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Sustained Hemodynamic Response to Flosequinan in Patients With Heart Failure Receiving Angiotensin-Converting Enzyme Inhibitors

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Objectives. **We evaluated the short- and long-term effects of flosequinan in 47 patients with severe heart failure despite ongoing captopril treatment.**

Background. **There have been no previous evaluations of the long-term hemodynamic effects of any direct-acting vasodilator in patients with heart failure receiving an angiotensin-converting enzyme inhibitor. Flosequinan is an arterial and venous vasodilator with actions similar to those of the hydralazine–isosorbide dinitrate combination.**

Methods. **After baseline hemodynamic measurements using balloon-tipped pulmonary artery and radial arterial catheters, patients were randomized to receive 50, 100 or 150 mg of flosequinan daily. Hemodynamic variables were measured immediately before and after short-term flosequinan administration and after 8 weeks of therapy.**

Results. **With short-term flosequinan administration, mean arterial, right atrial and left ventricular filling pressures decreased by 6.4 ± 1.1, 3.8 ± 0.5 and 7.3 ± 0.7 mm Hg, respectively (all $p < 0.001$). Cardiac index increased by 0.5 ± 0.1 liters/min per m^2, systemic vascular resistance decreased by 616 ± 105 dynes·s·cm^{-5} and heart rate increased by 4 ± 1 beats/min (all $p < 0.001$). After 8 weeks of long-term flosequinan administration, the vasodilator effect of a dose of flosequinan persisted. Compared with pretreatment baseline values, mean arterial, right atrial and left ventricular filling pressures at the peak effect of flosequinan were decreased by 3.5 ± 1.3, 2.8 ± 0.7 and 5.1 ± 1.3 mm Hg, respectively (all $p < 0.01$). Systemic vascular resistance had decreased by 585 ± 95 dynes·s·cm^{-5}, cardiac index had increased by 0.5 ± 0.1 liters/min per m^2 and heart rate had increased by 10 ± 2 beats/min (all $p < 0.001$).**

Conclusions. **The arterial and venous vasodilator flosequinan exerts both short- and long-term sustained hemodynamic effects in patients with heart failure receiving angiotensin-converting enzyme inhibitors.**

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It has recently been proposed that direct-acting vasodilators can be utilized as adjunctive therapy for the treatment of heart failure in patients receiving angiotensin-converting enzyme inhibitors (1). The results of the second Veterans Administration Heart Failure Trial (V-HeFT-II) suggested that the use of enalapril in patients with heart failure decreases mortality more than the use of hydralazine and isosorbide dinitrate but that the combination of hydralazine and isosorbide dinitrate might be a better treatment for increasing exercise capability (2). Concurrent administration of an angiotensin-converting enzyme inhibitor and a vasodilator could theoretically maximize both survival and exercise tolerance.

Flosequinan is a vasodilator that has actions similar to those of the hydralazine–isosorbide dinitrate combination, exerting balanced arterial and venous vasodilation in patients with congestive heart failure (3). After short-term administration of flosequinan in patients not receiving angiotensin-converting enzyme inhibitors, left ventricular filling, mean arterial and right atrial pressures decrease, and there is a consequent rise in cardiac index. After long-term therapy, the same response is observed (4,5). These beneficial hemodynamic effects produce improved exercise tolerance and decreased symptoms of heart failure (6).

Patients receiving angiotensin-converting enzyme inhibitors might have a similar clinical response to flosequinan if the drug exerts beneficial hemodynamic effects in such patients; however, because the extent of vasodilation induced by an agent is related to the basal vasoconstrictive state of the patient (7), patients receiving angiotensin-converting enzyme inhibitors might react differently to flosequinan (and other direct-acting vasodilators) than would those not being treated with these agents. Yet, there have been no previous evaluations of the long-term hemodynamic effects of any direct-acting vasodilator in patients with heart failure receiving an angiotensin-converting enzyme inhibi-

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tor. Using pulmonary artery thermodilution catheters, we therefore assessed both the short- and long-term hemodynamic effects of flosequinan in patients receiving captopril.

Methods

Study patients. We studied 47 patients with severe left ventricular dysfunction who were referred for treatment of refractory heart failure. There were 35 men and 12 women, aged 21 to 79 years (mean age 61 ± 2). All patients had a left ventricular ejection fraction <40% by radionuclide angiography (range 5% to 36%, mean 18 ± 1%). The cause of heart failure was ischemic heart disease or dilated cardiomyopathy; 28 patients were in New York Heart Association functional class III and 19 were in class IV. All patients had received constant doses of digitalis and diuretic agents for at least 5 days and had received angiotensin-converting enzyme inhibitors for at least 2 months. They were receiving captopril three times daily in a total daily dose of 37.5 mg (4 patients), 75 mg (20 patients), 112.5 mg (2 patients) or 150 mg (21 patients). Previous therapy with other vasodilator drugs was withdrawn for ≥5 days before entry into the study. Another 10 patients were initially entered into the study but were withdrawn before final evaluation because of death (7 patients), rash (1 patient), patient refusal (1 patient) and problems with the Swan-Ganz catheter (1 patient).

