The Effect of Propranolol on Left Ventricular Function at Rest and during Exercise in Patients With Ischemic Heart Disease

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SUMMARY

Twelve patients with ischemic heart disease were investigated by right and left heart catheterisation. All patients were studied at rest and during exercise, both before and after administration of β-blocker propranolol, Inderal (ICI). Left ventricular function decreased after administration of propranolol, but these changes were significant only during exercise. Contractility was depressed after administration of propranolol already at rest. On the other hand, left ventricular filling pressure decreased after administration of propranolol. Our results show the poor reliability of the evaluation of the left ventricular function based solely on the left ventricular filling pressure.

Additional Indexing Words:
Ischemic heart disease Central hemodynamics Left ventricular function Rest Exercise Propranolol

THE drugs which block beta adrenergic receptors have been well known to produce good effect in indicated cases. Nevertheless, in patients with ischemic heart disease (IHD), attention has been also drawn to some undesirable effects of these agents. In patients with IHD the cardiodepressive effect of beta blockers may further impair the mechanical function.

In this paper we were not concerned with the therapeutic effect of beta blockers, but we analyzed the undesirable effect on the left ventricular function during an acute experiment. We chose intravenous administration of propranolol to get negative inotropic effect on the myocardium.

METHODS

We examined 12 patients who had had acute myocardial infarction (MI) 3–6 months previously. Two patients had nontransmural MI, and 10 transmural MI; of these 10 patients, during the acute phase of MI 2 exhibited clinical, and
3 X-ray signs of left heart failure. At the time of our examinations, 9 patients reported effort angina pectoris, and 3 effort dyspnea. None of the patients had obvious and 2 patients had incipient X-ray signs of left heart failure. All patients felt well and had been included into a rehabilitation program. None of the patients received digitalis or beta blockers.

All patients underwent an outpatient hemodynamic examination; a floating catheter was inserted into the pulmonary artery. Second catheter was introduced into the left ventricle without X-ray control. Intracardiac pressures were measured by Statham P23 Db transducers and were recorded on Cardiopan Philips. The system was calibrated with the aid of a water column.

The left ventricular work index (LVWI) and the stroke work index (SWI) were calculated from the formulae:

\[
LVWI = (LVSP - LVEDP) \times 1.36 \times CI
\]

\[
SWI = \frac{LVWI}{HR}
\]

where \( LVSP \): left ventricular mean systolic pressure, \( LVEDP \): left ventricular enddiastolic pressure, \( CI \): cardiac index, and \( HR \): heart rate.

The LVSP during ejection was obtained by planimetry from ventricular pressure curve between the opening and closing of aortic valves drawn at a paper speed of 100 mm/s. Average of 5 consecutive beats was calculated. The ejection time was delimited with the aid of a tracing of the first derivative of the left ventricular pressure (dP/dt).

The cardiac output was obtained by the direct Fick's principle. Blood gases in arterial and mixed venous blood were analysed on a Radiometer Copenhagen Apparatus. Expired gases were analysed for the content of \( O_2 \) and \( CO_2 \) on a Zeiss interferometer. Exercise was performed on an Elema bicycle ergometer. The exercise load was chosen so that the patient was able to exercise in a relatively steady state.

All examinations were performed in recumbent position, both at rest and during exercise. After a 20 min rest, 10 mg of propranolol was injected into the pulmonary artery; each 1 mg portion was injected during 1 min, alternating with a 1 min break. During the administration, the heart rate, left ventricular pressure, and dP/dt were monitored. All examinations were repeated at rest and during exercise after application of propranolol. The same exercise load was used.

**Results**

The patient data and results of routine pulmonary function tests were given in the Table I. The hemodynamic results at rest and during exercise both before and after intravenous administration of propranolol were given in Table II.

