Prolonged Duration of Myocardial Ischemia in Patients With Coronary Heart Disease and Impaired Cardiopulmonary Baroreceptor Sensitivity

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To investigate the potential contribution of cardiopulmonary reflexes in myocardial ischemia, the coronary vascular response to cardiopulmonary baroreceptor unloading and the number and the duration of spontaneous episodes of symptomatic and asymptomatic myocardial ischemia were evaluated in 23 patients with coronary heart disease. Lower-body negative pressure at −10 mm Hg, which causes selective deactivation of cardiopulmonary receptors, reduced left ventricular filling pressure in all patients, but calculated coronary vascular resistance increased in only 14 patients (from 0.846±0.1 to 1.07±0.1 mm Hg/ml/min, p<0.01) (group 1). In the remaining nine patients, coronary resistance did not change during cardiopulmonary receptor unloading (group 2). A 60-mm Hg increase in neck tissue pressure, which induces arterial baroreflex-mediated sympathetic activation, caused comparable coronary vasoconstriction in the two groups. Clinical characteristics of the two groups were similar, except that a lower ejection fraction was measured in group 1 (45±2% vs. 56±1%, p<0.01). In the 14 patients in group 1, 24-hour electrocardiographic monitoring showed 151 episodes of myocardial ischemia (average individual value, 10.8±1), 137 of which were asymptomatic, with an individual daily ischemic period of 62±6 minutes. In contrast, the nine patients in group 2 had only symptomatic episodes of myocardial ischemia, and the daily ischemic period in these patients was longer than in patients of group 1 (104±10 minutes, p<0.01). After a 3-day treatment with digitalis, the patients of group 2 showed 38 asymptomatic episodes of myocardial ischemia and a shorter daily ischemic period (85±6 minutes, p<0.01 vs. control conditions). In contrast, no change in number and duration of the ischemic episodes was detected in group 1. The effects of acute administration of digitalis (Lanatostide-C 0.02 mg/kg body wt e.v.) on the coronary vascular response to cardiopulmonary receptor unloading were assessed in a separate group of patients with ischemic heart disease. Digitalis treatment did not significantly modify the magnitude of the coronary vascular response induced by −10 mm Hg lower-body negative pressure in the patients showing in control conditions an increase of coronary vascular resistance greater than 20% of the basal value during cardiopulmonary receptor unloading. On the contrary, digitalis potentiated the coronary reflex response to −10 mm Hg lower-body negative pressure in the patients with impaired cardiopulmonary responsiveness (Δ percent increase in coronary vascular resistance: 1±1% in control conditions; 23±3.9% after digitalis, p<0.001). In conclusion, in patients with coronary heart disease, impaired low-pressure receptor responsiveness is associated with prolonged duration of myocardial ischemia. When cardiopulmonary reflexes are restored by digitalis, the duration of myocardial ischemia is significantly reduced. (Circulation 1990;81:1792–1802)
possibility that an inhibitory hemodynamic reflex induced by myocardial ischemia attenuates or resolves the ischemic attack.

In a group of 13 patients, we recorded 204 episodes of transient acute myocardial ischemia, of which 166 were asymptomatic and resolved spontaneously.2 A sudden drop in heart rate and blood pressure either preceded or coincided with the resolution of the electrocardiographic signs of acute myocardial ischemia in 93% of these episodes. Because global myocardial ischemia, which results in left ventricular failure, has been reported to lead to prevalent stimulation of receptors with vagal afferents,3 we speculated that ischemic ventricular myocardium can generate a powerful depressor reflex that may contribute to the resolution of myocardial ischemia by reducing myocardial oxygen consumption and coronary vascular tone. In particular, the increase in ventricular pressure induced by myocardial ischemia may potentiate the inhibitory input from cardiopulmonary receptors with vagal afferents, which are sensitive to changes in cardiac filling pressures,4 thus reducing sympathetic activity.5 The possibility of a concurrent increase in the activity of the parasympathetic system cannot be ruled out. In fact, in experimental animals, we have demonstrated that the activation of sensory left ventricular receptors with vagal afferents also potentiates vagal discharge to coronary arteries.2

In this study, we investigated whether cardiopulmonary reflexes contribute to the buffering mechanisms activated during myocardial ischemia by assessing cardiopulmonary receptor responsiveness and duration of ischemic episodes in patients with ischemic heart disease.

