

Haemodynamic control and clinical outcomes in the perioperative setting

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Introduction

Death due to anaesthesia has become rare [1,2]. By contrast, morbid events related to anaesthetic care are more prevalent and difficult to classify. Haemodynamic changes may signal morbid events during anaesthesia. A decrease in blood pressure (BP), enabling detection of occult haemorrhage, is an obvious example of how haemodynamic monitoring contributes to the diagnosis of a morbid state. However, monitoring for BP variability outside acceptable target thresholds, because it may contribute to postoperative 30-day mortality, is a much more subtle example. It is estimated that 500 million surgeries will be performed worldwide annually by the year 2050, with approximately 2% of these in patients at high risk for the development of cardiovascular complications [3]. In the United States alone, 30 million non-cardiac surgical procedures are performed annually [4], and 2.5% to 10% of these procedures are associated with peri-operative cardiovascular morbidity and mortality [5]. Prospective and retrospective analyses have identified patient- and treatment-related factors (Table 1) that increase the risk for peri-operative complications, including mortality, myocardial infarction (MI), stroke, acute kidney injury, pulmonary embolism, atrial fibrillation, and excessive bleeding [3,6-14].

Preoperative haemodynamic abnormalities, such as increased or decreased heart rate or BP*, can adversely affect outcomes for patients undergoing either cardiac or non-cardiac procedures [5-7,13,15-19]. The risk for

adverse cardiovascular outcomes in surgical patients may be reduced by avoiding haemodynamic variability outside target parameters during the peri-operative period (Table 2) [4].

Haemodynamic control

HC has been defined as a physiologic state whereby adequate blood flow to and perfusion of organs is achieved [20]. Several parameters, including heart rate, BP, central venous pressure, pulmonary artery pressure, pulmonary artery occlusion pressure, and CO/cardiac index contribute to HC [21]. It has been suggested that BP and indices of flow or perfusion (e.g. CO/cardiac index, mixed-venous haemoglobin oxygen saturation [SvO₂]) may simply and most effectively reflect a state of HC [21]. Assessment of heart rate and BP (variously defined as systolic BP [SBP], diastolic BP [DBP], mean arterial pressure [MAP], and pulse pressure [PP]) is easily accomplished in the peri-operative setting and may provide a reasonable surrogate of adequate organ perfusion [22,23]. Furthermore, definitions of HC based on these and related parameters (Table 1) have been evaluated in prospective studies and meta-analyses [24-26].

Results from a large number of studies have shown that abnormal heart rate and BP are independent predictors of morbidity and mortality in the non-surgical setting [27-31] and also in patients undergoing cardiac and non-cardiac surgical procedures [5-7, 13, 15, 16, 18, 19, 32].

* Includes systolic BP, diastolic BP, mean arterial pressure, and pulse pressure.

Table 1: Risk factors in patients undergoing cardiac and non-cardiac surgical procedures

Cardiac Surgery	Non-cardiac Surgery
<p>Pre-operative risk factors</p> <ul style="list-style-type: none"> • Increased age • Myocardial infarction • Hypertension (systolic blood pressure, pulse pressure, diastolic blood pressure), hypotension • Tachycardia, bradycardia • Congestive heart failure • Chronic obstructive pulmonary disease • Renal failure • Diabetes mellitus requiring medication <p>Intra-operative risk factors</p> <ul style="list-style-type: none"> • Hypertension/hypotension • Tachycardia 	<p>Pre-operative risk factors</p> <ul style="list-style-type: none"> • Ischaemic heart disease • Congestive heart failure • Cerebrovascular disease • Diabetes mellitus requiring insulin therapy • Elevated serum creatinine (>2.0 mg/dL) • Hypertension <p>Intra-operative risk factors</p> <ul style="list-style-type: none"> • Tachycardia • Hypertension • High-risk surgical procedures (retroperitoneal, intrathoracic, supra-inguinal, vascular)

Data from 3,6,7,9,11-13,14

Normal BP and heart rate values in the peri-operative setting

Normal values for BP and heart rate in the peri-operative setting are not clearly defined. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) defines normal BP as SBP/DBP <120/80 mm Hg, hypertension as SBP/DBP >140/90 mm Hg, and postural hypotension as a decrease in standing SBP >10 mm Hg [33]. The JNC 7 guidelines also indicate that BP levels >180/100 mm Hg should be controlled prior to urgent surgery. However, for elective surgical procedures, control of acute hypertension can be achieved with treatment in an outpatient setting for several days to weeks prior to the procedure [34]. These guidelines, however, are written principally to guide ambulatory management, do not address nor recognize the need to achieve “acceptable targets”, and may have little, if anything, to do with management of HC in the peri-operative setting. In addition, these guidelines are not condition- or situation-specific to other patient comorbidities.

