Provocative Testing with Ergonovine to Evaluate the Efficacy of Treatment with Calcium Antagonists in Variant Angina

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SUMMARY Ten consecutive hospitalized patients with uncontrolled variant angina were studied to evaluate the efficacy of nifedipine and perhexiline maleate treatment and to determine if the results of incremental ergonovine testing during treatment predicted the short-term clinical response. During a mean control period of 5.2 days without treatment other than nitroglycerin, 3.9 ± 4.7 (mean ± SD) episodes of variant angina occurred per day. During the subsequent treatment period with nifedipine 20 mg every 6 hours, only 0.09 ± 0.15 episodes/day occurred (p < 0.02 vs control) and seven patients had no angina. During perhexiline treatment (400 mg twice daily), 2.3 ± 3.2 attacks/day were recorded; this was not significantly different than during the control period.

Without treatment all 10 patients had positive ergonovine tests at doses ranging from 0.025–0.3 mg. During nifedipine treatment nine of the 10 tests became negative at doses as large as 0.4 mg (p < 0.0001). The results of ergonovine testing during perhexiline treatment did not differ significantly from the control period. Overall, 11 of the 12 ergonovine tests positive at 0.1 mg or less occurred during observation periods with more than one episode/day of variant angina, and all 16 negative tests, or tests positive only at 0.2 mg or more, occurred during periods with less than one episode/day of variant angina.

We conclude that the results of ergonovine testing during treatment correlate with the short-term clinical response to therapy. Although the effect of chronic treatment with calcium antagonists on the natural evolution of this syndrome is unknown, nifedipine rapidly and effectively controls the acute clinical manifestation of variant angina.

IN 1959 PRINZMETAL et al.1 described a variant form of angina characterized by rest pain associated with transient ST-segment elevation. They postulated that the clinical features were caused by coronary artery spasm, and others substantiated that this was so.2,4 Recently the intravenous administration of small doses of ergonovine maleate has been shown to induce coronary artery spasm and its associated clinical manifestations in patients with variant angina, but not in normal subjects.5–8

Sublingual nitroglycerin promptly relieves acute episodes of variant angina11 but the efficacy of other modes of treatment has not been clarified.9,10 Long-acting nitrate preparations often reduce symptoms, but rarely provide complete relief.11 Propranolol has been reported to be both beneficial12 and detrimental,13 but most studies report that it is much less useful than in classic angina.14,16 Similarly, both excellent17,19 and poor13,14,17 results have been obtained with coronary artery bypass surgery. Several studies17–24 have reported excellent preliminary results using the calcium antagonists nifedipine,17–19 perhexiline maleate,20,21 verapamil22,23, and diltiazem24 to treat variant angina. Theoretically, this class of drugs prevents coronary artery spasm by inhibiting calcium uptake and thereby relaxing arterial smooth muscle cells. In patients with coronary artery spasm associated with severe fixed stenoses, Endo et al.13 had good results by combining coronary artery bypass surgery with long-term nifedipine treatment.

Since spontaneous variations in the frequency of symptoms occur in most patients with variant angina, the effect of any treatment is difficult to evaluate. An objective measurement of the effect of treatment would be very useful, both in managing individual cases and in conducting clinical trials. This study was undertaken to determine if the response to ergonovine testing during treatment with calcium antagonists correlated with the short-term clinical response to these drugs. A secondary purpose of the study was to compare the efficacy of nifedipine and perhexiline maleate in preventing clinical episodes of variant angina.

Methods

Patient Material

Ten consecutive patients hospitalized in our coronary care unit because of frequent, uncontrolled episodes of variant angina formed the study group. The clinical and coronary angiographic features of these patients are delineated in table 1. In this study the following criteria were required for the diagnosis of variant angina:

1) burning or squeezing retrosternal chest pain occurring at rest;
2) sublingual nitroglycerin always relieving the pain in less than 5 minutes;
3) ST-segment elevation of at least 3 mV not pres-

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ent on the resting ECG but documented during pain and disappearing after relief of pain;
4) no evidence of myocardial infarction.

Informed written consent was obtained from all patients before beginning the study. The study protocol was approved by the hospital ethics committee.

