Clinical Use of Inotropic Agents

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In the clinical practice of anesthesia, it may become necessary for the anesthetist to augment myocardial contractility in order to maintain circulatory integrity. The authors discuss the pharmacological agents which exert a positive inotropic effect on the myocardium and review their peripheral vascular effects.

Acute or chronic circulatory insufficiency is generally characterized by alteration of cardiac output (CO) and relative failure to deliver sufficient blood flow to meet the metabolic demands of the vital organs. Although cardiac output is a summation of multiple complex interrelationships, overall it may be simply expressed by the following equation:

\[ \text{SVR} \times \text{CO} = \text{AP} \]

By definition, AP is the mean arterial blood pressure and SVR equals systemic vascular resistance. The variables of this equation are interdependent. Alteration of any variable may change the other parameters. For example, AP may be elevated by increasing the SVR, CO, or both.

The advent of the Swan-Ganz™ catheter has allowed measurement of right- and left-sided ventricular filling pressures to perform therapeutic manipulations aimed at maximizing left ventricular performance. These manipulations include appropriate reduction of volume by diuretics in volume overload states, as well as intravascular volume expansion in patients with volume depletion syndromes.

Furthermore, exciting advances in afterload reduction therapy have greatly aided the management of circulatory insufficiency by allowing beneficial alterations in the systemic vascular resistance and augmentation of cardiac output. Because the underlying clinical states associated with power failure are not infrequently accompanied by low or borderline arterial blood pressure there has been a reluctance to routinely administer vasodilating drugs.

Accordingly, over the past several years, the mainstay of drug therapy for circulatory insufficiency has been various inotropic agents. The purpose of this article is to provide an overview of the cardiovascular actions of inotropic drugs in present clinical use.

L-Norepinephrine (Levophed®)

The cardiovascular effects of norepinephrine are mostly dose dependent and are related to the clinical setting. In man, administration of lower dosages (<5 µg/min) generally causes cardiac beta receptor stimulation resulting in...
the elevation of cardiac output due to increased contractility (inotropy) and heart rate (chronotropy).4 At higher doses, alpha receptor activity predominates, and AP may increase because of elevation in systemic vascular resistance. Unfortunately, at the higher dose ranges, despite increased cardiac output and systemic vascular resistance, compensatory vagal reflex may negate the beneficial effects of the drug by induction of bradycardia. Furthermore, large increases in systemic vascular resistance may depress left ventricular performance.

Beneficial utilization of norepinephrine requires constant monitoring. Use of a preselected blood pressure response, irrespective of the dosage given, is probably hazardous. Aside from the adverse actions of high doses of norepinephrine just described, excessive vasoconstriction may cause reduction of perfusion to the kidney, liver and skeletal muscle.5

It should be clear, therefore, that use of norepinephrine is most beneficial in patients with arterial hypotension and only the minimum dosage necessary to maintain perfusion of the vital organs should be used. Drug induced elevation of systolic blood pressure above 90-100 mmHg is rarely indicated (except in the patient with long standing hypertension).5

A consequence of prolonged therapy with norepinephrine is the development of volume depletion which may complicate the period of weaning from all vasopressors. Schmutzer and co-workers8 demonstrated that normal animals may develop hypotension after abrupt discontinuation of norepinephrine. This may be corrected by volume repletion during the weaning period.9

Epinephrine (Adrenalin®)

Epinephrine produces potent beta stimulation of the myocardium and pacemaker cells. Infusion of lower doses of epinephrine (0.2 μg/kg/min) will predictably produce increased contractility and heart rate, while slightly decreasing systemic vascular resistance due to peripheral beta-receptor mediated vasodilatation in excess of alpha-receptor mediated vasoconstriction.2,8

Higher dosages of epinephrine will increase systemic vascular resistance. Thus, while epinephrine may be helpful in initiating spontaneous myocardial contraction (as in cardiac arrest), its vasoconstricting effect increases afterload, which severely restricts any potential benefit to the failing circulation in states associated with depressed cardiac output.

Isoproterenol (Isuprel®)

Isoproterenol is a potent beta-receptor stimulant in both the myocardium and peripheral vasculature. Although it is a strong inotropic and chronotropic agent, it acts as a vasodilator in most organ beds.5,7 Accordingly, elevation in blood pressure due to isoproterenol is attributed to its cardiac effects as opposed to an increase in systemic vascular resistance.

Infusion rates vary from 1 to 5 μg/min and increases in cardiac output and blood pressure vary from patient to patient. Although isoproterenol is an effective inotropic agent, its value in the clinical setting must be strongly weighed against the potential deleterious effects. Isoproterenol is prone to result in rhythm disorders that include ventricular ectopy, as well as supraventricular tachyarrhythmias. Further, although isoproterenol increases cardiac output, it frequently decreases the mean arterial and diastolic perfusion pressure of the coronary arteries.