Short-term hemodynamic measurements. Right heart catheterization and arterial cannulation were performed at least 12 h before hemodynamic assessment. All cardioactive medications were withheld for ≥8 h, and hemodynamic variables were measured using previously described procedures (8). The baseline measurements were made before the administration of any doses of flosequinan.

Patients were then randomized to receive 50, 100 or 150 mg of flosequinan daily in addition to their previous medications. Because the full effects of flosequinan are not apparent after administration of only a single dose of the drug (9), the short-term hemodynamic assessment of flosequinan was performed on day 2 of flosequinan administration. Hemodynamic measurements were obtained before administration of flosequinan and periodically for 4 h. No other medications were given on that day until completion of hemodynamic assessment.

Long-term treatment. After the short-term measurements were made, patients were discharged from the hospital. For the next 8 weeks, they received their usual prestudy medications in addition to the daily flosequinan dose to which they were randomized.

Long-term hemodynamic measurements. Patients were readmitted to the hospital 8 weeks after baseline assessment, and hemodynamic measurements were obtained as initially performed. Long-term pretreatment values were obtained ≥12 h after placement of the catheter and the effects of drug administration were assessed the following day in a manner analogous to that of the initial evaluation.

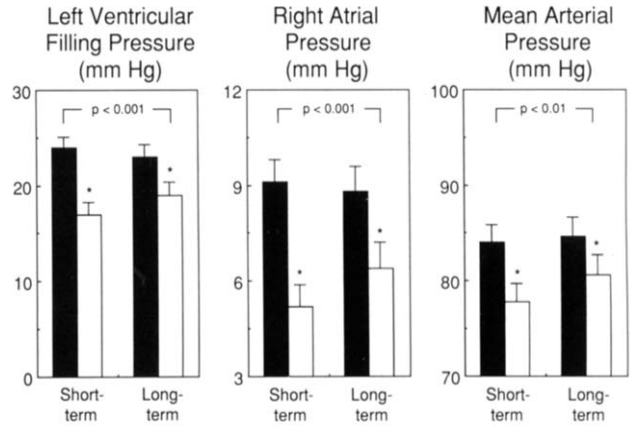

Figure 1. Mean arterial, left ventricular filling and right atrial pressures before and after 8 weeks of therapy with flosequinan in 47 patients with severe heart failure receiving long-term treatment with captopril. **Solid bars** indicate the values for each hemodynamic variable before flosequinan administration; **open bars** indicate values 1 h after the drug was given; *$p < 0.001$ compared with the period before flosequinan dosing for that evaluation period; p values shown compare short-term variables with those obtained before any flosequinan therapy. After long-term flosequinan therapy, a dose of this drug exerted effects similar to those initially seen.

Data analysis. Statistical comparisons were made using the two-tailed Student *t* test for paired data. The values obtained 1 h after flosequinan administration were used to evaluate the short-term effect of drug administration. The mean value ± SEM are given where appropriate.

Results

Despite long-term treatment with captopril, the patients studied were severely ill as demonstrated by the markedly abnormal hemodynamic variables assessed before flosequinan administration (Fig. 1 and 2). The mean left ventricular filling pressure was 24 ± 1.1 mm Hg and the mean cardiac index was 1.8 ± 0.1 liters/min per m^2.

Short-term flosequinan administration caused significant vasodilation and an increased heart rate. Mean arterial, right atrial and left ventricular filling pressures decreased by 6.4 ± 1.1, 3.8 ± 0.5 and 7.3 ± 0.7 mm Hg, respectively (all $p < 0.001$) (Fig. 1). Cardiac index increased by 0.5 ± 0.1 liters/min per m^2; systemic vascular resistance decreased by 616 ± 105 dynes·s·cm^{-5} and heart rate increased by 4 ± 1 beats/min (all $p < 0.001$) (Fig. 2).