Because acute administration of digitalis partially restores the responsiveness of impaired left ventricular receptors in patients with left ventricular dysfunction,6 we also investigated the effects of acute or chronic digitalis therapy on cardiopulmonary baroreflex and duration of myocardial ischemia.

Methods

Patients

The patients selected for the study had at least three daily episodes of chest pain at rest, which were of typical quality and location. History of angina in these patients varied from 1 to 3 years. Patients in whom a sudden increase in severity and frequency of angina had been experienced were excluded from the study. Patients with history or evidence of heart failure, arterial hypertension, valvular or pulmonary diseases, left bundle branch block, or other pathological baseline changes in the ST segment were also excluded from the study. The nature and the purpose of the investigation and its possible risks were explained in detail to each patient to obtain informed, written consent consistent with the rules of the ethical committee on clinical investigation of our institution. Twenty-three patients were studied. Electrocardiograms at rest were normal in nine; in eight, they showed old myocardial infarctions; and in six patients, they showed flat or inverted T waves.

Study Design

In the week preceding the study sessions, the patients were hospitalized. During this period, all pharmacological treatments were withdrawn, and only nitroglycerin was given to resolve episodes of angina. In a diary, the number, time, and circumstances of the anginal attacks and nitroglycerin consumption during a 24-hour period were charted daily. The patients received a standard daily diet containing 1,500 ml of fluids, 150 meq Na, and 70 meq K. Personal food preferences were allowed as much as possible. A stable sodium balance was achieved between days 4 and 7 as assessed by measurements of body weight, sodium intake, and urinary sodium output. Two days before the invasive study, the patients were familiarized with the lower-body negative pressure (LBNP) device and the neck chamber.

Hemodynamic Study

The study was undertaken in the morning with the patient in the supine position and in the postabsorptive state after an overnight fast. No premedication was used. Under local anesthesia with 2% lidocaine, a heparinized arterial catheter was introduced percutaneously into the right brachial artery and positioned under fluoroscopy in the ascending aorta for direct measurement of systemic blood pressure. Mean arterial pressure was obtained by integration of the pulsatile trace during 5-second periods. A multithermistor thermodilution catheter was introduced through an antecubital vein into the coronary sinus for measurement of coronary sinus blood flow. The position of the coronary sinus catheter was verified under fluoroscopy by injection of 2–3 ml of contrast medium and was rechecked frequently. Particular care was devoted to placing the proximal thermistor well within the coronary sinus, close to the origin of the great cardiac vein, and to avoid a position across the take off of a marginal vein. In addition, saline was injected into the right atrium to determine whether reflux of blood from the right atrium into the coronary sinus was present at rest.7 During the LBNP maneuver, we did not observe in any patient fluctuations of injectate and coronary sinus blood mixture synchronous with right atrial contractions, which is a clue to a reflux of blood into the coronary sinus.7 A Swan-Ganz thermodilution catheter was introduced through another antecubital vein into the pulmonary artery, and cardiac output was assessed in triplicate with a 9520-A cardiac output computer (American Edwards Laboratory, Santa Ana, California). Right atrial, pulmonary artery, and pulmonary capillary wedge pressures were also recorded. An electrocardiographic lead was continuously monitored during the study, and the patients were asked to breathe regularly. Systemic and pulmonary arterial pressures were measured with a Statham P23Db pressure transducer.
(Gould-Statham, Oxnard, California) and recorded simultaneously on a multichannel polygraph at a paper speed of 50 mm/sec. A polyethylene catheter was introduced percutaneously into an antecubital vein for drug administration. Baseline hemodynamic measurements included heart rate, arterial pressure, right heart pressure, pulmonary pressure, coronary sinus flow, and cardiac output. Arterial and coronary sinus blood samples were withdrawn for myocardial oxygen consumption determination.

LBNP was applied by means of a chamber placed around the patient’s body below the iliac crest, sealed, and connected to an adjustable vacuum according to the technique described by Mark and Kerber. Responses to 2 minutes of LBNP at -10 mm Hg were determined.

Systemic and coronary hemodynamic responses induced by reduction in carotid transmural pressure were also evaluated. An increase in external neck pressure (+60 mm Hg) was applied during a 1-second period and maintained for 120 seconds by means of a pneumatic chamber similar to that previously described by Ludbrook et al. The 60-mm Hg increase in neck tissue pressure was adopted to avoid changes in cerebral blood flow and the involvement of chemoreceptors in the reflex effect.

