Control of Arteriolar Resistance in Heart Failure

Partial Attenuation of Specific Phosphodiesterase Inhibitor–Mediated Vasodilation by Digitalis Glycosides

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Background. The vasodilatory response to local specific type III phosphodiesterase inhibition with amrinone was evaluated before and immediately after local administration of digoxin in 14 patients with severe congestive heart failure (CHF).

Methods and Results. A 3F polyethylene catheter was inserted into the common femoral artery for drug administration and pressure monitoring. Mean blood flow velocity (MBFV) was continuously determined in the superficial femoral artery by transcutaneous Doppler ultrasonography. After intra-arterial administration of 10 mg amrinone, group MBFV increased from 7.7±1.4 to 16.0±2.1 cm/sec (p<0.05, n=10). Local administration of 20 μg digoxin, which was infused over 20 minutes, did not alter group MBFV (i.e., 8.2±1.6 versus 7.6±1.5 cm/sec; p=NS, n=10). The second administration of 10 mg amrinone, which immediately followed completion of local digoxin infusion, increased group MBFV but to a lesser extent than that produced by the first amrinone administration (i.e., 11.9±1.9 versus 16.0±2.1 cm/sec; p<0.05, n=10). When placebo was administered instead of digoxin, group MBFV was similar after the first and second administrations of amrinone (i.e., 15.3±3.3 versus 15.6±3.8 cm/sec; p=NS, n=4).

Conclusions. Although local administration of digoxin did not significantly alter baseline vascular tone in patients with CHF, it substantially decreased the direct vasodilatory effect induced by specific type III phosphodiesterase with amrinone. (Circulation 1992;85:54–60)

A new class of cardiotonic agents, the specific type III phosphodiesterase inhibitors (PDEI), is currently under investigation for the treatment of congestive heart failure (CHF). Specific PDEI improve left ventricular performance by exerting mild-to-moderate positive inotropic action and potent direct vasodilatory effects in the peripheral circulation. The positive inotropic action of PDEI is not mediated by Na,K-ATPase inhibition or β-adrenergic stimulation and probably results from a rise in intracellular levels of cyclic AMP (cAMP), which increases the amount of calcium available to the contractile proteins. Similarly, elevated levels of cAMP in the vascular smooth muscle appear to mediate the direct vasodilatory effect of specific PDEI. Although specific PDEI consistently enhance left ventricular performance in digitalized patients with CHF, they do not reliably increase peak aerobic capacity in these patients. The apparent inability of specific PDEI to reliably enhance peak aerobic capacity in digitalized patients could be due in part to an adverse interaction of these two pharmacological interventions on the peripheral circulation.

When administered systemically, cardiac glycosides have an indirect vasodilatory action in patients with CHF that is secondary to withdrawal of heightened peripheral sympathetic tone. In contrast, direct administration of cardiac glycosides has a local vasoconstrictive action that has been well documented in isolated human arteries and in open-chest dogs under cardiopulmonary and cerebral bypass. Of interest, cardiac glycosides decrease specific type III PDEI–mediated relaxation in isolated aortic rings. Whether a similar interaction between cardiac glycosides and specific type III PDEI occurs in the peripheral circulation of patients with CHF is unknown.

Accordingly, the present study was undertaken to determine whether the local vasodilatory response to intra-arterial administration of amrinone was altered.

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by local administration of digoxin in the lower limb vasculature of patients with CHF.

Methods

Patient Population

Fourteen men and five women with New York Heart Association class I through IV CHF (average age, 62 years; age range, 45–80 years) were studied. Eleven patients were in functional class II, six were in functional class I, and the remaining two patients were in functional class IV. Left ventricular ejection fraction measured by radionuclide angiography averaged 29% (range, 20–35%). The etiology of heart failure was coronary artery disease in 11 patients (as evidenced by coronary angiography or previously documented myocardial infraction) and idiopathic dilated cardiomyopathy in eight patients. The therapeutic regimen varied among patients and included lasix in 13 patients, captoril in 10 patients, and long-acting nitrates in five patients. All medications were withheld at least 24 hours before the study. None of the patients was treated with cardiac glycosides or PDEI. All patients were clinically stable for at least 1 month before the study. Seventeen patients were in sinus rhythm, and the remaining two were in atrial fibrillation with ventricular response below 100 min⁻¹ while not treated with digitalis glycosides. None had peripheral edema or clinical evidence of peripheral vascular disease (as evidenced by a ratio of ankle pressure to arm pressure of less than 1, hair loss, absence of peripheral pulse, or femoral bruit).

