Systemic and Coronary Hemodynamic Effects of Diazepam in Patients with Normal and Diseased Coronary Arteries

By Pierre Côté, M.D., Pascal Guéret, M.D., and Martial G. Bourassa, M.D.

SUMMARY
In 12 patients with significant coronary artery disease (group I) and in eight patients with normal coronary arteries (group II), 5 to 8.5 mg of diazepam was given intravenously before coronary angiography. Adequate sedation was obtained in 17 patients. Hypoventilation occurred in all patients but was without clinical correlate. Coronary and cardiovascular effects were assessed before as well as 10 and 20 min after diazepam. Heart rate was unchanged and aortic pressure (AP) decreased significantly (P < 0.01) in most patients. Cardiac index decreased only in patients of group II (P < 0.01). Of particular interest was a constant fall in left ventricular end-diastolic pressure (LVEDP) in both groups, (P < 0.01) and (P < 0.05) at 10 and 20 min respectively in group I and (P < 0.01) at 10 and 20 min in group II. Tension-time index and myocardial oxygen consumption (MVO₂) were also significantly decreased (P < 0.05) after diazepam in both groups. Since neither coronary blood flow nor coronary vascular resistance were modified by diazepam, the fall in LVEDP could be due to a decrease in AP (afterload) and/or in venous return (preload). The combination of these effects could reduce intra-cavitary volume, myocardial wall tension and left ventricular MVO₂. Our data therefore suggest that, in addition to its central sedative effects, diazepam also has a nitroglycerin-like action on the coronary and systemic circulation.

Additional Indexing Words:
Coronary sinus blood flow  Left ventricular function  Myocardial metabolism
Nitroglycerin-like action  Left ventricular end-diastolic pressure

As a sedative-hypnotic agent, diazepam has been found very useful to induce analgesia and amnesia during direct-current cardioversion.1–3 Although it is generally accepted that diazepam produces less circulatory depression than morphine, other narcotics and barbiturates,1–6 these agents are still used much more commonly to alleviate apprehension and pain in cardiac patients, because during the course of an acute myocardial infarction or in the cardiovascular laboratory. In the latter clinical situation, this contrasts with the general acceptance of diazepam as an excellent mental relaxant prior to bronchoscopy,4 gastroscopy5 and other procedures.5, 7, 8

On the other hand, diazepam is frequently prescribed in the management of anginal patients. Since anginal pain is often related to stressful stimuli, the beneficial effects of this tranquilizing drug are thought to be mediated through its action on the psyche. However, recent studies have shown that diazepam increases coronary blood flow and thus enhances left ventricular contractility in dogs during cardiopulmonary bypass.9, 10 Hemodynamic studies following diazepam administration in humans have been few and fragmentary.11–13 For example, there are to our knowledge no available data on the effects of the drug on left ventricular end-diastolic pressure.

Therefore, the primary purpose of the present study was to reassess the sedative and hemodynamic effects of diazepam in patients undergoing cardiac catheterization. Since measurements of coronary blood flow are now easily feasible in the cardiovascular laboratory,14 we have also attempted to determine the coronary and metabolic effects of diazepam in patients with normal and diseased coronary arteries.

Methods

Subjects
Twenty unpremedicated subjects undergoing cardiac evaluation for coronary artery disease were studied after an overnight fast. Informed consent was obtained for the additional procedure; however, no information was given concerning the nature of the drug to be studied. Exclusion criteria were as follows: diabetes, valvular heart disease, arterial hypertension (diastolic pressure greater than 105
mm Hg), significant pulmonary disease, therapy with beta-blockers or other autonomic drugs as well as digitalis or other cardiotoxic drugs.

The study was undertaken after left heart and coronary sinus catheterization, prior to left ventriculography and coronary arteriography. Patients were then divided into two groups, according to the presence (group I: 12 patients) or absence (group II: 8 patients) of coronary artery disease, as determined by cinecoronary arteriography. Table 1 summarizes the clinical and biological characteristics of the two groups.