In a similar vein, normal heart rate for a healthy individual at rest may range from 60

to 100 beats per minute (bpm) [35]. However, “normal heart rate” has not been defined for the peri-operative setting. Guidelines from the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) indicate that patients undergoing elective, non-cardiac surgery should begin treatment with a β -blocker with careful titration for days to weeks prior to elective surgery to increase the likelihood of achieving benefit of β -blockade while minimizing the risk of hypotension and bradycardia. Titrated heart rate control should be continued in the intra-operative and postoperative periods to maintain a heart rate of 60 to 80 bpm in the absence of hypotension [23,36].

While some investigators have suggested acceptable ranges for heart rate (45 to 110 bpm), MAP (55 to 100 mm Hg), and SBP (80 to 160 mm Hg) in surgical patients [[37], there are few data to support such recommendations, and only recently have studies focused on the association and relationship between haemodynamic targets and outcomes.

Table 2: Benefits of peri-operative haemodynamic control

Benefit	Intervention
Decreased myocardial ischaemia	<p>β-Blockers:</p> <ul style="list-style-type: none"> • Atenolol^a [141] • Esmolol [142,143] • Labetalol^a [141] • Metoprolol [144-146] • Oxprenolol^a [141] <p>Calcium Channel Blockers:</p> <ul style="list-style-type: none"> • Diltiazem [147-150] • Verapamil [151]
Decreased cardiac death	<p>β-Blockers:</p> <ul style="list-style-type: none"> • Atenolol [4] • Bisoprolol [86]
Decreased nonfatal myocardial infarction	<p>β-Blockers:</p> <ul style="list-style-type: none"> • Atenolol [4,152] • Bisoprolol [86] • Metoprolol [153,154] <p>Calcium Channel Blocker:</p> <ul style="list-style-type: none"> • Diltiazem [147,155]
Decreased dysrhythmia	<p>β-Blockers:</p> <ul style="list-style-type: none"> • Esmolol [156,157] • Metoprolol [144,154,158]
Decreased unstable angina	<p>β-Blocker:</p> <ul style="list-style-type: none"> • Atenolol [4]
Decreased supraventricular tachyarrhythmia	<p>β-Blocker:</p> <ul style="list-style-type: none"> • Esmolol^b [159] <p>Calcium Channel Blockers:</p> <ul style="list-style-type: none"> • Diltiazem [155,160,161] • Verapamil [151,162]
Decreased congestive heart failure	<p>β-Blocker:</p> <ul style="list-style-type: none"> • Atenolol [4]
Decreased acute hypertension	<p>β-Blocker:</p> <ul style="list-style-type: none"> • Esmolol [163] <p>Calcium Channel Blocker:</p> <ul style="list-style-type: none"> • Clevidipine [97] • Diltiazem [164]
Decreased mortality/stroke/myocardial infarction/renal dysfunction ^c	<p>Calcium Channel Blocker:</p> <ul style="list-style-type: none"> • Clevidipine [97]
Decreased time between surgery and discharge	<p>β-Blocker:</p> <ul style="list-style-type: none"> • Metoprolol [153]
Increased cardiac event-free survival	<p>β-Blocker:</p> <ul style="list-style-type: none"> • Atenolol [4]
Decreased mortality	<p>β-Blocker:</p> <ul style="list-style-type: none"> • Atenolol^d 165 <p>Calcium Channel Blockers:</p> <ul style="list-style-type: none"> • Clevidipine [97] • Diltiazem [155,160] • Verapamil [162]

^aStudy results not distinguished between atenolol, labetalol, and oxprenolol. ^bEsmolol is effective for the treatment of supraventricular tachyarrhythmias in the peri-operative setting. ^cComposite of mortality, stroke, myocardial infarction, and renal dysfunction. ^dMortality 2 years following surgery.

Normal CO values in the peri-operative setting

Most individual tissues determine their own flow in proportion to need (i.e. metabolic rate, thermal rate). Brain, heart, skeletal muscle, and the splanchnic area all vary their blood flows according to local tissue metabolic rate. Summation of peripheral blood flows constitutes venous return, and thus, CO. Therefore, CO is largely determined by the metabolic rate of the peripheral tissues.

Patients undergoing cardiac surgery who are unable to sustain normal (or higher) levels of CO during the peri-operative period have substantially higher mortality rates compared with patients with low output syndrome [38-40]. The minimal normal threshold value for CO in normal patients is poorly described. Furthermore, an adequate circulatory function response to need may vary depending on the situation and other conditions, and, as a result, an optimal therapeutic goal is not always known.