The protocol was approved by the Albert Einstein College of Medicine Internal Review Board, and informed consent was obtained from all patients.

Femoral Artery Catheterization

The study was conducted in a quiet, temperature-controlled room. After local anesthesia with 1% lidocaine, a 3F polyethylene catheter was inserted into the common femoral artery for pressure monitoring and intraarterial administration of drugs. The catheter was flushed with heparinized 5% dextrose in water, and the patients were then allowed to rest for at least 30 minutes.

Drug Administration

Ten milligrams of amrinone lactate (Sterling Winthrop, Rensselaer, N.Y.) diluted in 10 ml of normal saline was administered by hand injection in the common femoral artery over 1 minute. Preliminary studies had shown that 10 mg amrinone was sufficient to consistently produce a peripheral vasodilatory response in patients with CHF. Assuming a lower limb blood flow of 400 ml/min in patients with CHF, the local concentration of amrinone was approximately 25 μg/ml (133 μM). This concentration in vitro has been shown to induce vasorelaxation in isolated vascular strips. Forty-five minutes after completion of amrinone administration, when mean blood flow velocity (MBFV) had returned to baseline value, 20 μg digoxin diluted in 30 ml of 5% dextrose in water was administered by volumetric pump over 20 minutes into the common femoral artery. This dosage was chosen to obtain a local concentration of digoxin equal to the higher end of the therapeutic range during chronic systemic administration (i.e., 2.5 ng/ml). In 10 patients, digoxin blood levels obtained from an antecubital vein immediately at the end of the digoxin infusion were less than 0.6 ng/ml in each patient and averaged 0.3 ng/ml. Immediately after completion of digoxin administration, a second dose of 10 mg amrinone was administered into the common femoral artery in a manner identical to the first administration; we reasoned that local effect of digoxin would last for at least 10 minutes (i.e., during the second amrinone injection) because half-time of tissue binding after intravenous administration of tritiated digoxin is 20 minutes. Four patients were randomly selected to receive placebo (i.e., 5% dextrose in water) instead of digoxin before the second administration of amrinone. Patients receiving placebo were similar to patients receiving digoxin with respect to age (57.6±6.5 versus 62.6±4 years), sex (three men and one woman versus eight men and two women), body weight (76 versus 77 kg), left ventricular ejection fraction (28% versus 30%), and functional class (1.6 versus 1.9) according to the New York Heart Association criteria.

Peak Reactive Hyperemia Response

The peak vasodilatory response was determined after 5 minutes of arterial occlusion produced by a cuff placed above the knee and inflated to suprasystolic pressure. Postischemic peak reactive hyperemia was measured at the onset of the study (i.e., 30 minutes after insertion of the catheter into the femoral artery) and at the end of the study (i.e., 45 minutes after the second administration of amrinone) to demonstrate the stability of the lower limb circulation and reproducibility of our blood flow velocity measurements.

Doppler Ultrasonography

Ultrasound examination was performed using a 7.5-MHz duplex mechanical transducer connected to a Hewlett-Packard Sonos 100 ultrasound system. While the patient was resting in the supine position, the transducer was positioned on the medial portion of the patient’s thigh, at the inferior border of the femoral triangle. The superficial femoral artery was identified and carefully scanned to determine its origin and course and the presence and extent of atheroma. Exclusion criteria for the study included extensive arterial wall atheromatous changes, arterial narrowing, and/or Doppler signal consistent with significant proximal arterial stenosis. Once the optimal portion of the artery had been visualized, the position of the transducer was marked on the skin. Before any Doppler measurements were attempted, great care was taken to visualize the vessel at its greatest diameter, with the plane of the two-dimensional image parallel to the long axis of the vessel.
When the walls of the vessels are parallel on the screen, one can assume that the ultrasound beam is directed parallel to the longitudinal axis of the vessel and that the incident angle in the longitudinal plane is therefore close to 0°. Transducer position was then adjusted to minimize the incident angle of the ultrasound beam. An angle of less than 60° was obtained in all instances. Automatic internal correction for the Doppler angle was made using an on-screen cursor. Sample volume was placed across the vessel. Under these circumstances, the maximal velocity corresponding to the central position in a parabolic profile was recorded, which tends to overestimate the actual velocity across the entire cross section of the vessel. However, the overestimation was systematic in all patients studied. This approach was chosen to maximize reproducibility of the Doppler signal. Doppler studies were recorded on 1/2-in. tape with a commercially available videocassette recorder for later analysis.