Protocol

Systemic, right atrial, and pulmonary pressures were determined continuously during 90 seconds at baseline and then during application of LBNP at -10 mm Hg for 120 seconds. Cardiac output, coronary sinus blood flow, and myocardial oxygen consumption were determined before and during each intervention period. The changes in arterial pressure, heart rate, and coronary hemodynamics elicited by the 60-mm Hg increase in neck tissue pressure were also assessed. Interventions were performed in random order.

At the end of the study, diagnostic coronary arteriography and left ventriculography were performed successfully in all patients.

Data Analysis

Coronary sinus blood flow (ml/min) was measured by the continuous thermodilution method of Ganz et al according to the formula: 60×1.08×[(Tb−Ti)/(Tb−Tm)]−1, where 60 is the injectate flow rate, 1.08 is a constant accounting for the different density of saline and blood, Tb is blood temperature, Ti is injectate temperature, and Tm is mixture temperature. Coronary vascular resistance (mm Hg/ml/min) was calculated by dividing mean aortic pressure by coronary blood flow. In a previous study, we assessed the variability of repeated measurements of coronary flow during an observation period of about 1 hour. We found that the coefficient of variability was about 3%. Cardiac output (l/min) was measured by thermodilution. Systemic vascular resistance (dyne·sec/cm5) was calculated as (mean arterial pressure−right atrial pressure)/(cardiac output)×80.

Myocardial oxygen consumption (ml/min) was calculated by the formula [(AO2−CSO2) CBF]/100, where AO2 is the arterial oxygen content, CSO2 is the coronary sinus oxygen content, and CBF is the coronary blood flow (ml/min). Blood oxygen content was measured by oximetry (American Optical, New York).

To analyze the hemodynamic effects of the increase in neck tissue pressure, the following measurements of systolic and diastolic blood pressures, RR interval, cardiac output, and coronary sinus blood flow were obtained: 1) control value in the 10 seconds preceding the change in neck tissue pressure, 2) early response (the average value in the 20-second period from 5 to 25 seconds after the change in neck tissue pressure), 3) late or steady-state response (the average value in the last 30 seconds of the increase in neck tissue pressure).

The second study session consisted of a continuous 24-hour two-lead frequency-modulated electrocardiographic monitoring (Medilog 2, Oxford Instruments, Bedford, Massachusetts). The frequency response of these recorders meets American Heart Association specifications for the detection of ST segment changes. The Holter study was performed as it is customarily implemented at our institution. In detail, after careful skin preparation and electrode placement, a 1-mV calibration signal was recorded for 5 minutes, and 24-hour recording was started, which initiated a built-in time clock. The leads selected for the recording were those showing the most pronounced reversible ischemic changes on the initial qualifying 12-lead electrocardiogram recorded during an episode of chest pain. Patients were given a diary to record angina and anginal equivalent symptoms; they were instructed to press the event button on the diary coincident with onset of symptoms. During the monitoring period, the number and duration of symptomatic ischemic episodes were recorded in angina diaries. All recordings were performed while the patients were resting in bed. Time of onset and duration for each symptomatic episode during this period were also recorded prospectively. The electrocardiographic monitoring tapes were scanned by an experienced physician for the occurrence, frequency, and duration of ischemic episodes, which were defined as transient ST segment elevation or depression of 1 mm or more from baseline, 0.08 second after the J point, lasting for at least 1 minute. The definition of transient ischemic episodes as detected with the continuous electrocardiographic recordings required ST segment shifts and did not depend on T wave changes. After any potential ischemic episode, as defined above, had been identified and its onset and duration noted, each episode was recorded on paper. In addition, hourly examples of baseline measurements without ST segment changes were recorded on paper. The electrocardiographic recordings were then blindly and independently reviewed by two investigators. Correspondence between each episode recorded on the Holter
monitoring tape and symptoms permitted the identification of symptomatic and silent episodes. Our Holter analog system had been validated by studying 60 normal volunteers without risk factors for coronary heart disease who underwent exercise stress testing and 24-hour Holter monitoring and 100 patients with ischemic heart disease in whom coronary arteriography was also performed. This validation has yielded an accuracy of 64%, a sensitivity of 46%, and a specificity of 95%.

To evaluate the spontaneous variability of the daily number of episodes of myocardial ischemia, three patients from each group underwent two 24-hour electrocardiographic monitoring sessions at a 3-day interval in absence of any treatment.