The time course of haemodynamic patterns in survivors and non-survivors has been described for the postoperative period after elective surgery. Shoemaker et al [41,42] described non-survivor patterns in patients who were prospectively treated for anticipated intra-operative circulatory deficiencies. Increased cardiac index and oxygen delivery were shown to enable a protective physiologic mechanism [41,42]. They evaluated high-risk elective surgical patients (N=356) with preoperative and intra-operative haemodynamic monitoring by the pulmonary artery thermodilution catheter [41], and observed that haemodynamic patterns in non-survivors included decreased cardiac index, stroke index (SI), and left ventricular stroke work index ≥ 2 hours after the initiation of surgery, reduced oxygen delivery after the first hour of surgery, and decreased oxygen consumption during the third through sixth intra-operative hours. They also observed that low oxygen consumption was partly compensated by increased oxygen extraction rates, and arterial pressures were maintained by increas-

ing systemic vascular resistance (SVR) [41]. The authors concluded that non-survivors' changes were similar to those described during the postoperative period that preceded development of organ failure and death, and that lethal circulatory dysfunctions may begin during the intra-operative period. In addition, the authors asserted that the survivors may compensate for tissue hypoxia with higher cardiac index and oxygen delivery (DO_2) [41].

Others have drawn different conclusions with regard to defining an optimal CO threshold. Hayes and colleagues [43] studied patients returning to the intensive care unit (ICU) postoperatively with organ failure. Nine of 109 patients were resuscitated with fluid administration alone and survived [43]. The remaining 100 patients were randomly assigned to a control group or a protocol group that was administered high-dose dobutamine to achieve supranormal CO values, but without beneficial effects [43]. Gattinoni et al used supranormal values for cardiac index or SvO_2 to prevent organ failure in a large series of ICU patients with organ failure as a condition for admission [44]. No significant differences were observed in mortality or organ dysfunction with the targeted haemodynamic therapy [44].

However, findings of additional clinical trials have demonstrated a beneficial effect of targeted haemodynamic therapy. Cesanek et al [45] showed that administration of an aggressive, heart rate-targeted intravenous (IV) dosing regimen of metoprolol compared with a fixed-dose regimen (control; usual care) resulted in a significantly lower percentage of heart rate measurements >80 bpm (16.1% vs. 34.5%; $P < 0.001$), and significant reduction in absolute heart rate change ($P = 0.034$) in patients scheduled to undergo major elective vascular surgery who were at moderate or high risk for peri-operative cardiac events (cardiac risk index ≥ 2). Although no significant differences were observed in overall mean heart rate through the preoperative and initial 24 h postoperative period among the 2 regimens, the authors concluded that

an aggressive, heart rate-targeted peri-operative treatment strategy was associated with more consistent maintenance of postoperative haemodynamic parameters (i.e. heart rate) within the range recommended by current guidelines, and did not result in increased drug-related adverse events (AEs). Pölonen and colleagues [26] reported positive findings upon evaluating the effect of targeted interventions (in addition to standard clinical care) to achieve specific haemodynamic goals (e.g. SvO₂ >70% and serum lactate concentrations ≤ 2.0 mmol/L) immediately following cardiac surgery (N=403). A higher percentage of patients who received targeted therapy achieved specific haemodynamic goals (84 patients; 42.9%) compared with patients who received standard care (114 patients; 57.9%). In addition, patients who achieved haemodynamic targets as a result of the targeted therapy had significant reductions in organ dysfunction on the first postoperative morning in the ICU ($P < 0.001$), postoperative morbidity ($P < 0.001$), and mortality rate at 6 and 12 months ($p < 0.05$ for each comparison) vs. patients who did not achieve haemodynamic targets. The authors concluded that goal-directed haemodynamic therapy of normal oxygen transport and lactate in the immediate postoperative period can improve clinical outcomes in cardiac surgery patients.

Why is HC important in the surgical setting?

Physiologic stress associated with surgical procedures may be associated with adverse peri-operative cardiovascular events (i.e. cardiac death, nonfatal MI, nonfatal cardiac arrest) [46]. These events both cause and are precipitated by decreased fibrinolytic activity, hypercoagulability, decreased vasomotor reactivity, vulnerable plaque rupture, catecholamine surges, decreased coronary perfusion, shorter diastolic intervals, tachycardia, and a heightened inflammatory state [47,48]. Specific events or conditions linked to the oc-

currence of peri-operative hypertension, tachycardia, and loss of HC include intubation, inadequate anaesthesia or ventilation, pain, anxiety, excessive fluid administration, emergence from anaesthesia, postoperative fluid mobilization, acute cardiac events, pheochromocytoma (rare), and malignant hyperthermia [49,50].