Off-line analysis was performed using Hewlett-Packard Sonos 100 software for Doppler measurements. Analysis of the Doppler MBFV was performed by integrating the maximum velocity throughout systole and diastole and dividing the integral by the RR interval. Extrasystolic and postextrasystolic beats were excluded from analysis. The results of five cycles were averaged in the 17 patients in sinus rhythm, and the results of 10 cardiac cycles were analyzed in the two patients in atrial fibrillation. This analysis was performed without knowledge of the study medication (i.e., digoxin or placebo).

MBFV was measured immediately before amrinone administration, continuously during amrinone administration, and as long as 60 seconds after amrinone administration. MBFV peaked immediately at the end of amrinone administration. MBFV was measured immediately before and at the end of digoxin infusion as well as during the second administration of amrinone in a manner identical to that of the first administration.

**Plethysmography**

In the first five patients, lower limb blood flow was determined by venous occlusion plethysmography to validate measurements of MBFV in the superficial femoral artery by Doppler ultrasonography. The Doppler ultrasonography method has been previously used and validated in patients with peripheral vascular disease but has not been applied to patients with CHF. A single mercury-in-rubber strain gauge was calibrated at a force of 10 g and then placed at the largest circumference of the calf and connected to a plethysmograph (model 271, Parks Medical, Aloha, Ore.). The lower limb was elevated to an angle of 60° above the horizontal. A cuff was placed on the lower part of the thigh so that the flow measured by plethysmography would approximate blood flow in the superficial femoral artery. Rapid inflation to 60 mm Hg was used to prevent venous return. Lower limb blood flow by venous occlusion plethysmography was measured immediately before amrinone administration, every 15 seconds during amrinone administration, and at 15 and 30 seconds after completion of amrinone administration. Subsequently, lower limb blood flow was measured immediately at the end of digoxin administration and during the second administration of amrinone in a manner identical to the first administration of amrinone. The alterations in lower limb blood flow closely correlated to those in MBFV in the superficial femoral artery, with a coefficient correlation of more than 0.88 in every patient (Figure 1). Similarly, MBFV by Doppler ultrasonography and lower limb blood flow by venous occlusion plethysmography were closely correlated during the peak hyperemic responses obtained at the onset and at the end of the study (r≥0.90 in all five patients). After local administration of amrinone, the increases in MBFV tended to be greater than the increases in lower limb blood flow. This disparity may be explained by the transient nature of the peak vasodilatory response to amrinone that occurred within a few beats of the completion of the drug infusion. The peak vasodilatory response to amrinone could be detected more readily by continuous Doppler ultrasonography than by venous occlusion plethysmography. Because the position of the lower limb during venous occlusion plethysmography was poorly tolerated by patients and Doppler ultrasonography more reliably measured the peak vasodilatory response to amrinone, venous occlusion plethysmography was deleted from the protocol in the 10 patients who received digoxin and the four patients who received placebo. All 14 patients were studied with the lower limb in the horizontal position.

**Data Analysis**

All data are presented as mean±SEM. Group MBFV was assessed with a two-factor within-subject analysis of variance. Patients were assessed at control and after the first and second administrations of amrinone in the presence of digoxin or placebo for a total of four observations per patient. In the presence of interactions, F tests for the single effect of digoxin or placebo were performed using orthogonal contrasts. Statistical significance was accepted at the 95% confidence level (p<0.05).

**Results**

**Superficial Femoral Artery Blood Flow Velocity**

Patterns of blood flow velocity in the superficial femoral artery of a representative patient were illustrated during the control period, after the first administration of amrinone, at the end of digoxin infusion, and after the second administration of amrinone (Figure 2). During the control period, blood flow pattern was characterized by a systolic forward flow followed by an early diastolic reversal and late diastolic oscillations of flow. The first administration of amrinone substantially altered the blood flow velocity pattern. The peak velocity and the
duration of the systolic forward flow increased, the early diastolic reversal nearly disappeared, and a forward flow was maintained throughout late diastole. Local administration of digoxin did not change blood flow pattern. The second injection of amrinone, which was administered immediately after the end of digoxin infusion, had a lesser effect on blood flow velocity pattern than the first injection of amrinone. The peak velocity was lower, the early diastolic reversal was more preserved, and the late forward diastolic flow was not maintained throughout late diastole.