The patients were divided into two groups according to their coronary response to cardiopulmonary baroreceptor unloading. In particular, group 1 included patients who showed coronary vasoconstriction during LBNP at −10 mm Hg, which is an increase in coronary vascular resistance greater than 20% of the basal value. This value was chosen according to the observation that only large changes in coronary flow are likely to be accurately assessed by the thermodilution method. Group 2 included patients who showed an increase in coronary resistance smaller than 20% of the baseline value.

All the patients in group 2 and seven in group 1 received digoxin (Lanatoside-C, 0.01 mg/kg body wt/day, divided in four intravenous daily doses) for 3 days and underwent a second 24-hour electrocardiographic monitoring session on day 3. This dose of digoxin was chosen according to the results of preliminary experiments showing that such a dosage schedule results in plasma levels of digoxin constantly near the upper limit of the therapeutic range within 3 days.

In the other two groups of patients with coronary heart disease who underwent diagnostic coronary arteriography, we assessed the effects of acute administration of digoxin on cardiopulmonary responsiveness. The reflex response was evaluated according to the protocol previously described for the main study, in control conditions, and 20 minutes after intravenous administration of digoxin (Lanatoside-C 0.02 mg/kg body wt). Finally, in two additional groups of five patients with coronary heart disease, we studied the influence of chronic digoxin treatment on cardiopulmonary reflexes. Because reflex changes in plasma norepinephrine concentrations during LBNP at −10 mm Hg are known to parallel changes in coronary vascular resistance, we used norepinephrine response as a marker for cardiopulmonary receptor responsiveness. This allowed us to repeat a relatively noninvasive study twice within 3 days. Right atrial pressure and venous plasma norepinephrine levels were measured in control conditions and during LBNP at −10 mm Hg before and after a 3-day digoxin treatment at the doses reported above.

Plasma norepinephrine assay was performed with reverse-phase high-performance liquid chromatography with electrochemical detector as previously described. The sensitivity of the assay was 10 pg injected. Intra-assay and interassay variation coefficients for norepinephrine were 5.7% and 13.8%, respectively.

Statistical Analysis

Baseline values of the two groups and the responses to LBNP and the mean number and duration of episodes of myocardial ischemia recorded in each group in control conditions and during the pharmacological treatment were compared by unpaired and paired t tests as appropriate. Analysis of variance and Duncan’s test were used to compare the responses to arterial baroreceptor unloading by neck chamber of each group.

Results

Responses to Lower-Body Negative Pressure

As specified above, the patients were divided into two groups according to their coronary response to cardiopulmonary receptor unloading. The two groups did not show significant differences in mean and pulse systemic blood pressures, systemic vascular resistance, right atrial pressure, left ventricular filling pressure (as estimated by pulmonary wedge pressure), cardiac output, and coronary blood flow (Table 1).

LBNP at −10 mm Hg reduced right atrial pressure, left ventricular filling pressure, and cardiac output (Table 1). It did not modify mean and pulse pressures and heart rate, and it increased systemic vascular resistance in both groups (Table 1). However, group 1 patients, but not those of group 2, showed a significant increase in coronary vascular resistance (Figure 1) and a significant reduction in coronary blood flow (Table 1) in response to LBNP. In addition, LBNP at −10 mm Hg decreased coronary sinus oxygen content and increased myocardial oxygen consumption only in group 1 (group 1: baseline, 16.0±0.8; −10 mm Hg LBNP, 18.1±0.7 ml/min, p<0.05; group 2: baseline, 16.7±0.8; −10 mm Hg LBNP, 16.5±0.8 ml/min, NS).

Neck Chamber Study

Carotid baroreceptor unloading significantly increased mean arterial pressure and reduced the RR interval in both groups (data not shown). A significant increase in coronary vascular resistance (group 1: baseline, 0.846±0.1; early period, 0.949±0.1, p<0.05; steady state, 0.986±0.1 mm Hg/ml/min, p<0.05; group 2, baseline, 0.869±0.1; early period, 0.965±0.1, p<0.05; steady state, 1.035±1 mm Hg/ml/min, p<0.01), which was accompanied by a decrease in coronary sinus oxygen content and an increase in myocardial oxygen extraction and consumption, was recorded in both groups (group 1: from 15.7±0.6 to 17.5±0.6 ml/min, p<0.01; group 2: from 16.1±0.7 to 19.2±1 ml/min, p<0.01).
TABLE 1. Effects of Lower-Body Negative Pressure at −10 mm Hg on Systemic and Coronary Hemodynamics