Unfortunately, patients with profound depression of cardiac output often have significant coronary artery disease and can ill afford the cardiac demands associated with isoproterenol. On the other hand, temporary use of
isoproterenol in the treatment of bradyarrhythmias, septic shock, or the low output state subsequent to cardiopulmonary bypass (especially after valve replacement) may be clinically helpful.

**Dopamine (Intropin®)**

Dopamine, the “third endogenous catecholamine” is the immediate precursor of norepinephrine and is similar in some respects, but is less potent in its alpha adrenergic stimulation at lower doses.8

Dopamine increases myocardial contractility and, to a lesser extent, heart rate by direct beta-receptor stimulation. Accordingly, at lower doses (2-5 µg/kg/min) dopamine may be expected to increase cardiac output and decrease systemic vascular resistance or increase heart rate to the same extent as isoproterenol.

It has gained attention because in lower and moderate dosages (5-20 µg/kg/min) this agent possesses the unique property of vasodilatation in the renal and mesenteric beds through dopamine specific receptors.8,9 This is an especially attractive and unique property of dopamine, because it is frequently found that patients with low output states additionally demonstrate depressed urine output and sodium excretion due to decreased glomerular filtration.

Although each patient responds somewhat differently to incremental dosage schedules with dopamine, at higher infusion rates (>20-30 µg/kg/min) the predominant effect of dopamine in all vascular beds is vasoconstriction. This increase in total systemic vascular resistance appears to be due to alpha-receptor stimulation and may be antagonized by alpha blocking agents such as phentolamine. Further, although higher infusion rates may result in greater increments in cardiac output, renal blood flow and natriuresis may not increase but instead may decrease due to vasoconstriction.10

It is important to note that, in general, dopamine as well as other sympathomimetic amines, should not be administered in the face of volume depletion. Accordingly, central venous pressure should be kept in the range of 10-15 cm of water or the pulmonary capillary wedge should be 14-18 mmHg.

Adverse reactions to dopamine include ventricular ectopy, development of angina pectoris due to increased contractility and heart rate, and nausea;10 however, in our experience, these are infrequently encountered. Moreover, though hypotension may be occasionally observed, this usually occurs at the lower dose rates when systemic vascular resistance has declined due to mild beta-receptor stimulation.

It should be emphasized that, although dopamine is very useful in most clinical states associated with depressed cardiac output, isoproterenol may produce greater increments in cardiac output and may be used in selected patients (that is, patients with septic shock) in whom vasoconstriction is problematic and who can tolerate isoproterenol induced tachycardia. Furthermore, modest doses of norepinephrine may be used in patients demonstrating inadequate perfusion—despite adequate dosages of dopamine.5

**Dobutamine (Dobutrex®)**

Dobutamine is structurally related to dopamine and isoproterenol and possesses pharmacologic properties of both. Dobutamine acts directly on beta-receptors of the myocardium but produces only slight beta and alpha response in the peripheral vasculature. Although the response of the peripheral vasculature is less than with isoproterenol (beta response) or norepinephrine (alpha response), there is a mixed response, with beta effects predominating slightly.11

Accordingly, administration of dobutamine in the usual doses (2-10 µg/kg/min) will result in dose related increments of cardiac contractility and cardiac output while mean arterial blood pressure remains unchanged or only slightly increased at lower doses and slightly decreased with higher dosage.

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rates. An important observation of Beregovich and co-workers\textsuperscript{1,2} is that patients with more profound depression in cardiac output usually respond to a more beneficial degree.

In contrast to dopamine, dobutamine lacks the specific receptor response of dopamine at the renal level, implying that the increased urine flow observed with dopamine administration may not occur with dobutamine. On the other hand, the substantial augmentation of cardiac output found with dobutamine may obviate the need for a specific vascular receptor response at the renal level found with dopamine.

Preliminary data generated by Leier, \textit{et al}\textsuperscript{13} support this. They administered dobutamine for as long as 72 hours to patients with left ventricular failure at dose rates from 2.5 to 15.0 $\mu$g/kg/min and found a sustained salutary effect on cardiac output, urine flow, and sodium excretion during the study period.

Most studies suggest that with dobutamine there is an absence of a significant chronotropic effect; instead, its effect is that of a powerful inotropic agent. However, dobutamine may cause rapid heart rates if given in sufficient doses. Further, dobutamine facilitates conduction through the atrioventricular node, and patients with atrial fibrillation may be at risk for developing a rapid ventricular response.\textsuperscript{11}

Overall dobutamine directly increases contractility while usually sparing the patient from significant alterations in systemic vascular resistance or the tachycardia found with other sympathomimetic agents such as isoproterenol. Dobutamine may be very useful for treatment of low cardiac output states not associated with substantive hypotension.