Study Protocol

On admission to the coronary care unit all cardiac medication was discontinued except sublingual nitroglycerin, which was given only to relieve angina. An electrocardiographic lead where ST-segment elevation had been documented during angina was monitored continuously throughout the study. Each spontaneous episode of variant angina was recorded in a separate clinical chart. Angina without ST-segment elevation and painless ST-segment elevation occurred infrequently and were not charted.

During an initial control period of at least 3 days no specific therapy was used. Coronary arteriography was performed during this period and, on a different day, an ergonovine test. Episodes of variant angina caused by either of these procedures were not counted in the clinical chart.

Upon completion of the control period, nifedipine was begun at an oral dose of 10 mg every 6 hours, increasing to 20 mg every 6 hours after the first four doses. After at least 2 days of nifedipine treatment an ergonovine test was performed 90 minutes after a regular dose.

Nifedipine was discontinued and perhexiline maleate begun at an oral dose of 300 mg every 12 hours, increasing to 400 mg every 12 hours after the first two doses. An ergonovine test was done after at least 2 days of treatment with perhexiline maleate.

In the original design of the study protocol, the duration of the control and each treatment period was established as 4 days. However, in practice, the control period varied from 3–9 days (mean 5.2 days) and the treatment periods varied from 2.5–8 days (mean 4.1 days). This variation occurred because coronary arteriography and ergonovine testing could not always be conveniently scheduled within the prescribed period, or because one of these tests had to be postponed due to frequent spontaneous episodes of variant angina.

Coronary Arteriography

Selective coronary arteriography was performed via a percutaneous femoral approach using preformed catheters, as previously described.25 Views with cranial angulation were routinely filmed.26 Particular care was taken to avoid catheter-induced coronary artery spasm. No attempt was made during catheterization to induce coronary spasm by administering ergonovine. Nitroglycerin was not given before the initial injections; however, when a lesion was noted, the vessel was filmed again in several views after nitroglycerin. All angiographic documents were routinely interpreted independently by an experienced cardiovascular radiologist. The left ventricular angiogram was filmed in the 30° right anterior oblique view before the arteriogram. Visual inspection and calculated ejection fractions (area-length method) of all ventriculograms were normal.

Ergonovine Testing

After recording a 12-lead ECG and cuff blood pressure, a bolus of 0.025 mg of ergonovine was injected intravenously within a 5-second interval. Blood

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Site of ST</th>
<th>Associated arrhythmias</th>
<th>Coronary arteriogram</th>
<th>Spontaneous spasm during angiography</th>
<th>LV angiogram</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>M</td>
<td>1, L, V1-4</td>
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<td>40% LAD</td>
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<td>2</td>
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<td>F</td>
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<td>3</td>
<td>47</td>
<td>M</td>
<td>1, L, V1-4</td>
<td>PVDs</td>
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<td>LAD</td>
<td>Normal</td>
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<tr>
<td>4</td>
<td>68</td>
<td>M</td>
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<td>Ventricular fibrillation</td>
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<td>Normal</td>
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<tr>
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<td>49</td>
<td>M</td>
<td>V1-4</td>
<td>None</td>
<td>40% RCA</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>M</td>
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<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>M</td>
<td>2, 3, F, V5-6</td>
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<td>M</td>
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<td>2º AV block, ventricular fibrillation</td>
<td>35% RCA</td>
<td>No</td>
<td>Normal</td>
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<tr>
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<td>50</td>
<td>M</td>
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<td>Normal</td>
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<tr>
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<td>M</td>
<td>V1-3</td>
<td>Ventricular tachycardia</td>
<td>75% LAD</td>
<td>No</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Abbreviations: ST = ST-segment elevation; AV = atrioventricular; PVD = premature ventricular depolarization; LAD = left anterior descending coronary artery; RCA = right coronary artery; LV = left ventricular.
pressure and a 12-lead ECG were recorded each subsequent minute for 5 minutes. If an episode of variant angina did not occur the procedure was repeated at each of the following dose levels of ergonovine: 0.05 mg, 0.075 mg, 0.1 mg, 0.2 mg, 0.3 mg and 0.4 mg. The interval between successive ergonovine doses was always maintained at 5–6 minutes; therefore, a negative test required 35–45 minutes to complete. The occurrence of angina during ergonovine testing was always accompanied by ST-segment elevation. An intravenous bolus of 0.3 mg of nitroglycerin was administered when angina developed during ergonovine testing, and always promptly relieved both pain and ST-segment elevation. If a positive response occurred, blood pressure and a 12-lead ECG were recorded each minute until both returned to pretest levels. An electrocardiographic lead where ST-segment elevation had been documented during angina was monitored continuously throughout the procedure. No complications occurred as a result of ergonovine testing.

