Comparative Effects of Ischemia and Hypoxemia on Left Ventricular Systolic and Diastolic Function in Humans

Bernard De Bruyne, MD; Jean G.F. Bronzwaer, MD; Guy R. Heyndrickx, MD, PhD; and Walter J. Paulus, MD, PhD

Background. During the initial phase of an ischemic insult, left ventricular (LV) performance depends on the complex interaction between oxygen deprivation, vascular turgor, and accumulation of metabolites. In experimental preparations, low-flow ischemia decreases systolic shortening and increases diastolic LV distensibility, whereas pacing-induced ischemia or hypoxic perfusion produces smaller decreases in systolic shortening but decreases LV diastolic distensibility. The purpose of this study was to investigate the different effects of low-flow ischemia, pacing-induced ischemia, and hypoxic perfusion on LV performance in humans.

Methods and Results. In 20 patients with a significant stenosis in the left anterior descending coronary artery, micromanometer-tip LV pressure recordings (n=20), LV angiography (n=18), and coronary sinus blood sampling (n=11) were obtained at rest and during the following conditions: pacing-induced ischemia (PI) (n=11), low-flow ischemia of balloon coronary occlusion (CO) (n=20), and hypoxemia induced by balloon coronary occlusion with hypoxic perfusion distal to the occlusion (CO+P) (n=11). LV stroke work index fell from 75±17 g·m at rest to 43±14 g·m at the end of CO (n=18; P<.002) and was lower at the end of CO than during PI (50±11 vs 77±15 g·m; n=11; P<.002) and was lower at the end of CO than at the end of CO+P (35±7 vs 46±9 g·m; n=9; P<.02). LV end-diastolic pressure rose from 16±5 mm Hg at rest to 22±6 mm Hg at the end of CO (n=20; P<.001). However, LV end-diastolic pressure was lower at the end of PI (20±5 vs 30±5 mm Hg; n=11; P<.002) and was lower at the end of CO than at the end of CO+P (26±5 vs 34±7 mm Hg; n=11; P<.01). LV end-diastolic volume index increased from 75±14 mL/m² at rest to 79±15 mL/m² at the end of CO (n=18; P<.05). Left ventricular end-diastolic volume index increased to values similar to those for CO during PI (79±13 mL/m²; n=11; P=NS) and at the end of CO+P (78±14 mL/m²; n=9; P=NS). Higher values of LV end-diastolic pressure and unchanged values of LV end-diastolic volume index for PI and CO+P, compared with CO, suggested a lower end-diastolic LV distensibility during PI and during hypoxemia, as compared with low-flow ischemia. Upward shifts of individual diastolic LV pressure-volume curves during PI (9 of 11 patients) and at the end of CO+P (7 of 9 patients), compared with CO, were also consistent with lower LV diastolic distensibility during pacing-induced ischemia and during hypoxemia, compared with low-flow ischemia. Coronary sinus lactate, H⁺, and K⁺ levels increased after balloon deflation (CO and CO+P) and during pacing (PI).

Conclusions. Thus, during low-flow ischemia, LV systolic performance was lower and LV diastolic distensibility larger than during pacing-induced ischemia or hypoxemia. The variable response of the human myocardium to different types of ischemia was probably related to the degree of vascular turgor and accumulation of tissue metabolites. *Circulation* 1993;88:461-471

Key Words • ischemia • hypoxia • angioplasty • diastole

Left ventricular performance during the initial phase of an ischemic insult results from a complex interaction between oxygen deprivation, accumulation of metabolites, and vascular turgor. These interactions have been investigated primarily in isolated, isovolumically beating, and retrogradely perfused guinea pig, rat, and rabbit hearts. In the buffer-perfused guinea pig and rabbit heart, a switch from aerobic to hypoxic perfusate induced a rise in resting tension and a progressive decline in developed tension. In the blood-perfused rabbit heart, a reduction in coronary perfusion pressure caused a rise in resting tension when pacing tachycardia was superimposed on the reduction in coronary perfusion pressure. In the rat heart, a complete interruption of coronary flow produced a fall in resting tension and a faster loss in developed tension than during hypoxic perfusion.

To investigate in humans these disparate initial left ventricular effects of different types of ischemia, the present study compared, in the same patients, left...
ventricular performance during balloon coronary occlusion (low-flow ischemia), during pacing-induced angina (low-flow, high-demand ischemia), and/or during balloon coronary occlusion with maintained hypoxic perfusion distal to the balloon occlusion (hypoxia).

Methods

Patients

Twenty patients (15 men, 5 women; mean age, 57 years; range, 42 to 72 years) were included in this study. All patients had exercise-induced angina and a clinically and electrocardiographically positive exercise stress test. There was no evidence of previous myocardial infarction on the ECG at rest or on the baseline left ventricular angiogram. Diagnostic left heart catheterization and coronary angiography revealed normal baseline global and regional left ventricular function and single-vessel coronary artery disease consisting of a significant proximal left anterior descending coronary artery (LAD) stenosis. Percent diameter and percent area of the proximal LAD stenosis, calculated by electronic caliper technique, were 67±8% and 88±5%, respectively. There were no visible collaterals to the distal LAD on contralateral coronary injection. Long-acting nitrates, β-blockers, and calcium entry blockers were withheld at least 24 hours before the procedure except in two patients who had experienced angina during mild exercise during the 48-hour period preceding hospital admission. Premedication consisted of 10 mg diazepam. The study protocol was approved by the ethical committee of the O.L.V. Ziekenhuis, Aalst (Belgium). All patients gave informed consent, and there was no complication related to procedure or study protocol.