Group superficial femoral artery MBFV during the control period, after the first administration of amrinone, at the end of digoxin infusion, and after the second administration of amrinone for the 10 patients are illustrated in Figure 3, whereas individual data are detailed in Table 1. The first administration of amrinone increased MBFV from 7.7±1.4 to 16.0±2.1 cm/sec (p<0.05). Group MBFV was not changed by the infusion of digoxin (i.e., 8.2±1.6 versus 7.6±1.5 cm/sec; p=NS). The second administration of amrinone increased group MBFV but to a lesser extent than that produced by the first administration (i.e., 11.9±1.9 versus 16.0±2.1 cm/sec; p<0.05). In the four patients who received placebo instead of digoxin, group mean MBFV increased similarly after the first and the second administration of amrinone (i.e., 15.3±3.3 versus 15.6±3.8 cm/sec). Group MBFV values reached during peak reactive hyperemia, produced by arterial occlusion for 5 minutes, were similar at the onset and at the end of the study (60.6±6.8 versus 59.1±7.4 cm/sec, p=NS; Figure 4).

Systemic Hemodynamic Parameters

Mean femoral artery pressure and heart rate were not changed significantly by the first administration of amrinone, at the end of digoxin infusion, and by the second administration of amrinone (Table 2).

Figure 1. Scatterplots of lower limb blood flow (LLBF) determined by venous occlusion plethysmography and transcutaneous Doppler-derived mean blood flow velocity (MBFV) in superficial femoral artery compared directly during control periods and after local intra-arterial infusions of amrinone and digoxin in first five patients. LLBF and MBFV closely correlated in every patient.

Figure 2. Spectral display of blood flow velocity obtained by transcutaneous Doppler ultrasonography in superficial femoral artery of a representative patient. Positive value indicates forward flow, and negative value indicates retrograde flow. Panel A: Control period. Panel B: After first intra-arterial administration of amrinone, peak velocity and duration of systolic forward flow increased, diastolic flow reversal nearly disappeared, and forward flow persisted throughout late diastole. Panel C: At end of intra-arterial administration of digoxin, blood flow pattern was unchanged. Panel D: After second administration of amrinone, which immediately followed that of digoxin, peak velocity was lower, early diastolic flow reversal was preserved and quite similar to that of control period, and diastolic forward flow was not maintained throughout late diastole compared with first administration of amrinone.
Discussion

Our data clearly demonstrate that although local administration of digoxin did not significantly alter baseline vascular tone in patients with CHF, it substantially decreased the direct vasodilatory effect induced by specific PDEI with amrinone. In the absence of digoxin, local administration of amrinone increased group MBFV by 130%; once digoxin had been locally administered, an identical dose of amrinone increased group MBFV by only 50%.

Because local administration of amrinone and digoxin did not change femoral artery pressures, alterations in regional blood flow induced by these drugs directly reflected changes in local vascular resistance. The change in MBFV pattern after the first administration of amrinone was consistent with marked peripheral arteriolar vasodilatation. Lower limb blood flow measured by venous occlusion plethysmography and superficial femoral artery MBFV were closely correlated in the first five patients. An increase in cross-sectional area of the superficial femoral artery could have contributed to the attenuation in MBFV noted after the second administration of amrinone, at the completion of digoxin infusion. However, the return to baseline values of local hemodynamic parameters after the first administration of amrinone and the lack of effect of digoxin on lower limb blood flow and MBFV argue against the possibility that superficial femoral artery diameter changed significantly after infusion of digoxin. Subsequently, the vasodilatory response to local administration of amrinone and digoxin was solely quantified by continuous determination of MBFV.

When administered systemically, digoxin indirectly lowers vascular tone in patients with CHF. The lowering of the vascular tone results from withdrawal of the augmented sympathetic tone, which is in turn mediated by a direct stimulation of the baroreceptors and a rise in aortic pressure induced by the positive inotropic effect of digoxin. Both mechanisms increase the inhibitory tone exerted by the baroreceptors on central sympathetic center and thereby decrease sympathetic tone. In contrast, systemic administration of digoxin in normal subjects increases vascular tone via central stimulation of sympathetic tone. Local administration of digoxin did not appear to exert any systemic action in our patients, as both heart rate and systemic blood pressure were unchanged, and the systemic level of digoxin was below the lower end of the therapeutic range in every patient. Although local administration of digoxin did not affect baseline vascular tone, it adversely interacted with the direct vascular smooth muscle relaxation induced by specific PDEI to blunt the increase in MBFV produced by amrinone.

