Group (DIG) trial (114), enrolling more than 6500 patients with an average follow-up of 37 mo, showed that digoxin reduced the incidence of HF exacerbations but had no effect on survival. Patients with mildly symptomatic chronic HF, who were randomized to digoxin withdrawal (PROVED and RADIANCE trials), had an increased likelihood of an acute exacerbation compared with those who continued to receive digoxin (115,116). On the other hand, doubling the dose of digoxin from 0.125 to 0.25 mg daily provided no significant benefit in terms of exercise tolerance or ventricular function, suggesting that doses of digoxin should be kept small (117).

**Perioperative Implications**

Chronic treatment with diuretics can lead to hypovolemia and an imbalance of electrolytes, particularly hypokalemia. These side effects are most common in the elderly (118). Chronic diuretic therapy can lead to hypotension and arrhythmias (119) during anesthesia. However, chronic use of diuretics for the management of HF has not been associated with perioperative CV death (within 30 days of surgery) in emergency and urgent surgical patients (120). In contrast, complications of digoxin therapy can be life-threatening and often difficult to diagnose and treat, given digoxin’s narrow therapeutic index. Aggravating conditions that predispose to digoxin toxicity include hypomagnesemia, hypercalcemia, and hypokalemia, all of which may occur during the perioperative period. Treatment of digoxin toxicity, which often manifests as nausea, arrhythmias, and visual symptoms consists of correcting any underlying electrolyte imbalances, administering antiarrhythmic drugs (most commonly phenytoin), and in refractory cases, commercially prepared antibodies to digoxin (e.g., digoxin-specific Fab (Digibind; Glaxo-SmithKline, Research Triangle Park, NC), a mixture of antidigoxin Fab fragments prepared from sheep sera). Despite continuing concerns about digoxin toxicity, perioperative discontinuation of digoxin therapy remains controversial. After adjustment for the confounding effect of HF, Sear et al. (120) report that digoxin therapy was associated with an increased cardiac risk in urgent and emergent surgical patients. Given that rate and rhythm control and positive inotropy can be achieved with other drugs with shorter half-lives and less toxicity, we tend to discontinue digoxin in elderly surgical patients where age-related alterations in drug distribution and excretion may make toxicity increasingly likely (121).

**PHARMACOLOGIC TREATMENT OF DIASTOLIC HF**

Abnormal diastolic ventricular function is present in nearly all patients with symptomatic HF (122). As many as one in three patients presenting with clinical signs of chronic HF have a normal or near-normal EF (≥40%). Although the prognosis of patients with isolated diastolic HF is better than for those with systolic HF (5%–8% versus 10%–15% annual mortality), the complication rate is the same (123). The 1-yr readmission rate for patients with isolated diastolic HF approaches 50% (124).

Large randomized trials have led to the treatment guidelines for systolic HF; however, there are few completed randomized, double-blind, placebo-controlled, multicenter trials performed in patients with diastolic HF. The CHARM-Preserved Trial (58) data of 3023 patients indicate that treatment with the ARB candesartan reduces hospitalization rates but does not alter mortality in patients with diastolic HF. Findings from the I-PRESERVE (Irbesartan in HF with preserved
systolic function) (125) trial of more than 4000 subjects will likely provide conclusive data regarding the primary end-point of death and the role of ARB blockade in the management of diastolic HF. Data from the Seniors trial (126) of nebivolol in 2128 HF patients, of whom 752 had diastolic HF (EF defined as >35%), suggest that β-adrenergic blockade is equally beneficial in patients with diastolic as with systolic HF. Preliminary findings from continuing studies suggest that aldosterone antagonists may also improve exercise tolerance and quality of life in patients with diastolic HF (127,128). However, until validation from adequately powered, randomized controlled trials becomes available, the contemporary treatment of chronic diastolic HF remains empiric (Table 4).

**MANAGEMENT OF ACUTE EXACERBATIONS OF CHRONIC HF**

Patients with chronic HF may experience episodes of acutely decompensated HF, heralded by the classic symptoms of dyspnea or fatigue. These patients will require all the standard medications as outlined in previous sections (except for perhaps holding ACE-I when systolic BP <80 mm Hg), and may also require infusions of vasodilators or positive inotropic drugs (129) (Table 5).

IV vasodilators have long been used to treat the symptoms of low cardiac output in patients with decompensated chronic HF. In general, vasodilators reduce ventricular filling pressures and systemic vascular resistance while increasing stroke volume and cardiac output. Nitroglycerin is commonly used for this purpose and has been studied in numerous clinical trials (129). In addition, recombinant brain natriuretic peptide (BNP) has received regulatory approval as a drug (nesiritide), indicated for patients with acute HF and dyspnea. Nesiritide binds to A- and B-type natriuretic peptide receptors on endothelial and vascular smooth muscle cells. It produces venous and arterial dilation, with subsequent reductions in preload and afterload, through increasing cGMP. Nesiritide does not increase heart rate, and has no effect on cardiac inotropy. Nesiritide exerts diuretic and natriuretic effects and causes coronary vasodilation. It has a rapid onset of action with a distribution half-life of 2 min and a terminal elimination half-life of 18 min. Onset of the drug’s effects is later than would be predicted based on its pharmacokinetic parameters. For example, with an initial loading dose and maintenance infusion, only 60% of the reduction in pulmonary wedge pressure that will be measured at 3 h is achieved 15 min after the bolus dose (130). Clinical effects have also been observed to persist longer than would be anticipated (based on drug levels) after the drug is discontinued.

Nesiritide is metabolized by three mechanisms: endocytotic internalization by its surface receptor, hydrolysis by neutral endopeptidase, and renal excretion (minor role) (131). When initiated in the perioperative setting (e.g., post-CPB), a starting infusion dose of 0.005 µg·kg⁻¹·min⁻¹, without a bolus, is recommended to avoid hypotension in patients with increased filling pressures and low systemic vascular resistance (<800 dyne·s·cm⁻²) who might also be receiving ACE-I and β-adrenergic blockers. Studies

**Table 5. Management of Decompensated Heart Failure**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Infusions</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Furosemide</td>
<td>5–20 mg/h</td>
<td>Hyponatremia, hypokalemia, hypomagnesemia; predisposes patients to toxicity of cardiac glycosides</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Bumetanide</td>
<td>2–5 mg slow infusion</td>
<td>Hypotension, nausea, headaches, tachycardia, tolerance</td>
</tr>
<tr>
<td></td>
<td>Nitroglycerin</td>
<td>10–200 µg/min</td>
<td>Hypotension, nausea, headaches, thiocyanate poisoning</td>
</tr>
<tr>
<td>Inotropes</td>
<td>Nitroprusside</td>
<td>0.1–5 µg·kg⁻¹·min⁻¹</td>
<td>Tolerance (beta receptor down-regulation) hypotension, supraventricular and ventricular tachyarrhythmias</td>
</tr>
<tr>
<td></td>
<td>Dobutamine</td>
<td>2.5–15 µg·kg⁻¹·min⁻¹ (load, 50 µg/kg) systolic blood pressure &lt;100 mm Hg) 0.375–0.75 µg·kg⁻¹·min⁻¹</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Milrinone</td>
<td>12 µg/kg over 10 min (load); 0.1 µg·kg⁻¹·min⁻¹</td>
<td>Dose-related increase in heart rate</td>
</tr>
<tr>
<td></td>
<td>Levosimendan*</td>
<td>g/kg over 10 min</td>
<td></td>
</tr>
<tr>
<td>Vasodilator/</td>
<td>Nesiritide</td>
<td>2 µg/kg load; 0.01 µg·kg⁻¹·min⁻¹ (preferred in perioperative setting)</td>
<td>Hypotension, nausea</td>
</tr>
<tr>
<td>Diuretic/</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natriuretic</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Used for treatment of acute, decompensated heart failure in Europe.*
have shown that nesiritide reduces symptoms of acute decompensated HF similarly to nitroglycerin, including a reduction of pulmonary artery pressure, without development of acute tolerance (132). In early studies, patients receiving nesiritide experienced fewer adverse events than those receiving nitroglycerin (133). Compared with dobutamine, nesiritide was associated with fewer instances of ventricular tachycardia or cardiac arrest (134). In the ADHERE registry (135) of more than 65,000 episodes of acute decompensated HF, treatment with either nesiritide or a vasodilator was associated with a 0.59 odds ratio for mortality compared with either milrinone or dobutamine. Recent data, however, suggest that not only may nesiritide not offer a compelling safety advantage, it may also be associated with an increased incidence of adverse side effects, including renal failure and mortality, when administered to patients with acutely decompensated chronic HF (136,137). These publications prompted the Food and Drug Administration to convene an expert panel, which made several recommendations, including that nesiritide be used only for hospitalized patients with acute decompensated HF and that the drug not be used to enhance diuresis or to “protect” the kidneys (138).

