Both the severity and duration of intraoperative arterial hypotension have been identified as significant risk factors for predicting surgical mortality (1, 2). Particularly in elderly patients (3), delayed or inadequate correction of hypotension comprises nearly 40% of substandard intraoperative care and is closely associated with postoperative myocardial ischemia and infarction (2). Consequently, the practicing anesthesiologist needs an efficient and effective approach to diagnosing the cause and appropriate management of intraoperative hypotension. This lecture will review basic cardiovascular physiologic principles that control blood pressure using the following algorithm.

### MYOCARDIAL PERFORMANCE

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<th>Physiologic Algorithm</th>
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A decrease in blood pressure warrants a noninvasive assessment of cardiac output whether by end-tidal CO\(_2\), arterial waveform pulse contour analysis, or echocardiography. A useful, simple indicator of cardiac output in the operating room is end-tidal carbon dioxide (CO\(_2\)) by capnography. Assuming constant minute ventilation and no exogenous source of CO\(_2\), a sudden drop in end-tidal CO\(_2\) by 3-4mmHg reflects a reduction in cardiac output by approximately 1 L/min/m\(^2\) (4, 5). Using the algorithm, a decrease in blood pressure with no change in end-tidal CO\(_2\) indicates a primary problem with systemic vascular resistance which can be readily treated with an alpha-agonist drug (phenylephrine or norepinephrine). A decrease in both blood pressure and end-tidal CO\(_2\) indicates a primary problem with cardiac output which, in turn, depends on heart rate and stroke volume. In anesthetized patients, increasing heart rate is not effective to improve cardiac output due to inadequate venous return (6). However, heart rhythm is an important, essential, and frequently overlooked component. Normal sinus rhythm should be verified by inspection of the electrocardiogram or the central venous waveform tracing.

In the hypotensive patient in normal sinus rhythm and with a reduction in end-tidal CO\(_2\), the next consideration is stroke volume which represents the difference between end-diastolic volume and end-systolic volume. In terms of assessing the adequacy of preload (end-diastolic volume), dynamic indices such as pulse pressure variability or systolic pressure variability with positive pressure ventilation are more sensitive indicators of fluid responsiveness to volume expansion than static indices such as measured filling pressures. On the other hand, end-systolic volume is
affected by afterload and contractility. A vasodilator to reduce afterload may be effective treatment of hypotension under the following conditions: aortic or mitral regurgitation; atrial or ventricular septal defect; pulmonary hypertension with right ventricular failure; severe left ventricular systolic failure. Afterload reduction in these conditions can improve blood pressure if the net increase in stroke volume exceeds the net reduction in systemic vascular resistance. Otherwise, an inotropic drug would be indicated to improve stroke volume. Use of this algorithm will be developed by incorporating the following basic cardiac physiologic principles that govern myocardial performance, namely afterload, heart rate, preload, and contractility.

A. Afterload

Afterload represents all forces that oppose left ventricular (LV) fiber shortening during ejection and includes ventricular shape, size, wall thickness, intracavitary pressure, aortic impedance, blood viscosity, and peripheral resistance. Systemic vascular resistance is frequently used as an indicator of LV afterload but a more accurate parameter is wall stress which by the Laplace relationship is proportionate to \((\text{radius} \times \text{pressure}) / \text{wall thickness}\). Wall stress is more difficult to precisely determine in patients than calculating systemic vascular resistance. Moreover, vasoactive medications can affect vascular resistance and wall stress differently.

For example, both phenylephrine and norepinephrine increase systemic vascular resistance but their effects on venous return, preload, and wall stress differ markedly. Experimental studies show that increasing preload accounts for 25% of the elevated blood pressure response to norepinephrine but nearly 67% for phenylephrine (7). The majority of the pressor response from norepinephrine is due to inotropy which is not seen with phenylephrine. When administered to patients with coronary disease and preserved LV function, phenylephrine (1 mcg/kg bolus) causes a significant impairment of global LV function with a doubling of end-systolic wall stress and a reduction in the velocity of circumferential shortening and fractional area change (8). Similar responses to phenylephrine are reported whether administered to normotensive, awake subjects (9) or to hypotensive, anesthetized patients (8, 10) and provokes a threefold higher incidence of myocardial ischemia in surgical patients (11). In contrast, norepinephrine (0.05mcg/kg bolus) increases mean arterial pressure without adversely affecting the fractional area of shortening, velocity of circumferential shortening, or heart rate (8). With norepinephrine, end-systolic wall stress does not change due to concomitant beta-adrenoreceptor agonist properties.

The ventricular response to an acute increase in afterload is closely linked to preload recruitable function. Initially, an afterload increment causes a transient reduction in stroke volume as end-systolic volume increases (12). This in turn causes a greater end-diastolic volume with a recovery of stroke volume using the Frank-Starling mechanism. As a result, a normal heart can maintain stroke volume in the face of increasing afterload (solid line). An increase in afterload is matched by an increase in preload so the force of contraction is augmented using the Frank-Starling mechanism. In contrast, a failing heart with reduced contractility will decrease stroke volume in the face of increased afterload due to reduced preload recruitable function (dotted line). The dilated heart has less preload reserve so an increase in afterload causes deterioration in function and reduction in stroke volume. Thus, a normal heart is insensitive to afterload due to preload sensitivity whereas a failing heart is sensitive to afterload due to preload insensitivity. Much of the hemodynamic response to phenylephrine administration in anesthetized patients can be explained by this concept.
Furthermore, even in normal hearts, if preload is inadequate then stroke volume will decrease in the face of increased afterload which is termed afterload mismatch with reduced preload reserve (13). Under this circumstance, the stroke volume response to increased afterload will be limited by ventricular filling despite normal contractile properties. A relevant clinical example of afterload-preload mismatch is the use of dynamic indices such as stroke volume variability or pulse pressure variability to predict the cardiac output response to volume infusion. Positive pressure inspiration with lung volume above functional residual capacity increases pulmonary vascular resistance and consequently right ventricular afterload while simultaneously reducing venous return and right-sided filling. This right ventricular afterload-preload mismatch places the right ventricle at a mechanical disadvantage which, in large part, is why stroke volume decreases with limited preload reserve and makes this parameter a sensitive clinical indicator of fluid volume responsiveness.

