Electrophysiological effects of labetolol on rabbit atrial, ventricular and Purkinje cells, in normoxia and hypoxia

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SUMMARY Labetolol, which blocks both α and β-adrenoceptors, was found to have direct actions on cardiac muscle which could themselves be antiarrhythmic. It depressed the maximum rate of depolarisation, and reduced conduction velocity, in atrial and ventricular muscle and in Purkinje cells, implying restriction of fast inward current (Class 1). It had twice the potency of procaine as a local anaesthetic on nerve. Labetolol abbreviated the action potential (AP) plateau in normoxic atrial muscle, but attenuated AP-shortening by hypoxia. It caused a significant slowing of all phases of repolarisation (Class 3) in normoxic ventricular muscle. It had no negative inotropic action in normoxia or hypoxia, and there was no evidence for slowing of A-V nodal conduction.

Labetolol has been in use for several years for the treatment of hypertension, and its general and clinical pharmacology was the topic of a symposium in 1976. The drug was estimated to be four to eight times more potent as a β-adrenoceptor blocker (0.6 to 0.3 activity of propranolol) than as an α-adrenoceptor blocker (0.2 to 0.1 activity of phentolamine). The hypotension induced by labetolol in human hypertensives was not accompanied by any reflex tachycardia, because the beta-blockade intervened; in exercise, heart-rate, cardiac output and vascular resistance were lowered, but stroke volume was raised. Although the main chronotropic and inotropic drives to the heart are mediated through β-adrenoceptors, the existence of cardiac α-adrenoceptors has long been recognised, but their functional significance in the myocardium is unclear. Ventricular arrhythmias occurring during reperfusion after acute experimental coronary occlusion could be controlled by phentolamine, and it has been suggested that the number of α-adrenoceptor binding sites may be increased by ischaemia.

Several α- and β-adrenoceptor blocking drugs have subsidiary properties which could be antiarrhythmic independently of their anti-adrenergic (Class 2) action. Propranolol, oxprenolol and alprenolol are local anaesthetics, and the Class 1 action of such compounds on cardiac muscle is increased by ischaemia. Sotalol is not a local anaesthetic, but it prolongs action potential duration (APD) in normoxic myocardium (Class 3 action). Since labetolol is both an α- and β-adrenoceptor blocking drug, it could be useful in the management of arrhythmias associated with ischaemia or recovery therefrom. The extent, however, to which the antiarrhythmic properties of any α- or β-adrenoceptor antagonist may be attributed to adrenoceptor blockade can only be assessed if it is known whether or not they also possess antiarrhythmic actions of another class.

In this paper the electrophysiological properties of labetolol have been studied. It has been concluded that labetolol has a powerful Class 1 antiarrhythmic action, which is augmented by hypoxia. It has a Class 3 action in ventricular muscle. In the atrium, although labetolol shortened APD slightly in normoxia, it afforded significant protection against APD shortening in hypoxia.

Methods

LOCAL ANAESTHESIA

Sciatic nerves were removed from pithed frogs, and the perineural sheaths were stripped from the central portions. The nerve was enclosed in a three-compartment chamber; supramaximal stimuli were applied at the proximal end, and action potentials were recorded from the distal end, the nerve being supported on platinum wires in moist air. Various concentrations of procaine or labetolol were applied to the stripped portion of the nerve, immersed in physiological solution in the central chamber, as previously described.

INTRACELLULAR POTENTIALS

Atrial records

Rabbits of either sex, weighing 1 to 1.5 kg, were
stunned and their hearts rapidly removed. The atria were separated from the ventricles, and were suspended horizontally to facilitate recording with microelectrodes from the endocardial surface of the atrial myocardium. Contractions were measured simultaneously. The temperature of the solution was 32°C and the oxygenation was external to the bath, to avoid disturbance of microelectrodes by bubbles.