After 8 weeks of therapy with flosequinan, but before administration of the daily dose of the drug, cardiac index had increased by 0.4 ± 0.1 liters/min per m^2 ($p < 0.001$), systemic vascular resistance had decreased by 392 ± 104 dynes·s·cm^{-5} ($p < 0.05$) and heart rate had increased by 9 ± 2 beats/min ($p < 0.001$). Nevertheless, the vasodilator effect of a dose of flosequinan persisted (Fig. 1 and 2). After administration of flosequinan, almost all variables were similar to those observed after short-term administration of flosequinan 8 weeks earlier. Only heart rate was significantly faster ($p < 0.01$). Compared

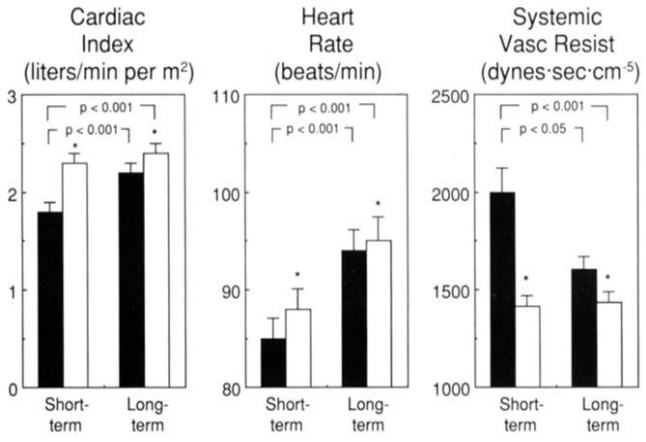

Figure 2. Effects of flosequinan administration on cardiac index, systemic vascular resistance and heart rate in 47 patients with severe heart failure receiving long-term treatment with captopril. Short-term administration of flosequinan increased heart rate and cardiac index and decreased systemic vascular resistance (Vasc Resist). After long-term flosequinan therapy, a dose of this drug exerted effects similar to those initially seen. Symbols as in Figure 1.

with pretreatment baseline measurements, mean arterial, right atrial and left ventricular filling pressures at the peak effect of flosequinan (after 8 weeks of long-term administration) had decreased by 3.5 ± 1.3, 2.8 ± 0.7 and 5.1 ± 1.3 mm Hg, respectively (all $p < 0.01$). Systemic vascular resistance had decreased by 585 ± 95 dynes·s·cm^{-5}, cardiac index had increased by 0.5 ± 0.1 liters/min per m^2 and heart rate had increased by 10 ± 2 beats/min (all $p < 0.001$).

Clinically, by functional classification, 22 patients improved by one class and 5 improved by two classes. The condition of three patients deteriorated, and functional class was unchanged in the remaining 17 patients.

Table 1 demonstrates the response to flosequinan therapy in patients who received the three different doses. Although not statistically significant, the highest dose, 150 mg, produced a greater decrease in mean arterial, left ventricular filling and right atrial pressures than either of the other two doses. In addition, increasing doses of flosequinan produced larger increases in cardiac index and heart rate and greater decreases in systemic vascular resistance.

Table 1. Change in Hemodynamic Variables as Related to Dose of Flosequinan

	Flosequinan Dose		
	50 mg (n = 18)	100 mg (n = 13)	150 mg (n = 16)
Cardiac index (liters/min per m^2)	+0.53 ± 0.1	+0.53 ± 0.1	+0.59 ± 0.1
Mean arterial pressure (mm Hg)	−3.9 ± 1.6	−2.2 ± 3.3	−4.1 ± 2.0
Right atrial pressure (mm Hg)	−2.0 ± 0.9	−3.2 ± 1.0	−3.2 ± 1.4
Left ventricular filling pressure (mm Hg)	−5.6 ± 1.9	−3.7 ± 2.4	−5.8 ± 2.6
Heart rate (beats/min)	+5 ± 3	+8 ± 4	+17 ± 3
Systemic vascular resistance (dynes·s·cm^{-5})	−493 ± 109	−529 ± 188	−733 ± 203

Values presented are mean value ± SEM and show the differences between pretreatment values and the peak effect (1 h after drug administration) after 8 weeks of long-term flosequinan therapy.

Discussion

This is the first study to demonstrate, using invasive monitoring, an additive hemodynamic effect of long-term administration of a vasodilator in patients receiving angiotensin-converting enzyme inhibitors. The hemodynamic effects of flosequinan persisted; the variables measured after drug administration after 8 weeks of long-term flosequinan therapy were similar to those observed with short-term drug administration. These findings support the concept that long-term therapy with a vasodilator may be effective in patients receiving angiotensin-converting enzyme inhibitors.

Hemodynamic effects of flosequinan. The short-term hemodynamic effects of flosequinan are predominantly related to its arterial and venous vasodilator effects. Mean arterial and both right atrial and left ventricular filling pressures decrease markedly after a single dose of flosequinan (3,10), with the peak decrease in systemic vascular resistance occurring between 1 and 2 h after dose administration. A dose-related positive inotropic effect of flosequinan has also been seen (11,12), but its importance at therapeutic concentrations in patients with heart failure is still unknown. The increased cardiac index seen after flosequinan administration is probably predominantly secondary to vasodilation. Heart rate also increases with flosequinan, although the mechanism is unknown; it does not appear to be related to reflex neurohormonal activation (13).