The direct vasodilatory response to another specific type III PDEI has been well documented with milrinone by Cody et al. Forearm blood flow measured by venous occlusion plethysmography was substantially increased by administration of milrinone into the brachial artery of digitized patients with CHF. The increase in forearm blood flow was dose related and not associated with alterations in systemic hemodynamic parameters.

The cellular mechanisms by which specific type III PDEI lower vascular smooth muscle tone are incompletely understood. Overall, the vascular smooth muscle relaxation produced by specific type III PDEI appears to be closely related to a rise in intracellular levels of cAMP and cAMP can promote relaxation of the vascular smooth muscle by phosphorylation of the myosin light-chain kinase. Phosphorylation of myosin light-chain kinase decreases its affinity for the calcium-calmodulin complex and, by preventing activation of the light chain of myosin, mediates vasorelaxation. cAMP can also promote vascular smooth
TABLE 2. Systemic Hemodynamic Parameters

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<th>A₁</th>
<th>C</th>
<th>D</th>
<th>A₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats per minute)</td>
<td>76.4±4.9</td>
<td>79.1±4.6</td>
<td>74.7±5.1</td>
<td>74.8±4.8</td>
<td>74.6±4.5</td>
</tr>
<tr>
<td>MFAP (mm Hg)</td>
<td>74.0±4.0</td>
<td>74.2±4.4</td>
<td>72.2±4.6</td>
<td>75.6±4.3</td>
<td>73.3±5.4</td>
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C, control; A₁, first intra-arterial administration of 10 mg amrinone; D, intra-arterial administration of 20 µg digoxin; A₂, second intra-arterial administration of 10 mg amrinone; HR, heart rate; MFAP, mean femoral artery pressure.

The adverse interaction of specific type III PDEI and cardiac glycosides on the peripheral circulation may occur at different sites. Of interest, ouabain has been well demonstrated to decrease the relaxant effect of dibutylryl-cAMP on arterial strips in various species. Inhibition of the Na,K-ATPase pump by cardiac glycosides leads to an increase in intracellular calcium concentration that may offset the lower affinity of myosin light-chain kinase for the calcium-calmodulin complex and/or the decrease in intracellular calcium concentration induced by specific type III PDEI. In addition, cardiac glycosides can facilitate liberation of norepinephrine from sympathetic nerve endings and thereby promote vasoconstriction.

Clinical Implications

Clinical experience with long-term administration of specific type III PDEI has been disappointing as they do not appear to produce steady clinical improvement and are associated with increased mortality. At the present time, only parenteral use of amrinone is approved, and its therapeutic usefulness is limited to acute situations. Although newer specific type III PDEI appear to produce steady clinical improvement in patients with severe CHF, their safety is still unproven. Nevertheless, with these limitations in mind, our methodology and data appear useful as they offer a model with which to study the local interaction of different pharmacological interventions on the peripheral circulation.

The precise clinical implications of our findings are difficult to determine. Our findings are pertinent to local administration of digoxin and amrinone, whereas systemic administration of these drugs modifies peripheral vascular tone by both a local action and reflex-mediated mechanisms. Of importance is that the hemodynamic benefits of specific PDEI have been mostly demonstrated after systemic administration of these agents to patients with severe CHF who were already digitalized. Similarly, the direct vasodilatory effect of milrinone was demonstrated by Cody et al in digitalized patients with CHF. The local vascular adverse interaction between digoxin and specific type III PDEI could in part explain the lack of long-term clinical benefits of this combined pharmacological approach. The effects of these drugs on the peripheral circulation appear to be an important determinant of their overall effect on maximum exercise tolerance.

FIGURE 4. Bar graphs of group mean blood flow velocity (MBFV) in superficial femoral artery of 14 patients with congestive heart failure during control and peak reactive hyperemia at onset of study (C₁, PRH₁) and at end of study (C₂, PRH₂). *p<0.001 versus C₁ or C₂.

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KEY WORDS • blood flow velocity • amrinone • digoxin
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