Catheterization Protocol

In all patients, a 7F pigtail Sentron tip-micromanometer (Cordis Europe, Rooden, The Netherlands) was advanced from the left femoral artery to the left ventricle, and an 8F angioplasty guiding catheter was advanced from the right femoral artery. All pressures were referenced to atmospheric pressure at the level of the midchest. The tip-micromanometer catheter was calibrated externally against a mercury reference and matched against luminal pressure. A left ventricular dP/dt signal was derived from the high-fidelity left ventricular pressure signal with an electronic differentiator. The pressure signals, the left ventricular dP/dt signal, and three leads of the ECG were recorded on a Gould ES 1000 multichannel recorder (Fig 1). In patients 1 through 11, a 7F NIH catheter was positioned in the coronary sinus from a left antecubital vein or from the right femoral vein, and its position was confirmed by injection of contrast agent. During angioplasty balloon inflation, the coronary wedge pressure, which was measured through the fluid-filled lumen of the balloon catheter, was 29±11 mm Hg (range, 11 to 45 mm Hg), and the mean pressure difference between coronary wedge pressure and left ventricular end-diastolic pressure at the end of the balloon coronary occlusion was 8±6 mm Hg (range, 3 to 15 mm Hg). All left ventricular angiograms were performed on conventional cine film at 50 or 25 frames per second in 30° right anterior oblique projection by injection of 45 mL ioxaglate over a period of 3 seconds. An angiographic frame marker was used to match the high-fidelity left ventricular pressure recording and the left ventricular angiogram.

Comparative effects of pacing ischemia and balloon coronary occlusion. In 11 patients (Tables 1 and 2, patients 1 through 11), the effects of pacing-induced ischemia and balloon coronary occlusion ischemia on left ventricular function and washout of tissue metabolites were investigated. After baseline left ventricular angiogram and simultaneous left ventricular tip-micromanometer pressure recordings, left ventricular filling pressures were allowed to return to control level. Subsequently, right ventricular pacing was initiated at a rate of 120 beats per minute and was increased stepwise by 20 beats per minute every 2 minutes. Pacing was continued for a total pacing period of 6 minutes and stopped prematurely only if the patient experienced severe angina. In two patients, pacing was continued for more than 6 minutes and maintained at a rate of 160 beats per minute for an additional 3- or 4-minute period until appearance of chest pain. Immediately upon cessation of pacing, a second left ventricular angiogram

FIG 1. Tracings of (from left to right) two surface leads (I and II) and one precordial lead (V5) ECG, the left ventricular dP/dt signal, and the left ventricular tip-micromanometer pressure recording at rest, at cessation of pacing during pacing-induced angina, at the end of a regular balloon coronary occlusion, and at the end of an equally long balloon coronary occlusion with distal hypoxic perfusion (Tables 1 and 2, patient 10). Left ventricular diastolic pressures were higher during pacing angina and at the end of balloon coronary occlusion with distal hypoxic perfusion than at the end of the regular balloon coronary occlusion.
Table 1. Effects of Pacing-Induced Angina, Balloon Coronary Occlusion, and Balloon Coronary Occlusion With Distal Perfusion on Left Ventricular Systolic Function

<table>
<thead>
<tr>
<th>Patient</th>
<th>LVSP (mm Hg)</th>
<th>LVEF (%)</th>
<th>LV dP/dt_max (mm Hg/s)</th>
<th>LVSWI (g·m)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>PI</td>
<td>CO</td>
<td>CO+P</td>
</tr>
<tr>
<td>1</td>
<td>156</td>
<td>152</td>
<td>123</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>162</td>
<td>172</td>
<td>165</td>
<td>...</td>
</tr>
<tr>
<td>3</td>
<td>133</td>
<td>167</td>
<td>175</td>
<td>...</td>
</tr>
<tr>
<td>4</td>
<td>197</td>
<td>225</td>
<td>161</td>
<td>...</td>
</tr>
<tr>
<td>5</td>
<td>175</td>
<td>158</td>
<td>160</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>152</td>
<td>155</td>
<td>159</td>
<td>...</td>
</tr>
<tr>
<td>7</td>
<td>140</td>
<td>162</td>
<td>150</td>
<td>...</td>
</tr>
<tr>
<td>8</td>
<td>153</td>
<td>173</td>
<td>156</td>
<td>...</td>
</tr>
<tr>
<td>9</td>
<td>138</td>
<td>177</td>
<td>99</td>
<td>...</td>
</tr>
<tr>
<td>10</td>
<td>187</td>
<td>183</td>
<td>173</td>
<td>190</td>
</tr>
<tr>
<td>11</td>
<td>162</td>
<td>195</td>
<td>155</td>
<td>142</td>
</tr>
<tr>
<td>12</td>
<td>126</td>
<td>132</td>
<td>150</td>
<td>...</td>
</tr>
<tr>
<td>13</td>
<td>162</td>
<td>138</td>
<td>162</td>
<td>...</td>
</tr>
<tr>
<td>14</td>
<td>134</td>
<td>152</td>
<td>134</td>
<td>65</td>
</tr>
<tr>
<td>15</td>
<td>142</td>
<td>145</td>
<td>192</td>
<td>73</td>
</tr>
<tr>
<td>16</td>
<td>150</td>
<td>160</td>
<td>178</td>
<td>72</td>
</tr>
<tr>
<td>17</td>
<td>152</td>
<td>135</td>
<td>145</td>
<td>67</td>
</tr>
<tr>
<td>18</td>
<td>176</td>
<td>161</td>
<td>130</td>
<td>60</td>
</tr>
<tr>
<td>19</td>
<td>150</td>
<td>117</td>
<td>165</td>
<td>...</td>
</tr>
<tr>
<td>20</td>
<td>157</td>
<td>152</td>
<td>176</td>
<td>67</td>
</tr>
<tr>
<td>Mean</td>
<td>155</td>
<td>174</td>
<td>148</td>
<td>160</td>
</tr>
</tbody>
</table>

