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CARDIAC DRUGS



Kanu Chatterjee
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JAYPEE

2nd Edition

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CHAPTER

Positive Inotropic Drugs: A Limited but Important Role

Carl V Leier, Garrie J Haas, Philip F Binkley

INTRODUCTION

Positive inotropic agents are drugs that increase the velocity and strength of contraction of the cardiomyocyte in which the myocardium and heart are the primary target organs. The classic measurement of cardiac function is ejection fraction, but it only indirectly represents a measurement of contractility. It is a way of determining the extent of contraction but does not account for the rate or strength of myocardial contraction. The more accurate measurements of myocardial contractility or inotropy include end-systolic elastance from the left ventricular (LV) pressure-velocity loop, ΔLV systolic upstroke pressure/Δtime, peak slope of LV developed pressure and velocity of circumferential fiber shortening.

The positive inotropes will also augment the magnitude of contraction (i.e., ejection fraction), but this effect can also be achieved to varying degrees by a wide variety of non-inotropic agents (e.g., angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers and vasodilators). Therefore, this is not a unique characteristic of positive inotropic agents.

This chapter will discuss the pharmacologic drugs employed clinically to directly enhance cardiac contractility or the inotropic state of the myocardium, the so-called positive inotropic drugs. These agents are directed at the patients whose overall cardiovascular function is impaired by loss of cardiac contractility to the extent that there are symptoms and signs of reduced stroke volume, cardiac output, hypotension and hypoperfusion of vital organs and systems.

Positive inotropic agents augment cardiac contractility through a number of different mechanisms, but most of them act by modulating calcium handling by the myocardial cell. The various mechanisms of action on the cardiomyocyte by the major positive inotropic drugs are presented in Figure 1.

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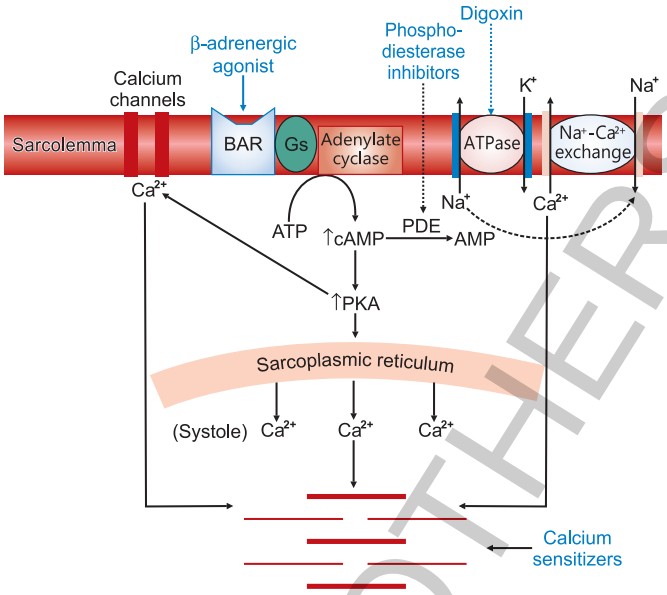

BAR, β-adrenergic receptor; Gs, G protein; ATPase, adenosine triphosphatase; K^+, potassium; Na^+, sodium; Ca^{2+}, calcium; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PDE, phosphodiesterase; AMP, adenosine monophosphate; PKA, protein kinase A.

FIG. 1: Mechanisms of actions of positive inotropic drugs on cardiomyocytes. The major positive inotropic groups generally act through mechanisms that increase the concentration and availability of intracellular calcium for the actin-myosin contractile apparatus. β-adrenergic agonists attach to the β-adrenergic receptor, activating the Gs protein-adenylate cyclase complex to convert ATP to cAMP. cAMP activates protein kinase A, which phosphorylates several intracellular sites resulting in Ca^{2+} influx into the cell and Ca^{2+} release from sarcoplasmic reticulum to augment systole. Phosphodiesterase inhibitors impair the breakdown of cAMP. Calcium sensitizers act by making the troponin-actin-myosin complex more responsive to available intracellular Ca^{2+}. By blocking the Na^+/K^+ ATPase pump, digoxin increases intracellular Na^+ loading of the Na^+-Ca^{2+} exchanger, resulting in less extrusion of Ca^{2+} from the myocyte. Dashed arrow indicates inhibition. The comprehensive mechanisms of actions of these positive inotropic agents are considerably more numerous and complex.