Clinical trials showed that chronic treatment with positive inotropes such as inamrinone and milrinone led to increased mortality (139–141). Nevertheless, positive inotropic drugs, principally dobutamine or milrinone, have long been used to treat decompensated HF (Fig. 4). There is a lack of data supporting their discretionary administration (142), e.g., on a monthly schedule to patients awaiting cardiac transplantation to avoid the need for ventricular assist devices. Levosimendan, a new cAMP-independent positive inotrope, may prove to have no negative outcome effects when used to treat acute decompensation of chronic HF (143). Levosimendan acts by increasing myocyte sensitivity to calcium via stabilizing the calcium-bound conformation of troponin C (Fig. 5). Levosimendan also opens K_{ATP} channels in vascular smooth muscle inducing vasodilation and in cardiac muscle, where these channels may protect against ischemia (144). When compared with dobutamine, levosimendan reduced 1-mo mortality (and reduced mortality compared with placebo at 14 days (145). Calcium sensitivity is increased during systole without causing calcium overload during diastole. This results in enhanced inotropic performance and preserved diastolic performance.

When drug treatment proves unsuccessful, HF patients may require invasive therapy, including ventricular assist devices, resynchronization with biventricular pacing, coronary bypass with or without surgical remodeling, or even cardiac orthotopic transplantation (146). These important modalities are beyond the scope of this review.

Current Clinical Practice

Diagnosis

For most patients, the diagnosis of HF will have been made long before they arrive for surgery or intensive care. Current guidelines provide a helpful framework by which primary care physicians and cardiologists can make the appropriate diagnoses and follow the disease process over time (6). On the other hand, how does a perioperative physician determine quickly, conveniently, and inexpensively whether a dyspneic patient’s symptoms are the result of new or worsening HF, lung disease, or a combination of the two? Clearly the issue can be settled using the medical history and physical examination, electrocardiogram, echocardiogram, chest radiograph, and consultation with either a pulmonary medicine specialist or cardiologist. On the other hand, measurements of BNP in blood are widely used to help triage patients presenting with acute dyspnea (147). Taken together with physical examination and history, if the BNP is <100 pg/mL, then HF is highly unlikely; negative predictive value, 90%, and if the BNP level is >500 pg/mL, then HF is highly likely, positive predictive value is 90%. For BNP levels of 100–500 pg/mL, one must consider whether the baseline is increased as a result of advanced age, underlying stable left ventricular dysfunction, right ventricular failure secondary to pulmonary hypertension or acute pulmonary embolism (148,149).

Treatment

Current guidelines begin pharmacotherapy of HF with primary prevention of left ventricular dysfunction (6,7) (Fig. 1). Because hypertension and coronary artery disease are leading primary causes of left ventricular dysfunction, adequate control of both hypertension (according to the Joint National Committee-7 guidelines) (150) and hypercholesterolemia has been endorsed after encouraging results in prevention trials (151). ACE inhibitors, and possibly β-adrenergic blockers, should be initiated in diabetic, hypertensive, and hypercholesterolemia patients (AHA/ACC, Stage A HF) who are at increased risk for CV events, despite normal contractile function, to reduce the onset of new HF (HOPE trial) (30). In patients with asymptomatic left ventricular dysfunction (EF ≤ 40%) (Stage B), treatment with ACE inhibitors and β-adrenergic blockers can blunt the disease progression. In the symptomatic HF patient (Stage C), diuretics are titrated to relieve symptoms of pulmonary congestion and peripheral edema and to restore a normal state of intravascular volume (152). ACE inhibitors and β-adrenergic blockers are recommended to blunt disease progression. Although digoxin has no effect on patient survival, it may be considered in Stage C if the patient remains symptomatic despite adequate doses of ACE inhibitors and diuretics. An alternative for patients (particularly African-American patients) with systolic dysfunction
and contraindications, intolerance, or unresponsiveness to ACE inhibitors or ARBs is isosorbide dinitrate three times a day in combination with hydralazine three times a day (153) or BiDil (fixed dose combination of isosorbide dinitrate and hydralazine hydrochloride (A-HeFT trial) (31). The use of an NO donor (isosorbide) in HF heralds the new suggestion that “NO balance” may be important in the pathophysiology of HF (154).

In general, the primary treatment objectives for Stages A–C HF are: 1) improved quality of life, 2) reduced morbidity, and 3) reduced mortality. At this time, the most important way to improve long-term outcome is through inhibiting disease progression by counteracting neurohormonal effects. Pharmacologic therapy in patients with severe, decompensated HF (Stage D) is based on hemodynamic status. Symptomatic treatment with diuretics, vasodilators, and, in palliative circumstances, IV inotropic infusions is added to “standard” treatment. Finally, some of these patients may require device therapies or surgical procedures, such as cardiac transplants.

What is an anesthesiologist to do when faced with a patient with Stage D or decompensated Stage C HF who requires emergency surgery? If tracheal intubation and positive pressure ventilation are needed to manage pulmonary edema, then there is little reason to select a regional anesthesia technique. When feasible (this will be rare because these patients often cannot lie flat on the operating table), regional nerve block techniques, rather than general anesthesia or neuroaxial block techniques, may avoid intraoperative crystalloid infusions. There is no evidence basis by which to select either an induction or a maintenance anesthetic drug in these patients. We have successfully used most IV induction drugs in these patients (including thiopental, propofol, ketamine, etomidate, midazolam, and diazepam) and have seen no obvious reason to recommend any one of them over the others. Similarly, while many authors advocate maintaining anesthesia in these very sick patients using benzodiazepines and opioids, our usual practice is to maintain anesthesia with inhaled anesthetics. We find intraoperative fluid and medical management considerably more challenging than anesthetic choice in these patients. Accordingly, when HF patients must undergo major surgery, we suggest invasive arterial BP monitoring and transesophageal echocardiography (TEE) to help guide intraoperative decision-making. TEE is especially useful in diagnosing whether hypotensive episodes are the result of inadequate circulating blood volume, worsening ventricular function, or arterial vasodilation (155–157). Pulmonary artery catheters have long been used in these patients for this purpose; if TEE is not available, pulmonary artery catheters may be a useful, if controversial, alternative (158).

Large volumes of blood, colloid, or crystalloid should be used to treat hypotension in HF patients only when there is a reasonable suspicion that true hypovolemia is present. This advice may be even more important for patients receiving spinal or epidural anesthesia (in the latter case there seems to be an even greater tendency to use IV fluid/colloid/blood rather than vasoactive drugs to treat hypotension). Patients receiving loop diuretics on an outpatient basis may prove refractory to the usual IV doses of furosemide and continuous infusions of furosemide (20 mg/h) or nesiritide (0.005–0.01 μg·kg⁻¹·min⁻¹) may be needed. Finally, transfusion for perioperative anemia in a hemodynamically stable patient with a history of HF (e.g., stage C) must be approached with greater caution than usual. It is easy to produce intravascular volume overload in these patients (159).

When we consider our aging patient population in which prolonged survival with hypertension and/or coronary artery disease is expected and the better HF treatment strategies now available to them, we conclude that anesthesiologists will encounter an increasing number of patients with either a predisposition to HF (stages A and B) or a history of HF (stages C and D). Thus, knowledge of the evolving pharmacologic strategies for the management of chronic HF is essential both for patient care and for our continued credibility as perioperative physicians.

**APPENDIX**

REFERENCES


Peripartum cardiomyopathy (PPCM) is a disorder in which initial left ventricular systolic dysfunction and symptoms of heart failure occur between the last month of pregnancy and the first 5 months postpartum.1,2 Elkayam and colleagues1 described an identical clinical condition that appeared earlier in pregnancy; these women (n=23) were diagnosed with “pregnancy-associated” cardiomyopathy at 17–36 weeks of gestation, and did not differ clinically from women with the usual presentation of PPCM (n=100). Some reports of PPCM4–6 also include women who presented with first heart failure in the sixth month postpartum. All these conditions might be part of the same clinical entity, with an expanded time interval for onset of heart failure.