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>LBNP</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>92±1</td>
<td>93±2</td>
</tr>
<tr>
<td>PP (mm Hg)</td>
<td>47±4</td>
<td>47±4</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>71±2</td>
<td>72±2</td>
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<tr>
<td>RAP (mm Hg)</td>
<td>7.0±0.3</td>
<td>5.4±0.3†</td>
</tr>
<tr>
<td>LVFP (mm Hg)</td>
<td>16.8±0.7</td>
<td>13.6±0.7†</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>7.4±0.3</td>
<td>6.4±0.2†</td>
</tr>
<tr>
<td>SVR (dyne · cm/sec⁻³)</td>
<td>1,008±29</td>
<td>1,162±32†</td>
</tr>
<tr>
<td>CBF (ml/min)</td>
<td>111±6</td>
<td>89±4†</td>
</tr>
<tr>
<td>CVR (mm Hg/ml/min)</td>
<td>0.846±0.1</td>
<td>1.07±0.1†</td>
</tr>
</tbody>
</table>

Values are mean±SEM; group 1, n=14; group 2, n=9 patients. LBNP, lower-body negative pressure at −10 mm Hg; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; RAP, right atrial pressure; LVFP, left ventricular filling pressure; CO, cardiac output; SVR, systemic vascular resistance; CBF, coronary blood flow; CVR, coronary vascular resistance.

* p<0.05, †p<0.01 baseline vs. LBNP.

**FIGURE 1. Plot of coronary vascular response to lower-body negative pressure at −10 mm Hg in the two study groups. CVR, coronary vascular resistance.**
TABLE 2. Baseline Clinical Characteristics of Patients With and Without Silent Ischemia Detected by Continuous Electrocardiographic Recording

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n=14)</th>
<th>Group 2 (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54±3</td>
<td>54±3</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>9/5</td>
<td>6/3</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Prior MI</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Vessel stenosis ≥70% (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vessel</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>2 vessels</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>≥3 vessels</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>LAD</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Vessel stenosis ≥90% (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 vessels</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>1 vessel</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>2 vessels</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>45±2</td>
<td>56±1*</td>
</tr>
</tbody>
</table>

Values are mean±SEM where applicable; n is number of patients.

Group 1, patients with silent ischemia; group 2, patients without silent ischemia.

MI, myocardial infarction; LAD, left anterior descending coronary artery.

*p<0.01 by unpaired t test. There was no significant difference between the two groups for any other characteristics listed.

Patient Population and Continuous Electrocardiographic Monitoring

There was no significant difference between group 1 and 2 with regard to clinical characteristics including age, sex, prevalence of diabetes, and cigarette smoking (Table 2).

The extent of fixed coronary artery diseases, as defined by the number of arteries with stenosis diameter of 70% or more or of 90% or more or by the presence of previous myocardial infarction, was also comparable in the two groups (Table 2). However, former anterior myocardial infarction was prevalent in patients of group 1, and former infarction of the inferior wall of the left ventricle was more frequent in patients of group 2. This observation could explain the lower mean left ventricular ejection fraction in group 1 (45±2%) than in group 2 (56±1%) (p<0.01). Standard electrocardiography during ischemic episodes, thallium scintigraphy or radionuclide ventriculography in patients who developed myocardial ischemia during the test, and coronary arteriography indicated that the two groups showed a comparable distribution of myocardial ischemia.

A total of 151 ischemic episodes was recorded in group 1 patients during 24-hour continuous electrocardiographic monitoring (10.8±1 for each patient). More than 90% of these episodes resolved spontaneously and were asymptomatic, whereas the remaining were resolved only by nitroglycerin administration. All patients in group 1 had at least one episode of silent ischemia, and in 12 patients, symptoms were associated with at least one episode. Figure 2 shows the electrocardiographic tracing in a patient from group 1 at the beginning and during an episode of asymptomatic myocardial ischemia. Immediately after heart rate fell, the electrocardiographic signs of myocardial ischemia progressively disappeared, and finally, the electrocardiographic tracing returned to the preischemic aspect. In this patient, as well as in all the others included in this group, the development of asymptomatic myocardial ischemia was not associated with any significant increase in heart rate (73±2 vs. 70±2 beats/min). On the contrary, heart rate significantly decreased immediately before the resolution of the asymptomatic episodes of myocardial ischemia (57±2 beats/min, p<0.01). Heart rate progressively returned to the preischemic values after the resolution of the ischemic episode. Heart rate did not change at the beginning of the symptomatic episodes of angina, and actually during these ischemic episodes, heart rate significantly rose (75±4 vs. 70±2 beats/min, p<0.05), and myocardial ischemia resolved only after nitroglycerin administration. The electrocardiographic signs of myocardial ischemia observed during the asymptomatic episodes were quite comparable to those recorded during symptomatic angina. The mean duration of myocardial ischemia was 5.04±0.22 minutes for asymptomatic and 11.86±0.81 minutes for symptomatic episodes. The mean individual total daily duration of ischemia was 62±6 minutes.