LVSP, left ventricular peak systolic pressure; LVEF, left ventricular ejection fraction; LV dP/dt_max, maximum left ventricular dP/dt; LVSWI, left ventricular stroke work index; R, rest; PI, pacing-induced ischemia; CO, balloon coronary occlusion ischemia; CO+P, balloon coronary occlusion ischemia with distal perfusion.

*P<.01 vs CO; †P<.01 vs R; ‡P<.02 vs CO.

and simultaneous left ventricular tip-micromanometer pressure recordings were obtained. To allow diastolic left ventricular pressures to return to control level, a 15-minute time interval separated the end of the pacing run from the beginning of the angioplasty procedure. A third left ventricular angiogram and simultaneous left ventricular tip-micromanometer pressure recordings were obtained at the end of the second angioplasty balloon inflation of 60-second duration. All patients experienced chest pain and ischemic ST segment changes at the end of the balloon coronary occlusion. Coronary angioplasty was successful in all patients with minimal residual coronary stenosis.

Comparative effects of pacing ischemia, balloon coronary occlusion, and balloon coronary occlusion with distal perfusion. In two patients (Tables 1 and 2, patients 10 and 11), the effects of pacing-induced ischemia, balloon coronary occlusion, and balloon coronary occlusion with distal perfusion on left ventricular function and washout of tissue metabolites were investigated. After the pacing stress test, the first two balloon coronary occlusions and return of left ventricular filling pressures to control level, a third balloon coronary occlusion of the same duration as the second balloon coronary occlusion (60 seconds) was performed. During this third balloon coronary occlusion, saline was perfused through the distal lumen of the balloon catheter. To mimic resting LAD coronary artery flow, the flow rate was set at 1 mL/s. This value was based on previous measurements in humans of great cardiac vein flow (44±4 mL/min; 69±17 mL/min) or of LAD graft flow in the presence of an occluded anterior descending artery (49±5 mL/min). As the saline solution equilibrated with room air in the perfusion pump, the amount of oxygen dissolved in the saline solution was calculated to equal ±5 mL/L, or approximately 38 times less than the amount of oxygen contained in arterial blood at 95% saturation. Hence, a saline infusion at 1 mL/s corresponded to hypoxemic conditions as it approximated normal LAD flow and as it resulted in an oxygen delivery 38 times lower than normal. At the end of this third balloon coronary occlusion, a left ventricular angiogram and simultaneous left ventricular pressure recordings were obtained. Both patients experienced more severe chest pain during the balloon occlusion with distal perfusion than during the regular first two balloon occlusions.

Comparative effects of balloon coronary occlusion and balloon coronary occlusion with distal perfusion. In nine patients (Tables 1 and 2, patients 12 through 20), the effects of balloon coronary occlusion and balloon coronary occlusion with distal perfusion on left ventricular function were investigated. After baseline recordings and a first angioplasty balloon inflation, a second angioplasty balloon inflation with distal perfusion was performed. At the time of chest pain, a second left ventricular angiogram and simultaneous left ventricular pressure recordings were obtained. After return of left ventricular pressure to baseline value, a regular third angioplasty balloon inflation of the same duration as the
TABLE 2. Effects of Pacing-Induced Angina, Balloon Coronary Occlusion, and Balloon Coronary Occlusion With Distal Perfusion on Left Ventricular Diastolic Function