Heart rate (HR) and cardiac index (CI) decreased significantly after injection of Propranolol both at rest and during exercise (Table II and Fig. 1). Oxygen consumption (\( \dot{V_o}_2/M^2 \)) and stroke index (SI) were not influenced significantly by injection of propranolol. Exercise did not influence SI signi-
Table I. The Subject Data, Lung Volume and Forced Expiratory Volume

<table>
<thead>
<tr>
<th>Name</th>
<th>Age &amp; Sex</th>
<th>BSA (M²)</th>
<th>VC (ml)</th>
<th>VC % pred.</th>
<th>TLC (ml)</th>
<th>RV/TLC (%)</th>
<th>FRC (ml)</th>
<th>FEV/ls (%)</th>
<th>FEV 3/4'' x40 (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. V.</td>
<td>51 M</td>
<td>1.96</td>
<td>3,486</td>
<td>82</td>
<td>5,154</td>
<td>32.4</td>
<td>1,946</td>
<td>77</td>
<td>96</td>
</tr>
<tr>
<td>E. J.</td>
<td>54 M</td>
<td>1.83</td>
<td>3,336</td>
<td>89</td>
<td>5,180</td>
<td>35.6</td>
<td>2,267</td>
<td>70</td>
<td>85</td>
</tr>
<tr>
<td>K. CH.</td>
<td>59 M</td>
<td>2.09</td>
<td>4,893</td>
<td>104</td>
<td>7,974</td>
<td>38.6</td>
<td>3,384</td>
<td>67</td>
<td>118</td>
</tr>
<tr>
<td>A. K.</td>
<td>53 M</td>
<td>1.81</td>
<td>3,862</td>
<td>98</td>
<td>5,894</td>
<td>38.5</td>
<td>2,785</td>
<td>78</td>
<td>114</td>
</tr>
<tr>
<td>J. G.</td>
<td>59 M</td>
<td>1.94</td>
<td>4,287</td>
<td>101</td>
<td>6,823</td>
<td>37.2</td>
<td>3,305</td>
<td>62</td>
<td>92</td>
</tr>
<tr>
<td>A. C.</td>
<td>52 M</td>
<td>1.86</td>
<td>2,942</td>
<td>70</td>
<td>5,274</td>
<td>44.2</td>
<td>2,596</td>
<td>79</td>
<td>91</td>
</tr>
<tr>
<td>K. P.</td>
<td>47 M</td>
<td>2.08</td>
<td>5,073</td>
<td>100</td>
<td>7,348</td>
<td>31.0</td>
<td>3,011</td>
<td>64</td>
<td>115</td>
</tr>
<tr>
<td>K. S.</td>
<td>51 M</td>
<td>1.95</td>
<td>4,389</td>
<td>97</td>
<td>6,090</td>
<td>27.9</td>
<td>2,260</td>
<td>73</td>
<td>117</td>
</tr>
<tr>
<td>V. J.</td>
<td>49 M</td>
<td>1.93</td>
<td>4,484</td>
<td>99</td>
<td>6,178</td>
<td>27.4</td>
<td>2,185</td>
<td>71</td>
<td>116</td>
</tr>
<tr>
<td>K. K.</td>
<td>68 M</td>
<td>1.84</td>
<td>4,166</td>
<td>109</td>
<td>6,254</td>
<td>33.4</td>
<td>2,770</td>
<td>52</td>
<td>78</td>
</tr>
<tr>
<td>M. S.</td>
<td>35 M</td>
<td>1.89</td>
<td>4,817</td>
<td>100</td>
<td>6,755</td>
<td>28.7</td>
<td>2,875</td>
<td>78</td>
<td>137</td>
</tr>
<tr>
<td>J. H.</td>
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<td>1.84</td>
<td>4,179</td>
<td>104</td>
<td>5,307</td>
<td>21.3</td>
<td>2,106</td>
<td>60</td>
<td>91</td>
</tr>
</tbody>
</table>

BSA = body surface area; VC = vital capacity; VC % pred. = vital capacity in percent of predicted values; TLC = total lung capacity; RV/TLC = residual lung volume in percent of TLC; FEV/ls. = forced expiratory volume in 1 second in percent of vital capacity.