B. Heart Rate

In exercising individuals, tachycardia represents a major component of the sympathetic cardiovascular response to increase cardiac output by nearly five-fold (14). However, in anesthetized, supine patients, increasing heart rate produces a negligible effect on cardiac output due to a limitation in cardiac filling. In patients undergoing coronary revascularization before and after cardiopulmonary bypass, sequentially increasing heart rate from 80 bpm to 110 bpm causes a reduction in right ventricular end-diastolic volume and consequently stroke volume so that cardiac output remains unchanged (6). Similar findings have been found in experimental animals (15) as well as patients undergoing radionuclide angiography (16). Increasing heart rate reduces cardiac filling and may have detrimental effects in patients with coronary disease by increasing myocardial oxygen consumption while reducing the diastolic time period for coronary blood flow.

Heart rhythm is an important component of blood pressure particularly in patients with noncompliant ventricles where the volume contribution from a properly timed atrial contraction may represent 25-40% of end-diastolic volume. Note the significant reduction in blood pressure in the patient with aortic stenosis in nodal rhythm (see below). Although the diagnosis of nodal rhythm may be possible from the electrocardiogram, a more exact physiologic method is examination of the central venous pressure waveform where a normal biphasic wave pattern is replaced with uniphasic cannon “a” waves (17). Treatment of nodal rhythm should be directed towards restoring normal sinus rhythm.
C. Preload

Preload is the force or load acting to stretch ventricular myofibrils at end-diastole. Preload recruitable function refers to the intrinsic ability of the heart to increase the force of contraction and stroke volume at greater end-diastolic volumes. Originally, this Frank-Starling relationship was explained by the sliding filament theory with greater actin-myosin overlap as sarcomere length approaches 2.25 microns. More recent studies show the steepness of the ascending limb is due to length-dependent calcium availability and sensitivity of myofibrils (18). Furthermore, there is no descending limb of the Starling function curve. Under the experimental conditions of constant coronary perfusion pressure and prevention of mitral regurgitation, left ventricular developed pressure is maintained at 60 mmHg end-diastolic pressure and decreases by only 5% at 100 mmHg (19). Rupture of myofibrils at elevated filling pressures is prevented by the restraining effect of the pericardium as well as the cardiac cytoskeleton and collagen. Any apparent descending limb of the Starling curve at high filling pressures is attributable to the development of mitral regurgitation or secondary coronary ischemia (12, 20).

The curvilinearity of the stroke volume – LV end-diastolic pressure relationship (Frank-Starling relationship; panel a) is due to the intrinsic diastolic pressure-volume relationship (21). If stroke volume is plotted against left ventricular end-diastolic volume instead of pressure (panel b), the relationship becomes linear in normal patients as well as in patients with heart failure (22). This finding means that stroke volume increases in normal individuals as well as heart failure patients at greater end-diastolic volumes (23). However, because of the steep curvilinear slope of the diastolic pressure-volume relationship after filling pressures of 12-15mmHg (panel c), the risk of subsequent fluid volume expansion in terms of markedly elevated filling pressure becomes too great. This concept has important clinical implications.
D. Contractility

Inotropic drugs increase cardiac contractility so the heart ejects to a lower end-systolic volume thereby increasing stroke volume. The net effect of increasing contractility on myocardial oxygen consumption depends on baseline ventricular size and wall stress. With a dilated ventricle, increasing contractility can reduce end-systolic volume and consequently end-diastolic volume so that overall wall stress actually decreases (24). Acutely, an inotrope could improve contractile function and myocardial oxygen consumption as long as heart rate does not change. However, when chronically administered, inotropic drugs become cardiotoxic secondary to calcium overload from sarcolemmal permeability changes and alterations in the sarcoplasmic reticulum (25). These effects may occur from the oxidative metabolites of catecholamines rather than from epinephrine or norepinephrine per se. A potential exception to inotropic cardiotoxicity is levosimendan which works by increasing the calcium sensitivity of troponin C rather than increasing intracellular calcium seen with calcium mobilizers such as beta-adrenoreceptor agonists and phosphodiesterase inhibitors. Levosimendan has been extensively utilized in Europe but is not approved for use in this country.

Another influential factor that can directly affect the amount of ischemic injury is the level of myocardial oxygen consumption at the time of coronary occlusion. In experimental animals, increasing oxygen demand with an inotrope before the onset of ischemia worsens the amount of myocardial injury. In contrast, starting an inotrope after coronary occlusion has little detrimental effect on infarct size (26) although recent evidence shows that increasing calcium influx after infarction increases apoptotic cell death, exacerbates depressed pump function, and hastens heart failure progression (27). Long-term catecholamine administration can induce pump dysfunction by beta adrenoreceptor downregulation, increased myocardial norepinephrine release, and left ventricular dilatation (28).

In conclusion, intraoperative hypotension is a frequent and morbid complication of general anesthesia and warrants prompt diagnosis and correction. The use of a physiologic algorithm which incorporates all components of myocardial performance – namely afterload, heart rate, preload, and contractility – provides a reliable and inclusive approach to improve patient management.
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Disclosure

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