Treatments

The control measurements described below were not carried out until at least 10 min after catheter manipulations in order to achieve a stable basal state. The following measurements were made over a 5 min period: blood samples were withdrawn from central aorta and mid-coronary sinus for biochemical determinations; all pressures were recorded; cardiac output was determined and, finally, coronary sinus blood flow was measured. During the last 3 min, expired air was collected for determination of body O2 consumption. After completion of basal measurements, diazepam in a dosage of 0.1 mg/kg body weight was injected as a bolus into an arm vein through the side-arm of an infusion tubing and was flushed immediately to avoid phlebitis.13 The patient was unaware that the drug was being administered. Measurements were repeated at 5 and 15 min after diazepam over a 5 min period. Expired air was collected once for determination of body O2 consumption during the 12th to 15th min. The drug study was completed within 30 min after diazepam injection. Left ventriculography and selective coronary arteriography were then carried out14 and a precise diagnosis of the obstructions was made.

Measurements

Systemic Hemodynamics and Derived Variables

Left ventricular and aortic pressures were measured through an end-hole, 100 cm, size 7F, polyethylene catheter (USCI, Billerica, Mass.) passed percutaneously from the femoral artery. A 100 cm, size 8F, Ganz thermodilution catheter was inserted from the right or left antecubital vein into the main coronary sinus. Catheters were connected to Statham P23Db transducers, which were adjusted so that the zero pressure was at the mid-chest position. Pressures were amplified and recorded on high and normal sensitivity and at paper speed of 100 mm/sec on a multichannel Sanborn photographic recorder. Pressure readings were always the mean of 10 beats. Cardiac output was measured after rapid injection of 5 mg of indocyanine green into the coronary sinus, followed immediately by a saline flush. Central aortic blood was withdrawn by a Harvard infusion pump at a rate of 20 ml/min through a cursive dye densitometer. Computation of the cardiac output was performed with the use of the Williams formula.15

Systemic vascular resistance (SVR in dynes-cm⁻² − min⁻¹) was calculated as follows:

\[
SVR = \frac{\text{map} \times 80}{\text{CO}}
\]

where MAP indicates mean aortic pressure in mm Hg, CO is cardiac output in L/min, and 80 is the conversion factor to express resistance in absolute units.

Left ventricular stroke work index (LVSWI in gm/beat/m²) was determined as follows:

\[
LVSWI = \frac{\text{SI} \times (\text{MSAP} - \text{LVEDP})}{1000}
\]

where SI indicates stroke index in ml/beat/m², MSAP is mean systolic aortic pressure and LVEDP is left ventricular end-diastolic pressure, both in mm Hg.

Tension-time index (TTI in mm Hg/sec/min) was measured as follows:

\[
TTI = (\text{HR}) \times (\text{SEP}) \times (\text{MSAP})
\]

where HR represents heart rate in beats/min, SEP is systolic ejection period in sec/beat and MSAP is mean systolic aortic pressure in mm Hg.

Mean systolic ejection rate (MSER in ml/sec/m²) was calculated as follows:

\[
\text{MSER} = \frac{\text{SI}}{\text{SEP}}
\]

where SI is the stroke index in ml/beat/m² and SEP is the systolic ejection period in sec/beat.

Coronary Hemodynamics and Metabolism

Coronary sinus blood flow was measured by the ther-

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**Table 1**

<table>
<thead>
<tr>
<th>Clinical and Biological Data</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Coronary artery disease: group I</td>
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<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Clinical data</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Age: range (mean)</td>
</tr>
<tr>
<td>Sex: male</td>
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<tr>
<td>Female</td>
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<tr>
<td>Angina</td>
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<tr>
<td>Old myocardial infarction</td>
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<tr>
<td>Functional classification*</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>Other diseases:</td>
</tr>
<tr>
<td>Mild essential hypertension</td>
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<tr>
<td>Chronic bronchitis</td>
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<tr>
<td>Angiographic data</td>
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<tr>
<td>Vessels with 75% obstruction</td>
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<tr>
<td>or more</td>
</tr>
<tr>
<td>1 vessel disease</td>
</tr>
<tr>
<td>2 vessel disease</td>
</tr>
<tr>
<td>3 vessel disease</td>
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<tr>
<td>Abnormal left ventriculogram</td>
</tr>
</tbody>
</table>