Enhancement of cardiac contractility by these agents with resultant improvement of compromised hemodynamics is not achieved without a price to be paid. Unless the positive inotropic agent also has substantial cardiac unloading properties (preload- and afterload-reduction) and/or substantially causes other favorable effects (e.g., increase of diastolic perfusion time, improvement of autonomic imbalance), these agents invariably increase the metabolic and oxygen demands of the heart. This undesirable characteristic is accentuated by other pharmacologic properties not uncommonly associated with positive inotropes, such as positive chronotropy (increase in heart rate), an increase in systemic vascular resistance, and cardiac dysrhythmias. These unfavorable properties can be especially troublesome in the clinical setting of occlusive

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coronary artery disease (CAD), where the oxygen-metabolic supply to a threatened region can be limited by the coronary obstructing lesions. For these reasons, intravenous positive inotropic therapy should generally be directed at acute short-term intervention and must be administered properly.

At present, chronic oral inotropic therapy is primarily delivered by digoxin, an agent with a relatively mild positive inotropic effect. It is quite possible that any favorable response to digoxin is largely secondary to other accompanying beneficial properties (*See* the heading "Digoxin"). The development of newer orally administered positive inotropic agents to enhance cardiac function has received a lot of attention and research activity over the past four decades, but to date, most have been burdened with adverse effects and outcomes.

For the purpose of clinical application, this chapter is divided into those agents directed at the short-term support of cardiac contraction with the intravenous inotropes, followed by a discussion on chronic long-term inotropic therapy with digoxin.

INTRAVENOUS SHORT-TERM POSITIVE INOTROPIC THERAPY

The drugs placed under this category represent a wide spectrum of pharmacologic effects in addition to their positive inotropic properties. The predominant distinguishing feature among these agents is their effect on peripheral vasculature, which can range from vasodilatation (milrinone) to balanced vascular tone (dobutamine) to vasoconstriction (norepinephrine) (Fig. 2 and Table 1). The cellular mechanisms for the positive inotropic properties of these intravenous agents are centered on increasing intracellular cyclic adenosine monophosphate (cAMP) by either adrenergic receptor stimulation or inhibition of cAMP degradation with subsequent elevation of intracellular calcium available for contraction (Fig. 1).

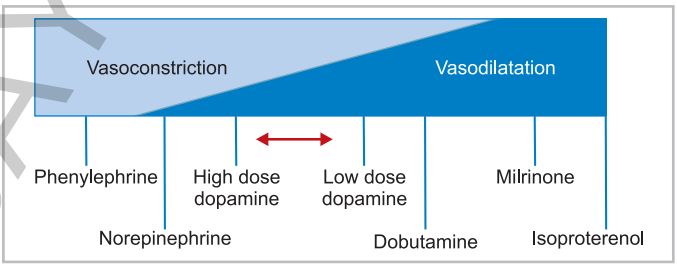

FIG. 2: Effects of short-term positive inotropic agents on peripheral vasculature. The wide range of vascular effects is presented for the agents currently available for short-term positive inotropy and cardiovascular support. The vascular properties are the major determinants for selection of these agents in individual patients.

