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Editorial Comment

Management of Patients With Heart Failure and Angina: Do Coexistent Diseases Alter The Response to Cardiovascular Drugs?*

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Poisons and medicine are oftentimes the same substance given with different intents.

Peter Mere Latham

Because coronary artery disease is the most frequent cause of left ventricular dysfunction in the United States and Europe, it is common to see patients with heart failure who complain of angina pectoris either at rest or on exertion. Anginal symptoms may be mild and add little to exercise intolerance, or they may be severe and emerge as the primary reason for the patient's disability. Physicians have long assumed that when cardiac failure and cardiac ischemia coexist, the two conditions should be managed independently: each disease should be treated as if the other were not present. This approach has been strongly supported by the beliefs that 1) each condition can aggravate the other, and 2) most drugs used in the treatment of angina and heart failure share a common mechanism of action (since they all function to reduce ventricular size or pressure). Therefore we might expect that drugs used for one condition would help to treat the other, and thus, we see patients with both left ventricular dysfunction and ischemia who are receiving as many as *seven* different cardiovascular drugs: digoxin, a diuretic drug, a converting enzyme inhibitor, nitrates, a beta-adrenergic blocking agent, a calcium channel blocking agent and aspirin. Yet, despite such intensive medical therapy, many of these patients continue to experience both dyspnea and angina.

Why are these patients so difficult to treat? Certainly, we have effective drugs for both heart failure and angina pectoris. Controlled trials have shown that digitalis, diuretics and converting-enzyme inhibitors are useful in the management of heart failure, and that nitrates, beta-blockers, calcium channel blockers and aspirin are useful in the management of ischemic heart disease. Why then are the clinical responses to these drugs so disappointing when both conditions are present? Controlled clinical trials generally exclude patients who have more than one cardiovascular condition. For example, patients with exertional angina are not included in clinical trials of drugs for heart failure, and patients with heart failure or severe left ventricular dysfunction are excluded from controlled trials of drugs for angina pectoris. As a result, there is virtually no information on the efficacy and safety of cardiovascular drugs for one disorder when other conditions coexist. The dilemma is similar to the one physicians face when they treat patients with heart failure who have serious ventricular arrhythmias. For many years, patients with heart failure were excluded from studies that investigated the utility and safety of antiarrhythmic agents, and thus, physicians treated heart failure and ventricular arrhythmias as if they were independent entities, since they had little reason to believe that drugs used in the management of these conditions might interact unfavorably. Only recently have we learned that left ventricular dysfunction markedly decreases the efficacy and increases the toxicity of antiarrhythmic agents (1); the presence of heart failure produces a marked deleterious shift in the risk-to-benefit relation governing the use of these potent drugs.

Given this experience with antiarrhythmic agents, we ask: does the presence of ischemia alter the response to drugs for heart failure? Does the presence of heart failure alter the efficacy and safety of antianginal agents? The study by Cleland et al. (2) in this issue of the Journal provides strong support for the occurrence of such adverse interactions.

Effect of Ischemia on Drugs for Heart Failure

Digitalis. Controlled trials (3) have shown that digitalis improves the hemodynamic and clinical status of patients with chronic heart failure, whether or not they have coronary artery disease. However, patients with active angina were never enrolled in these studies, and theoretically, such patients may be less responsive to and tolerant of digitalis than are patients without symptomatic ischemia. The symptoms of heart failure in patients with active angina are frequently related to diastolic dysfunction, which responds poorly to digitalis (4), possibly because digitalis exerts unfavorable effects on ventricular relaxation (5). Furthermore, although digitalis rarely produces serious arrhythmias when administered in therapeutic doses to patients with heart failure in stable condition, its proarrhythmic effects may be enhanced in the presence of active ischemia (6).

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These experimental observations are consistent with clinical concerns about a possible adverse effect of digitalis on the survival of patients who have recovered from an acute myocardial infarction (7).

Angiotensin-converting enzyme inhibitors. Angiotensin-converting enzyme inhibitors lessen symptoms and reduce the risk of death in patients with chronic heart failure, whether or not they have coronary artery disease (3). Although these drugs occasionally produce marked decreases in systemic blood pressure (and thus, in coronary perfusion pressure), these hypotensive effects are rarely associated with end-organ ischemia, and their use in controlled clinical trials has not been accompanied by reports of worsening angina. In fact, preliminary data (8–10) suggest that converting enzyme inhibitors may exert *favorable* effects on myocardial ischemia by dilating coronary arteries, reducing sympathetic stimulation of the heart and decreasing myocardial oxygen consumption. These physiologic actions may explain why converting enzyme inhibitors have been reported to ameliorate the development of stress-induced angina in patients with coronary artery disease who do not have heart failure (10,11). Furthermore, converting enzyme inhibitors have been used with increasing frequency during the early hours and days after an acute myocardial infarction to prevent the adverse hemodynamic effects of neurohormonal activation and ventricular dilation (12,13).