*New York Heart Association.
†A 37-year-old male was asymptomatic at the time of the study, but he had suffered an acute myocardial infarction 3 months before.
‡An acute myocardial infarction was well documented in this 27-year-old female, 3 months prior to the study.
modulation method. Estimation of total coronary flow by this simple method was found highly reproducible in our laboratory, provided that certain technical requirements were observed. The external thermistor or distal pacing electrode of the Ganz catheter was positioned just inside the coronary sinus ostium and was maintained in that position throughout the study. Location of the coronary sinus ostium was acknowledged by a small hand injection of contrast material. A physiological saline solution at 22–25°C was injected into the coronary sinus, using a calibrated Harvard pump and twin-syringes of 20 ml, at a constant rate of about 35–40 ml/min for 20–30 sec. As previously indicated, this relatively high injection rate allows adequate mixing of the injectate with blood and the short period of injection prevents contamination for recirculation. Under these conditions, variations between two successive measurements in our laboratory did not exceed 5%.

Coronary sinus blood flow (CSBF in ml/min) was calculated using the following formula:

\[ \text{CSBF} = F_1 \left( \frac{T_b - T_i}{T_b - T_m} \right) \times 1.19 \]

where \( F_1 \) represents the volume of injectate (ml/min), \( T_b \), \( T_i \), \( T_m \) are temperatures of blood, injectate and mixture of blood and injectate (°C); 1.19 is a constant derived from the density and specific heat of the saline solution and blood.

Blood samples were obtained simultaneously from the central aorta and the coronary sinus and immediately analyzed for pH, pO2, and pCO2 by a Micro-Astrup analyzer. Hemoglobin saturation was obtained from the oxyhemoglobin dissociation curve with correction for pH and temperature, as described by Severinghaus. Samples of arterial and coronary sinus blood were also taken for determinations of lactate concentration by the enzymatic method of Hohorst.

The following calculations were made:

Left ventricular oxygen and lactate extraction (%)

\[ \text{left ventricular oxygen extraction} = \left( \frac{\text{arterial} - \text{coronary sinus}}{\text{arterial}} \right) \times \text{oxygen or lactate} \]

Left ventricular oxygen consumption (ml/min)

\[ \text{left ventricular oxygen consumption} = \left( \frac{\text{arterial} - \text{coronary sinus O}_2 \text{ content (ml/100 ml)}}{\text{coronary sinus blood flow (ml/min)}} \times 10^2 \right) \]

coronary vascular resistance (units)

\[ \text{coronary vascular resistance} = \frac{\text{mean aortic pressure (mm Hg)}}{\text{coronary sinus blood flow (ml/min)}} \]

Ventilatory Indexes

Before the administration of diazepam and midway through the drug study, expired gas was collected and measured in a Tissot spirometer. From the composition of expired air, oxygen consumption (VO2 in ml/min) and alveolar ventilation (VA in L/min) were calculated. Respiratory rate was measured by visual inspection of the respiration.

Statistical analysis was performed with the use of a paired Student’s t-test for comparison of data within the same subjects in each group. Diazepam values at 10 and 20 min were compared to control values. No statistical comparison between the two groups of patients was attempted.

Results

Clinical and Respiratory Effects of Diazepam

The average diazepam dosage was 7.2 mg (range: 5 to 8.5 mg) and 6.4 mg (range 5 to 8 mg) in groups I and II, respectively. Adequate sedation was achieved in 17 of the 20 patients. In 5 subjects, light sleep was induced within one to 3 min and lasted 5 to 15 min; the patients were easily arousable. Three patients became euphoric and one was slightly agitated for a short period, but not disoriented. A few patients experienced transient drowsiness after a bolus injection of diazepam. Six patients had venous irritation at the injection site, manifested by local pain; however, none developed phlebitis in the subsequent days.