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TABLE 1: Hemodynamic profiles of the agents currently employed to deliver short-term inotropic and vasoactive support

	Phosphodiesterase inhibitor	Adrenergic agonists				
	Milrinone	Dobutamine	Dopamine		Norepinephrine	Phenylephrine
			Low dose	Higher dose		
Contractility (inotropy)	↑	↑↑↑	↑	↑↑	→↑	↗
Cardiac output	↑↑	↑↑↑	↑	↑	→↑	↗
Heart rate (chronotropy)	→↑	→↑	→↑	↑↑	→↑	→↗
LV filling pressure	↓↓↓	↓↓	↓	→↑	→↑	→↑
Systemic blood pressure	→↓	→↑	→	↑↑	↑↑↑	↑↑↑
Systemic vascular resistance	↓↓↓	↓↓	→	↑↑	↑↑	↑↑↑
Pulmonary vascular resistance	↓↓↓	↓↓	→	→↑	↑	↑

↓, decrease; →, minimal to no change; ↗, mild increase; ↑, increase.

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ADRENERGIC AGENTS

Although the adrenergic receptor agonists can provoke tachycardia and dysrhythmias, they generally have a short elimination half-life. This is an ideal pharmacokinetic property for patients in the monitored critical care setting, where a quick onset and offset of cardiovascular effects allow immediate and tightly controlled hemodynamic support. An undesirable effect can be expected to be reversed shortly, within minutes, after the dose of the agent is lowered or discontinued.

The 3, 4-hydroxyphenyl ring is the essential structure of the catechols, the major component for the adrenergic agents employed for positive inotropic therapy. The molecular structures of the most commonly used adrenergic agents available and applied clinically are shown in Figure 3.

The adrenergic receptor agonists evoke most of their pharmacodynamic effects through activation of β-and α-adrenergic receptors. The myocardium is heavily populated with β-adrenergic receptors and, to a lesser extent, with α-adrenergic receptors; all capable of augmenting cardiac contraction in varying degrees. Stimulation-activation of both β1- and β2-adrenergic receptors augments the inotropic and, in some instances, the chronotropic states of the cardiac cell through mechanisms shown in Figure 1. β-adrenergic receptors are also present in other regions and organs of the body with the β2-adrenergic receptor being the most ubiquitous; accounting for concomitant vasodilatation and bronchodilation during β2-receptor agonism. α-adrenergic receptors are predominantly located in vasculature, such that their stimulation evokes vasoconstriction (also calcium-mediated) in excess of any positive inotropic effect.

The pharmacotherapeutic properties of the adrenergic receptor agonists used clinically for inotropic and hemodynamic support are individually presented under the heading of each. The pharmacologic properties are summarized in Table 1.

Dobutamine

Dobutamine is discussed first, because it is currently the agent most commonly employed for short-term intravenous positive inotropic support. Its overall cardiovascular effects in the setting of LV systolic dysfunction and failure result predominantly from positive inotropic enhancement of depressed cardiac contractility.

Dobutamine was formulated and developed in the laboratory by Tuttle and Mills[1] from a methodical manipulation and branch substitutions of the basic catechol-phenylethylamine molecule. Out of over 15 molecules developed and then studied