All 10 study patients had an ergonovine test during the control period and again during treatment with nifedipine. Eight of the patients were retested during perhexiline treatment, but two were not. Patient 1 developed perhexiline-induced ataxia and in patient 5 the drug seemed ineffective; both patients questioned the need for repeat testing since the drug obviously would not be used for their long-term management.

Data Analysis

Differences in the number of episodes of variant angina between control and treatment periods were compared using the paired t test. The Fisher exact test was applied to evaluate differences in the number of positive ergonovine tests between different periods of the study. Using the unpaired t test the number of anginal episodes per day were compared between groups classified according to their ergonovine test results.

Results

Patient Characteristics

The clinical and angiographic features of the study patients are outlined in table 1. Nine patients were men and one was a woman. Their ages ranged from 32–68 years (mean 47.8 years). The electrocardiographic site of variant angina was anterior in five, inferior in four and both anterior and inferior in one patient. Coronary arteriography was entirely normal in three cases and three other patients had no fixed coronary stenoses greater than 50% of the arterial luminal diameter. Four patients had > 50% coronary artery stenosis in one vessel, and in three of them the involved artery corresponded to the electrocardiographic site of ST elevation. Spontaneous coronary artery spasm occurred during angiography in two patients.

Results of Treatment

The clinical chart of patient 8 is illustrated in figure 1. Forty-six spontaneous episodes of variant angina occurred during the 3-day observation period, none during the 5-day treatment period with nifedipine and 30 during the 3-day treatment period with perhexiline maleate. After the end of the study he was again treated with nifedipine, and again, no attacks of variant angina occurred.

Table 2 shows that the mean number of variant anginal episodes per day decreased from 3.9 ± 4.7 (mean ± sd) to 0.09 ± 0.15 (p < 0.02) between the control period and the nifedipine treatment period. Seven patients were angina-free during nifedipine therapy, compared with only one patient during the control period. Each of the three patients with variant angina during nifedipine treatment had only one attack.

In contrast, only two patients were entirely angina-free during treatment with perhexiline maleate and the mean number of episodes per day increased to 2.3 ± 3.2 (p < 0.05 vs nifedipine period, but not significantly different from control period). Compared with the control period, six patients had fewer attacks while taking perhexiline, two patients more attacks and two patients the same number of attacks. The only patient to have fewer episodes of variant angina with perhexiline than with nifedipine had only one episode with nifedipine and none with perhexiline.

Ergonovine Testing

The results of ergonovine testing are listed in table 2. All 10 patients had positive tests during the control period, and the dose required varied from 0.025–0.3 mg. During treatment with nifedipine the ergonovine test became negative to the maximal dose of 0.4 mg in nine of the 10 patients (p < 0.0001 vs control). The ergonovine test persisted positive in patient 9, but at a dosage level eight times higher than during the control period.

During the perhexiline treatment period two patients had negative tests, six had positive tests and in two cases no test was done (p = NS vs control period). Of the six positive tests, three occurred at the same dosage level as during the control period, two at a higher level and one at a lower level.