Detailed ventilatory effects, between 12 and 15 min after diazepam, and blood gas data at 5 and 15 min are shown in table 2. Minute ventilation decreased from 7.7 to 6.6 L/min (\( P < 0.05 \)) in group I and 7.0 to 5.4 L/min (\( P < 0.01 \)) in group II. Respiratory rate was unchanged and thus hypventilation was due primarily to a decrease in tidal volume. Analysis of arterial blood gases reflected the observed hypventilation, more pronounced in group I. In this group, there was a significant (\( P < 0.001 \)) mean decrease in PO2 of 14 mm Hg at 5 min. In group II, PO2 decreased by 6 mm Hg at 5 min but this was not significant. PCO2 increased significantly (\( P < 0.001 \)) in both groups at 5 min. There was a corresponding decrease in arterial pH 5 min after diazepam: mean decrease of 0.05 in group I (\( P < 0.001 \)) and 0.03 in group II (\( P < 0.05 \)). By 15 min, PO2, PCO2 and pH had returned to control values in both groups, with the exception of PO2 in group II, which was still significantly (\( P < 0.05 \)) lower than control.

Systemic Hemodynamic Effects of Diazepam

These data are shown in table 3 for both groups.

Heart Rate

There was no change in cardiac rhythm. Only two subjects, with heart rates over 100 beats per min, slowed down after diazepam, from 122 to 98 and 112 to 104 beats/min, respectively.

Pressures

At 5 and 15 min after administration of diazepam, aortic pressures (systolic, diastolic and mean) were significantly lower (\( P < 0.01 \)) than control values in both groups. Aortic pressures were unchanged in only 3 patients. The observed changes were without clinical correlates and did not require therapy.

Left ventricular end-diastolic pressure (LVEDP) fell significantly in the normal group (group II) from 9.5 to 6.6 mm Hg at 5 min (\( P < 0.01 \)) and to 6.8 mm Hg at 15 min (\( P < 0.01 \)). In the coronary artery disease group (group I), LVEDP also decreased from 13.3 to 9.8 mm Hg at 5 min (\( P < 0.01 \)) and to 9.6 mm Hg at 15 min (\( P < 0.05 \)). In the latter group, 5
Table 2
Respiratory Effects of Diazepam in Patients with Normal and Diseased Coronary Arteries

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>5 to 10 min*</th>
<th>15 to 20 min*</th>
<th>After diazepam</th>
<th>Control</th>
<th>5 to 10 min*</th>
<th>15 to 20 min*</th>
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</thead>
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<tr>
<td><strong>Arterial blood gases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.48 ± 0.02†</td>
<td>7.43 ± 0.01</td>
<td>7.47 ± 0.02</td>
<td>7.43 ± 0.02</td>
<td>7.42 ± 0.02</td>
<td>7.43 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>pO₂ (mm Hg)</td>
<td>77 ± 4</td>
<td>63 ± 2</td>
<td>71 ± 3</td>
<td>87 ± 10</td>
<td>81 ± 9</td>
<td>87 ± 10</td>
<td></td>
</tr>
<tr>
<td>pCO₂ (mm Hg)</td>
<td>26 ± 1</td>
<td>32 ± 3</td>
<td>25 ± 1</td>
<td>24 ± 3</td>
<td>29.2</td>
<td>25 ± 3</td>
<td></td>
</tr>
</tbody>
</table>
| *Data collected over a 5 min period.*  
†Mean = SEM.  
‡Paired t-test; difference from control values (NS indicates no significance).  
§Air collected through the mid-period of the drug study.