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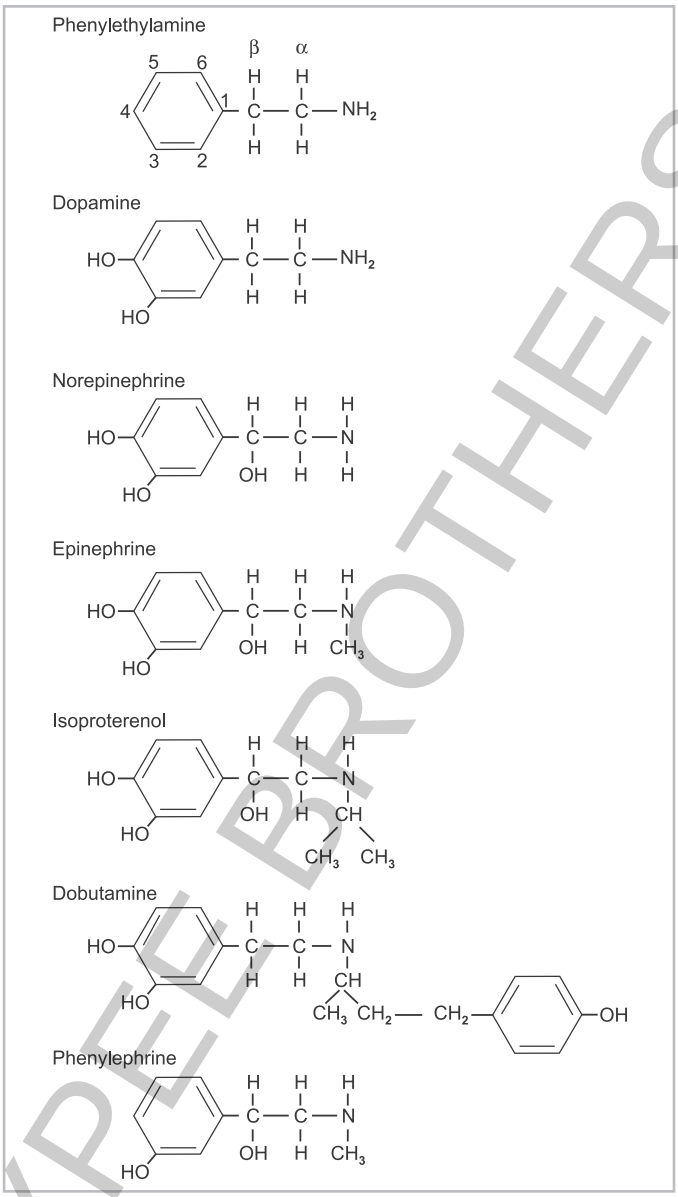

FIG. 3: The molecular structures of the most commonly used adrenergic agents. The phenylethylamine molecule is the basic molecular structure for the adrenergic compounds under discussion. Variations in the hydroxyl attachment at the β-site and the groups at the amino end determine many of the pharmacologic properties and consequent clinical applications of the catechols. Very little modification of the molecular structure is needed to change an intense vasodilator (isoproterenol) to a strong vasopressor (norepinephrine). Deletion of the 4-hydroxyl group from the epinephrine molecule results in phenylephrine, a powerful vasoconstrictor.

in large animal models, dobutamine achieved the greatest increase of cardiac contractility and performed with the least effect on vasculature and heart rate.

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Pharmacologic Effects

Dobutamine is a racemic compound: dextro- and levo-isomers. It activates myocardial β1- and β2-adrenergic receptors to generate cAMP, which enhances calcium entry and release (the downstream mechanisms are depicted in Figure 1); thereby, increases the velocity and extent of myocardial contraction. In chronic heart failure (HF), the number and responsiveness of β1-adrenergic receptors are depleted such that dobutamine's cardiac effects in this clinical setting are largely rendered by activation of β2-receptors.[2] β-adrenergic receptor stimulation also accounts for the chronotropic properties and any dysrhythmias noted with higher dose dobutamine.

In the setting of LV systolic dysfunction and HF, dobutamine generally evokes a mild overall vasodilatory effect, reducing systemic and pulmonic vascular resistances through arteriolar β2-receptor stimulation (and secondary reduction of sympathetic vasoconstriction) exceeding the relatively modest vasoconstricting effects of its α-receptor agonism (Fig. 2 and Table 1). Studies by Binkley et al.[3-5] indicated that the pharmacology of dobutamine in human HF was considerably more complex. Their studies demonstrated that dobutamine favorably affected aortic impedance and vascular-ventricular coupling, allowing further enhancement of ventricular contractility and overall cardiac performance. In the total artificial heart model of the calf, dobutamine augmented cardiac output in the absence of myocardium and its associated positive inotropic mechanisms.[4] This response was the result of the vascular effects of dobutamine: its dextro-isomer (+ enantiomer) reduced systemic vascular resistance and afterload via β2-adrenergic receptor stimulation, and its levo-isomer (– enantiomer) reduced venous capacitance with enhanced venous return via α-receptor agonism.[4,6] The result is augmentation of cardiac output.