The conditions that cause an acute change in systemic haemodynamics during surgery are common and include acute changes in endogenous and exogenous systemic catecholamines due to anaesthesia depth, surgical stimulation, aortic occlusive clamping and unclamping, fluid shifts, haemorrhage, secondary drug effects, and many other examples. These changes commonly occur in the setting of insufficient intravascular volume and likely affect patients differently, depending on their underlying vascular physiology and compliance. With loss of HC (i.e. increased or decreased heart rate, MAP, or SAP, or prolonged, elevated heart rate [>95 bpm for >12 h in a 24-h period]), the risk for adverse cardiac outcomes is increased [14,51,52]. Results from several studies indicate that both presenting BP and either a rise or fall in BP (SBP, MAP, or PP) may result in a progressively elevated risk for adverse outcomes, including stroke, death from cerebrovascular complications [6,16,17], cognitive dysfunction, and other neurologic complications [53].

A closer look at BP and heart rate

BP consists of a steady component (MAP) and a pulsatile component (PP), the difference between SBP and DBP. Arterial compliance relates to the change in stroke volume and inversely to the ensuing change in pressure. The fluid-pressure dynamic of BP is determined by different parameters depending on its component subtype; for example, the determinants of MAP are left ventricular (LV) ejection and peripheral vascular resistance (PVR), whereas the determinants of SBP are stroke volume, LV ejection, distensibility, and

wave reflection. The determinants of PP are LV ejection, viscoelasticity, and wave reflection. The actual observed pulse contour that is displayed on a monitor is a summation of forward and returning pressure waves. It also has been suggested that a patient's haemodynamic state is modulated with each heart beat and that organ perfusion may be best predicted by cardiac index, defined as heart rate times SI [54].

PP is an index of conduit vessel stiffness and the rate of pressure wave propagation within the arterial tree [55,56]. When stiffening of the aorta occurs, propagated and reflected waves within the arterial tree travel much more rapidly, resulting in an early return of the propagated wave to the central aorta during late systole as opposed to early diastole. This augmented systolic component thereby effectively increases afterload, and the ensuing loss of DBP augmentation may decrease organ perfusion, including coronary, cerebral, and renal perfusion pressure. This condition is exacerbated in the setting of tachycardia, as the potential for the reflected pressure wave propagation to occur in late systole vs. early diastole is greater. The waveform obtained with PP monitoring can provide indications of adequate or inadequate end-organ perfusion [57]. Further, there is an inverse relationship between heart rate and the augmentation index of the PP wave, a parameter measured by pulse wave analysis that is used as a surrogate measure of arterial stiffness [58].

There is a close relationship between aging, long-standing arterial hypertension, vascular disease, and PP, all acting in concert to limit organ flow and reserve [55]. In patients undergoing cardiac or major vascular surgery, the combination of such pre-existing vasculopathy and aortic-wall injury from surgical manipulation (aortic clamping/declamping, cannulation, and decannulation) provide a compelling pathophysiologic basis for the increased postoperative vascular complications observed in patients with non-compliant arteries, and is manifested by increased PP [17,56].

This is also true of the inflammatory response associated with cardiopulmonary bypass (CPB) [59]. Stiff vessels have altered vascular smooth muscle cell phenotypes with arterial remodelling of the blood vessels in vital organs. It is possible that the autoregulatory range is distinctly different across individuals with different vascular properties and with different types of superimposed surgery and anaesthesia. An altered autoregulatory range might lead to organ hypoperfusion in some individuals, despite what may be deemed to be a "clinically acceptable" BP. Moreover, an increased, isolated SBP may serve as a pathophysiologic marker of underlying cardiovascular disease [28,60,61].

In addition, chronic SBP overload leads to LV hypertrophy and impaired DBP filling. Management of diastolic heart failure should be directed at central volume reduction and heart rate control, as tachycardia is poorly tolerated. Decreased diastolic compliance is a consequence of altered passive elastic properties due to fibrosis or increased muscle mass, as well as derangements in the dynamics of ventricular relaxation [62].

The conditions that affect vascular tone (e.g. neural, endothelial, and mechanical) can cause acute changes in local and/or systemic haemodynamics by dilatory or constrictive stimuli and can trigger acute procoagulation or inflammatory reactions. Endothelial cells release various relaxing and constricting factors to maintain normal vascular tone. The impact that acute, haemodynamic fluctuations may have on endothelial function and potential destabilization of vulnerable plaque has been studied. An essential and common consequence of endothelial dysfunction is reduced endothelial nitric oxide synthase and the loss of a protective effect from nitric oxide with increased production of reactive oxygen species due to decreased scavenging of oxygen free radicals [63]. The changes of stretch and/or stress, endothelial function, and central nervous system stimulation often exist in combination with one another. Nevertheless, adverse vascular outcomes associated with acute fluctuations in BP superim-

posed on pre-existing hypertension appear to be accelerated in the surgical setting, manifesting over days vs. decades [14,51,52,64].