Table 3
Systemic Hemodynamic Effects of Diazepam in Patients with Normal and Diseased Coronary Arteries

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>5 to 10 min*</th>
<th>15 to 20 min*</th>
<th>After diazepam</th>
<th>Control</th>
<th>5 to 10 min*</th>
<th>15 to 20 min*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (/min)</td>
<td>77 ± 3†</td>
<td>79 ± 3</td>
<td>77 ± 3</td>
<td>85 ± 8</td>
<td>86 ± 5</td>
<td>81 ± 5</td>
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<tr>
<td>Pressures (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aortic, systolic</td>
<td>147 ± 7</td>
<td>136 ± 7</td>
<td>135 ± 7</td>
<td>138 ± 4</td>
<td>126 ± 3</td>
<td>126 ± 4</td>
<td></td>
</tr>
<tr>
<td>Aortic, diastolic</td>
<td>84 ± 3</td>
<td>79 ± 3</td>
<td>81 ± 3</td>
<td>85 ± 3</td>
<td>80 ± 3</td>
<td>81 ± 3</td>
<td></td>
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<tr>
<td>Aortic, mean</td>
<td>112 ± 5</td>
<td>105 ± 5</td>
<td>105 ± 5</td>
<td>107 ± 4</td>
<td>99 ± 4</td>
<td>100 ± 4</td>
<td></td>
</tr>
<tr>
<td>LV, end-diastolic</td>
<td>13.3 ± 1.7</td>
<td>9.8 ± 1.2</td>
<td>9.6 ± 1.4</td>
<td>9.5 ± 0.9</td>
<td>6.6 ± 0.5</td>
<td>6.8 ± 0.6</td>
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<tr>
<td>SVR (dynes, sec, cm⁻²)</td>
<td>1945 ± 171</td>
<td>1818 ± 170</td>
<td>1916 ± 186</td>
<td>1228 ± 85</td>
<td>1290 ± 107</td>
<td>1314 ± 136</td>
<td></td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.7 ± .2</td>
<td>2.8 ± .3</td>
<td>2.7 ± .2</td>
<td>4.4 ± .3</td>
<td>3.8 ± .2</td>
<td>3.9 ± .3</td>
<td></td>
</tr>
<tr>
<td>Stroke index (cc/beat/m²)</td>
<td>36 ± 3</td>
<td>36 ± 4</td>
<td>35 ± 4</td>
<td>33 ± 3</td>
<td>44 ± 2</td>
<td>49 ± 4</td>
<td></td>
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<tr>
<td>Tension time index (mm Hg/sec/min)</td>
<td>2981 ± 217</td>
<td>2741 ± 206</td>
<td>2730 ± 175</td>
<td>2944 ± 204</td>
<td>2586 ± 129</td>
<td>2532 ± 140</td>
<td></td>
</tr>
<tr>
<td>LV stroke-work index (gm/beat/m²)</td>
<td>34 ± 5</td>
<td>30 ± 6</td>
<td>30 ± 5</td>
<td>60 ± 8</td>
<td>63 ± 4</td>
<td>69 ± 5</td>
<td></td>
</tr>
<tr>
<td>Mean systolic ejection rate (ml/sec/m²)</td>
<td>118 ± 10</td>
<td>120 ± 11</td>
<td>115 ± 10</td>
<td>180 ± 12</td>
<td>165 ± 10</td>
<td>174 ± 14</td>
<td></td>
</tr>
</tbody>
</table>

*Data collected over a 5 min period.  
†Mean = SEM.  
‡Paired t-test; difference from control values (NS indicates no significance).  
Abbreviations: LV = Left ventricular; SRV = Systemic vascular resistances.

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patients had a resting LVEDP greater than 14 mm Hg (upper limit of normal for this laboratory) and all except one had a substantial fall.

Basal systemic vascular resistance was higher in group I (1945 dynes-cm⁻⁴/sec) than in group II (1228 dynes-cm⁻⁴/sec); there was no significant change after diazepam in either group, although a mean decrease of 127 dynes-cm⁻⁴/sec was encountered in group I.