Clinical Effects

The major clinical indication for dobutamine administration is short-term positive inotropic support in patients afflicted with ventricular systolic dysfunction and failure, resulting in a problematic drop in blood pressure and systemic perfusion. Short-term support will vary somewhat, but generally, until the patient recovers adequately or is advanced into more definitive interventions (e.g., mechanical support, remedial cardiac surgery). The typical patient requiring inotropic support presents with acute systolic HF or decompensated chronic HF, a reduced stroke volume and cardiac output, elevated ventricular filling pressures, mild-to-moderate reduction in systemic pressure (systolic blood pressure 70–100 mmHg), and notably impaired systemic perfusion (e.g., prerenal azotemia, impaired mentation, elevated liver enzymes); the clinical setting is the "cold and wet"patient.[7]

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Clinical Indications and Applications

Major indications

Short-term (hours to days) positive inotropic and hemodynamic support for patients with ventricular systolic dysfunction resulting in a depressed stroke volume and cardiac output, mild-to-moderate systemic hypotension (systolic blood pressures of 70–100 mmHg), systemic hypoperfusion and an elevated LV diastolic filling pressure (≥18 mmHg).

The support is maintained until the patient recovers or is directed into more advanced cardiovascular support (e.g., intra-aortic balloon counterpulsation and ventricular assist device) and/or remedial intervention (e.g., coronary artery intervention, valvular repair or replacement, and cardiac transplantation).

Additional considerations

- Pharmacologic support as needed for patients with severe HF undergoing major diagnostic or surgical procedures.
- Cardiovascular hemodynamic support for the HF patient as needed during the course of a major illness.
- Pharmacologic bridge in severe HF to standard therapies (e.g., ACEI, β-adrenergic blockade).
- As a continuous infusion via indwelling central venous catheter to provide the only means of stabilizing an unstable or decompensated HF patient to allow discharge from the hospital (to extended care, home or hospice).
- For hemodynamic support during weaning from cardiopulmonary bypass and during immediate recovery from cardiac surgery.
- To facilitate recovery of myocardial stunning in the setting of low-output cardiac failure.
- As a means of improving renal function and urine output in patients hospitalized for low-output, systemic hypoperfusion and volume-overloaded congestive HF when renal responsiveness to standard therapy and diuretics is impaired.
- For hemodynamic support during management of cardiac transplant-rejection complicated by hemodynamic low-output and volume-overloaded decompensation.
- To augment systolic function of problematic systolic failure of the right ventricle.
- To assess ventricular (right or left) contractile reserve.
- To evaluate the severity of aortic valvular stenosis in low-flow and low-gradient aortic stenosis.
- As pharmacologic stress for myocardial perfusion imaging or echocardiographic imaging.

The therapeutics in this general clinical setting can include diuretics for volume overload and elevated ventricular

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filling pressures (>18 mmHg), vasopressor infusion (e.g., norepinephrine, moderate-to-high dose dopamine, phenylephrine) for marked hypotension and shock, dobutamine for systemic systolic pressures of 70–100 mmHg, and combined with a positive inotrope—vasodilator or inodilator (e.g., milrinone) or a vasodilator (e.g., nitroprusside, nitroglycerin and nesiritide) for patients with systolic blood pressure more than 90–100 mmHg. It is relatively common to administer two or more of these agents simultaneously or in succession to attain and maintain the optimal and safest clinical and hemodynamic stability on the way to more definitive interventions. For example, a patient may be receiving a diuretic, dobutamine and nitroprusside, and yet another patient, dobutamine and norepinephrine.

With proper patient selection, specifically the patient with ventricular systolic dysfunction resulting in a fall in stroke volume and cardiac output, an abnormal rise in LV end-diastolic filling pressure, systemic hypoperfusion, and mild-to-moderate reduction in systemic blood pressure, dobutamine increases stroke volume, cardiac output, systemic systolic blood pressure and pulse pressure, and systemic perfusion, while decreasing the elevated LV filling pressure and pulmonary and systemic vascular resistances[8-10] (Fig. 4). In patients with concomitant mitral regurgitation, the reduction in systemic vascular resistance, ventricular volume and mitral orifice area likely account for the decrease in mitral regurgitation; the reduction in mitral regurgitation further augments stroke volume, and cardiac output during dobutamine administration.[10] While there appears to be a dose-related separation of positive inotropy or enhanced contractility with beneficial hemodynamic effects from the potential detrimental effects of positive chronotropy, higher dosing will elicit a faster heart rate and can provoke atrial and ventricular ectopic beats and various forms of tachydysrhythmias (Fig. 4).