An essential element in diagnosis of PPCM is the demonstration of left ventricular systolic dysfunction. Because echocardiography was not available at the time of Demakis’ original description of the condition,7 specific echocardiographic measures of left ventricular systolic dysfunction have been proposed as additional criteria.8 These measures include an ejection fraction of less than 45%, fractional shortening of less than 30%, or both, and end-diastolic dimension of greater than 2.7 cm/m² body surface-area. The need for echocardiographic confirmation of left ventricular systolic dysfunction often presents a difficulty in developing countries where the necessary technology is not available. However, even in settings of poverty, echocardiographic strategies have been shown to be possible and practical.9

PPCM remains a diagnosis of exclusion. No additional specific criteria have been identified to allow distinction between a peripartum patient with new onset heart failure and left ventricular systolic dysfunction as PPCM and another form of dilated cardiomyopathy. Therefore, all other causes of dilated cardiomyopathy with heart failure must be systematically excluded before accepting the designation of PPCM. Recent observations from Haiti11 suggest that a latent form of PPCM without clinical symptoms might exist. The investigators identified four clinically normal postpartum women with asymptomatic systolic dysfunction on echocardiography, who subsequently either developed clinically detectable dilated cardiomyopathy, or improved and completely recovered heart function.

Epidemiology

Although it seems likely that women of reproductive age all over the world have some risk of developing PPCM, good data about incidence are unavailable because so few population-based registries exist. Recent reports suggest an estimated incidence of one case per 299 livebirths in Haiti,9 one case per 1000 livebirths in South Africa,12 and one case per 2289 livebirths11 to one case per 4000 livebirths in the USA.1 These more recent data from the USA suggest a higher incidence than reported in earlier studies.11,12 The reasons for this variation in incidence between countries remain unknown.

Cases of PPCM that adhere to the stated diagnostic criteria probably represent a similar disease, despite geographical variation in contributing factors. The remarkable propensity for recovery of left ventricular function observed in the diverse locations provides further evidence for a similar disease process. It should not be surprising that varying genetic pools and diverse environmental factors play parts of varying importance.
in different areas. However, cultural practices in some areas such as heavy intake of lake salt and body heating in clay beds, might precipitate pregnancy-associated heart failure that does not always fit the diagnostic criteria for PPCM.16–20

Although not clearly delineated, suggested risk factors associated with PPCM have included age, gravidity or parity, African origin, toxaemia or hypertension of pregnancy, use of tocolytics, and twin pregnancy. The incidence of these presumed risk factors reported in the three largest series of patients with PPCM3,8,9,11,21 and in Demakis and colleague’s1,22 original report of the condition are shown in the table.

Although PPCM is thought to be more prevalent in the upper and lower extremes of childbearing age, and in older women of high parity,12,23 it is important to note that 24–37% of cases may occur in young primigravid patients.1,3,9,11,12,21,22 The largest prospectively-identified case series reports, from Haiti and South Africa, did not show a disproportionate role for older age, multiparity, and long-term use of tocolytic agents in the development of PPCM. The association with race might be confounded by the observed increased frequency of PPCM in women of lower socioeconomic status.

### Aetiology

The cause and mechanism of pathogenesis of PPCM remain unknown, and many hypotheses have been proposed (figure 1).24–29 Early suggestions that nutritional disorders, such as deficiencies in selenium and other micronutrients, might contribute could not be confirmed in studies of Haitian patients with PPCM,27 although unidentified nutritional factors might exist. Because of immune-system changes related to pregnancy, associations with autoimmune mechanisms and inflammation have been studied since the 1970s. Melvin and colleagues30 proposed myocarditis as the cause for PPCM and reported a dense lymphocyte infiltrate with variable amounts of myocyte oedema, necrosis, and fibrosis in right ventricular biopsy specimens. Treatment with prednisone and azathioprine resulted in clinical improvement and loss of inflammatory infiltrate on repeated biopsies in the three patients studied. Sanderson and colleagues,31 and subsequently Midei and colleagues,32 emphasised the association between myocarditis and development of PPCM. Although their findings were intriguing, they failed to establish a causal link. Additionally, Rizeq and colleagues33 found an inflammatory component in less than 10% of biopsy samples from patients with PPCM, a proportion similar to that found in age-and-sex-matched patients with idiopathic dilated cardiomyopathy. A decade later, Felker and colleagues34 confirmed that the absence or presence of inflammation on endomyocardial biopsy tissue did not predict outcome in patients with PPCM.

A viral trigger for the development of PPCM has been postulated and investigated in several studies. Bultmann and colleagues35 identified viral genomic material in endomyocardial biopsy tissue from patients with PPCM; however, the same incidence and types of viral positivity were noted in controls. The findings of Kuhl and colleagues25 in idiopathic dilated cardiomyopathy are

<table>
<thead>
<tr>
<th></th>
<th>Haiti, 2005 (n=98)*</th>
<th>South Africa, 2005 (n=100)*</th>
<th>USA, 2005 (n=100)†</th>
<th>USA, 1971 (n=27)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31·8 (8·1, 16–51)</td>
<td>31·6 (6·6, 18–45)</td>
<td>30·7 (6·4, 16–43)</td>
<td>14 patients &gt;30, 13 patients &lt;30</td>
</tr>
<tr>
<td>Gravidity</td>
<td>4·2 (1–10)</td>
<td>3·1 (1–7)</td>
<td>2·6 (1–10)</td>
<td>8 patients (29%) G1–2, 19 patients (71%) G3</td>
</tr>
<tr>
<td>Primigravida</td>
<td>24 (24·5%)</td>
<td>20 (20%)</td>
<td>37 (37%)</td>
<td>8 (29%)</td>
</tr>
<tr>
<td>Hypertension/toxaemia</td>
<td>4 (4%)</td>
<td>2 (2%)</td>
<td>43 (43%)</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>Use of tocolytics</td>
<td>0</td>
<td>9 (9%)</td>
<td>19 (19%)</td>
<td>0</td>
</tr>
<tr>
<td>African descent</td>
<td>98 (100%)</td>
<td>100 (100%)</td>
<td>19 (19%)</td>
<td>25 (93%)</td>
</tr>
<tr>
<td>Twin pregnancy</td>
<td>6 (6%)</td>
<td>6 (6%)</td>
<td>13 (13%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>15 (15·3%)</td>
<td>15 (15%)</td>
<td>9 (9%)</td>
<td>11 (40·7%)</td>
</tr>
</tbody>
</table>

For Haiti, South Africa, and USA (2005), data are mean (SD, range) for age and mean (range) for gravidity.*Single centre prospective study. †Multicentre retrospective study, including survey questionnaire. ‡Single centre retrospective study. §Report included gravida 1–2 together as a group.

Table: Comparison of potential risk factors and mortality rates in PPCM

![Figure 1: Proposed factors investigated contributing to the pathogenesis for PPCM](#)

References for factors listed: protective signalling pathway,24 viral antigen persistence,25 stress-activated cytokines,26 autoimmunity,26 micronutrients,27 microchimerism,26 myocyte apoptosis,21,22 prolactin.24,29
more convincing evidence for the role of virus as a trigger for cardiomyopathy. The investigators demonstrated the presence of viral genomic material in endomyocardial biopsy tissue, including enterovirus (coxsackievirus), parvovirus B19, adenovirus, and herpesvirus. They also showed that clinical improvement of left ventricular systolic function was associated with viral clearing. If future results show that viruses play a part in the development of PPCM (and some forms of idiopathic dilated cardiomyopathy), endomyocardial biopsy could become increasingly important in PPCM and unexplained cardiomyopathy, especially in patients who do not improve with conventional treatment in the early weeks after diagnosis.24-27

Ansari and colleagues28 investigated the role of fetal microchimerism (fetal cells in maternal blood during and after pregnancy) in patients with PPCM. In a small sample of patients, the amount of male chromosomal DNA in maternal plasma was significantly greater in patients with PPCM than in control mothers without PPCM during the third trimester of pregnancy, at term, and in the first week postpartum. The lower concentrations of this foreign protein could possibly contribute to tolerance of the fetus, permitting successful completion of this foreign protein could possibly contribute to tolerance of the fetus, permitting successful completion of pregnancy; increased levels could theoretically lead to the initiation of autoimmune disease, including an autoimmune myocarditis.