Cardiac Output and Ventricular Performance

Average cardiac index and stroke index were higher in group II; they fell significantly in this group at 5 (P < 0.01) and 15 min (P < 0.05). This was probably due to an elevated resting cardiac index in 4 patients (normal value for this laboratory is 2.5 to 4.5 L/min/m²). In group I, patients with coronary artery disease, cardiac index was lower at rest, and did not change significantly after diazepam, even in patients with the lowest values.

Tension-time index decreased significantly at 5 and 15 min in both groups (P < 0.05 in group I and P < 0.01 in group II). Left ventricular stroke work index decreased slightly but not significantly in most patients. Mean systolic ejection rate (MSER) was decreased significantly only in group II (P < 0.001) and only at 5 min. Basal MSER was 180 ml/sec/m² in group II as compared to 118 ml/sec/m² in group I.

Coronary and Metabolic Data

Myocardial extraction of oxygen, higher in group I, was unchanged after diazepam in either group. However, left ventricular oxygen consumption (LVO₂) decreased significantly at 5 and 15 min in both groups. In group I, LVO₂ decreased from 16.3 to 13.9 (P < 0.001) and 14.2 ml/min (P < 0.05), and in group II from 13.5 to 11.6 (P < 0.01) and 11.4 ml/min (P < 0.05).

Basal myocardial lactate extraction was low in 3 patients with normal coronary arteries, and lactate extraction increased in these subjects at 5 and 15 min after diazepam. Of the 12 patients with coronary artery disease, 4 had either a decrease of lactate extraction or abnormal production of lactate at rest. One patient reversed myocardial lactate production to extraction after diazepam and 3 remained unchanged.

Discussion

Diazepam has been widely used in patients with heart disease, either orally to relieve emotional tension or parenterally to induce sedation, analgesia, amnesia and narcosis as a pre-anesthetic agent and during electrocardioversion.¹⁻⁸

The present study was undertaken to determine 1) whether diazepam was a safe and efficient premedicant agent for cardiac catheterization and coronary

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>After diazepam</th>
<th>Normal coronary arteries: Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary sinus blood flow (ml/min)</td>
<td>134 ± 13†</td>
<td>124 ± 14</td>
<td>112 ± 17</td>
</tr>
<tr>
<td>Coronary vascular resistance (mm Hg/ml/min)</td>
<td>1.26 ± 0.15</td>
<td>1.24 ± 0.15</td>
<td>1.03 ± 0.15</td>
</tr>
<tr>
<td>Myocardial oxygen extraction (%)</td>
<td>67 ± 3</td>
<td>67 ± 3</td>
<td>61 ± 3</td>
</tr>
<tr>
<td>Left ventricular oxygen consumption (ml/min)</td>
<td>16.3 ± 1.2</td>
<td>14.2 ± 1.3</td>
<td>11.4 ± 1.9</td>
</tr>
<tr>
<td>Myocardial lactate extraction (%)</td>
<td>16 ± 6</td>
<td>19 ± 6</td>
<td>22 ± 5</td>
</tr>
</tbody>
</table>

*Data collected over a 5 min period.
†Mean ± SD.
‡Paired t-test; difference from control values (NS indicates no significance).
angiography and 2) whether the drug would produce significant cardiovascular alterations. We were particularly interested to know whether drug-induced acute depression or enhancement of the peripheral and coronary circulation could interfere with proper evaluation of left ventricular function in the cardiovascular laboratory.

The rapidly induced sedation was impressive and was sufficient to keep the patient fully relaxed throughout the catheterization and angiographic studies. Significant changes in ventilation have previously been noted\textsuperscript{12, 13} and were confirmed in our study. The modest rise in PCO\textsubscript{2} that we have observed was not different from that reported by Robin and associates in normal individuals during physiological sleep,\textsuperscript{20} or by Dalen et al.\textsuperscript{13} and Rao et al.\textsuperscript{19} in the catheterization laboratory. Decreases in PO\textsubscript{2} and pH were also consistently seen. This blood gas derangement was maximal within 5 min after diazepam administration and returned to near control values after 15 min.\textsuperscript{12} This mild and transient respiratory depression after diazepam suggests that the drug should be administered cautiously to patients with severe bronchopulmonary disease.