Impact of inadequately controlled heart rate and BP in cardiac surgery

It is well understood that peri-operative hypertension and tachycardia increase myocardial oxygen consumption and LV end-DBP and contribute to subendocardial hypoperfusion and myocardial ischemia [65]. It also increases the risk of stroke, neurocognitive dysfunction, and renal dysfunction, and contributes to surgical bleeding from anastomotic sites. In addition, it is now understood that poor HC (elevated heart rate and BP) during surgery can trigger hyperinflammatory and procoagulation conditions, including platelet activation [47], which may compromise microvascular blood flow [66-68].

The assessment, characterization, and management of HC in the setting of cardiovascular surgery is confounded by acute mechanical and physiologic perturbation involving aortic occlusive clamps, excessive release of catecholamine, reperfusion injury, humoral and cellular inflammatory response, and platelet activation, which can compromise microvascular blood flow. Several studies have provided information about the association between poor heart rate control and increased risk for morbidity and mortality in cardiac surgery patients [13,15,69]. In a study of 2149 patients undergoing coronary artery bypass grafting (CABG) surgery, both preoperative bradycardia (low heart rate defined as 30 to 39 bpm; very low heart rate defined as <30 bpm) and tachycardia (high heart rate defined as 101 to 120 bpm; very high heart rate defined as >120 bpm) were significant predictors of perioperative MI ($P = 0.007$ and $P = 0.028$, respectively) [13]. Further, both postbypass tachycardia and hypotension (MAP <49 mm Hg) during CPB were significant predictors of mortality ($P = 0.025$ and $P = 0.001$, respectively). In a study of 566 patients undergoing CPB, the duration

of hypotension (SBP <90 mm Hg) after CPB also was a significant predictor of MI, determined by Q-wave, myocardial fraction of creatine kinase, or at autopsy ($P = 0.04$) [70]. The incidence of early postoperative complications (a composite of mortality, MI, stroke, or transient ischemic attack) was assessed in 1022 patients undergoing CABG surgery [15]. Both elevated heart rate (69.9 vs. 64.9 bpm) and PP >70 mm Hg were correlated with significantly elevated risk for the composite end point ($P < 0.0001$ and $P < 0.03$, respectively). A separate study of 5934 CABG patients found that pre-induction heart rate ≥ 80 bpm was correlated with an increased risk for in-hospital mortality ($P < 0.0001$) [69]. The authors suggested that heart rate, while not definitive, may be either a cause of the observed mortality, a marker for irreversible myocardial damage, or an indicator of patients with limited cardiac reserve at risk for further injury.

There also is circumstantial evidence that risk for adverse cardiac events in cardiac surgery is increased when BP is not controlled preoperatively. A prospective epidemiologic study of 2147 CABG patients indicated that isolated systolic hypertension (SBP >140 mm Hg) was present in 29.6% of the study cohort and was independently associated with a 30% increased risk for adverse outcomes, including LV dysfunction, cerebral vascular dysfunction or events, renal insufficiency or failure, and all-cause mortality, after adjustment for other risk factors (odds ratio [OR] = 1.3; $P = 0.008$) [6].

An association between predictor variables and postoperative renal dysfunction and/or renal failure was established in a prospective and descriptive study of patients who had undergone CABG surgery with CPB. Of a total of 4801 patients, postoperative renal events occurred in 231 patients (4.8%). Among these patients, significant independent risk factors were age >75 years (OR = 2.04; 95% confidence interval [CI], 1.23 - 3.37; $P = 0.006$), preoperative congestive heart failure (CHF) (OR = 2.38; 95% CI = 1.55-3.64; $P < 0.001$), prior MI (OR = 1.75; 95% CI =

1.08–2.83; $P = 0.023$), pre-existing renal disease (OR, 3.71; 95% CI = 2.41–5.70; $P < 0.001$), intra-operative multiple inotrope use (OR = 2.75; 95% CI = 1.75–4.31; $P < 0.001$), intra-operative intra-aortic balloon pump insertion (OR = 4.41; 95% CI = 2.21–8.80; $P < 0.001$), CPB >2 h (OR = 1.78; 95% CI = 1.15–2.74; $P = 0.01$), and preoperative PP (every additional 20 mm Hg increment in PP >40 mm Hg), (OR = 1.49; 95% CI = 1.17–1.89; $P = 0.001$). Patients with PP hypertension >80 mm Hg were 3 times more likely to experience a renal-related death vs. those without PP hypertension (3.7% vs. 1.1%) [7].

In other studies among patients undergoing cardiac surgery, the mean PP was greater in those patients who suffered a stroke (81 vs. 65 mm Hg), with each additional 10 mm Hg contributing additive risk (OR = 1.35; 95% CI = 1.13–1.62; $P = 0.001$) [16].