**Ventricular records**

The heart was immersed in ice-cold physiological saline continuously oxygenated during the dissection. The left atrium, the part of the right atrium containing the sinoatrial node (SAN), and the left ventricular free wall were removed. The right ventricular wall was cut free anteriorly and peeled back, revealing the anterior papillary muscles which, in the rabbit, both originate from the septum. A thread was tied to one of the chordae tendineae. Dissection was continued, to leave a preparation consisting of: (1) a portion of right atrium and interatrial septum within 3 to 4 mm of the A-V node; (2) the A-V node and His bundle; (3) a strip of interventricular septum containing the right bundle branch and two papillary muscles; and (4) the moderator band and other free-running strands of Purkinje cells, together with a small portion of the right ventricular free wall. The preparation was then transferred to the organ bath, as described for atrial recording. The septum was anchored by threads tied to a rectangular grid to stabilise the origin of one of the papillary muscles, and the thread attached to the tendon was tied to a strain gauge. The other papillary muscle was left slack and was used for microelectrode recordings. Stimuli, of twice threshold strength and at a frequency just fast enough to 'capture' spontaneously beating preparations (usually 1.5 to 1.8 Hz) were applied to the atrium. Intracellular records were obtained from His bundle cells, terminal Purkinje cells and papillary muscle cells. 

**Table 1**

<table>
<thead>
<tr>
<th>Drug concentration in μmol-litre⁻¹ and number of fibres (n)</th>
<th>0.0 (31)</th>
<th>2.74 (29)</th>
<th>5.48 (42)</th>
<th>10.96 (37)</th>
<th>Recovery (1 h) 0.0 (42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>±SEM Action potential amplitude mV</td>
<td>95.56 2.13</td>
<td>-5.5 -8.6* -11.0** +4.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum rate of depolarisation 106.3 8.65</td>
<td>-17.8 -28.5* -50.9*** +25.9**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum follow frequency beats-min⁻¹ 447 29.6</td>
<td>-8.9** -14.1** -22.2*** +2.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduction velocity m⁻¹ 0.78 0.057</td>
<td>-20.5 -33.3** -33.3** 0.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Action potential duration ms 57.9 1.48</td>
<td>-12.3** -15.5*** -13.7* -2.3 +20</td>
<td>1 h 2 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>to 50% repolarisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APDw 100.82 1.93</td>
<td>-7.6* -7.6 -1.1 -5.2 +14.8**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistical significance: * P<0.05; ** P<0.01; *** P<0.001. When the difference approaches significance (P<0.1) the actual value is given in brackets.
Electrophysiological effects of labetolol

Drugs: Labetolol hydrochloride was donated by Glaxo Research Ltd.; procaine HCl (B.D.H.).

Results

LOCAL ANAESTHESIA

Dose-response curves relating depression of action potential amplitude to the log concentration of procaine were obtained on six desheathed frog nerves; the calculated regression (r=0.76) gave an ED50 of 0.83 mmol-litre⁻¹. Recovery was complete after 30 min washout. Log-dose response curves were then constructed for labetolol on the same nerves, yielding an ED50 of 0.42 mmol·litre⁻¹ (r=0.87), and indicating a local anaesthetic activity twice that of procaine. On washout recovery was rapid and complete.

ISOLATED RABBIT ATRIA

Labetolol had no significant effect on electrical threshold in concentration up to 11 μmol·litre⁻¹, but spontaneous frequency was depressed in a dose-dependent manner. Concentrations of 2.74, 5.48 and 10.96 μmol·litre⁻¹ caused mean (n=5) percentage falls in rate of 1.8, 6.0 (P=0.006) and 21.8 (P=0.049) respectively. The spontaneous frequency returned towards, but did not reach, control values after one hour’s washout following exposure to the highest concentration.

Labetolol had no statistically significant effect on atrial contractions. The highest concentration had a small negative inotropic action (-12.6%, P=0.12) which was probably real, because the contractions returned to control values on washout. There was no effect on the time to peak of contractions, however.