<table>
<thead>
<tr>
<th>Patient</th>
<th>LVEDP (mm Hg)</th>
<th>LVMDP (mm Hg)</th>
<th>LVEDVI (mL/m²)</th>
<th>LV dP/dtmin (mm Hg/s)</th>
<th>T0 (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>31</td>
<td>19</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>27</td>
<td>16</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>28</td>
<td>17</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>37</td>
<td>19</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>33</td>
<td>13</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>20</td>
<td>21</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>23</td>
<td>14</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>31</td>
<td>26</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>9</td>
<td>16</td>
<td>28</td>
<td>17</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>10</td>
<td>23</td>
<td>35</td>
<td>29</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>11</td>
<td>16</td>
<td>35</td>
<td>24</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>26</td>
<td>41</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>13</td>
<td>15</td>
<td>25</td>
<td>36</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>14</td>
<td>17</td>
<td>38</td>
<td>36</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>15</td>
<td>17</td>
<td>23</td>
<td>34</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>16</td>
<td>25</td>
<td>32</td>
<td>38</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>17</td>
<td>10</td>
<td>17</td>
<td>17</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>18</td>
<td>18</td>
<td>24</td>
<td>29</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>19</td>
<td>10</td>
<td>24</td>
<td>34</td>
<td>R</td>
<td>PI</td>
</tr>
<tr>
<td>20</td>
<td>24</td>
<td>25</td>
<td>37</td>
<td>R</td>
<td>PI</td>
</tr>
</tbody>
</table>

LVEDP, left ventricular end-diastolic pressure; LVMDP, left ventricular minimum diastolic pressure; LVEDVI, left ventricular end-diastolic volume index; LV dP/dtmin, minimum left ventricular dP/dt; T0, time constant of left ventricular pressure decay with zero asymptote; R, rest; PI, pacing-induced ischemia; CO, balloon coronary occlusion ischemia; CO+P, balloon coronary occlusion ischemia with distal perfusion.

*P<.01 vs CO; †P<.01 vs R; ‡P<.05 vs R; §P<.02 vs CO.

Data Analysis

Hemodynamic data. All hemodynamic data (Tables 1 and 2) were averaged throughout a complete respiratory cycle. The time constants of left ventricular pressure decay (T0 and Tp) were derived from exponential curve fits with zero and variable (PB) asymptote pressures to the digitized left ventricular pressure data points of isovolumic left ventricular relaxation.10 Pressure data points were obtained at 3-millisecond intervals by digitizing the left ventricular pressure signals from the moment of left ventricular dP/dtmin to a time at which left ventricular pressure equaled left ventricular end-diastolic pressure plus 5 mm Hg.

Angiographic data. Left ventricular volumes were calculated from single-plane left ventricular cineangiograms performed in 30° right anterior oblique projection using the area-length method and a regression equation.11 Frame-by-frame analysis was performed on the third to fourth beat after contrast appearance, and nonsinus and potentiated beats were excluded from the analysis. In two patients (Tables 1 and 2, patients 12 and 19), no volumetric data were reported because of ventricular premature beats on one of the left ventricular angiograms. Left ventricular pressure-volume plots were constructed by matching corresponding points of left ventricular pressure and volume using the cine frame marker. Left ventricular stroke work index (Table 1) was calculated as the product of stroke volume index and mean systolic left ventricular pressure. Each individually reported angiographic value (Tables 1 and 2) is the average of three measurements (intraobserver variability for left ventricular volume, 1.5%).

Metabolic data. Blood samples were obtained from the coronary sinus and from the femoral artery before pacing, during the last 15 seconds of each pacing step, and 10, 30, and 120 seconds after cessation of pacing (Tables 1 and 2, patients 1 through 11). Similar samples were obtained before balloon inflation, at the end of the balloon inflation period, and 10, 30, and 120 seconds after deflation of the balloon (Tables 1 and 2, patients 1 and 19).
through 11) and before balloon inflation with distal perfusion, at the end of the balloon inflation period with distal perfusion, and 10, 30, and 120 seconds after deflation of the balloon and cessation of the distal perfusion (Tables 1 and 2, patients 10 and 11). The timing of sampling was based on previously reported K⁺ concentration measured by catheter electrode in the coronary sinus during and after balloon inflations of coronary angioplasty. 12 On each blood sample, pH and K⁺ and lactate concentrations were determined. For determination of lactates, blood was rapidly centrifuged, and the supernatant fluid was stored at −20°C. Lactate in the supernatant was analyzed by oxidase-catalyzed lactate to pyruvate and hydrogen peroxide in the presence of oxygen. Potassium concentration was assessed by indirect potentiometry, and pH was determined by an ABL 30 blood gas analyzer.

Statistical analysis. Results are given as mean±SD. Differences were considered significant when P<.05. A paired t test was used for single comparisons and a Bonferroni method for multiple comparisons.