Fig. 1. Changes in cardiac index (CI) and heart rate (HR) after administration of propranolol at rest and during exercise. Mean percentual changes and statistical significance are marked at the bottom.
Table II. Hemodynamic Data before

<table>
<thead>
<tr>
<th></th>
<th>( \dot{V}_{O_2}/M^2 )</th>
<th>HR</th>
<th>CI</th>
<th>SI</th>
<th>PLV syst.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(ml/min/M^2)</td>
<td>R</td>
<td>E</td>
<td>R</td>
<td>E</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>R</td>
<td>E</td>
<td>R</td>
<td>E</td>
</tr>
<tr>
<td>( \bar{x} )</td>
<td>141</td>
<td>71</td>
<td>106</td>
<td>3.7</td>
<td>5.6</td>
</tr>
<tr>
<td>SD</td>
<td>16</td>
<td>9.2</td>
<td>7.3</td>
<td>0.99</td>
<td>1.31</td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
<td>R</td>
<td>E</td>
<td>R</td>
<td>E</td>
</tr>
<tr>
<td>( \bar{x} )</td>
<td>136</td>
<td>65</td>
<td>94</td>
<td>3.1</td>
<td>4.6</td>
</tr>
<tr>
<td>SD</td>
<td>25</td>
<td>3.7</td>
<td>7.2</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td>( d )</td>
<td></td>
<td></td>
<td></td>
<td>-6.0 -11.8</td>
<td>-0.57 -0.98</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td>6.8</td>
<td>6.5</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td>-8.5 -11.2</td>
<td>-15.49</td>
</tr>
<tr>
<td>p</td>
<td>n. n.</td>
<td>&lt;0.025 &lt;0.001</td>
<td>&lt;0.05 &lt;0.001</td>
<td>n.</td>
<td>n.</td>
</tr>
</tbody>
</table>

\( \dot{V}_{O_2}/M^2 \) = oxygen uptake per square meter of BSA; HR = heart rate; CI = cardiac index; SI = stroke index; \( P_{LV syst.} \) = mean systolic pressure in the left ventricle; LVEDP = left ventricular filling pressure.

Fig. 2. Correlation between cardiac index (CI) at rest and during exercise and oxygen consumption (\( \dot{V}_{O_2}/M^2 \)). The dotted lines give the range of values normal according to Ekelund and Holmgren 1967. Black circles denote pathological values.
and after application of propranolol.

The response of CI to exercise was normal in the majority of our patients; only 3 patients (closed circles in Fig. 2) had subnormal CI. These circles belong to patients with X-ray manifestation of left heart failure. After injection of propranolol the response of CI to exercise was abnormal in 9 patients.

Left ventricular filling pressure (LVEDP) was abnormal (>12 mmHg) in all patients but 1. LVEDP decreased after injection of propranolol in all but 1 patient (Fig. 3). There was a significant increase in LVEDP during exercise by 56% before and by 68% after injection of propranolol. Mean pulmonary arterial pressure ($P_{PA}$) decreased after injection of propranolol but the decrease was significant only at rest (Table II). LVWI and SWI decreased after injection of propranolol at rest (by 15 and 7%, resp.) but significantly, only during exercise (by 23 and 16%, resp.) (Table II and Fig. 4). The indices of contractility $dP/dt$ and $(dP/dt)/P$ decreased significantly after injection of propranolol at rest and during exercise. Exercise led to a significant increase in $dP/dt$ and $(dP/dt)/P$ (by 69 and 29%, resp.). After injection of propranolol these indices increased by only 49 and 17%, respectively (Fig. 5). Injection of propranolol did not influence left ventricular systolic pressure at rest. During exercise, however, this pressure decreased significantly after injection of (Table II). Administration of propranolol, to a certain extent, inhibited the increase in systolic pressure.

During exercise without propranolol 7 patients reported incipient retro-
Fig. 3. Changes in left ventricular enddiastolic pressures (LVEDP) after administration of propranolol (Inderal) at rest and during exercise.

Fig. 4. Changes in left ventricular work index (LVWI) and stroke work index (SWI) after administration of propranolol (Inderal) at rest and during exercise.
sternal pain, but none of the patients reported pain after administration of propranolol. Eight patients reported diminished effort dyspnea after administration of propranolol. In no instance the dyspnea became more intense.

**DISCUSSION**

Hemodynamic effects of beta blockers, particularly of propranolol, are well known.\(^2\),\(^10\),\(^14\),\(^15\),\(^17\),\(^18\) The hemodynamic changes are to a certain extent dose-related. Beta blockers produce also a considerable negative inotropic effect. This effect became the subject of our attention, particularly in IHD, mainly because left ventricular function has been already impaired in such patients and any additional cardiodepressive influence may further worsen the mechanical cardiac function. Recently, several drugs with weaker negative inotropic activities have been developed, to which propranolol is considerably inferior in this respect.\(^7\)–\(^9\),\(^11\) We intentionally chose a marked negative inotropic drug, propranolol, enabling us to investigate, in an acute experiment, some changes associated with incipient left heart insufficiency. Propranolol is widely used in our clinical practice, and we felt obliged to point out its cardiodepressive activity.