Findings from South Africa25-27 and Haiti26-28 lend support to the hypothesis that immune activation contributes to the pathogenesis of PPCM. Sliwa and colleagues29-31 identified increased concentrations in plasma of the inflammatory cytokine tumour necrosis factor α (TNFα), C-reactive protein, and a plasma marker of apoptosis, Fas/Apo-1, in a large population of newly diagnosed patients with PPCM. Baseline concentrations of C-reactive protein correlated positively with baseline left ventricular end-diastolic and end-systolic diameters and inversely with left ventricular ejection fraction. Concentrations of Fas/Apo-1 in plasma were significantly higher in patients with PPCM than in healthy controls, and were a predictor of mortality. Concentrations of C-reactive protein in plasma can vary substantially between different ethnic groups, and as much as 40% of this variation is genetically determined.32 Hypothetically, an increase in the intensity of an inflammatory response could be one of the many factors contributing to development of PPCM. The importance of raised high-sensitivity C-reactive protein in plasma of patients with new and evolving PPCM28-34 merits additional evaluation.

A high incidence of postpartum mortality in mice with a cardiac-tissue-specific signal transducer and activator of transcription 3 (STAT 3) knockout of has been reported.35 Before death, female mutant mice presented with symptoms of heart failure, reduced cardiac function, and apoptosis. Data from this study suggested that the cardiomyocyte-specific STAT3 pathway is necessary for protection of the heart from postpartum stress, and that prolactin cleavage is crucially involved in the pathogenesis of PPCM. Additionally, data from another mouse model of PPCM suggest that apoptosis of cardiomyocytes has a causal role in PPCM, and that pharmacological inhibition of apoptosis by a caspase inhibitor might offer novel therapeutic strategies.36 The finding of raised Fas/Apo-1 in women with PPCM37 provides additional evidence for a role of apoptosis.

Warrach and colleagues38 investigated the effect and clinical relevance of PPCM on humoral immunity and evaluated the immunoglobulins (class G and subclasses G1, G2, G3) against cardiac myosin in 47 patients with PPCM from South Africa, Mozambique, and Haiti. The immunoglobulin profiles were similar in the three regions and were markedly and non-selectively present (figure 2).

Although various causes for PPCM have been proposed, including abnormal hormonal regulation, the role of innate and adaptive immune systems, and the participation of autoantibodies, progenitor dendritic cells, T and B lymphocytes, cytokines, and chemokines,39-48 so far no cause has been clearly identified. It is likely that the aetiology is multifactorial, and that the search for a cause is hampered by the rarity of this condition in the developed countries, where more research funds are available, by the lack of adherence to diagnostic guidelines, and by the heterogeneity of the populations studied.

Clinical presentation
The most common presentation of PPCM is with symptoms and signs of systolic heart failure.14-17 Clinical examination of 97 patients seen in South Africa39 over 4 years revealed a displaced hypodynamic apical impulse in 72% and gallop rhythm in 92% of the patients. Functional mitral regurgitation was present in 43%. Left ventricular hypertrophy by electrocardiographic voltage criteria was present in 66% and ST-T wave abnormalities in 96% of the patients. Additional symptoms and signs include
dependent oedema, dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea, persistent cough, abdominal discomfort secondary to passive congestion of the liver and other organs, precordial pain, and palpitations. In the later stages postural hypotension may be prominent, reflecting low cardiac output and low blood pressure.

Early signs and symptoms of heart failure can be obscured by pregnancy, because often the patient considers them to be a normal part of pregnancy. New York Heart Association (NYHA) cardiac functional classification varies from NYHA I to IV, although most frequently initial presentation is with NYHA III and IV. Sudden cardiac arrest might occur in a situation where cardiopulmonary resuscitation is neither available nor successful. Delayed diagnosis can be associated with increased morbidity and mortality. Clinicians should think of PPCM in any peripartum patient with unexplained disease. A broad index of suspicion is important, since unusual and non-heart failure presentations are also possible, as illustrated by the following evidence.

Left ventricular thrombus is common in PPCM patients with a left ventricular ejection fraction of less than 0.35. With progression of disease, four-chamber dilation may be seen, with thrombus formation in the left atrium and right ventricle. Peripheral embolisation then becomes possible to any part of the body, including arterial occlusion of the right ventricle. Peripheral embolisation then becomes possible to any part of the body, including arterial occlusion of the lower extremities with compromised circulation.

With progression of disease, four-chamber dilation may be seen, with thrombus formation in the left atrium and right ventricle. Peripheral embolisation then becomes possible to any part of the body, including arterial occlusion of the lower extremities with compromised circulation. In the left atrium, the left ventricular ejection fraction is often less than 0.3, and acute myocardial infarction secondary to coronary artery embolism is a frequent feature of co-existing pulmonary embolus, for which the patient is at risk.

A recent report identified a 5-weeks postpartum 35-year-old woman who progressively deteriorated with acute hepatic failure and was being considered for liver transplant. An echocardiogram identified dilated cardiomyopathy as the reason for heart failure with subsequent passive congestion of the liver and severe hepatic failure. Appropriate treatment led to survival and recovery from liver failure as well as complete recovery of left ventricular systolic function.

Management and prognosis

The medical management of patients with PPCM is similar to that for other forms of heart failure, and has been reviewed in detail. Treatment aims to reduce afterload and preload, and to increase contractility. Angiotensin-converting enzyme (ACE) inhibitors are usually used to reduce afterload by vasodilatation if PPCM occurs after pregnancy. Because of potential toxic effects on the fetus, hydralazine (with or without nitrates) replaces ACE inhibitors during pregnancy. β blockers are used, since high heart rate, arrhythmias, and sudden death often occur in patients with PPCM. Digitalis, an inotropic agent, is also safe during pregnancy and may help to maximise contractility and rate control, but has to be closely monitored since excessive digoxin concentrations in serum have been associated with worse outcomes in women.

Although PPCM shares many features with other forms of non-ischaemic cardiomyopathy, an important distinction is that women with PPCM have a higher rate of spontaneous recovery of ventricular function. However, in a single centre prospective study of 100 South African patients with the condition, 15% died, and only 23% recovered normal left ventricular function after 6 months of treatment, despite optimal medical therapy with ACE inhibitors and β blockers. In a longer follow-up study of prospectively identified patients in Haiti over 5 years, the mortality rate was also 15%, and 29 of 92 (31.5%) recovered normal left ventricular function. Continuing improvement was observed in the second and third years after diagnosis, confirming that the recovery phase is not limited to the first 6–12 months.

Subsequent monitoring depends on response to treatment, and includes a follow-up echocardiogram in the first several weeks to confirm improvement of left ventricular systolic function. After that, an echocardiogram is indicated about every 6 months until recovery is confirmed or a plateau is reached. The best time to discontinue ACE-inhibitors or β blockers is unknown; however, one or both of these medications should be continued for at least 1 year. Where resources exist, left ventricular assist devices and heart transplantation may be used if necessary.

Limited studies have been done with the use of immunosuppressive drugs such as azathioprine and steroids, and have shown mixed results. Use of these agents should be reserved pending further assessments, and perhaps should be restricted to patients with biopsy-proven lymphocytic myocarditis in the absence of viral particles. Recent studies in some patients with idiopathic dilated cardiomyopathy suggest a prominent role for cardiotoxic viruses. As noted previously, only one investigation to date has identified viral genomic material in endomyocardial tissue from patients with PPCM. Hence, PCR testing for a range of cardiomyotropic viruses could become important in the investigation of patients who do not improve in the early weeks following diagnosis.

Aside from their haemodynamic benefits, the angiotensin-converting enzyme inhibitors, β blockers, and angiotensin-receptor blockers may have an additional benefit to dampen an over-active immune system that plays a role in the basic pathophysiology of PPCM.
Given the potential inflammatory nature of PPCM there may also be a role for other immunomodulatory therapy. A prospective study of 59 consecutive women with PPCM reported a significant reduction in the inflammatory marker TNFα and improved outcome in patients receiving the immunomodulating agent pentoxifylline in addition to conventional therapy.64

**Long-term prognosis**

Very few studies have been done to investigate the long-term survival and recovery outcomes in patients with PPCM. Felkner and colleagues65 assessed the survival of patients with initially unexplained cardiomyopathy referred for endomyocardial biopsy Johns Hopkins hospital. Patients with PPCM seemed to have a better prognosis than those with other forms of cardiomyopathy. However, patients who died soon after diagnosis were probably not included in that study. Fett and co-workers,11 with over 5 years of echocardiographic observations, noted continuing improvement in cardiac function well beyond the initial 6–12 months after diagnosis (figure 3).