Results

Effects on Left Ventricular Systolic Function

Table 1 shows individual values of indices of left ventricular systolic function, and Fig 1 shows a set of recordings obtained in a representative patient. At the end of balloon coronary occlusion, heart rate was significantly higher than at rest (79±13 vs 74±12 beats per minute; P<.01; n=20). In the patients in whom left ventricular function was compared at rest, at cessation of pacing, and at the end of balloon coronary occlusion, heart rate during pacing ischemia was significantly higher than at rest (85±12 vs 78±11 beats per minute; P<.01; n=11) and comparable to heart rate at the end of balloon coronary occlusion (85±12 vs 83±13 beats per minute; NS; n=11). In the patients in whom left ventricular function was compared at rest, at the end of balloon coronary occlusion, and at the end of balloon coronary occlusion with distal perfusion, heart rate at the end of balloon coronary occlusion with distal perfusion was higher than at rest (78±11 vs 69±13 beats per minute; P<.01; n=11) and comparable to heart rate at the end of balloon coronary occlusion (78±11 vs 76±13 beats per minute; NS; n=11). At the end of balloon coronary occlusion, left ventricular ejection fraction (LVEF) was significantly lower than at rest (39±9% vs 68±7%; P<.001; n=18). In the patients in whom left ventricular function was compared at rest, at cessation of pacing, and at the end of balloon coronary occlusion, LVEF during pacing ischemia was lower than at rest (59±9% vs 68±7%; P=.002; n=11) but higher than at the end of balloon coronary occlusion (59±9% vs 43±7%; P<.001; n=11). In the patients in whom left ventricular function was compared at rest, at the end of balloon coronary occlusion, and at the end of balloon coronary occlusion with distal perfusion, LVEF at the end of balloon coronary occlusion with distal perfusion was lower than at rest (36±8% vs 65±5%; P<.001; n=9) and comparable to LVEF at the end of the regular balloon coronary occlusion (36±8% vs 32±6%; NS; n=9). Left ventricular stroke work index (LVSWI) at the end of balloon coronary occlusion was significantly lower than at rest (43±14 vs 75±17 g·m; P<.001; n=18). In the patients in whom left ventricular function was compared at rest, upon cessation of pacing, and at the end of balloon coronary occlusion, LVSWI during pacing ischemia was higher than at the end of balloon coronary occlusion (77±15 vs 50±11 g·m; P<.002; n=11). In the patients in whom left ventricular function was compared at rest, at the end of balloon coronary occlusion, and at the end of balloon coronary occlusion with distal perfusion, LVSWI at the end of balloon coronary occlusion with distal perfusion was lower than at rest (46±9 vs 74±17 g·m; P<.01; n=9) but higher than at the end of the regular balloon coronary occlusion (46±9 vs 35±7 g·m; P<.02; n=9).

Effects on Left Ventricular Diastolic Function

Table 2 shows individual values of indices of left ventricular diastolic function. Left ventricular end-diastolic pressure (LVEDP) was significantly higher at the end of balloon coronary occlusion than at rest (23±6 vs 16±5 mm Hg; P<.001; n=20). In the patients in whom left ventricular function was compared at rest, at cessation of pacing, and at the end of balloon coronary occlusion, LVEDP during pacing ischemia was significantly higher than at rest (34±7 vs 17±5 mm Hg; P<.001; n=11) and than at the end of regular balloon coronary occlusion (34±7 vs 26±5 mm Hg; P<.01; n=11). In the patients in whom left ventricular function was compared at rest, at the end of balloon coronary occlusion, and at the end of balloon coronary occlusion with distal perfusion, LVEDP at the end of balloon coronary occlusion with distal perfusion was significantly higher than at rest (34±7 vs 17±5 mm Hg; P<.001; n=11) and than at the end of the regular balloon coronary occlusion (34±7 vs 26±5 mm Hg; P<.01; n=11). As evident from Table 2, the results for left ventricular minimum diastolic pressure were similar to those for LVEDP. The time constant of left ventricular pressure decay with zero asymptote pressure (T₀) was significantly larger at the end of balloon coronary occlusion than at rest (58±10 vs 41±10 milliseconds; P<.001; n=20). During pacing-induced ischemia, T₀ was significantly larger than at rest on single-comparison analysis but not on multiple-comparison analysis (48±12 vs 39±8 milliseconds; NS; n=11). At the end of balloon coronary occlusion with distal perfusion, T₀ was significantly larger than at rest (73±10 vs 43±11 milliseconds; P<.01; n=11) and than at the end of the regular balloon coronary occlusion (73±10 vs 59±12 milliseconds; P<.02; n=11). The time constant of left ventricular pressure decay with variable asymptote pressure (Tₘ₀) was significantly larger than at rest (67±24 milliseconds), at the end of balloon coronary occlusion (112±57 milliseconds; P<.05; n=20), during pacing-induced ischemia (98±33 milliseconds; P<.02; n=11), and at the end of balloon coronary occlusion with distal perfusion (112±59 milliseconds; P<.02; n=11). At the end of balloon coronary occlusion, left ventricular end-diastolic volume index (LV EDVI) was significantly larger than at rest (79±15 vs 75±14 mL/m²; P<.05; n=18). During pacing ischemia and at the end of balloon coronary occlusion with distal perfusion, LV EDVI was comparable with LV EDVI at the end of the regular balloon coronary occlusion. The higher LV EDVI observed during pacing ischemia and at the end of balloon coronary occlusion with distal perfusion, therefore, indicated lower left ventricular end-diastolic distensibility than at the end of the regular balloon coronary occlusion.
Fig 2 shows individual diastolic left ventricular pressure-volume relations at rest, during pacing-induced ischemia at cessation of pacing, and at the end of balloon coronary occlusion. In 9 of the 11 patients, the diastolic left ventricular pressure-volume relation during pacing-induced ischemia was shifted upward compared with both the diastolic left ventricular pressure-volume relations at rest and at the end of balloon coronary occlusion. In one patient (patient 10), both the diastolic left ventricular pressure-volume relation during pacing-induced ischemia and at the end of balloon coronary occlusion shifted upward compared with the diastolic left ventricular pressure-volume relation observed at rest. In one patient (patient 6), both the diastolic left ventricular pressure-volume relation during pacing-induced ischemia and at the end of balloon coronary occlusion fell on the relation observed at rest. Fig 3 shows individual diastolic left ventricular pressure-volume relations at rest, at the end of balloon coronary occlusion, and at the end of an equally long balloon coronary occlusion with distal perfusion. In seven of the nine patients, the diastolic left ventricular pressure-volume relation at the end of balloon coronary occlusion with distal perfusion was shifted upward compared with both the diastolic left ventricular pressure-volume relations observed at rest and at the end of the regular balloon coronary occlusion. In two patients (patients 14 and 17), the diastolic left ventricular pressure-volume relations at the end of balloon coronary occlusion and at the end of balloon coronary occlusion with distal perfusion showed a similar upward shift compared with the relation at rest.