The relationship between preoperative hypertension (systolic, diastolic, PP), ischaemic cardiac and cerebral outcomes, and death was assessed in a prospective, observational study of patients who had elective CABG surgery that required CPB. Of a total of 5436 patients, 917 patients (19.1%) had fatal and nonfatal vascular complications, including 146 patients (3.0%) with cerebral events and 715 patients (14.9%) with cardiac events. Renal events were observed in 231 patients (4.8%). In-hospital mortality occurred in 147 patients (3.1%). Of all BP preoperative parameters examined, PP was most strongly associated with an increased risk of postoperative complications. PP increments of 10 mm Hg were associated with an increased risk of cerebral events (adjusted OR = 1.12; 95% CI = 1.002–1.28; $P = 0.026$). A near doubling of the incidence of a cerebral event and/or death from neurologic complications was demonstrated for patients with PP >80 mm Hg compared with ≤ 80 mm Hg (5.5% vs. 2.8%; $P = 0.004$). PP greater than a threshold of 80 mm Hg was found to be associated with cardiac complications, with an increased incidence of CHF by 52%, and cardiac-related death by nearly 100% [17].

Impact of inadequately controlled heart rate and BP in non-cardiac surgery

Several studies have investigated the risks associated with loss of HC in patients undergoing non-cardiac surgery (Table 3). In a retrospective study of 797 patients undergoing major non-cardiac surgery, both intra-operative tachycardia (defined as heart rate >110 bpm: OR = 2.704; $P = 0.01$) and hypertension (defined as SBP >160 mm Hg: OR = 2.095; $P = 0.009$) were independently associated with negative surgical outcome (postoperative hospital LOS >10 days with a morbid condition or death) after major non-cardiac surgery of long duration (>220 minutes) [14]. MAP also has been evaluated as an intra-operative index of peri-operative risk during non-cardiac surgery. It has been reported that high-risk patients who experience a drop in MAP >20 mm Hg for more than 1 hour or the same, in addition to an increase in MAP >20 mm Hg for more than 15 minutes from baseline while undergoing elective non-cardiac surgery, had the greatest risk of complications [72].

Basali and colleagues evaluated the relationship between peri-operative hypertension (BP $\geq 160/90$ mm Hg) and postoperative intracranial haemorrhage (ICH) following craniotomy. In this case-control study of 69 patients who developed ICH postoperatively and 138 control subjects, 62% of patients with ICH had peri-operative hypertension vs. 34% of controls ($P < 0.001$) [5]. A retrospective study of operative morbidity and mortality in 621 patients undergoing surgery for non-small cell lung cancer also indicated that risk for complications was significantly increased in those with peri-operative hypertension (OR = 4.0; $P < 0.05$ based on 95% CI) [12]. Further, results from the Peri-Operative ISchemic Evaluation (POISE) trial, which evaluated the effect of peri-operative β -blockers vs. placebo on the 30-day risk of major cardiovascular events, demonstrated that hypotension (SBP <100 mm Hg: OR = 4.97; 95% CI = 3.62–6.81) and bradycardia (heart

Table 3. Consequences of poor peri-operative heart rate and blood pressure control in non-cardiac patients

Poor Heart Rate Control	Poor Blood Pressure Control
Ventricular dysrhythmias [52]	Nonfatal stroke [13,16]
Nonfatal cardiac arrest [52]	Hypotension [37,70,73,87,91]
Nonfatal myocardial infarction [13,51,166]	Intracranial haemorrhage [5]
Myocardial ischaemia [92,142,166-168]	Neurological complications [53]
Cardiovascular death [13,17,52,166]	Renal failure or insufficiency [6]
Atrial fibrillation [169]	Cerebrovascular accident [6]
Atrial flutter [52]	Left ventricular dysfunction [6]
Postoperative myocardial infarction [52]	Peri-operative myocardial infarction [13]
Longer stay in the intensive care unit [52]	Life-threatening cardiorespiratory complications [12]
Mortality [13]	Mortality [12]
Congestive heart failure [17]	

rate <45 bpm: OR = 2.13; 95% CI = 1.37-3.32) are both associated with significantly increased mortality, and that hypotension is also correlated with increased risk for peri-operative stroke (OR = 2.14; 95% CI = 1.15-3.96) [73].

Management of heart rate and BP in the peri-operative setting

An often-cited goal of treatment in the peri-operative surgical setting is to rapidly and effectively achieve, and then maintain, targeted BP and heart rate [49]. Current treatment recommendations for peri-operative HC in patients undergoing either cardiac or non-cardiac procedures provide only limited guidance with respect to establishing target goals, monitoring standards, or intervention options [23]. However, evidence from randomized, controlled clinical studies now support the benefit of interventions aimed at achieving and maintaining HC (i.e. BP and heart rate) in low- or high-risk surgical patients (Table 2) [4,85,86].