The present study. Unfortunately, all of the controlled studies using converting enzyme inhibitors in patients with heart failure have excluded patients with active angina—at least until the publication in this issue of the Journal of the study by Cleland et al. (2). Their report presents the results of the first placebo-controlled study to evaluate the effects of a converting enzyme inhibitor (captopril) in patients with both angina and heart failure. In contrast to its beneficial effects in patients without ongoing ischemia, captopril *reduced* exercise tolerance and *increased* both the severity of angina and the consumption of nitroglycerin in patients with active angina. The risk of these adverse effects was directly related to the magnitude of the hypotensive effects of the drug. Angina was increased primarily in patients who experienced marked decreases in systemic blood pressure; this was especially true when the hypotensive effects of captopril and nifedipine were combined.

Why does the presence of angina alter the risk to benefit relation that governs the use of converting enzyme inhibitors in patients with heart failure? In patients with heart failure but without angina, a critical stenosis is primarily found in coronary arteries that supply hypocontractile (i.e., infarcted) myocardial segments. In the absence of viable myocardium distal to the stenosis, changes in coronary perfusion pressure in these segments may be functionally unimportant. In contrast, angina is a common finding if stenoses are present in coronary arteries that supply *actively contracting* regions of the left ventricle, and it is likely to be exacerbated if coronary perfusion pressure is compromised. In the study of Cleland et al. (2), this anatomic substrate was present in most patients who responded unfavorably to captopril.

Effect of Heart Failure on Drugs for Ischemia

Beta-adrenergic blocking drugs. Although controlled studies have shown that beta-blockers are potent antianginal agents, none of these trials enrolled patients with congestive heart failure, because of fears that a beta-blocker would aggravate heart failure. Such concerns seem reasonable, since any increase in cardiac size and wall stress produced by the negative inotropic effects of beta-blockers could act to limit their anti-ischemic actions. As a result, most clinicians have avoided the use of a beta-blocker in patients with coexistent heart failure and angina pectoris. However, the need for such caution has been recently questioned after the publication of the results of two long-term controlled trials (14,15) that showed that a beta-blocker may produce hemodynamic and clinical improvement in chronic heart failure. Yet the benefits of beta-blockade noted in these two studies were observed in patients *without* coronary artery disease; patients with such disease may not respond favorably to these drugs (16). Any long-term benefit that beta-blockers may produce in patients with ischemic heart failure may be related primarily to their antiarrhythmic—rather than their anti-ischemic—effects (17).

Calcium channel blockers. As in the case of other antianginal drugs, the controlled trials that have demonstrated the utility of calcium channel blockers as antianginal agents have generally excluded patients with heart failure. In the few studies (18) that included such patients, patients with heart failure experienced the least benefit and most adverse reactions during treatment. Although the deleterious effects of calcium channel blockers in patients with left ventricular dysfunction have traditionally been attributed to their negative inotropic effects, recent evidence (19) has indicated that the hormone-stimulating actions of these drugs may underlie many of their detrimental effects. This hypothesis has led some physicians to suggest that the neurohormonal activation produced by calcium channel blockers might be reduced by the concomitant administration of a converting enzyme inhibitor. The observations of Cleland et al. (2) however, indicate that this combination may cause a marked hypotensive reaction that can aggravate myocardial ischemia.

Drug–Drug Interactions

To make matters more complicated, drugs used in the treatment of heart failure and myocardial ischemia may interact with each other, both favorably and unfavorably. On the one hand, beta-blockers may reduce the arrhythmogenic potential of digitalis in subjects with ischemic heart disease (6). On the other hand, aspirin (which is widely used in

patients with angina) may attenuate the favorable hemodynamic actions of the converting enzyme inhibitors (20).

Therapeutic Implications

These observations indicate that disease states may interact to modify the efficacy and safety of cardiovascular drugs. Although much attention has recently been directed toward the interplay of drugs and disease in patients who have both heart failure and ventricular arrhythmias (1), the report by Cleland et al. (2) underscores the fact that similar adverse interactions may occur in patients who have both heart failure and angina pectoris. The presence of angina pectoris may decrease the efficacy and increase the risks of drugs for heart failure; the presence of heart failure may reduce the benefits and enhance the toxicity of antianginal agents.

How then should we treat patients with active symptoms of both heart failure and angina? Although both diuretics and nitrates would appear to be first-line drugs in such individuals, many patients remain unresponsive to both agents. What should the clinician do when symptoms persist? Controlled trials indicate that, despite a higher operative risk (21), patients with both heart failure and angina pectoris are ideal candidates for coronary bypass surgery. Revascularization offers these severely ill patients a better chance of survival and lessened symptoms than does pharmacologic therapy (22). Similarly, surgery (specifically, implantation of a cardiac defibrillator) may also provide an ideal remedy for the patient with heart failure and serious ventricular arrhythmias. Hence, when cardiovascular diseases and cardiovascular drugs interact unfavorably, physicians may accomplish more by withdrawing—rather than adding—drugs. Under such circumstances, mechanical approaches may provide the only therapeutic solution.

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