As illustrated in figure 2, the results of ergonovine testing during both control and treatment periods correlated well with the frequency of spontaneous variant anginal episodes. In the 17 periods with a positive ergonovine test, the number of episodes of variant angina per day was 3.4 ± 4.2 (mean ± sd), compared with 0.10 ± 0.15 episodes per day in the 11 study periods associated with a negative ergonovine test (p < 0.02). Furthermore, when the ergonovine test was positive only at doses of 0.2 mg or greater, the number of attacks of variant angina in the associated study period was always less than one per day. Thus, in the 16 periods with a negative ergonovine test or a positive test at 0.2 mg or more, the number of episodes averaged 0.13 ± 0.17 per day compared with 4.7 ± 4.4 episodes per day in the 12 periods with a positive ergonovine test at 0.1 mg or less (p < 0.001). Positive tests at this low dose were associated with more than one episode of variant angina per day in 11
of 12 instances; however, in all 16 instances when the ergonovine test was negative, or positive only at 0.2 mg or more, less than one episode of variant angina occurred per day.

Discussion

Treatment of Variant Angina

This study demonstrates that nifedipine can rapidly and effectively control the clinical manifestations of variant angina. In 10 consecutive patients hospitalized with uncontrolled variant angina, 187 attacks occurred during a 5-day control period, but only three attacks occurred during nifedipine treatment in the following 4-day period. Our study design does not eliminate the possibility that spontaneous variations in symptoms or the nonspecific effects of hospitalization might partially account for the marked improvement during nifedipine treatment. However, this possibility is unlikely, because immediately after the nifedipine treatment period frequent episodes of variant angina recurred during therapy with perhexiline maleate.

Although angina and ST-segment elevation were effectively controlled by nifedipine in this study, the duration of treatment was limited to several days. Excellent short-term results from nifedipine therapy have also been reported by Endo et al. in 34 cases. In a preliminary report, Goldberg et al. treated six patients who all showed improvement. However, longer periods of follow-up are required to determine

Table 2. Variant Angina Episodes and Ergonovine Test Results During Control and Treatment Periods

<table>
<thead>
<tr>
<th>Patient</th>
<th>VA/day (Control)</th>
<th>VA/day (Nifedipine)</th>
<th>VA/day (Perhexiline)</th>
<th>Results of ergonovine testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59/7</td>
<td>8.1</td>
<td>0/3</td>
<td>+, 0.1 mg</td>
</tr>
<tr>
<td>2</td>
<td>9/7</td>
<td>1.3</td>
<td>0/3</td>
<td>+, 0.1 mg</td>
</tr>
<tr>
<td>3</td>
<td>18/5.5</td>
<td>3.3</td>
<td>1/8</td>
<td>+, 0.075 mg</td>
</tr>
<tr>
<td>4</td>
<td>13/3.5</td>
<td>3.7</td>
<td>1/2.5</td>
<td>+, 0.025 mg</td>
</tr>
<tr>
<td>5</td>
<td>29/9</td>
<td>3.2</td>
<td>0/4</td>
<td>+, 0.05 mg</td>
</tr>
<tr>
<td>6</td>
<td>1/5</td>
<td>0.20</td>
<td>0/3</td>
<td>+, 0.3 mg</td>
</tr>
<tr>
<td>7</td>
<td>7/3.6</td>
<td>1.9</td>
<td>0/5.5</td>
<td>+, 0.1 mg</td>
</tr>
<tr>
<td>8</td>
<td>46/3</td>
<td>15.3</td>
<td>0/5</td>
<td>+, 0.025 mg</td>
</tr>
<tr>
<td>9</td>
<td>5/4</td>
<td>1.3</td>
<td>0/3</td>
<td>+, 0.05 mg</td>
</tr>
<tr>
<td>10</td>
<td>0/4</td>
<td>0</td>
<td>0/3</td>
<td>+, 0.05 mg</td>
</tr>
</tbody>
</table>

Mean ± SD 3.9 ± 4.7 0.09 ± 0.15* 2.3 ± 3.2

*p < 0.02 vs control, p < 0.05 vs perhexiline.

Abbreviations: VA = episodes of variant angina; + = positive test at dose indicated; — = negative test up to 0.4 mg of ergonovine.