Pharmacotherapy for maintaining HC

A crucial issue with peri-operative maintenance of HC is achieving and maintaining desired BP and heart rate targets while avoiding the risk of treatment-associated AEs, notably hypotension and bradycardia [37,87]. The properties of the agents most commonly used for controlling heart rate and BP in the peri-operative setting are summarized in Table 4.

Conclusions

Loss of HC (increased heart rate and/or BP) is common during cardiac and non-cardiac surgical procedures. It is estimated that hypertensive episodes requiring intervention occur in approximately 50% of patients undergoing major surgery [49]. As the occurrence of hypertension increases, there is a concomitant increase in risk for adverse cardiac outcomes [14,51,52]. Several studies have clearly demonstrated that elevated BP and heart rate in the cardiac and non-cardiac surgery setting place patients at increased risk for poor surgical outcomes [5,6,13-

Table 4: Agents commonly used to achieve/maintain haemodynamic control in the peri-operative setting

Agent	Mechanism of Action	Contraindications/ Cautions	Adverse Events
β-Blockers			
Atenolol [4]	<ul style="list-style-type: none"> • β₁-, β₂-blocker • β₁-selective (cardioselective) <p>Inhibits β₂ adrenoreceptors at higher doses</p>	<ul style="list-style-type: none"> • Sinus bradycardia • Heart block greater than first degree • Cardiogenic shock • Overt cardiac failure 	<ul style="list-style-type: none"> • Systolic hypotension • Bradycardia • Dizziness • Vertigo • Fatigue • Diarrhea • Nausea • Generally mild and transient
Esmolol [49,88]	Short-acting cardioselective β-blocker	<ul style="list-style-type: none"> • Sinus bradycardia • Heart block greater than first degree • Cardiogenic shock or overt heart failure 	<ul style="list-style-type: none"> • Asymptomatic hypotension (25%) • Symptomatic hypotension (12%) • Both usually reversed within 30 minutes of dose decrease or infusion termination
Labetalol [49,90]	α-, β ₁ -, β ₂ -blocker	<ul style="list-style-type: none"> • Heart block greater than first degree • Sinus bradycardia • Acute heart failure • Asthma 	<ul style="list-style-type: none"> • Bronchospasm
Metoprolol [90]	<ul style="list-style-type: none"> • Highly selective β₁-blocker • Inhibits β₂ adrenoreceptors at higher doses 	<ul style="list-style-type: none"> • Known hypersensitivity to product components • Severe bradycardia • Heart block greater than first degree • Cardiogenic shock • Decompensated cardiac failure • Sick sinus syndrome* 	<ul style="list-style-type: none"> • Bronchospasm • Nausea • Vomiting • Scalp tingling
Calcium Channel Blockers			
Clevidipine [97,170,171]	<ul style="list-style-type: none"> • Rapidly metabolized dihydropyridine calcium channel blocker • Decreases arterial pressure via direct arterial vasodilation 	<ul style="list-style-type: none"> • Allergy to soy or eggs • Defective lipid metabolism • Severe aortic stenosis 	<ul style="list-style-type: none"> • Flushing • Fever • Atrial fibrillation • Sinus tachycardia • Acute Renal failure • Systemic hypotension • Nausea

Table 4 - Continuation: Agents commonly used to achieve/maintain haemodynamic control in the peri-operative setting

Agent	Mechanism of Action	Contraindications/ Cautions	Adverse Events
Diltiazem [90]	Non-dihydropyridine calcium channel blocker	<ul style="list-style-type: none"> • Severe hypotension (<90 mm Hg systolic) • Hypersensitivity to the drug • Patients with acute MI and pulmonary congestion documented by x-ray on admission 	<ul style="list-style-type: none"> • Asymptomatic hypotension (4.3%) • Symptomatic hypotension (3.2%) • Injection site reactions (3.9%) • Generally mild and transient
Nicardipine [49]	Rapidly acting dihydropyridine calcium channel blocker	<ul style="list-style-type: none"> • Advanced aortic stenosis 	<ul style="list-style-type: none"> • Headache • Hypotension • Nausea • Vomiting • Tachycardia
Verapamil [90]	Non-dihydropyridine calcium channel blocker	<ul style="list-style-type: none"> • Severe hypotension or cardiogenic shock • Second- or third-degree AV block* • Sick sinus syndrome* • Severe congestive heart failure (unless secondary to a supraventricular tachycardia amenable to verapamil therapy) • Coadministration of IV β-adrenergic blocking drugs • Atrial flutter/atrial fibrillation associated with an accessory bypass tract • Ventricular tachycardia 	<ul style="list-style-type: none"> • Symptomatic hypotension (1.5%) • Bradycardia (1.2%) • Severe tachycardia (1.0%)
Class III Antiarrhythmic			
Amiodarone [172]	<ul style="list-style-type: none"> • Class III antiarrhythmic • Lengthens cardiac action potential 	<ul style="list-style-type: none"> • Cardiogenic shock • Severe sinus-node dysfunction causing marked sinus bradycardia • Second-or third-degree AV block • When episodes of bradycardia have caused syncope* <p>Known hypersensitivity to the drug or any of its components, including iodine</p>	<ul style="list-style-type: none"> • Hypotension • Cardiogenic shock • Bradycardia • Liver function test abnormalities • Thyroid toxicity • Pulmonary toxicity