**Digitalis (Lanoxin\textsuperscript{®})**

The cardiac glycosides increase the amount of calcium released to the contractile elements of the myocardium at the time of excitation-contraction coupling. This increase in intracellular calcium availability appears secure as a critical step in the augmentation of cardiac output, even though the exact details remain uncertain.\textsuperscript{14}

Rapid intravenous administration of the digitalis glycosides will result in an increase in arterial blood pressure due to elevation of systemic vascular resistance.\textsuperscript{15,16} Thus, elevation of blood pressure after acute administration of digitalis may not reflect increases in contractility (which occur later) but, instead, appear to be due to direct vasoconstriction. It follows that rapid administration of digitalis preparations for acute depression of cardiac output may cause an elevation in afterload and temporarily depress left ventricular performance\textsuperscript{16} \textit{before} the inotropic effects of the agent appear.

Once the direct inotropic effects of the agent occur, elevations of cardiac output are generally accompanied by relaxation of the peripheral vascular beds, which results in arterial and venous dilatation. Further, improvement in myocardial contractility will promote diuresis and thereby reduce pulmonary vascular congestion and central venous pressure.

Digitalization of the patient with chronic mild depression of cardiac output who is to undergo major stress, such as surgery, is controversial. Without enlargement of the heart or clinical evidence of obvious congestive heart failure, most clinicians withhold digitalis.

Because hypokalemia results in a relatively rapid uptake of digitalis by the myocardium, there is a well known tendency for hypokalemic patients to exhibit findings of digitalis toxicity. The same is true with patients demonstrating low extracellular magnesium levels. This is especially pertinent because patients with diminished cardiac reserve frequently are exposed to diuretics that cause renal loss of both potassium and magnesium.

It should also be noted that calcium potentiates the effects of digitalis glycosides, and caution should be exercised.
when calcium is administered to the digitalized patient or if hypercalcemia is present. Moreover, patients with chronic obstructive pulmonary disease are apt to exhibit decreased tolerance to digitalis as a result of hypoxemia and alterations of acid-base balance.

Adverse effects of digitalis due to toxicity include anorexia, nausea, vomiting, and occasionally diarrhea. Elderly patients frequently exhibit central nervous system findings such as fatigue, lethargy, or confusion. The most common manifestation of digitalis toxicity, however, is alteration in cardiac rhythm. Surprisingly, prospective studies indicate slightly more than 20% of hospitalized patients receiving digitalis demonstrate findings consistent with toxicity.

The most common rhythm disturbances associated with digitalis excess are paroxysmal atrial tachycardia with block, atrial and junctional tachycardias, complete heart block or atrioventricular dissociation and ventricular ectopy. However, all rhythm disorders have been reported. It should be clear, therefore, that these patients deserve continuous electrocardiographic monitoring.

Improvement of myocardial contractility by digitalis is not mediated by beta-adrenergic stimulation. Therefore, digitalis also may be helpful in the treatment of cardiac depression resulting from beta-blocking agents, such as propranolol.

**Glucagon**

Glucagon is a potent inotropic agent that exerts its effects through pathways other than those of the previously described agents. The exact mechanism by which glucagon exerts its effects has not been clarified, although administration of glucagon is associated with elevation of intracellular cyclic 3', 5'-AMP.

Glucagon in doses of 3 to 5 mg given intravenously significantly raises cardiac output, mean arterial blood pressure, and heart rates without substantial change in systemic vascular resistance. The effectiveness of glucagon is not attenuated by prior digitalization nor by beta-blocking agents, such as propranolol. Further, elevation in glomerular filtration and sodium excretion are prominent renal effects.

There are few clinical studies in the literature examining the time efficacy of glucagon. Accordingly, its appropriate place in the spectrum of inotropic agents aimed at augmentation of cardiac function is unknown. Thus far, it has been used with variable benefits in low output states following cardiopulmonary bypass, chronic heart failure, and acute myocardial infarction with heart failure.

Because of facilitation of atrioventricular conduction, glucagon should be used with caution in patients demonstrating atrial fibrillation or flutter, since the ventricular response may abruptly increase. In addition, nausea and vomiting may occur in selected patients.

**Conclusion**

Based on this discussion of the inotropic agents in current clinical use, it should be clear that no agent is perfect. On the other hand, each has its place in the therapy of various states associated with circulatory insufficiency. Furthermore, use of a particular agent must be tailored to the specific situation encountered and the physiologic manipulation desired. Finally, no drug should be used to the exclusion of another, as multiple pharmacologic agents (such as norepinephrine used in conjunction with dopamine or isoproterenol) may be useful in selected situations.

**REFERENCES**


AUTHORS

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