**Subsequent pregnancy and long term outcome**

One of the greatest concerns of PPCM patients is the safety of additional pregnancies. Since many patients with PPCM develop the disease during or shortly after their first pregnancy, it is especially important to be able to provide them with information about relapse. In a retrospective study, Elkayam and colleagues65 found that subsequent pregnancy in women with PPCM was associated with significant decrease in left ventricular function that resulted in clinical deterioration and even death. Symptoms of heart failure occurred in 21% of those who entered the subsequent pregnancy with normal left ventricular systolic function and 44% of those who entered the subsequent pregnancy with abnormal left ventricular systolic function. However, all deaths (three of 44, 7%) occurred in the group who entered the subsequent pregnancy with abnormal systolic function. Eventual recovery of left ventricular systolic function occurred more frequently in women who had an ejection fraction of greater than 30% at original diagnosis of PPCM.

Serial studies of left ventricular function and TNFα in prospectively-studied African patients with subsequent pregnancy after PPCM showed that deterioration of left ventricular function occurred postpartum to the subsequent pregnancy in five of six patients and was accompanied by raised concentrations of TNFα in plasma.66

In a study67 of 15 prospectively-identified Haitian patients with a subsequent pregnancy after PPCM, seven patients tolerated the subsequent pregnancy without worsening heart failure whereas eight had a relapse. Of those who relapsed, only one regained normal left ventricular systolic function during the 2-year follow-up after the subsequent pregnancy. All those who did not relapse went on to recover normal left ventricular systolic function. The longer follow-up allowed identification of both late recovery and late deterioration, again emphasising that recovery of heart function is not limited to the first 6–12 months after diagnosis or relapse.

Family-planning counselling is an important aspect of the care of patients after a diagnosis of PPCM. Subsequent pregnancy after a diagnosis of PPCM carries higher risk of relapse if left ventricular systolic function is not fully recovered first; and even with full recovery some additional risk of relapse remains.

**Implications for research**

Reliable population-based information about incidence and prevalence of PPCM is essential to the development of national and international health policies for prevention and control of this condition. These should include a genetic epidemiological design to estimate the contribution of genetic susceptibility factors to this condition. While investigation continues on the molecular basis of PPCM, controlled trials are also needed for potential new treatments—including apheresis, immunoabsorption, immunosuppression, and antiviral agents—all of which might have a role, as suggested by initial reports from research in idiopathic dilated cardiomyopathy.68–71 The promising results64 that have been obtained with pentoxifylline in a non-randomised trial need to be tested in large multicentre randomised trials with the power to assess mortality and morbidity benefits.

**Conflict of interest statement**

We declare that we have no conflict of interest.

**References**


Cardiogenic shock

Simon Topalian, MD; Fredric Ginsberg, MD, FACC; Joseph E. Parrillo, MD, FACC

Cardiogenic shock is the most common cause of death in patients hospitalized with acute myocardial infarction and is associated with a poor prognosis. More than 75% of cases are due to extensive left ventricular infarction and ventricular failure. Other causes include right ventricular infarction and papillary muscle rupture with acute severe mitral regurgitation. Activation of neurohormonal systems and the systemic inflammatory response worsens shock. To improve outcomes, cardiogenic shock needs to be diagnosed rapidly. Treatment strategies using intra-aortic balloon counterpulsation and emergency revascularization by percutaneous coronary interventions or coronary bypass surgery have been shown to improve outcomes. To decrease the incidence of cardiogenic shock, public education regarding early presentation to hospital in the course of acute chest pain is important. Emergency medical transport systems may need to take patients with complicated acute myocardial infarction to hospitals with the capability to perform urgent revascularization. (Crit Care Med 2008; 36[Suppl.]:S66–S74)

Cardiogenic shock is a life-threatening emergency and the most common cause of death in patients hospitalized with acute myocardial infarction. Studies of this condition over the past 10 yrs have changed the approach to cardiogenic shock patients so that there is now an opportunity to improve on the high mortality rate of this condition.

Definition

Cardiogenic shock (CS) is defined as persistent hypotension and tissue hypoperfusion due to cardiac dysfunction in the presence of adequate intravascular volume and left ventricular filling pressure. Clinical signs include hypotension, tachycardia, oliguria, cool extremities, and altered mental status. Hemodynamic findings are sustained hypotension with systolic blood pressure <90 mm Hg for >=30 mins, low cardiac index <2.2 L/min/m², and elevated pulmonary artery occlusion pressure >15 mm Hg (1).

Incidence and Epidemiology

CS is a major complication of myocardial infarction. The incidence of CS has remained stable over the past 3 decades despite advances in diagnostic and therapeutic modalities. In an early trial of thrombolytic therapy for acute myocardial infarction, the incidence of CS complicating acute myocardial infarction was 7.2% (2). In an observational community-wide study, the incidence of CS averaged 7.1% over a 23-yr period from 1975 through 1997 (3). In a more recent analysis of the National Registry of Myocardial Infarction (NRMI) covering the period from June 1995 through May 2004, CS developed in 8.6% of patients with acute myocardial infarction (ST-segment elevation or left bundle branch block) hospitalized in 775 U.S. hospitals with revascularization capability (4) (Fig. 1). The prognosis of CS is extremely poor. Mortality rates were reported at 50% to 80% in older series (1). In-hospital mortality in the Should we emergently revascularize Occluded Coronaries for cardiogenic shock (SHOCK) Trial Registry was 60% (5). In the NRMI data, the overall in-hospital mortality decreased from 60.3% in 1995 to 47.9% in 2004 (4).

In the NRMI database, 29% of patients with CS were in shock as they presented to hospital, and 71% developed CS after admission (4) (Fig. 1). Patients >75 yrs old were slightly more likely to present with CS. Patients were more likely to have a history of hypertension, dyslipidemia, and prior coronary angioplasty. In the SHOCK Trial Registry, the median time from onset of myocardial infarction to shock was 7 hrs (5). Rates of recurrent myocardial infarction or ischemia precipitating CS were 9.3% and 19.7%, respectively. Infarction location was anterior in 55% of cases and in multiple locations in 50% (5).

CS can occur in the setting of ST-elevation myocardial infarction (STEMI) as well as non-ST-elevation myocardial infarction (NSTEMI). In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-IIb trial, CS developed in 4.2% of STEMI and 2.5% of NSTEMI patients. In the latter group, CS tended to occur later after presentation (76.3 hrs vs. 9.6 hrs). NSTEMI patients with CS were older and had higher rates of diabetes mellitus, prior myocardial infarction, heart failure, azotemia, bypass surgery, peripheral vascular disease, and three- vessel coronary disease. In-hospital and 30-day mortality rates in STEMI and NSTEMI patients were similar (6, 7).

Patients with CS have extensive coronary artery disease. Angiographic data from the SHOCK Trial Registry revealed that 53.4% of patients had three-vessel disease and 15.5% had significant left main stenosis (8).

Etiology

Many conditions may lead to CS (Table 1). However, left ventricular failure due to extensive acute myocardial infarction remains the most common cause. In
Figure 1. Frequency of cardiogenic shock among patients in the National Registry of Myocardial Infarction. Includes total shock at hospital presentation and shock that develops after hospital presentation as a clinical event. For hospitals with open-heart surgery and percutaneous coronary intervention capability, the ST-elevation myocardial infarction population was 293,633. Data are through May 2004. Reproduced with permission from Babaev A, Frederick PD, Paste DJ, et al: Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. JAMA 2005; 294:448–454.