Figure 1. Clinical chart of variant angina episodes for patient 8. During the 3-day control period he had 46 episodes of variant angina. During the nifedipine period (10 mg p.o.q. 6 hr on day 4; 20 mg p.o.q. 6 hr days 5–8) no attacks of variant angina occurred. During the 3-day treatment period with perhexiline maleate (300 mg p.o.q. 12 hr on day 9; 400 mg p.o.q. 12 hr days 10–11) 30 episodes of variant angina were recorded. At the end of the study (days 12–14) he was again treated with nifedipine (20 mg p.o.q. 6 hr) and no subsequent attacks of variant angina occurred before hospital discharge (day 15).
if the short-term clinical improvement with nifedipine is sustained, and if myocardial infarction and death are prevented by this drug.

In contrast to the excellent results obtained with nifedipine, perhexiline seemed to be of little value in controlling the clinical manifestations of refractory variant angina over the short period in which these patients were evaluated. Although a slight reduction in the number of attacks was noted when the control period was compared to the perhexiline treatment period, 3.9 ± 4.7 to 2.3 ± 3.2 (mean ± sd), the difference was not statistically significant. In the long-term management of patients with variant angina our preliminary results and those of Curry et al. have suggested that perhexiline is beneficial. The failure of perhexiline to control symptoms in the present short-term study and its apparent success in long-term studies may be related to the relatively long serum half-life of the drug and its accumulation during prolonged therapy. Thus, the inability of perhexiline to block the positive response to ergonovine may not have occurred if testing had been performed during chronic therapy. Unfortunately, large loading doses of the drug cannot be safely administered because of the high incidence of dose-related side-effects. The maximal dose we used was 400 mg twice daily, but in the chronic treatment of angina the usual dose is 200 mg twice daily or less; even at this lower level, side effects during prolonged therapy are frequent and seem to be dose-related. Therefore, although perhexiline may have a role in the long-term management of patients with variant angina, nifedipine is a superior drug to provide rapid control of frequent variant anginal attacks refractory to conventional therapy for angina.

Of the 10 patients in our study, only four had a fixed coronary stenosis > 50% at arteriography and none had multivessel disease. In no case did a fixed coronary stenosis obstruct the arterial luminal diameter by more than 80%. Therefore, we evaluated the response to treatment with calcium antagonists in these patients and did not refer them for coronary artery bypass surgery. Many patients with variant angina have extensive coronary disease, often with critical, proximal stenoses; the results of our study may not apply to them. Endo et al. have reported complete relief of symptoms in eight patients who underwent coronary bypass surgery followed by nifedipine treatment.

**Role of Ergonovine Testing**

The discovery that the clinical manifestations of variant angina can be provoked by small intravenous doses of ergonovine maleate has provided a sensitive and specific diagnostic test for this syndrome. Most studies of this drug have been limited to the cardiac catheterization laboratory, where coronary spasm can be documented directly; however, these studies have shown that when angina and ST-segment elevation occur after ergonovine administration in a patient with variant angina, coronary spasm is invariably present. Therefore, we have now performed 120 ergonovine tests in our coronary care unit using the protocol outlined in the Methods section of this paper. Except for transient arrhythmias that did not require treatment, no complications have occurred as a result of this procedure. Unwanted physiologic changes induced by catheters or contrast media are avoided when the test is performed in a coronary care unit. More important, the test can begin with very small doses which are gradually increased to cover a wide range; such a protocol would not be feasible in a catheterization laboratory because of time constraints. By beginning
with 0.025 mg of ergonovine and increasing gradually to 0.4 mg, a high degree of safety is theoretically attained, since the patient receives the lowest dose of ergonovine which will precipitate his symptoms. In addition, the test is highly sensitive, since all 10 variant angina patients in our study had positive tests at ergonovine doses of 0.025–0.3 mg.

The availability and safety of ergonovine testing in a coronary care unit have increased the potential use of the drug. The present study was designed to determine if ergonovine testing could be useful as an objective method of evaluating or predicting the response to therapy in variant angina. An excellent correlation was found between the results of ergonovine testing and the frequency of attacks of variant angina. Less than one episode of variant angina per day occurred during all 16 periods in the study associated with a negative ergonovine test or a test positive only at 0.2 mg or more. In contrast, 11 of the 12 positive tests at 0.1 mg or less were associated with more than one episode of variant angina per day. Therefore, the results of ergonovine testing in these patients appears to correlate with the short-term response to treatment.

