Inotropic Therapy for Cardiac Failure Associated with Acute Myocardial Infarction

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COMPARISON OF ACUTE AND CHRONIC FAILURE

Cardiac failure is the second most common complication of myocardial infarction, occurring in 40-50 percent of patients, usually evident within hours of onset of symptoms, reflecting 20-25 percent involvement of the myocardium. The pathogenesis is quite distinct from that of chronic failure and requires different treatment; however, this is still not fully recognized. In most cases, the failure is transient, the underlying pathology is probably a combination of necrosis and ischemia, with the latter associated with transient ischemic dysfunction. The basic defect is sudden loss of contractile function in association with decreased ventricular compliance. The predominant relevant compensatory effects from increased catecholamines are an increase of the heart rate and myocardial contractility, the latter primarily of the remaining normal myocardium, but to some extent of the ischemic but non-necrotic myocardium. The decreased ventricular compliance results in a higher end-diastolic pressure than normal for a given end-diastolic volume. Since the pressure-volume relationship is on the ascending limb, the cardiac output is very sensitive to any decrease in circulatory volume. For example, a patient in severe failure with acute pulmonary edema from acute myocardial infarction, who has lost 500-700 ml of fluid in his/her lungs at the expense of the vascular volume, may be hypotensive and administration of a diuretic would precipitate a decrease in coronary perfusion. In contradistinction to chronic cardiac failure, such as secondary to valvular, congenital, or end-stage ischemic heart disease, institution of a diuretic would be helpful and well tolerated. The feature of acute ischemic cardiac failure and chronic failure exhibit several important differences as follows: 1) patients are normovolemic or hypovolemic as opposed to hypervolemic; 2) cardiac output is often normal; 3) sodium and water retention, a feature of chronic failure is not present in the initial days of acute cardiac failure, and in patients with inferior infarction, there is a tendency to lose salt and water; 4) cardiomegaly from either dilatation or hypertrophy is absent; 5) catecholamines are markedly elevated; 6) failure is usually transient. This refers primarily to those patients with no previous history of cardiac failure, whereas when superimposed on chronic failure the combined pathophysiology exists.

It was assumed for some time that the pathogenesis of acute failure of ischemic heart disease and of chronic failure was the same, so the traditional regimen of administration of diuretics and digoxin developed for chronic failure was considered appropriate for acute failure. The experience of the CCU has highlighted the lack of hypervolemia and cardiomegaly in acute failure, but habits have changed slowly. Despite the increasing recognition of the different pathogenesis, only now are we beginning to change our treatment. There is widespread appreciation of the inappropriateness of therapy with digoxin and the beneficial effect of vasodilators, but the frequent use of diuretics continues despite hypovolemia and the potential for hypotension. The cardiac failure of acute myocardial infarction is usually left ventricular, with only about 5 percent due to failure of the right ventricle. The clinical picture of left ventricular failure is dominated by that of pulmonary congestion, the symptoms of which are often the primary indications for treatment. In patients with mild failure, as evidenced by basal rales and no other symptoms or evidence of hypoxemia, no specific treatment is recommended other than oxygen and morphine.

DIURETICS AND VASODILATORS

In patients with moderate failure, in whom there is an S3, and symptoms of pulmonary congestion, specific therapy is indicated. For immediate relief in the patient who is normotensive or hypertensive, the administration of a vasodilator initially is the most appropriate therapy, preferably with nitroglycerin as an intravenous infusion. If this is inadequate, an inotropic agent should be initiated. Diuretics are frequently administered in this situation and do indeed relieve the symptoms as there is a prompt decrease in