Coronary Sinus Washout of Lactate, H⁺, and K⁺

Fig 4 shows coronary sinus lactate concentrations measured in patient 10 of Tables 1 and 2. During pacing, there was a progressive rise of coronary sinus lactate, and before
cessation of pacing, coronary sinus lactate concentration was significantly different from the baseline value (8.8±3.8 vs 6.5±3.8 mmol/L; *P* < .05). Ten seconds after cessation of pacing (8.7±3.8 mmol/L; *P* < .05) and 30 seconds after cessation of pacing (8.4±3.7 mmol/L; *P* < .05), there was persistent elevation of coronary sinus lactate concentration. During balloon coronary occlusion, coronary sinus lactate concentration remained unaltered, but a significant rise in coronary sinus lactate concentration was observed 10 seconds after deflation of the balloon (16.5±6.7 mmol/L; *P* < .05), 30 seconds after deflation of the balloon (14.2±4.3 mmol/L; *P* < .05), and 120 seconds after deflation of the balloon (9.5±3.8 mmol/L; *P* < .05). During balloon coronary occlusion with distal perfusion, coronary sinus lactate concentration followed a pattern similar to the regular balloon coronary occlusion.

A significant rise in coronary sinus K⁺ concentration was observed with respect to baseline value (3.8±0.4 mEq/L) at the end of the first pacing step (4.0±0.1 mEq/L; *P* < .01), at the end of the second pacing step (4.0±0.1 mEq/L; *P* < .01), and at the end of the third pacing step (4.0±0.1 mEq/L; *P* < .01). Upon cessation of pacing, coronary sinus K⁺ concentration dropped below baseline value. A significant rise in serum K⁺ was observed after release of the balloon (4.4±0.6 mEq/L; *P* < .01) but not during the balloon occlusion periods.

No significant change in coronary sinus pH was observed during pacing, after pacing, during balloon coronary occlusion, and during balloon coronary occlusion with distal perfusion. With respect to baseline value (7.38±0.04), a significant drop in coronary sinus pH was observed 10 seconds (7.26±0.06; *P* < .01) and 30 seconds (7.34±0.07; *P* < .01) after release of the balloon. Arterial lactate and K⁺ concentrations and pH remained unaltered throughout the study.

**Discussion**

**Experimental and Clinical Evidence on Left Ventricular Performance in Different Types of Ischemia**

In the guinea pig left ventricle, hypoxic buffer perfusion induced, within 5 minutes, a decline in developed tension and a rise in resting tension² consistent with a drop in left ventricular distensibility. In a similar rabbit heart preparation, the acute effects of hypoxia were compared with low-flow ischemia.³ Hypoxia caused a
rise and low-flow ischemia an initial fall in left ventricular filling pressures, and hypoxia resulted in a slower decline of left ventricular developed pressure. Replacement of buffer by blood perfusion induced a rise of left ventricular filling pressures, when pacing tachycardia was superimposed on low-flow ischemia.4

During brief single-vessel coronary occlusion in anesthetized or conscious dogs,13-21 myocardial shortening of the affected segment was replaced by passive bulging, and the diastolic pressure–segment length relation showed a rightward shift.13,15,16,21 In conscious dogs with a single-vessel coronary stenosis, exercise resulted in an upward shift of the early portion of the left ventricular diastolic pressure–volume relation,20 and in anesthetized pigs with single-vessel coronary stenosis,22 pacing resulted in an upward shift of the entire left ventricular diastolic pressure–segment length relation. In anesthetized dogs with two-vessel coronary stenoses,17-19 pacing resulted in subendocardial ischemia, a drop in left ventricular systolic performance, and an upward shift of the diastolic left ventricular pressure–volume relation. When pacing tachycardia in the presence of two-vessel coronary stenoses resulted in transmural myocardial ischemia,21 there was more profound impairment of left ventricular systolic performance with occasional bulging and unaltered diastolic left ventricular distensibility. In isovolumic dog hearts, global ischemia increased left ventricular diastolic distensibility23 even in the presence of pacing tachycardia,24 but a hypoxic perfusate of methemoglobin-containing red blood cells25 decreased left ventricular diastolic distensibility.