As expected from its potency as a local anaesthetic on nerve, labetolol had a considerable Class 1 action on cardiac muscle, implying restriction of fast inward current, as shown in table 1. There were dose-related falls in action potential amplitude (APA), maximum rate of depolarisation (MRD), in the maximum frequency at which a pacing stimulus could be followed, and in conduction velocity. Action potential duration to 20% repolarisation (APD20) was not significantly altered by any concentration, but the APD50 was significantly shorter. APD90 was shorter at the lower two concentrations but not at the highest, an observation which may be related to opposing effects on APD of α- and β-adrenoceptor activation (see Discussion).

TABLE 2 Ventricular preparation. Comparison of effects of labetolol on ventricular muscle, and on Purkinje cells in the terminal pathway and bundle of His.

<table>
<thead>
<tr>
<th>Drug concentration (μmol·litre⁻¹)</th>
<th>APA (mV)</th>
<th>MRD (V/s⁻¹)</th>
<th>APD20 (ms)</th>
<th>APD90 (ms)</th>
<th>A-H (ms)</th>
<th>H-P (ms)</th>
<th>P-V (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>85.2</td>
<td>97.8</td>
<td>82.3</td>
<td>157.9</td>
<td>49.2</td>
<td>12.76</td>
<td>10.72</td>
</tr>
<tr>
<td>2.74</td>
<td>71.2</td>
<td>91.5</td>
<td>76.2</td>
<td>147.7</td>
<td>44.2</td>
<td>12.07</td>
<td>9.91</td>
</tr>
<tr>
<td>5.48</td>
<td>57.5</td>
<td>86.8</td>
<td>68.3</td>
<td>137.8</td>
<td>40.3</td>
<td>11.59</td>
<td>9.44</td>
</tr>
</tbody>
</table>

Statistical significances indicated as in table 1.
There were some marked quantitative differences between the actions of labetolol on atrial and ventricular muscle, and different parts of the conduction pathway, as may be seen from a comparison of tables 1 and 2.

**DEPOLARISATION**

Action potential amplitude was not altered in the bundle of His or ventricular muscle; although it was reduced by 7 mV in the terminal Purkinje fibres at 5.48 μmol-litre⁻¹, this change did not reach statistical significance (P=0.16). Likewise the maximum rate of depolarisation was much less affected in the ventricle than in the atrium, a significant depression being observed at 5.48 μmol-litre⁻¹ in the terminal Purkinje fibres only. It may be concluded that whereas labetolol exerted a potent Class 1 action in the atrium, it had quantitatively rather less effect on fast inward (sodium) current in ventricular tissue.

**REPOLARISATION**

There are marked differences in APD in the different parts of the normal ventricular conduction pathway. For example, in the terminal Purkinje cells APD₉₀ is greater than in the bundle of His and more than 100 ms longer than in the ventricular muscle fibres into which they are inserted.¹⁴ Another point of note is that in these terminal Purkinje cells the existence of an early transient outward current (the ‘notch’) makes the APD₉₀ very short (<10 ms), whereas in the Purkinje cells of the His bundle the notch is absent, and the plateau is long (table 2).

Labetolol did not alter significantly any phase of APD in the bundle of His. In the terminal Purkinje fibres, however, although the tail of the action potential (APD₉₀) was little affected, there was a highly significant extension of the plateau (APD₉₀). In the ventricular muscle, there was a uniform and dose-related prolongation of all phases of APD, which could constitute a useful Class 3 antiarrhythmic action. These effects in the ventricular muscle are in complete contrast to the action of labetolol on the atrium, in which APD₉₀ was significantly shortened (an effect reversed on washout).

**CONDUCTION TISSUES**

The A-H conduction time represents the whole interval between the stimulus applied to the atrial remnant and the start of the action potential recorded from the bundle of His, and thus includes, in addition to the conduction time through the A-V node proper, the times for conduction in the atrial muscle proximal to it and in some His bundle cells beyond it. The significance, but small (+15%), increase in A-H conduction time induced by labetolol is probably attributable to conduction delays in the atrial and His portions of this pathway, rather than in the A-V node itself, because 5.48 μmol-litre⁻¹ labetolol reduced atrial conduction velocity by 33%, and increased H-P conduction time (in the right bundle branch) by 182%.