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venomotor tone resulting in pooling of the blood and decreased ventricular filling pressure, analogous to vasodilators. This vasodilatory response occurs rapidly and is independent of the diuresis. The diuresis occurs some time later and often precipitates a significant decrease in cardiac output and not infrequently hypotension, depending upon the circulatory volume and the pressure-volume relationship of the ventricle. It is recommended that if one initiates therapy with a diuretic rather than a vasodilator, it should be with a low dose such as 20 mg of furosemide administered intravenously. The patient should be checked carefully over the next one to two hours for possible hypotension. Diuretics have no effect per se on cardiac performance, but in patients with chronic failure and fluid overload, they help to relieve the symptoms of congestion while the cardiac output remains the same or decreases slightly. In contrast, in patients with failure caused by acute myocardial infarction, the use of diuretics almost always decreases the cardiac output, the extent of which depends upon the fluid status. In patients with inferior infarction and failure, particularly with significant right ventricular involvement, the administration of a diuretic may be catastrophic, simulating cardiogenic shock. Until one is certain of the fluid status, diuretics should be withheld from patients with inferior infarction, as not infrequently fluid may be required. In patients with acute pulmonary edema and borderline blood pressure, it is preferable to initiate therapy with an inotropic agent. In patients with predominant right ventricular failure due to right ventricular infarction, therapy with diuretic and vasodilator drugs are contraindicated. If therapy other than fluid is required, an inotropic agent should be administered intravenously. In patients with high pulmonary occlusive pressure who do not respond to therapy with vasodilators and/or inotropic agents, diuretic drugs should be administered in high doses.

**Indications for Inotropic Therapy**

In summary, the indications for inotropic therapy in patients with cardiac failure caused by acute myocardial infarction are as follows: 1) initial therapy in patients with moderate to severe failure and borderline blood pressure; 2) initial therapy in patients with right ventricular failure and adequate vascular volume or patients who do not respond to a fluid challenge; and 3) secondary therapy if vasodilator therapy is inadequate, either alone or in combination with vasodilator therapy. The preferred inotropic agent should have: 1) rapid onset of action; 2) short plasma half-life; 3) potent inotropic effect; 4) minimal chronotropic effect; and 5) relieve pulmonary congestion while maintaining a reasonable balance between oxygen supply and demand such that infarct size is not increased. The inotropic agents to date that have been evaluated clinically are digoxin, dobutamine, dopamine and most recently, amrinone. However, the two agents preferred are dobutamine and dopamine.

**Digoxin**

Digoxin may be used appropriately for control of atrial fibrillation, but is rarely used now for acute failure of myocardial infarction. Digoxin administered intravenously exhibits peak action between 60 and 90 minutes with a half-life of about 31 hours. Optimal effect is probably achieved when loading occurs over 24 hours. In a study performed in patients with acute myocardial infarction and failure, digoxin given intravenously was compared to dobutamine. Digoxin had minimal inotropic effect compared to dobutamine and induced only a minimal change in the cardiac output while dobutamine markedly increased the cardiac output. More importantly, digoxin had no effect on left ventricular filling pressure in contrast to dobutamine which decreased it significantly. The vascular resistance was also decreased by dobutamine, but unaffected by digoxin. These hemodynamic effects were achieved by dobutamine while maintaining the heart rate to within only a 10 percent increase over baseline. Once a patient is digitalized, because of the long half-life, it requires at least a week to determine whether therapy should be sustained. Consequently, even if the failure is transient, the patient is often discharged on digoxin. Thus, the delayed onset of action, long plasma half-life, minimal inotropic effect, lack of effect on pulmonary congestion, and the potential for increased ventricular irritability precludes the use of digoxin for the treatment of failure in acute myocardial infarction. If the patient is receiving digoxin on admission, therapy may be continued; similarly, it does not preclude the concomitant use of dobutamine, dopamine or amrinone.