Previous studies in humans on the initial effects of ischemia on left ventricular performance investigated a single type of ischemic insult such as pacing-induced ischemia,26-28 exercise-induced ischemia,29 spontaneous coronary spasm,30 and balloon coronary occlusion ischemia31-34 except for the study of Bronzwaer et al,35 who compared left ventricular performance during both pacing-induced and balloon coronary occlusion ischemia in the same patient. The present study confirmed the findings of Bronzwaer et al and was the first to compare, in the same patient, left ventricular function at the end of a regular balloon coronary occlusion and at the end of an equally long balloon coronary occlusion during which saline was perfused through the distal lumen of the balloon catheter (hypoxemia). The present comparison of the left ventricular effects of balloon occlusion ischemia, pacing-induced ischemia, and hypoxemia revealed pacing-induced ischemia and hypoxemia to cause less depression of left ventricular systolic performance and a larger reduction of left ventricular diastolic distensibility than balloon occlusion ischemia. Pathophysiological mechanisms, which could contribute to the variable response of human myocardium subjected to different types of ischemia include (1) vascular turgor during the ischemic episode or during the hyperemic phase after the ischemic episode, (2) buildup or washout of tissue metabolites during the ischemic episode, and (3) unequal intensity of the ischemic stress episodes.
Vascular Turgor During Ischemic Episode and Hyperemic Phase

Coronary perfusion pressure, coronary flow, or both influence left ventricular systolic performance (Gregg phenomenon)\(^5\) and left ventricular diastolic distensibility (Salisbury effect).\(^6\) The Gregg phenomenon was recently reappraised by the slower decline of left ventricular developed pressure in the microembolized heart without coronary depressurization than after interruption of coronary flow.\(^7\) The slower loss of left ventricular systolic performance in the microembolized heart was attributed to persistent vascular turgor, which stretched cardiac sarcomeres by mechanical coupling of the vascular network and the myocardium. The better preservation of left ventricular stroke work during balloon coronary occlusion with distal perfusion, as observed in the present study, was consistent with a similar interaction between coronary vascular turgor and initial ischemic contractile failure. Recent insights on how cardiac muscle stretch affects cardiac muscle performance suggested an intrinsic molecular property of troponin-C to mediate the rising limb of the cardiac muscle length-active tension relation.\(^8\) Hence, vascular turgor could affect cardiac muscle performance by a mechanism similar to tissue metabolites, namely, modulation of myofilamentary calcium sensitivity. Moreover, the vascular network could also affect myofilamentary calcium sensitivity through release of substances from the coronary endothelium.\(^9\) In this respect, patients experienced more severe chest pain during the balloon inflation with distal perfusion. This could be consistent with a larger production of bradykinin, which is known to stimulate cardiac afferent nerve endings or nociceptors and to trigger a release of substances from endothelial cells. The increased severity of chest pain during the balloon inflation with distal perfusion could have resulted in increased cardiac sympathetic stimulation. The comparable heart rate at the end of both balloon inflations and the larger prolongation of the time constant of left ventricular pressure decay (\(T_{1/2}\)) during the balloon inflation with distal perfusion, however, argue against unequal sympathetic stimulation.

Coronary perfusion influences left ventricular diastolic distensibility by changing coronary vascular engorgement. An increase in LVEDP at increased coronary perfusion pressure was first observed in an isovolumic canine left ventricle (Salisbury effect)\(^10\) and confirmed by other investigators, who observed larger changes in diastolic left ventricular wall stiffness when coronary perfusion pressure was altered in a failing left ventricle.\(^11\) During balloon occlusion ischemia, the drop of coronary perfusion pressure could increase diastolic left ventricular distensibility. A rightward and downward shift of the diastolic left ventricular pressure-volume relation was indeed observed in the present study during balloon coronary occlusion in 5 of the 20 patients (Figs 2 and 3, patients 2, 7, 16, 18, and 20). Even when the presence of a critical coronary stenosis permits no change in total coronary blood flow, a reactive hyperemic response to the ischemic subendocardium after the pacing stress episode could contribute to the observed decrease in diastolic left ventricular distensibility.\(^12\) During balloon occlusion with distal saline perfusion, coronary perfusion pressure was preserved and probably contributed in the present study to the larger decrease in diastolic left ventricular distensibility compared with regular balloon coronary occlusion. Hypoxic whole blood perfusion instead of saline perfusion could have resulted in an even larger reduction in left ventricular diastolic distensibility because in an isovolumic rabbit heart, replacement of buffer by blood perfusion was a prerequisite for a consistent fall in left ventricular diastolic distensibility during low-flow, high-demand ischemia.\(^13\) These experiments favored the notion of higher mechanical vascular support of surrounding tissues during whole-blood perfusion.