In contrast to the well documented respiratory effects of diazepam, few hemodynamic studies of the drug are available. Moreover, there is still uncertainty as to whether or not diazepam modifies the cardiovascular system directly, through reflex sympathetic or parasympathetic vasodilatation or via the central nervous system.

In a recent experimental study,\textsuperscript{9} it was demonstrated that diazepam produces coronary vasodilatation following administration to the neurally intact heart isolated from the circulation, but that systemic administration does not produce coronary vasodilatation. With separate perfusion of the coronary and systemic circulations in dogs, the same authors\textsuperscript{10} have shown that intracoronary diazepam decreases coronary vascular resistance, while systemic diazepam does not.

In our study, heart rate was not altered by diazepam and aortic pressures decreased significantly in most patients, the average drop in mean aortic pressure being 7 and 8 mm Hg. Patients with low basal arterial pressures usually showed no decrease after diazepam administration, and this could possibly be explained by variations in sympathetic or parasympathetic activity. None of our patients experienced a hypotensive reaction, thus making diazepam a safe agent to use. These changes are comparable to those observed by Dalen and coworkers\textsuperscript{13} using the same dosage of diazepam under similar conditions. Other workers\textsuperscript{8, 11, 18} have found changes similar to ours or no change, although the conditions of the studies were often markedly different.

Following a simultaneous drop in arterial pressure and cardiac output in individuals with normal coronary arteries, systemic vascular resistances remained unchanged. In patients with coronary artery disease, the basal cardiac output was lower and was unchanged following diazepam injection; the relatively small drop in arterial pressure did not alter systemic vascular resistances in these patients.

Of particular interest was the constant fall in left ventricular end-diastolic pressure (LVEDP). As far as we know, this has not previously been investigated in man. This substantial fall was more obvious when basal LVEDP was elevated in some patients of the coronary artery disease group. A diminution in preload, possibly through a reduced venous return, associated with a fall, although moderate, in aortic pressure or a decrease in afterload could have contributed to the decrease in LVEDP in our patients.

The fall in LVEDP could also be due to increase in contractility and/or increase in coronary blood flow. This appears unlikely, however, since cardiac index was either decreased or unchanged, left ventricular stroke work index was unaltered and neither coronary blood flow nor coronary vascular resistance were modified by diazepam in this study.

As a result of its tendency towards a reduction in cardiac output and aortic pressure, tension-time index and myocardial oxygen consumption were significantly decreased after diazepam. Since total coronary blood flow was not increased, diazepam could most likely be regarded as a nitroglycerin-like agent. Nitroglycerin has been shown to lower arterial pressure, cardiac output, the rate of rise of left ventricular pressure and venous return.\textsuperscript{21, 22} The combination of these effects reduces intracavitary volume of the left ventricle, myocardial wall tension and oxygen requirements. It is also possible that the sedative action of diazepam yielded a more basal resting state, as manifested by a significantly decreased total body oxygen consumption.

Mean myocardial extraction ratio of lactate was unchanged in our patients; in a few individual subjects, lactate extraction was increased or even reversed from production to extraction.

In conclusion, this study demonstrates that diazepam is the agent of choice to produce sedation in patients with heart disease. It causes minimal depression of respiration and has negligible side effects. It has no deleterious effect on the cardiovascular system; on the contrary, its effects tend to bring about an improvement in cardiac function. This should be considered when the drug is used as a premedicant in the cardiovascular laboratory. Although further studies are needed in man, besides its central action,
diazepam seems to act directly upon the circulation, its mode of action being similar to that of nitroglycerin but of longer duration.

Acknowledgment

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