Table 1. Causes of cardiogenic shock

<table>
<thead>
<tr>
<th>Cause</th>
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<tbody>
<tr>
<td>Acute myocardial infarction</td>
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<tr>
<td>Pump failure</td>
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<tr>
<td>Large infarction</td>
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<tr>
<td>Smaller infarction with preexisting left</td>
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<tr>
<td>ventricular dysfunction</td>
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<tr>
<td>Infarction extension</td>
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<tr>
<td>Severe recurrent ischemia</td>
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<tr>
<td>Infarction expansion</td>
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<tr>
<td>Mechanical complications</td>
</tr>
<tr>
<td>Acute mitral regurgitation caused by</td>
</tr>
<tr>
<td>papillary muscle rupture</td>
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<tr>
<td>Ventricular septal defect</td>
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<tr>
<td>Free-wall rupture</td>
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<tr>
<td>Pericardial tamponade</td>
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<tr>
<td>Right ventricular infarction</td>
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<tr>
<td>Other conditions</td>
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<tr>
<td>End-stage cardiomyopathy</td>
</tr>
<tr>
<td>Myocarditis</td>
</tr>
<tr>
<td>Myocardial contusion</td>
</tr>
<tr>
<td>Prolonged cardiopulmonary bypass</td>
</tr>
<tr>
<td>Septic shock with severe myocardial</td>
</tr>
<tr>
<td>depression</td>
</tr>
<tr>
<td>Left ventricular outflow tract obstruction</td>
</tr>
<tr>
<td>Aortic stenosis</td>
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<tr>
<td>Hypertrophic obstructive cardiomyopathy</td>
</tr>
<tr>
<td>Obstruction to left ventricular filling</td>
</tr>
<tr>
<td>Mitral stenosis</td>
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<tr>
<td>Left atrial myxoma</td>
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<tr>
<td>Acute mitral regurgitation (chordal rupture)</td>
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<tr>
<td>Acute aortic insufficiency</td>
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<tr>
<td>Acute massive pulmonary embolism</td>
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<tr>
<td>Acute stress cardiomyopathy</td>
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<tr>
<td>Pheochromocytoma</td>
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</tbody>
</table>

Acute myocardial infarction accounted for 6.7%.

Pathophysiology

Most commonly, CS occurs after a massive and extensive myocardial infarction or severe myocardial ischemia leading to impaired left ventricular function, reduced systolic contractility, and decreased cardiac output and arterial blood pressure. Coronary perfusion will decrease and further compromise coronary reserve. Compensatory neurohormonal responses take place, which include activation of the sympathetic and renin-angiotensin systems, leading to systemic vasoconstriction, tachycardia, and fluid retention. These mechanisms are maladaptive and worsen myocardial ischemia. Thus, “ischemia begets ischemia,” leading to a progressive downward spiral of worsening ischemia, progressive deterioration of myocardial function, and worsening shock (1) (Fig. 2).

At the cellular level, inadequate oxygen delivery to myocytes affects cellular adenosine triphosphate production. Immediately, energy metabolism shifts from aerobic to anaerobic glycolysis with resultant lactic acid production. Intracellular calcium rises and intracellular sodium competes to expel calcium (9). If hypoperfusion and ischemia are severe, as occurs in CS, myonecrosis ensues with mitochondrial swelling and subsequent plasma membrane disruption.

This ischemic cascade results in metabolic and biochemical alterations, which lead to left ventricular diastolic dysfunction from impaired myocardial relaxation and decreased compliance. This leads to increased left ventricular filling pressures, manifesting as pulmonary congestion and edema. This in turn increases wall stress and further compromises coronary perfusion. Echocardiographic data from the SHOCK Trial showed that restrictive left ventricular filling, as assessed by Doppler mitral inflow deceleration time, was present in most patients (60.9%) (10). This restrictive pattern predicted pulmonary artery occlusion pressures >20 mm Hg.

New evidence has emerged that has led to expansion of the CS paradigm (11). Wide variations in left ventricular ejection fraction, left ventricular size, and systemic vascular resistance in patients with CS suggest that pathophysiologic mechanisms of CS may vary among patients. About one fifth of patients with CS complicating myocardial infarction in the SHOCK Trial had clinical evidence of a systemic inflammatory response syndrome, marked by fever, leukocytosis, and low systemic vascular resistance (12). Attempts to inhibit this inflammatory response focused on nitric oxide (NO), an endogenous vasodilator, which is produced by nitric oxide synthase (NOS). Inducible NOS (iNOS) is expressed at pathologic levels in many cells, especially myocytes, and has many deleterious effects (11). High levels of iNOS are associated with left ventricular dysfunction (13). Early work with a nonspecific inhibitor L-arginine (L-NMMA), had promising effects on the hemodynamics of patients with CS, including significantly increasing urine output and mean arterial blood pressure (14). A mortality benefit was seen in a small group of CS patients treated with this inhibitor (15) and led to larger randomized studies. However, the Tilarine Acetate Injection Randomized International Study in Unstable AMI Patients/Cardiogenic Shock (TRIUMPH) Trial, a phase III randomized trial to study the benefit of the NOS inhibitor L-NMMA in patients with cardiogenic shock complicating AMI, did not show any benefit (16).

Approach to the Patient With Cardiogenic Shock

The most important aspects of the initial care of the patient with cardiogenic shock are recognizing the condition early in its course and understanding its cause. Rapid assessment of the history, physical examination, and chest radiograph is mandatory, recognizing the signs of heart failure, pulmonary edema (sometimes with clear lung fields on examina-
Differential diagnoses to consider in patients with CS include hemorrhage, sepsis, aortic dissection, and massive pulmonary embolism. Patients must be assessed regarding the need for sedation, intubation, and mechanical ventilation in order to correct hypoxemia and reduce the work of breathing (1, 18, 19). Initial medical therapy includes intravenous fluid challenge for patients with significant hypotension, if there is no evidence for pulmonary edema or significant elevation of jugular venous pressure. If CS is due to acute myocardial infarction or ischemia, emergency cardiac catheterization and revascularization need to take place in patients believed suitable for this approach (discussed subsequently).

The use of an intra-arterial catheter is helpful in managing patients in shock (20). Pulmonary artery catheterization can assist in the precise measurement of volume status, left and right ventricular filling pressures, and cardiac output. It is also valuable in diagnosing right ventricular infarction and the mechanical complications of acute myocardial infarction (Table 2). Hemodynamic measurements can help guide fluid management and the use of inotropic agents and vaspressors.

The goal of the initial medical therapy of CS is to maintain arterial pressure adequate for tissue perfusion. Initially, dopamine is the drug of choice because it acts as an inotrope as well as a vasopressor. Intravenous norepinephrine is a more potent vasoconstrictor, with somewhat less effect on heart rate, and should be used in patients with more severe hypotension. These drugs increase heart rate and systemic vascular resistance and thus increase myocardial oxygen demand, and they may aggravate ischemia and lead to cardiac arrhythmias. Doses should be adjusted to the lowest levels that improve tissue perfusion (1, 18, 20).

Dobutamine, an inotrope with arterial dilator properties, can be used in patients with less severe hypotension or can be combined with vaspressors to improve cardiac output (18). There also have been reports of the effective use of vasopressin in patients with CS (22). Intravenous diuretics are used in patients with pulmonary edema and elevated pulmonary artery occlusion pressure. Aspirin should be given to patients with acute myocardial infarction. Intravenous amiodarone can be given for patients with severe arrhythmia. The use of β-blockers and nitrates should be avoided in the acute phase (20).

Some patients will demonstrate signs of tissue hypoperfusion with systolic blood pressure >90 mm Hg. This has been termed nonhypotensive cardiogenic shock or preshock. In the

Table 2. Hemodynamic profiles

<table>
<thead>
<tr>
<th>Condition</th>
<th>Signs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricular shock</td>
<td>High RA, RA/PAOP &gt; 0.8</td>
<td>vasopressors, inotropes</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>Large PAOP V wave</td>
<td>inotropes, diuretics</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>Large PAOP V wave, oxygen saturation step-up (&gt; 5%)</td>
<td>inotropes, diuretics</td>
</tr>
<tr>
<td>Pericardial tamponade</td>
<td>Equalization of diastolic pressures –20 mm Hg</td>
<td>inotropes, diuresis</td>
</tr>
</tbody>
</table>

PAOP, pulmonary artery occlusion pressure; CO, cardiac output; SVR, systemic vascular resistance; RA, right atrial; RV, right ventricular.
SHOCK Trial Registry, these patients demonstrated the hemodynamic profile of elevated pulmonary artery occlusion pressure with low cardiac index and high systemic vascular resistance. The hospital mortality rate in this group of patients was 43%, very high but lower than in patients diagnosed with full-blown cardiogenic shock. The mortality in patients with preshock compares with a mortality rate of 26% in patients with hypotension without signs of hypoperfusion. This preshock state needs to be recognized early so that appropriate, urgent diagnostic and therapeutic measures can be prescribed (23) (Fig. 3).

**Intra-Aortic Balloon Counterpulsation (IABP)**

IABP is very useful to support patients with CS. This device will increase coronary blood flow, decrease left ventricular afterload, and decrease left ventricular end-diastolic pressure without increasing oxygen demand (1, 19, 24). Cardiac output is increased only modestly, and this device does not provide total circulatory support (24).