After long-term treatment with flosequinan, a dose of flosequinan causes vasodilation (4,14), but the short-term effect is smaller than that seen after the first dose of flosequinan. It has been suggested that this attenuated hemodynamic response to flosequinan administration may be secondary to activation of the renin-angiotensin system. The present study counters this view because the response observed in our patients with inhibition of the renin-angiotensin system was very similar to that previously observed in patients not receiving angiotensin-converting enzyme inhibitors. Rather, the similarity of the peak hemodynamic effects of flosequinan administration both before and after long-term therapy with flosequinan supports another explanation. Persistent vasodilation secondary to the long-acting, hemodynamically active metabolite (12) probably prevents additional flosequinan-induced vasodilation to the same extent possible before accumulation of this metabolite.

A long-term effect of the sulfone metabolite of flosequinan is also suggested by comparison of the hemodynamic variables measured before administration of a dose of the drug both before and after long-term flosequinan therapy. Analysis of hemodynamic variables obtained 8 weeks apart is fraught with danger in an uncontrolled study; any actions

of flosequinan might be hidden by the natural course of the disease and by the fluctuations that occur over a 2-month period. It appears, however, that after 2 months of treatment, but before dosing, both heart rate and cardiac index are greater than those initially seen, and systemic vascular resistance is decreased.

Addition of flosequinan to angiotensin-converting enzyme inhibitors. The present study demonstrates a clear, persistent hemodynamic effect of flosequinan administered for 8 weeks to patients receiving angiotensin-converting enzyme inhibitors. Although this effect appears similar to those previously reported in patients not receiving angiotensin-converting enzyme inhibitors, a number of observations are interesting. First, even the smallest dose of 50 mg produced a hemodynamic response. In previous studies demonstrating efficacy of flosequinan in patients with heart failure, the dose administered was ≥100 mg. It is thus unknown whether the smaller 50-mg dose would also be effective in patients not receiving angiotensin-converting enzyme inhibitors. However, activation of the renin-angiotensin system can limit the hemodynamic actions of vasodilators (15), and prevention of this activation could theoretically *increase* the vasodilator response to a drug. Thus, the inability of patients receiving angiotensin-converting enzyme inhibitors to activate the renin-angiotensin system could potentially prevent attenuation of the vasodilator effects of flosequinan and enhance the actions of low doses of the drug.

In certain circumstances, the ability to dilate the vasculature is related to the extent of basal vasoconstriction (7), and patients receiving angiotensin-converting enzyme inhibitors might therefore be expected to respond *less* intensively to vasodilators. However, our data clearly demonstrate that the vasodilation caused by angiotensin-converting enzyme inhibition does not limit the extent of vasodilation induced by flosequinan. The actions of flosequinan reported in this study are as great as those previously reported in patients not receiving angiotensin-converting enzyme inhibitors.

Dose response. The present study supports the concept that increasing the dose of flosequinan causes an increased hemodynamic effect. Although the study group was too small to show statistically significant differences among doses, the trend is clear; however, these data should not be interpreted as demonstrating the optimal dose of flosequinan. The dose causing the largest hemodynamic effect may not be the optimal clinical dose. This has been demonstrated with phosphodiesterase inhibitors (16) and angiotensin-converting enzyme inhibitors (17) and could be true with flosequinan as well. Still, the dose-response curve does support the conclusion that flosequinan continues to exert hemodynamic actions after 8 weeks of therapy. Even though the present study was not placebo controlled, both the marked hemodynamic changes seen with the administration of flosequinan after 8 weeks of therapy and the relation of this response to the various administered doses demonstrate the long-term hemodynamic actions of flosequinan.

Relevance to other vasodilators. The mechanism of action of flosequinan has not been fully elucidated but may be related to the dose-dependent attenuation of the inositol triphosphate pathway seen in vitro (18). Flosequinan is not a phosphodiesterase inhibitor, and it does not act via actions on cyclic guanosine monophosphate or cyclic adenosine monophosphate (19). The unique mechanism of flosequinan makes extrapolation of the results of this study difficult. Nevertheless, there are data to suggest that other vasodilators may be similarly beneficial. Although this is the first demonstration of the long-term effects of any direct-acting vasodilator in patients receiving angiotensin-converting enzyme inhibitors, it has previously been demonstrated that the hemodynamic effects of both hydralazine and nitroprusside are additive to those of short-term captopril administration (20,21).

The present study demonstrates that even in patients with long-term angiotensin-converting enzyme inhibition, marked vasodilation can be produced with a direct-acting vasodilator. This finding supports the concept that vasodilators can successfully be added to the drug regimen of patients with heart failure who are receiving angiotensin-converting enzyme inhibitors.

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