Since frequent remissions and exacerbations often complicate the clinical course of patients with variant angina, the results of ergonovine testing during initial treatment may not be closely related to the long-term response to therapy. In addition, the correlation between ergonovine test results and the frequency of symptoms demonstrated in this study was no longer evident when only tests done during the control periods were considered. A correlation between the frequency of variant anginal episodes and the dose of ergonovine required to induce a positive test might have occurred if patients with less frequent symptoms had been included in the study.

Does the dose of ergonovine required to induce a positive test vary in each patient with the degree of clinical activity? It may be that a positive test converts to negative or becomes positive only at higher doses in a patient whose symptoms spontaneously disappear. The dose level at which a test is positive might predict subsequent complications. We speculate that ergonovine testing may be useful in investigating the pathogenesis and natural history of variant angina in addition to its value in diagnosis and the evaluation of treatment.

Acknowledgments

We are indebted to the nurses of our coronary care unit for their skillful care of the study patients, to Drs. Jean de L. Migneault, Michel Samson, Denis Desrochers, Pierre Saillant, Lucien Campeau and Bertrand Tardif for permitting us to study their patients and to Diane Roy for preparing the manuscript.

References

The Influence of Left Ventricular Late Diastolic Filling on the A Wave of the Left Ventricular Pressure Trace

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with the technical assistance of William B. King, B.A.

SUMMARY. To study the influence of left ventricular (LV) late diastolic filling on the A wave of the LV pressure, simultaneously recorded echocardiographic LV dimensions and high-fidelity LV pressure measurements were taken in 24 patients. Group 1 comprised eight patients without LV hypertrophy (LVH) and LV end-diastolic pressure (LVEDP) ≤ 13 mm Hg. Group 2 comprised 16 patients with LVH secondary to aortic stenosis, idiopathic hypertrophic subaortic stenosis, or hypertension and increased LVEDP. Patients in group 2 had significantly thicker left ventricles, decreased mitral E-to-F slopes, and larger A waves in the LV pressure curve. On the basis of end-diastolic chamber stiffness, we divided group 2 into two populations: 12 patients (group 2A) with end-diastolic chamber stiffness similar to that in group 1, and four patients (group 2B) with markedly elevated end-diastolic chamber stiffness. Patients in group 2A had a larger atrial contribution to LV filling than those with markedly abnormal stiffness (group 2B). Therefore, in LVH an increased A wave in the LV pressure may be related to either elevated end-diastolic chamber stiffness or augmented left atrial volume transport.

IN LEFT ventricular hypertrophy (LVH), the left ventricular end-diastolic pressure (LVEDP) is often increased, usually in association with a prominent A wave in the left ventricular pressure curve. The A wave reflects the rise in left ventricular pressure as a result of left atrial contraction; its increased magnitude in LVH has been attributed to increased left ventricular chamber stiffness; that is, a large change in pressure relative to the change in volume. However, recent angiographic and echocardiographic analyses have shown increased late diastolic filling in some patients with coronary artery disease, aortic stenosis, and idiopathic hypertrophic subaortic stenosis, reflecting augmented left ventricular filling secondary to a forceful atrial contraction. Although Grossman et al. studied the relationship of left atrial contraction and the left ventricular pressure A wave in a few patients with LVH secondary to aortic stenosis, none of their patients had unusually increased late diastolic filling. In this study, we have reexamined the relationship between the height of the A wave in the left ventricular pressure curve and the magnitude of the left atrial volume contribution to ventricular filling in patients with LVH.

Methods

Twenty-four patients undergoing diagnostic cardiac catheterization at the Mount Sinai Medical Center were studied. Simultaneous echocardiographic dimensions and high-fidelity pressure measurements of the left ventricle were recorded during catheterization either before injection of any contrast material or at least 20 minutes after contrast injection when heart rate, aortic pressure, and LVEDP had returned to baseline. All catheterizations were performed through the right brachial artery.

Eight patients (group 1) had no LVH on the ECG and normal or borderline elevated LVEDP (≤ 13 mm Hg). Four of these patients had atypical chest pain without evidence of cardiovascular disease; one patient had one-vessel coronary artery disease with normal left ventricular function, and three had mild or...
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