The efficacy of IABP in acute myocardial infarction complicated by CS has not been evaluated in a randomized controlled trial. In nonrandomized trials, the use of IABP is associated with decreased mortality, but the use of this device is consistently associated with more frequent use of revascularization therapies and other aggressive supportive measures (25). Its use was not associated with improved survival in patients undergoing primary percutaneous coronary intervention (PCI) in the NRMI database.

Complications of IABP include bleeding, thrombocytopenia, hemolysis, leg ischemia, aortic dissection, femoral artery injury, thromboembolism, and sepsis. The complication rate has been reduced with percutaneous insertion and with smaller pumps (26). Complication rates have been reported at 10% to 30%, with major complication rates of 2.5% to

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onset of infarction, often after hospitalization who develop CS do so hours after presentation (2, 4, 5, 27). Shock that has a delayed onset results from infarction extension, reocclusion of a previously patent coronary artery, recurrent ischemia, or decompensation of left ventricular function in the noninfarcted zone because of metabolic derangements (1). The most successful strategy to successfully treat acute myocardial infarction is rapid restoration of flow in the infarct-related artery (28), and primary coronary angioplasty results in better outcomes than fibrinolytic therapy (29). Many reports have suggested that early mechanical revascularization with either PCI or coronary artery bypass graft surgery (CABG) is associated with survival benefit. The landmark SHOCK trial prospectively randomized 302 patients with CS due to acute myocardial infarction and left ventricular failure to emergency early revascularization (ERV) with PCI or CABG vs. initial medical stabilization (IMS) with drug therapy and IABP. PCI accounted for 64% of revascularization and CABG was performed in 36%. The 30-day mortality rate, the primary outcome measured, was lower in the early revascularization group (47% vs. 56%), which was not statistically significant. However, late mortality rates were significantly improved in patients who received ERV (30). At 6 months, 1 yr, and 6 yrs, a statistically significant absolute survival difference of 13% was seen in patients who received ERV (31, 32). At 6 yrs, overall survival was 32.8% in the ERV group and 19.6% in the IMS group. In patients who survived hospitalization, the 6-yr survival rate in patients with ERV was 62.4% vs. 44.4% in IMS patients. (Fig. 4) There was no significant difference in long-term survival between patients treated with PCI or CABG. Quality of life measures were also better in patients who had received ERV (33).

Unfortunately, invasive procedures continue to be underused in patients with CS (4, 5) In the NRMI, primary PCI use increased from 27.4% in 1995 to only 54.4% in 2004 (4 yrs after the SHOCK trial was published). CABG was used in only 3.2% of patients. This increased use of PCI for CS was likely translated into a mortality benefit (60.3% mortality in 1995, declining to 47.9% in 2004) (4). Patients who were transferred to hospitals with revascularization capability also had better outcome with ERV (34). This benefit from early mechanical revascularization was incorporated in the ACC/AHA practice guidelines. Both PCI and CABG are class I recommendations for patients <75 yrs old with STEMI or acute myocardial infarction with left bundle branch block, who develop shock within 36 hrs of onset of myocardial infarction (20, 35).

Patients >75 yrs old had worse outcomes with ERV in the SHOCK trial compared with IMS. However, the number of patients treated with ERV in this age group was relatively small (30–32). Analysis from the SHOCK registry showed that elderly patients were treated less aggressively, and their in-hospital mortality was higher compared with younger patients (76% vs. 55%). However, outcomes in elderly patients in the registry who were treated with ERV were better than in patients who were not revascularized (36). Clearly, patient selection plays a key role. Elderly patients with good functional status, shorter duration of shock,
and absence of serious medical comorbidities should be carefully selected for aggressive therapies, including revascularization (21).

**Fibrinolytic Therapy in Cardiogenic Shock**

Urgent transfer to the cardiac catheterization laboratory for coronary angiography and emergency coronary intervention has largely supplanted thrombolytic therapy as first-line treatment for patients with acute myocardial infarction and CS. Fibrinolytics are not as effective as accomplishing reperfusion in STEMI with CS as in patients with STEMI without cardiogenic shock (1, 18). This is hypothesized to be due to decreased penetration of the coronary thrombus by fibrinolytics in hypotensive patients, a greater incidence of coronary artery reocclusion after thrombolysis, and longer times required to achieve coronary patency (1, 18, 19). In an overview of fibrinolytic trials, analysis of patients in CS showed nonsignificant reductions in mortality with fibrinolytic therapy. Subgroup analyses in individual trials have shown no effect on mortality (18). In the NRMI database, IABP combined with thrombolytic therapy was associated with a significantly lower mortality rate (49%) compared with thrombolytic therapy alone (67%) (25). In the SHOCK Trial Registry, the addition of IABP to thrombolytic therapy decreased mortality significantly from 63% with thrombolysis alone to 47% with thrombolysis and IABP. Thrombolytic therapy was associated with a lower mortality than in patients who did not receive any reperfusion therapy (37). However, mortality in CS patients treated with fibrinolytic therapy combined with IABP was still higher than in patients who received revascularization with PCI or coronary bypass surgery.

The development of CS after fibrinolytic therapy is more likely to occur in older patients, patients with Killip class II–III heart failure on presentation, and patients with higher heart rate and lower blood pressure on admission (38). When thrombolytic therapy was given to patients with acute myocardial infarction before hospital arrival, during ambulance transport, the incidence of subsequent CS was lowered from 11.5% to 6.8% (39).

Current guidelines have relegated thrombolytic therapy for CS as a class I recommendation only in patients with STEMI who are unsuitable for invasive therapy with PCI or bypass surgery (20). In the NMRI observational database, the use of thrombolytic therapy for acute myocardial infarction and CS declined from 19.9% to 5.6% of cases in the years 1995–2004 (4). The strategy of administering fibrinolytics with or without IABP is recommended if patients present to a hospital that does not have a catheterization laboratory or when there will be unavoidable delays in transport to the catheterization laboratory (1).

**Mechanical Complications of Acute Myocardial Infarction (Figure 5)**

*Right Ventricular Infarction.* Right ventricular myocardial infarction (RVI) can accompany acute inferior wall myocardial infarction and lead to cardiogenic shock. It is estimated that 10% to 15% of inferior wall myocardial infarctions are complicated by hemodynamically significant RVI (1, 20). RVI accounted for 2.8% of cases of CS in the SHOCK Trial Registry (5). Acute right ventricular dysfunction and right ventricular failure lead to decreased left ventricular preload, decreased cardiac output, and cardiogenic shock. Right ventricular dilation and shift of the intraventricular septum toward the left ventricle can further compromise left ventricular function and worsen cardiogenic shock.

RVI results from occlusion of the right coronary artery proximal to the origin of the right ventricular branches. In the era before PCI for acute myocardial infarction, in-hospital mortality from RVI was around 7.1%, less than the mortality rate for anterior myocardial infarction but higher than that for inferior myocardial infarction without RVI (40). RVI was also an independent predictor of 6-month mortality and was associated with higher rates of CS and sustained ventricular arrhythmia.

The diagnosis of RVI should be strongly considered in patients who present with acute inferior wall myocardial infarction with hypotension, clear lung fields, and elevated jugular venous pressure or a positive Kussmaul’s sign. Diagnostic findings on electrocardiogram include >1-mm ST-segment elevation in V1 and in the right precordial lead V4R, although these findings may be transient. Emergency transthoracic echocardiogram will show a dilated, hypocontractile right ventricle and may show bulging of the septum into the left ventricle. Right heart catheterization will demonstrate a mean right atrial pressure >10 mm Hg and right atrial pressure >80% of pulmonary artery occlusion pressure. Cardiac index will be low.

Initial therapy for hypotensive patients with RVI is a fluid challenge if jugular venous pressure is not elevated. Up to 1 L of intravenous saline should be infused, which may correct hypotension. Larger volumes may cause significant right ventricular dilation and impair left ventricular output. Inotropic medica-
tions and IABP are useful in patients who do not respond to fluid challenge (20). IABP helps to decrease wall stress and increase coronary perfusion pressure (1). Bradycardia and heart block should be corrected, and atroventricular sequential pacing may be necessary to maintain atroventricular synchrony and effective cardiac output.