The significant decreases in HR and CI following administration of pro-
pranolol are well known\textsuperscript{2,8,10,13-15,18}. We found, however, somewhat lesser decreases in both HR and CI than that reported in the literature. SI decreased but statistically not as significantly as was reported in the literature\textsuperscript{2,8,10,13,14,18}.

LVEDP after injection of propranolol decreased significantly, by 17\% (p<0.01) at rest and by 10\% (0.05<p<0.10) during exercise. A decrease was observed in all, except 1 patient, both at rest and during exercise. In this patient LVEDP was normal at rest and during exercise before administering of propranolol. If this patient was excluded from the statistical analysis, the mean decrease was highly significant (p<0.001). In the literature there are no concordant data about the changes of LVEDP. Most authors reported an increase after administration of beta blockers, both at rest\textsuperscript{9,10,13,17} and during exercise\textsuperscript{10,17}. Few authors found a decrease of LVEDP after administration of propranolol\textsuperscript{18}. In 1 of our patients (with a normal LVEDP) we found an increase of the LVEDP after administration of propranolol (Fig. 3). This finding is in accordance with Parker et al\textsuperscript{10} who found that propranolol during exercise produced greater increase of LVEDP in patients with normal LVEDP than in patients with abnormal LVEDP at rest. A decrease of LVEDP is also accompanied by a decrease of P\textsubscript{PA} in 9 patients at rest but only in 5 during exercise. The difference between the attitudes of LVEDP and P\textsubscript{PA} can be explained hypothetically by changes in pulmonary vascular resistance after administration of pranorolol. Previous data concerning changes of P\textsubscript{PA} are also discordant\textsuperscript{10,15,17}.

If we used only LVEDP as an indicator of a left ventricular function, we would not be able to prove a negative inotropic effect of propranolol in the present subjects. When evaluating the response of CI to exercise, however, we did find, in agreement with literature\textsuperscript{2,9,10,14,15,17} a cardiodepressive effect of propranolol (Fig. 2).

Further indicators of left ventricular function, LVWI and SWI decreased after administration of propranolol significantly during exercise (Fig. 4). Comparable results have also been published\textsuperscript{2,9,10,13,15,17}. An unequivocal evidence about negative inotropic effect of propranolol was obtained when the left ventricular myocardial contractility was evaluated. In agreement with the literature the dP/dt and the (dP/dt)/P decreased highly significantly both at rest and during exercise (Fig. 5).\textsuperscript{9,13,14} Consequently it can be stated that indicators of left ventricular function decreased after administration of propranolol, but these changes were significant only during exercise, although the contractility was depressed already at rest.

Deterioration of the left ventricular function after administration of propranolol is apparent from “left ventricular function curves”. During
exercise an increase of LVEDP was accompanied by an increase of SWI (Fig. 6). After administration of propranolol a similar increase in LVEDP was accompanied by a minimal increase in SWI. In the right part of Fig. 6, the patients were classified into 2 groups according to the slope of their function curves during exercise. Group A loses the favorable slope of functional curve after injection of propranolol as an evidence of depression of myocardial function. In group B with considerably pathological functional curves already before administration of propranolol the slope does not significantly change any more. SWI, however, decreases further, but simultaneously LVEDP decreases.

From our results we can conclude, that the beta blocker, propranolol, really has a negative inotropic effect. The cardiodepressive effect of propranolol becomes apparent when studying all indicators of the left ventricular function: CI, LVWI, SWI, as well as dP/dt and (dP/dt)/P and finally the shifts of the left ventricular function curves. On the other hand, LVEDP, if used as an indicator of left ventricular function, is incapable of proving the cardiodepressive activity of propranolol. A decrease of LVEDP itself following administration of propranolol might be interpreted falsely as an improvement of the left ventricular function. Consequently, our results leave no doubt about poor reliability of the evaluation of the left ventricular function based solely on the LVEDP.
REFERENCES