Table 4 - Continuation: Agents commonly used to achieve/maintain haemodynamic control in the peri-operative setting

Agent	Mechanism of Action	Contraindications/ Cautions	Adverse Events
ACE Inhibitor			
Enalaprilat [90]	ACE inhibitor (reduces production of angiotensin II resulting in decreased mean arterial pressure)	<ul style="list-style-type: none"> • Hypersensitivity to any product component • History of angioedema related to previous treatment with ACE inhibitor • Hereditary or idiopathic angioedema 	<ul style="list-style-type: none"> • Hypotension • Angioedema
Direct Vasodilators			
Hydralazine [90]	Reduces BP by increasing cyclic-guanosine monophosphate in vascular smooth muscle	<ul style="list-style-type: none"> • Hypersensitivity to hydralazine • Coronary artery disease, mitral valvular rheumatic heart disease 	<ul style="list-style-type: none"> • Reflex tachycardia • Headache • Flushing • Vomiting
Sodium nitroprusside [49,97,110]	Reduces peripheral resistance by acting on arterial and venous smooth muscle	<ul style="list-style-type: none"> • Treatment of compensatory hypertension • Known inadequate cerebral circulation in moribund patients coming to emergency surgery • Controlled hypotension during surgery in patients with inadequate cerebral circulation • Tobacco amblyopia • Treatment of acute congestive heart failure associated with reduced peripheral vascular resistance 	<ul style="list-style-type: none"> • Atrial fibrillation • Sinus tachycardia • Hypotension • Cyanide toxicity
Nitroglycerin [97,110]	Relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins	<ul style="list-style-type: none"> • Allergy to nitroglycerin • Early MI, severe anaemia, increased intracranial pressure, and hypersensitivity to nitroglycerin (sublingual nitroglycerin) 	<ul style="list-style-type: none"> • Atrial fibrillation • Tachyphylaxis • Hypotension • Headache
Other Agents			
Fenoldopam [49]	<ul style="list-style-type: none"> • Short-acting peripheral dopamine D1 receptor agonist • Mediates peripheral vasodilation 	<ul style="list-style-type: none"> • Intraocular pressure • Allergy to sulfite 	<ul style="list-style-type: none"> • Headache • Flushing • Nausea • Hypotension

*Except in the presence of a functioning ventricular pacemaker

Abbreviations: ACE, angiotensin-converting enzyme; AV, atrioventricular; BPM, beats per minute; IV, intravenous; SBP, systolic blood pressure.

17,53,57], which are improved when these haemodynamic factors are controlled. However, it is important to balance control of heart rate and BP against the increased risk of hypotension and bradycardia.

The mechanisms responsible for loss of peri-operative HC include hyperadrenergic response to surgery, increased SVR, preload shifts, rapid intravascular volume shifts, renin angiotensin activation, adrenergic stimulation (cardiac and neural), serotonergic overproduction, baroreceptor denervation, altered cardiac reflexes, inadequate anaesthesia, and regional mechanical forces (application of vascular occlusive clamps). In addition, it is known that adverse vascular outcomes associated with acute fluctuations in heart rate and BP, superimposed on pre-existing hypertension (acute on chronic phenomenon), appear to be accelerated in the surgical setting [137,138].

While haemodynamic indices developed and evaluated in large cohorts have identified patients at high risk for complications during surgical procedures [55], there is still a lack of agreement regarding thresholds for intervention and appropriate treatment goals [49,139]. A wide range of agents, including short- and long-acting β -blockers, CCBs, inotropes/chronotropes, and inosodilators are available for management of peri-operative heart rate, BP, and CO. Treatment selection should be based on the clinical situation and patient's condition, and should consider important pharmacokinetic and pharmacodynamic parameters of the various agents available. An ideal agent should have an immediate onset of action, a short duration of action, be easy to titrate precisely, and have demonstrated safety and efficacy in the treatment of peri-operative hypertension [49]. The clinician's challenge is to choose the optimal therapy to accomplish this goal and avoid heart rate and BP levels that are too high (hypertension, tachycardia) or too low (hypotension, bradycardia). Just as we were reminded in the story of *Goldilocks and the Three Bears*, "not too hot and not too cold", so it is

with achieving this "Goldilocks balance" that defines the art of HC.

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