Regional blood flow studies at rest in decompensated chronic HF revealed that dobutamine increases limb blood flow proportional to the increase in cardiac output. Dobutamine augments renal blood flow, but generally less than the proportional rise in cardiac output. However, dobutamine favorably affects renal function, glomerular filtration rate, and urine output, and can be expected to augment the renal effects (natriuretic and diuretic responses) of diuretics.[8] There is no statistical change in hepatic-splanchnic flow.[11]

In patients with LV systolic dysfunction and non-obstructed coronary arteries, dobutamine increases coronary blood flow proportional to or greater than the augmented cardiac output and myocardial oxygen consumption.[12,13] This favorable effect on myocardial oxygen balance is related to several mechanisms, including dobutamine-induced enhancement

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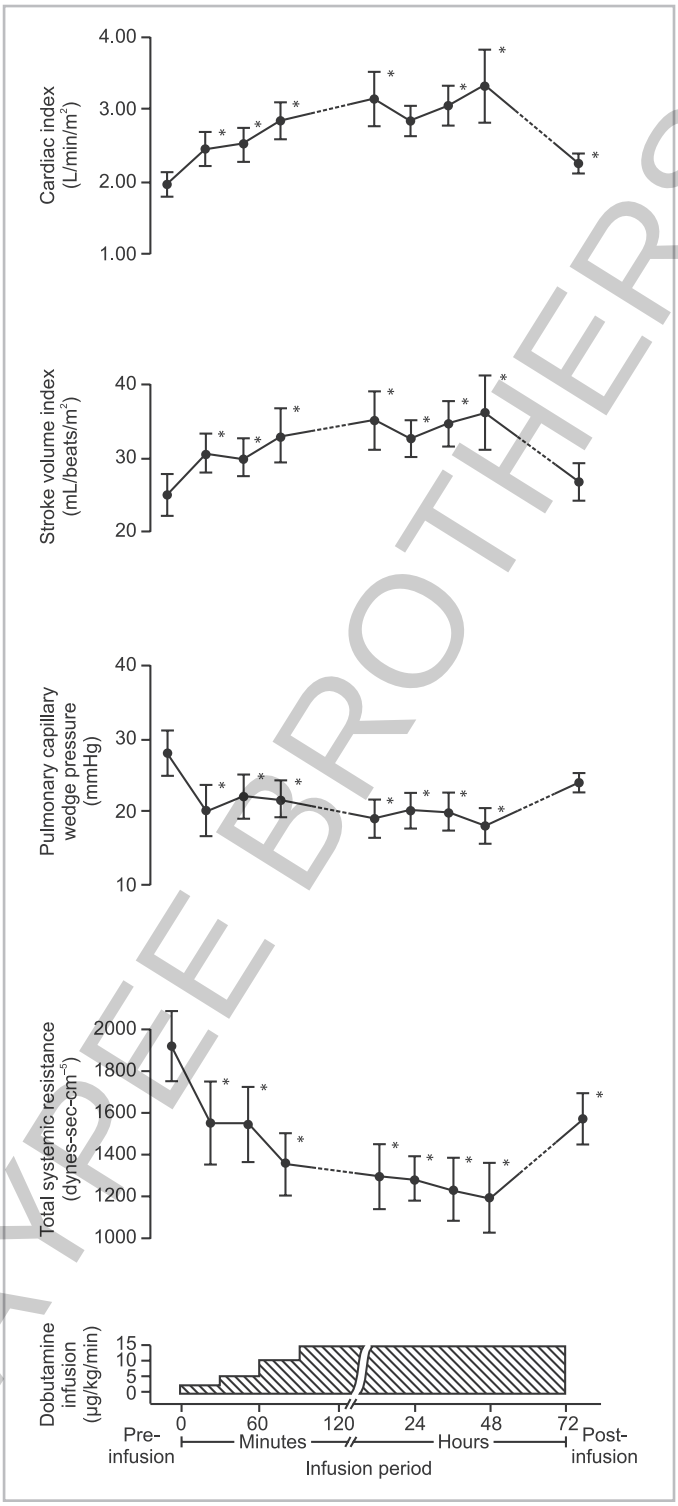