In the nine patients in group 2, we recorded 90 episodes (10±1 episodes for each patient) of myocardial ischemia during the 24 hours of electrocardiographic monitoring. All these episodes were symptomatic and required nitroglycerin therapy. Despite the favorable effect of this pharmacological treatment, which reduced the duration of all the episodes of myocardial ischemia, the individual daily ischemic period in this group was 104±10 minutes, which was significantly longer than in group 1 (p<0.001) (Figure 3). Also, in this case, heart rate was unchanged at the beginning of the ischemic episodes but increased significantly during ischemia (73±2 vs. 71±2, NS; 81±2 beats/min, p<0.01, respectively).

The individual coronary vascular responses to LBNP and the corresponding individual daily ischemic period showed a highly significant correlation (r = −0.614, n=23, p<0.001).

In all patients in group 2 and in seven of those in group 1, the effects of digitalis administration were tested. This treatment did not modify heart rate and blood pressure in either group (data not shown).

During digitalis treatment, no significant change in the total daily number of ischemic episodes (10±1 vs. 10±1) or in the percentage of symptomatic (88±3% vs. 84±2%) and asymptomatic episodes (12±3% vs. 16±2%) was observed in group 1. Therefore, the duration of the daily ischemic period of this group was unchanged (62.6±7.9 vs. 58.4±4.7 minutes, NS).
In group 2, the mean number of episodes of myocardial ischemia during digitalis treatment was comparable to that recorded in control conditions (10.0±1 vs. 10.7±0.9, NS). The symptomatic episodes of ischemia, however, significantly decreased (from 10.0±1 to 6.4±0.9, p<0.01), and there were 4.2±0.6 episodes of asymptomatic ischemia in each patient. Consequently, the total daily duration of ischemia in group 2 was significantly lower than in control conditions (85±6 vs. 104±10 minutes, p<0.001), and it was no longer different from that in group 1 (Figure 3). Also in these patients, as in those of group 1, resolution of the ischemic episodes was preceded by a significant fall in heart rate (62±3 vs. 74±2 beats/min, p<0.01).

The coefficient of variability of the total daily duration of myocardial ischemia calculated in the six patients who underwent two 24-hour electrocardiographic monitoring sessions at a 3-day interval in absence of any treatment was 8.33%.

The effects of digitalis on cardiopulmonary receptor sensitivity were defined in patients clinically comparable to those included in the main study. Acute digitalis administration raised arterial pressure and systemic vascular resistance (data not shown), reduced heart rate, reduced right atrial and left ventricular filling pressures, and did not modify coronary blood flow (Table 3) in all the patients. On the contrary, coronary vascular resistance rose after digitalis treatment only in the patients showing an increase in this parameter greater than 20% of the basal value during cardiopulmonary receptor unloading performed in control conditions. In these patients, digitalis treatment failed to modify the reflex response to LBNP at -10 mm Hg (Table 3). In contrast, in five patients with impaired reflex response to cardiopulmonary receptor unloading, there was a more marked increase in coronary vascular resistance during LBNP at -10 mm Hg after digitalis administration than during control conditions (Δ%, 23±3.9 vs. 1±1, p<0.001) despite a similar decrease in right atrial and left ventricular filling pressures (Table 3).

Also in the two groups of patients in the study with chronic digitalis treatment, there were no significant differences in age and sex of patients and number
and type of coronary lesions. Furthermore, the patients showing the expected increase in norepinephrine levels during LBNP at −10 mm Hg (norepinephrine, +38±13 pg/ml) and those showing a blunted increase in norepinephrine levels during control conditions (norepinephrine, +4±4 pg/ml) showed comparable values of basal norepinephrine plasma levels (195±15 and 199±29 pg/ml, respectively). In the “responders,” the ratio between the percent increase in plasma norepinephrine levels and the simultaneous decrease in right atrial pressure induced by LBNP at −10 mm Hg was 13±3 in control conditions and 17±6 (NS) after digitalis treatment. In the remaining five patients (“nonresponders”), the mean ratio was 1±1 in control conditions and 18±5 after digitalis administration (p<0.01). The LBNP-induced reduction in right atrial pressure remained unchanged in both groups after digitalis administration, whereas the increase in plasma norepinephrine concentration was potentiated in the nonresponders (from 198±24 to 244±23 pg/ml; Δ norepinephrine, 46±10 pg/ml; p<0.01 vs. control conditions) and not modified in the responders (from 189±16 to 238±31 pg/ml; Δ norepinephrine, 45±17 pg/ml; NS vs. control conditions).