Buildup or Washout of Tissue Metabolites

Coronary occlusion ischemia, pacing-induced ischemia, and hypoxemia exert unequal effects on buildup of tissue metabolites, such as \(H^+\) and inorganic phosphate. These tissue metabolites, especially inorganic phosphate,\(^14\)–\(^16\) induce contractile failure by reducing calcium sensitivity of myofilaments, despite increased amplitude of the calcium transient and myoplasmic calcium overload. In the present studies, coronary sinus lactate, \(H^+\), and \(K^+\) concentrations were measured at rest, during and after the pacing-stress episode, during and after the regular balloon coronary occlusion, and during and after the balloon coronary occlusion with distal coronary perfusion (see Fig 4). In the absence of simultaneous coronary sinus flow measurements, the coronary sinus lactate, \(H^+\), and \(K^+\) concentrations provided information on the time course of metabolite handling but not on metabolite production. During pacing-induced ischemia, washout of tissue metabolites started during the pacing-stress episode and continued after pacing. Since left ventricular function was measured immediately at cessation of pacing, the better preservation of left ventricular systolic performance could be related to the ongoing washout of tissue metabolites. Balloon coronary occlusion ischemia caused metabolites to appear in the coronary sinus at a different time than pacing-induced ischemia. During the actual balloon coronary occlusion, there was no rise of coronary sinus lactate concentration (Fig 4), the peak of which was observed after release of the angioplasty balloon during the hyperemic phase. At the end of the balloon inflation, when left ventricular function was measured, buildup of tissue metabolites could explain the larger decrease of LVSWI compared with pacing-induced ischemia. During balloon coronary occlusion with distal perfusion, the time pattern of coronary sinus lactate concentration was comparable to the regular balloon coronary occlusion. This observation, however, did not exclude unequal intracellular accumulation of metabolites during both coronary occlusions because of failure to measure inorganic phosphate concentrations and because of failure to perform great cardiac vein sampling to selectively assess LAD drainage.

During balloon inflation with distal perfusion, the perfusate was a mixture of blood obtained from coronary collaterals (mean coronary wedge pressure, 29±11 mm Hg) and regular saline (pH, 7.0) infused through the distal lumen of the balloon catheter. The saline infusion rate was set at a value of 1 mL/s to mimic resting LAD flow.\(^17\) The perfusate was of lower pH, hypokalemic, and hypocalcemic relative to whole-blood perfusion. In isolated cardiac muscle preparations, both
acidosis and combined hypokalemia-hypocalcemia exerted a negative inotropic effect. The higher LVSWI observed during balloon inflation with distal perfusion compared with the regular balloon inflation was therefore unrelated to the altered composition of the perfusate relative to whole blood. The lower pH of the perfusate relative to whole blood could have reduced diffusion of hydrogen ions out of the myocardium, and hypoxic whole-blood perfusion could probably have resulted in even better preservation of LVSWI.

Unequal Intensity of the Ischemic Stress Episodes

Unequal intensity of the ischemic stress of pacing-induced ischemia, of balloon coronary occlusion, and of hypoxemia could have influenced left ventricular performance in the three conditions. In a study on anesthetized open-chest, open- pericardium dogs, pacing-induced ischemia and coronary occlusion ischemia produced similar changes in contractile function of the ischemic region, when both ischemic stress episodes achieved the same elevation of LVEDP, which was used as a marker of the intensity of the ischemic stress. In the present study, LVEDP was lowest at the end of balloon coronary occlusion. Despite lowest LVEDP at the end of balloon coronary occlusion, LVSWI showed the largest reduction. Hence, when elevation of LVEDP is used as a marker of the intensity of the ischemic stress episode, the reduction of left ventricular systolic performance appears to be larger at the end of the least severe ischemic stress episode. This implies that factors other than the intensity of the ischemic stress episode modulate left ventricular performance during the initial stages of ischemia.

During balloon occlusion with distal perfusion, myocardial oxygen delivery could have been higher than during regular balloon occlusion because of oxygen dissolved in the perfusate. Because of the use of blood-free perfusate, the amount of oxygen dissolved was minimal (±5 mL/L) and approximately 38 times less than in arterial blood. Moreover, during balloon occlusion with distal perfusion, oxygen delivery to the ischemic region from collateral flow must have been less than during regular balloon inflation because of higher intravascular pressure created by the perfusion pump in the epicardial coronary arteries distal to the balloon occlusion.

Conclusions

Left ventricular function was compared in the same patient with single-vessel LAD coronary stenosis at the end of balloon coronary occlusion, immediately after a pacing stress test, and/or at the end of balloon coronary occlusion with hypoxic perfusion distal to the balloon occlusion (hypoxemia). At the end of balloon coronary occlusion, left ventricular systolic performance was lower and left ventricular diastolic distensibility larger than during pacing-induced ischemia or hypoxemia. Degree of vascular turgor and unequal accumulation of tissue metabolites could explain the variable response of human myocardium to different types of ischemia.

Acknowledgments

We gratefully acknowledge Stanislas U. Sys, MD, PhD, and Johan De Vriese, RN, for their technical support.

References


43. Ross J Jr. Is there a true increase in myocardial stiffness with acute ischemia? Am J Cardiol. 1989;63:87E-91E.


Comparative effects of ischemia and hypoxemia on left ventricular systolic and diastolic function in humans.
B De Bruyne, J G Bronzwaer, G R Heyndrickx and W J Paulus

Circulation. 1993;88:461-471
doi: 10.1161/01.CIR.88.2.461

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/88/2/461

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/