Figure 4 (*continued*)

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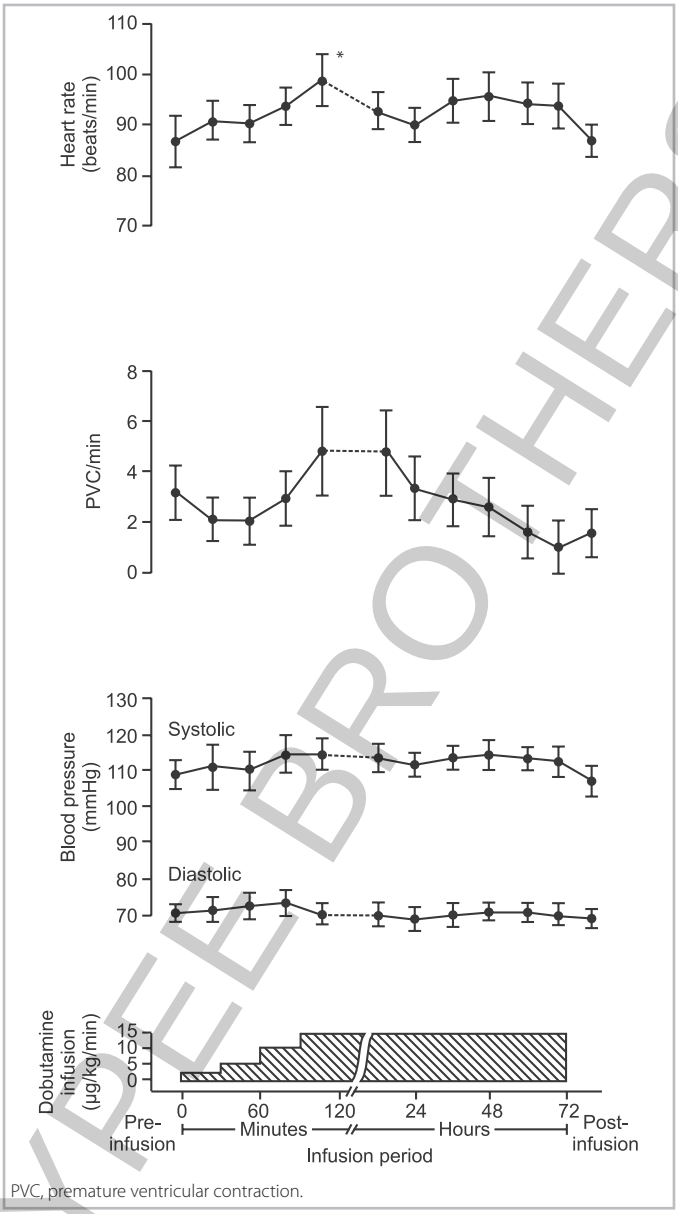
(*continued*)



PVC, premature ventricular contraction.

FIG. 4: Pharmacodynamic curves for the dose-response and sustained infusions (72 hours) of dobutamine in chronic systolic heart failure. The infused dose is presented in the bottom panel.[8] $\bar{X} \pm SD$, n = 25, *p < 0.05 vs. preinfusion baseline.

of coronary perfusion pressure (reduction in LV diastolic pressure is more than the little to no drop in systemic diastolic pressure), an increase in coronary diastolic perfusion time, and a decrease in coronary vascular resistance.[8,12-14] Furthermore, the reduction in aortic impedance, systemic and pulmonary vascular resistances, ventricular afterload, and ventricular

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