Discussion

Our results demonstrate that among patients with ischemic heart disease some show a coronary vasoconstriction in response to simulated orthostatic stress similar to that found in normal subjects, whereas others do not have appropriate reflex coronary vascular adaptation in response to low-pressure receptor deactivation.

The lack of reflex coronary vasoconstriction observed in a subgroup of patients with coronary heart disease seems to be accounted for by the impaired responsiveness of cardiopulmonary receptors with vagal afferents, which exert an inhibitory influence on vasomotor discharge. In fact, the changes in coronary vascular resistance induced by LBNP at −10 mm Hg were well above the spontaneous variability reported for repeated measurements of coronary flow. Also, it can be excluded that the changes in coronary blood flow induced by LBNP represent a consequence of changes in aortic perfusion pressure, myocardial compression of coronary vasculature, or vasomotion in response to myocardial metabolism, because no changes in blood pressure and heart rate were produced by this level of LBNP. Moreover, because a 60-mm Hg increase in neck tissue pressure induced a comparable coronary vasoconstriction in the two groups, we have ruled out the possibility that coronary vascular responsiveness was impaired in the patients of group 2. Because available evidence sug-
suggests that the supraspinal influence of renal afferents is inhibitory,17,18 we can exclude the possibility that coronary and systemic vasoconstriction induced by LBNP at −10 mm Hg results from excitatory reflexes originating in abdominal visceral receptors by distension of abdominal or pelvic veins.17,19

The observation that arterial pressure did not change during LBNP at −10 mm Hg rules out also a possible involvement of arterial baroreflexes in the mediation of the coronary vasoconstriction. Finally, cardiopulmonary receptors with sympathetic afferents mostly mediate excitatory influences,20,21 and thus, their deactivation during LBNP should have promoted an inhibitory response rather than the excitatory reflex observed in our study.

The finding that systemic vascular resistance increased in response to LBNP at −10 mm Hg also in patients in group 2 is not in contrast with the conclusion that the lack of changes in coronary vascular resistance during cardiopulmonary baroreceptor unloading in these patients is due to altered cardiopulmonary receptor responsiveness. In fact, we showed that the peripheral vascular response to LBNP at −10 mm Hg in patients with impaired cardiopulmonary responsiveness is not mediated by increased sympathetic tone.15

Although our present results demonstrate that in patients with coronary heart disease an altered responsiveness of cardiopulmonary receptors is associated with prolonged duration of myocardial ischemia, these results cannot define the relations of causality of these two events. A close inverse correlation was found between the duration of the daily ischemic period and the corresponding LBNP-induced increase in coronary vascular resistance in each patient, which strongly suggests a relation between left ventricular receptor function and duration of ischemia in coronary heart disease.

Maseri and coworkers22 demonstrated that even totally silent ST segment elevation is associated with severe impairment of left ventricular function. Thus, the increase in end-diastolic pressure, which stimulates cardiopulmonary receptors, may trigger a reflex response that reduces heart rate and coronary vascular resistance and attenuates or resolves myocardial ischemia. Indeed, we observed a reduction in heart rate that preceded or coincided with the spontaneous resolution of myocardial ischemia in group 1 patients. However, the possibility that bradycardia represents an arterial baroreflex response to systemic hypertension rather than a reflex response to cardiopulmonary receptor unloading cannot be completely ruled out. In this regard, it should be mentioned that in a previous study,2 in which we monitored blood pressure and heart rate, the spontaneous resolution of the ischemic episode was associated with a simultaneous fall in heart rate and blood pressure. There-
fore, it seems unlikely that bradycardia represents the reflex response to arterial baroreceptor activation.

Furthermore, because we were able to demonstrate such a response in group 2 only after the potentiation of cardiopulmonary receptors responsiveness induced by digitalis treatment, further support is given to the hypothesis that the activation of cardiopulmonary receptors induced by the increase in end-diastolic pressure elicits the fall in heart rate.

