Careful examination of the results of the Multicenter Diltiazem Postinfarction Trial (MDPIT) by the Adverse Experience Committee and the MDPIT Research Group, reported in this issue of Circulation, 1 offers further substantiation that diltiazem is associated with enhancement of congestive heart failure in patients with moderately severe left ventricular dysfunction. However, there are well-known drawbacks to using large data bases to evaluate treatment effects. It is quite possible, perhaps likely, that significant differences will be discovered during any posthoc subset analysis. Therefore, the conclusions drawn from the MDPIT are somewhat tenuous, but still consistent with previous findings.

There is a long-standing concern that the use of calcium channel blockers contributes to the worsening of heart failure in patients with preexisting left ventricular dysfunction. 2–4 The issue of whether calcium channel blockers aggravate or unmask heart failure is of more than passing interest because these drugs are widely used to treat angina pectoris in patients with underlying left ventricular dysfunction.

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Their use as first-line therapy for overt congestive heart failure may be questioned as several important issues remain to be addressed: How do they exacerbate heart failure? Do the more “vascular-selective” second generation agents have the same propensity to depress myocardial function? The question of whether all calcium channel blockers unmask or aggravate congestive heart failure in patients with inherent left ventricular dysfunction takes on growing importance as many new and more potent dihydropyridines are brought on the market.

How do calcium channel blockers contribute to the worsening of heart failure? By their basic mechanism of action, all such agents have intrinsic myocardial depressant activity and can further depress an already reduced inotropic state. Some have more intrinsic negative inotropic activity than others, and on a per molar basis, nifedipine most potently reduces the contractile state, with diltiazem being least potent in vitro and in vivo and verapamil having an intermediate potency. 5 The potencies of the newer dyhydropyridines like nicardipine, nitrrendipine, amlopidine, nisoldipine, isradipine, and felodipine have not been as rigorously studied. If the negative inotropic effects of calcium channel blockers are not counterbalanced by their vasodilator effects, acute marked hemodynamic and clinical deterioration can occur. 6–9 Therefore, the direct negative inotropic effects of these agents undoubtedly play some role in their ability to exacerbate heart failure, particularly if the heart has baseline severe left ventricular dysfunction. However, this is probably not the whole story. In the MDPIT, the magnitude of risk for heart failure was not substantially enhanced in patients receiving β-blockers, implying that mechanisms other than direct cardiodepression may contribute to the adverse long-term effects of diltiazem in patients with left ventricular dysfunction. There was, however, a trend toward exacerbation of late heart failure in patients assigned to diltiazem who were also taking a β-blocker. 1

Calcium channel blockers increase plasma norepinephrine and plasma renin activities in normal volunteers and patients with hypertension. 10–13 The primary stimulus to the release of these hormones is a fall in blood pressure, although a direct release of renin might occur as a result of interference of the inhibiting effect of calcium on renin release. 14,15 The increase in renin release may also be related to an influence of Ca2+ channel blockers on the juxtaglomerular apparatus, because direct-acting vasodilators with similar hypertensive effects do not raise plasma renin activity in patients with heart failure. 16,17 Nifedipine and nitrrendipine do not consistently raise plasma norepinephrine in patients with heart failure. 16–19 Patients with advanced heart failure are far less likely to mount a brisk sympathetic response to a modest drop in blood pressure because they have defective baroreceptor activity. Aldosterone release is also not observed following the use of calcium channel blockers in congestive heart failure, 10,11,13 possibly because calcium channel blockers inhibit angiotensin II-mediated aldosterone release. 20 It is possible that calcium channel blocker—
induced activation of the renin-angiotensin system contributes importantly to worsening heart failure. However, other agents widely used to treat congestive heart failure, like diuretics, are also well known to stimulate the renin-angiotensin system and are hardly considered to cause any worsening of congestive heart failure. In summary, neither the direct negative inotropic effects nor neuroendocrine activation seems solely responsible for the propensity of calcium channel blockers to unmask or aggravate underlying congestive heart failure. What, then, is the basis for the increase in late onset of congestive heart failure when diltiazem is used in patients with left ventricular dysfunction?

The systolic load that the left ventricle must empty against is a combination of many elements, including left ventricular wall stress and the impedance provided by the large conductance and smaller resistance vessels. The characteristics of the peripheral vasculature are important in determining left ventricular performance in patients with congestive heart failure. The systemic vascular resistance and the distal compliance of the vasculature are two independent properties of the vascular impedance load.21 It is entirely possible that the responses of distal compliance and proximal compliance to vasodilator drugs are different from that of the systemic vascular resistance. Preliminary data suggest that the vascular compliance is a dynamic process that can be differentially affected by various vasodilator agents.22 For example, although diltiazem has rather weak negative inotropic properties, it may fail to improve peripheral vessel compliance to the same extent as the more potent dilating dihydropyridines, although data for this are lacking. The ability to improve the compliance of the arterial tree may be an important factor in determining whether a particular calcium channel blocker will have a favorable, neutral, or unfavorable effect on the natural course of congestive heart failure. This brings us to the more vascular selective second generation dihydropyridines: amloidipine, nitrendipine, nisoldipine, nicardipine, isradipine, and felodipine. It is possible, but certainly not proven, that those agents that markedly improve vascular compliance may unload the ventricle to a far greater extent and thereby more than offset any negative inotropic effect or tendency to activate neuroendocrine systems. The effects of calcium channel blockers on vascular compliance may provide a clue as to whether the agent will be useful in treatment of patients with heart failure.

In summary, according to the post hoc analysis of the MDPIT group, the aggregate available data should dissuade clinicians from using diltiazem as the primary vasodilator therapy for patients with overt congestive heart failure or severely depressed left ventricular dysfunction (ejection fraction <40%). The mechanisms by which calcium channel blockers aggravate or unmask congestive heart failure are not entirely clear, but do not seem to be a simple matter of direct myocardial depression or neuroendocrine activation. Although the effects of calcium channel blockers on vascular compliance are largely unknown, information regarding peripheral vascular effects may be helpful in predicting their usefulness as vasodilators in the treatment of heart failure. Opinion regarding the newer, more vascular selective dihydropyridines in the setting of congestive heart failure should be reserved until more information is available. However, it is possible that the dihydropyridines, when used in conjunction with angiotensin converting enzyme inhibitors, may still prove useful as vasodilator therapy for patients with heart failure.

References


Calcium channel blockers and congestive heart failure.
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