**Dobutamine**

Therapy with dobutamine, a semi-synthetic catecholamine which stimulates the β1 receptors of the myocardium, results in an increase in contractility equal in potency to that of isoproterenol. Its onset of action is within minutes and its half-life is about two minutes, as with all catecholamines including dopamine. However, unlike isoproterenol, the improved stroke volume and decrease in ventricular filling pressure occurs without a significant change in heart rate or blood pressure. With increasing doses, one sees an increase in vasodilation due to peripheral β2 receptor stimulation with an increase in heart rate. In moderate to high doses, any minimal α-adrenergic effect is completely overdriven by the β1 and β2 effects. Dobutamine has been studied extensively in patients
with acute myocardial infarction and has consistently been shown to be effective in relieving the symptoms of pulmonary congestion in association with a significant increase in cardiac output. Studies show dobutamine, when administered such that there was not more than a 10 percent increase in heart rate, is associated with improved hemodynamics including a decrease in ventricular filling pressure without an increase in arrhythmias or infarct size. Recent studies suggest coronary flow is increased over and above that required to meet the increased demand by one or more of the following mechanisms: 1) improved coronary perfusion due to the decrease in left ventricular filling pressure; 2) decreased oxygen consumption from decreased intramyocardial tension; 3) a direct vasodilatory effect on the coronary vessels. In experimental animals, several studies have shown dobutamine either has no effect or, when given early, is associated with a significant reduction of infarct size. In patients with acute myocardial infarction, the use of a Swan-Ganz catheter is recommended when administering dobutamine; otherwise, one can titrate the dose so that the heart rate does not increase by more than 10 percent. It is recommended to initiate therapy at a dose of 2.5 μg/kg/min and increase, if necessary, to 10 μg/kg/min with the average dose being 5 to 10 μg/kg/min. Since dobutamine increases coronary blood flow, improves hemodynamics and relieves pulmonary congestion without a deleterious effect on infarct size, it is presently the inotropic agent of choice in the treatment of cardiac failure with acute myocardial infarction.

Dopamine

Dopamine is an endogenous catecholamine which acts on β-receptors in the heart to increase contractility and α-adrenergic receptors in the periphery to induce vasoconstriction. The effects are through either direct stimulation of the receptors or indirectly through release of norepinephrine. In low doses (<5μg/kg/min) it has an additional effect through stimulation of specific dopamine receptors which increases renal and mesenteric blood flow, although in moderate to high doses, vasoconstriction predominates in all vascular beds. While the inotropic effect of dopamine and dobutamine are similar, dopamine exerts greater chronotropic effects. The major difference between dopamine and dobutamine in the treatment of acute cardiac failure relates to the ventricular filling pressure and the systemic peripheral vascular resistance. In low doses, dopamine has no effect on ventricular filling pressure, while in moderate to high doses, it actually increases ventricular filling pressure, and therefore is not particularly suitable for relief of pulmonary congestion. Similarly, dopamine increases peripheral vascular resistance which increases the work load of the heart. In contrast to the balanced effect of dobutamine on myocardial oxygen consumption and supply, dopamine exerts a negative effect, although there is no study available assessing specifically the effect of dopamine on infarct size. Doxamine in low doses selectively increases renal blood flow, whereas the increase in renal blood flow from dobutamine is secondary to an overall increase in systemic circulation, the latter being the more appropriate objective in the treatment of cardiac failure. Dopamine, like dobutamine, should be initiated at a dose of 2.5 μg/kg/min and titrated to the desired hemodynamics with an average dose of 10 to 15 μg/kg/min. In cases where there is need to increase renal blood flow selectively, a combination of dopamine in low dose (<5μg/kg/min) with dobutamine may be administered. The combination of therapy with dopamine and a vasodilator drug is frequently used, dopamine to increase contractility, and the vasodilator to relieve pulmonary congestion and prevent the increase in systemic vascular resistance. In patients who are hypotensive, dopamine may be more appropriate to increase coronary perfusion pressure which will be discussed under the section on cardiogenic shock.

Amrinone

Amrinone is a new inotropic agent that inhibits phosphodiesterase, indirectly elevates cyclic AMP, and increases calcium availability. Amrinone is administered intravenously as a loading dose of 1.5 mg/kg followed by an infusion at a rate of 10-20 μg/kg/min. Its onset of action is rapid as with catecholamines, but its half-life is much longer, averaging about two hours. Amrinone has a much less potent inotropic effect compared to catecholamines, but has a similar vasodilating effect to that of dobutamine with minimal chronotropic effect.

BIBLIOGRAPHY