To demonstrate a possible causal link between cardiopulmonary receptors and duration of myocardial ischemia, we assessed the effects of digitalis treatment on low-pressure receptor responsiveness and myocardial ischemia.

Ferguson and coworkers reported an improved cardiopulmonary receptor function after acute digitalis administration, and Thames et al. observed that in dogs chronic digoxin treatment sensibilizes the vagal afferents mediating the cardiopulmonary baroreflex. An evaluation of the effects of chronic digitalis treatment on coronary reflex response to cardiopulmonary receptor unloading, however, would have required a second invasive study. To avoid this, we assessed the effects of acute digitalis administration on coronary vascular response to cardiopulmonary receptor unloading. Furthermore, we evaluated the effects of chronic digitalis therapy on cardiopulmonary responsiveness in control conditions and after chronic digitalis treatment, by measuring the LBNP-induced changes in plasma norepinephrine concentrations, which correlate well with changes in coronary vascular resistance during cardiopulmonary receptor unloading. The results of these experiments show unequivocally that digitalis improves the reflex response to cardiopulmonary receptor unloading only in patients with impaired low-pressure receptor responsiveness. Simultaneously, only in these patients did digitalis treatment reduce the total daily duration of myocardial ischemia and asymptomatic episodes of myocardial ischemia.

In particular, the finding that digitalis reduced the daily ischemic period by favoring the spontaneous resolution of myocardial ischemia may indirectly support the role of an impaired cardiopulmonary receptor responsiveness in exacerbating myocardial ischemia. In fact, previous data obtained in experimental animals and in humans support the hypothesis that the reflex response elicited by cardiopulmonary receptor activation not only reduces myocardial oxygen consumption but also improves oxygen delivery through a reduction in coronary vascular resistance.

Therefore, an impaired cardiopulmonary receptor responsiveness would result in the abolition of a mechanism of spontaneous interruption of myocardial ischemia. Thus, all the ischemic episodes are symptomatic and resolve only after nitroglycerin administration. The occurrence of asymptomatic episodes of myocardial ischemia in these patients during digitalis treatment may be accounted for by the improved cardiopulmonary receptor responsiveness that would allow the spontaneous resolution of ischemic episodes before they become symptomatic. Finally, the different putative effect of cardiopulmonary receptors with vagal afferents in asymptomatic and symptomatic episodes of myocardial ischemia may be due to the increase in sympathetic discharge that occurs during symptomatic myocardial ischemia and may counterbalance the effect of cardiopulmonary receptor activation.

Although the existence of a causal link between improved cardiopulmonary reflex sensitivity and reduction in the daily ischemic period is suggested by our present data, other possibilities need to be considered.

A spontaneous variability in the number of ischemic episodes, as noted by Parodi et al. during repeated electrocardiographic monitoring in the same patient, may partially account for the changes in the Holter findings described above. For this reason, we assessed in some of our patients the variability of the number of ischemic episodes by repeating two 24-hour electrocardiographic monitoring sessions without any pharmacological treatment. The results rule out the possibility that the changes in the number of asymptomatic episodes or the reduction in total daily ischemic period during digitalis therapy could represent the mere consequence of spontaneous variability.

In addition, sensitization of cardiac vagal afferents induced by digitalis therapy might have facilitated the occurrence of asymptomatic episodes in patients of group 2 by interfering with the sensation of cardiac pain without altering ischemia per se. In fact, Ammons and coworkers have presented evidence that vagal afferents can interact neurophysiologically to inhibit nociceptive transmission triggered by myocardial ischemia. Such a possibility, however, is minimized because of the significant reduction in the total daily duration of ischemia during digitalis therapy. This latter finding also excludes the hypothesis that the occurrence of asymptomatic episodes of myocardial ischemia during digitalis therapy in patients who did not show such an event in control conditions may be the consequence of the influence of digitalis on the electrocardiographic ST segment. In fact, if this were the case, we should have found an increase, rather than a decrease, in the total number of ischemic episodes. The observation that the administration of digitalis reduced the daily ischemic period in group 2 but not in group 1 patients further supports this conclusion.

References


KEY WORDS • ventricular receptors • myocardial ischemia • digitalis • coronary heart disease
Prolonged duration of myocardial ischemia in patients with coronary heart disease and impaired cardiopulmonary baroreceptor sensitivity.

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