Most patients with RVI will have spontaneous recovery of right ventricular function, but this may occur slowly and may be incomplete. Urgent revascularization with PCI is now the cornerstone of therapy. In a study of 53 patients with acute inferior wall myocardial infarction complicated by RVI, all 53 patients underwent emergency PCI (41). The right coronary artery was the culprit vessel in all cases. Seventy-seven percent of patients had successful intervention and reperfusion, and these patients demonstrated recovery of right ventricular function, decreased right heart pressures, and reduction in right ventricular size within 1 hr, with 95% recovery of normal right ventricular function in 3–5 days. In-hospital mortality was 2.4%. In the 12 patients with unsuccessful reperfusion, right ventricular dysfunction persisted at 24 hrs and only improved slowly during hospitalization. Ten of these 12 patients required support with inotropic drugs or IABP, and in-hospital mortality was 58.3%. Emergency revascularization efforts in these patients is now a class I recommendation in ACC/AHA guidelines for the treatment of acute myocardial infarction. If coronary bypass surgery is believed to be needed for multivessel disease and significant right ventricular dysfunction is present, then coronary bypass should be delayed for 4 wks, if possible, to allow for recovery of right ventricular function (20).

Acute Severe Mitral Regurgitation. Acute severe mitral regurgitation, due to infarction and rupture of the head of a papillary muscle, is an uncommon cause of cardiogenic shock. In the SHOCK Trial Registry, 6.9% of 1,190 patients with cardiogenic shock had acute severe mitral regurgitation (5, 42). Acute severe mitral regurgitation was more likely to complicate inferior and/or posterior myocardial infarction (87% of cases of acute mitral regurgitation) than anterior myocardial infarction (34%). Acute severe mitral regurgitation usually occurs within the first 24 hrs of acute myocardial infarction or may present at days 3–5. The diagnosis of acute severe mitral regurgitation should be suspected in patients who present with acute pulmonary edema complicating acute myocardial infarction, especially inferior wall myocardial infarction. The murmur of mitral regurgitation may be loud but also may be relatively unimpressive due to high left atrial pressures and a lower left ventricular/left atrial systolic gradient. Diagnosis is made by urgent echocardiography.

Acute severe mitral regurgitation is associated with a high in-hospital mortality. In the SHOCK Trial Registry, patients who underwent urgent mitral valve surgery had a 40% mortality rate. Patients who did not receive surgery had a 71% mortality rate. The overall 55% hospital mortality rate was not different from the registry cohort with cardiogenic shock due to left ventricular failure (42).

In patients with acute severe mitral regurgitation, early diagnosis and aggressive support with inotropic drugs, IABP, and vasodilators (if blood pressure allows) are vital in appropriately selected patients. The ACC/AHA guidelines list urgent cardiac surgical repair as a class I recommendation (20).

Postinfarction Ventricular Septal Rupture. Rupture of the intraventricular septum (VSR) can complicate acute myocardial infarction and lead to CS. This often occurs in the first 24 hrs of infarction. This condition occurred in <1% of patients with STEMI in the GUSTO I study (20, 21) and accounted for 3.9% of the cases of CS in the SHOCK Trial Registry (15, 31). VSR may complicate either anterior or inferior wall STEMI. Patients will present with shock and pulmonary edema, and a loud holosystolic murmur is present on physical examination. Diagnosis is made by urgent Doppler echocardiography. A pattern of right ventricular volume overload is seen, with Doppler evidence of left-to-right shunting at ventricular level. The septal rupture may be visualized. Right heart catheterization will show higher oxygen saturations in the pulmonary artery than in the right atrium due to left-to-right shunting. However, when the diagnosis of VSR is made by echocardiography, performance of right heart catheterization should not delay surgical therapy.

Urgent surgical repair of VSR is a class I recommendation in the ACC/AHA guidelines. However, this condition is associated with a very high mortality rate with surgical or medical therapy. Waiting for several days before surgery in order to let healing occur is not recommended because many patients will die during this waiting period. In the SHOCK Trial Registry, 31 of 55 patients with VSR underwent surgery, with a mortality of 81%. Only 4% of patients survived without surgery (43). In the GUSTO I trial, 30-day mortality was 73.8% (21). Another series of 76 patients with VSR who underwent surgery reported that 79% of patients presented with CS, and 30-day postoperative mortality was 49% for these patients (44).

Left Ventricular Free Wall Rupture and Cardiac Tamponade. Left ventricular free wall rupture is an uncommon, lethal complication of acute myocardial infarction. It is estimated to occur in 1% to 6% of patients with acute myocardial infarction (20), although the true incidence is difficult to ascertain as the majority of patients will die immediately after rupture from electromechanical dissociation. However, possibly 30% of free wall rupture may be spontaneously sealed off by elevated intrapericardial pressure from hemopericardium, and these patients may present with CS complicating acute myocardial infarction. The incidence of free wall rupture has decreased in the era of thrombolytic and primary angioplasty therapy for acute myocardial infarction. The diagnosis is made by emergency echocardiography, which shows a significant-sized pericardial effusion, either loculated or diffuse, and may show the area of rupture.

In the SHOCK Trial Registry, 1.4% of cases of CS were caused by free wall rupture and usually occurred in the first 24 hrs of infarction (2, 45). Twenty-one of 28 patients underwent surgery, with a 62% mortality rate. Six patients underwent pericardiocentesis only, and three survived. Another series listed operative mortality rates of 24% to 52% (46).

Ventricular Assist Devices (VADs)

VADs have been used in small series of highly selected patients with CS refractory to IABP and reperfusion strategies. The use of VADs should be considered in patients with very low cardiac output, <1.2 L/min/m² (19). Newer VADs can be inserted percutaneously. The TandemHeart percutaneous VAD, inserted in the catheterization laboratory, uses a catheter directed into the left atrium via a transseptal puncture, unloading the left atrium and left ventricle. Blood is then pumped into a 15- to 17-Fr catheter inserted in the femoral artery, producing...
flows of 3.5–4.0 L/min. One report described 11 patients with acute myocardial infarction and CS refractory to inotropic and IABP therapy who received percutaneous VADs. These patients were supported for an average of 89 hrs, with mean cardiac index during VAD therapy of 2.6 L/min/m². It was concluded from this small series that percutaneous VADs could be effective as a bridge to implanted VADs or cardiac transplant therapy, with a low incidence of adverse effects. This device cannot be used in patients with right ventricular failure or severe peripheral vascular disease (24, 47).

Implanted VADs have also been used in patients with CS. In 49 patients treated with this device, 78% were successfully bridged to transplant. VADs were placed at an average of 6 days after myocardial infarction, and patients were supported for a mean time of 56 days until transplant. In-hospital mortality was only 33% in this group of patients (48). These patients had a 31% incidence in need for dialysis and had a relatively high rate of infectious complications. Another series of 18 patients with CS received support with extracorporeal membrane oxygenation and/or VAD and cardiac transplant therapy. In these highly selected patients, hospital mortality was 33% and 5-yr survival was 30% (49).

Prevention of CS

Since most patients who develop CS after acute myocardial infarction do so at some time after presentation to hospital, there is an opportunity to prevent the occurrence of CS in individual patients, to reduce the overall incidence of CS, and to significantly improve outcomes in patients who develop this potentially lethal complication. The first step in prevention of CS involves educating the public, encouraging patients to present to hospital very early after the development of significant chest pain or other symptoms of acute myocardial infarction. Patients should be directed to call the emergency ambulance system, so that transport to an emergency department can occur quickly. In addition, hospital transport systems need to be developed to allow patients with STEMI to be transported directly to hospitals with PCI and coronary surgery capabilities, avoiding delays inherent when acute cardiac infarction patients are admitted to hospitals without these facilities and then emergently transferred to tertiary centers. If patients receive thrombolytic therapy for acute myocardial infarction in hospitals without revascularization capabilities, signs of failed thrombolysis should be recognized early, and these patients should be transferred quickly to tertiary centers with revascularization capabilities.

In patients hospitalized with acute myocardial infarction, prompt recognition of the preshock state or the early signs of CS is vital. Once the diagnosis of CS is made, rapid evaluation and institution of supportive medical therapy, insertion of the IABP, and emergency revascularization need to be performed. Admission of patients to hospitals with revascularization capabilities, or even directly to the catheterization laboratory, has led to the greater utilization of these lifesaving therapies with improved mortality rates in several nonrandomized studies (30, 31, 50). It is unlikely that further large randomized controlled trials in patients with CS will be carried out. It is now necessary to improve systems of care in order to translate the benefits of early revascularization to widespread implementation.

REFERENCES


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