H-P and P-V conduction times were both highly significantly prolonged, as is consistent with the reduction of MRD in the Purkinje cells themselves.

**EFFECTS OF HYPOXIA**

In Langendorff-perfused guinea-pig hearts, the APD-shortening induced by hypoxia or by reduced coronary flow was accelerated and exacerbated when successive periods of hypoxia were alternated with periods of normoxic reperfusion.¹⁶ ¹⁷ The effect was maximal at the third hypoxic period. Langendorff preparations may be mildly hypoxic even during perfusion with fully oxygenated fluid, and it was thought advisable to employ isolated atria to study the effects of labetolol in hypoxia. The protocol adopted was similar to that used previously, three hypoxic periods of 15 min (H₁, H₂, H₃) following three 25 min periods of normoxia (N₁, N₂, N₃). In view of the fact that the response to a second hypoxic period was not the same as the response to the first, it was not possible to study the effects of labetolol in the same preparations as were used for control studies, but exactly similar protocols were used for the control and labetolol experiments.

In the control series, there was complete recovery during the normoxic periods from the changes induced by hypoxia. Mean RP and APA, for example, in the periods N₁, N₂ and N₃ were -75.7, -73.8, -74.2 mV and 92.0, 88.0 and 93.3 mV respectively. MRD and conduction velocity in the corresponding three normoxic periods were 99.9, 90.3, and 106.5 V.s⁻¹, and 0.4, 0.45 and 0.4 m.s⁻¹. There was no change in the time from start to peak of contractions or in APD₉₀ (91.1, 85 and 91.8 ms), and there was even some ‘rebounce’ of the contractions themselves during the recovery periods (0.28, 0.35 and 0.41 g). It was evident, therefore, that these short periods of hypoxia caused no apparent ‘irreversible damage’ in the atrial muscle. In the three periods of hypoxia there was evidence of a cumulative effect, as previously observed, most obvious in the third period, possibly due to the progressive loss of intracellular glycogen.¹⁶ ¹⁷ The main effects of hypoxia, recorded as percentage changes from the initial normoxic pre-drug values (rows 1 and 6), have been presented in table 3. The concentration of labetolol chosen (4.1 μmol-litre⁻¹) was midway between the two lowest concentrations studied earlier. In the normoxic solution this concentration had no statistically significant effects (rows 2 and 8), except on conduction velocity, though very small changes in the same direction as those observed previously at higher concentrations were apparent. The effects of the three
successive periods of hypoxia (H₁, H₂ and H₃) are presented in rows 3 to 5 and 8 to 10, 4.1 μmol-litre⁻¹ being present in the labetolol series throughout (L columns). In all the measurements made the effects of hypoxia were greater in the third than in the first period, in confirmation of previous findings.

**DEPOLARISATION**

The Class 1 effect of labetolol was increased by the hypoxia, depression of MRD and conduction velocity being much greater relative to that of the hypoxic controls, than was apparent in normoxia. Resting potential was now significantly reduced by labetolol relative to the hypoxic controls, whereas in normoxia much higher concentrations of labetolol had no effect on resting potential.

**REPOLARISATION**

In contrast to the effects of labetolol in normoxia in the atrium, in which APD was shortened relative to pre-drug values, APD was shortened less by hypoxia in the labetolol treated group than in the controls. Pooling the effects of the 2.74 and 5.48 μmol-litre⁻¹ concentrations in normoxia (to compare with the effects of the intermediate concentration 4.1 μmol-litre⁻¹ in hypoxia) the reductions of APD₂₀, APD₅₀ and APD₉₀ were −2.1, −8.2 and −7.65 ms respectively. Again pooling the effects of the three periods of hypoxia, APD₂₀, APD₅₀ and APD₉₀ in the labetolol group were longer than in the controls by means of +8.45, +6.53 and +12.3 ms respectively; analysis of variance showed these differences between the effects of labetolol in normoxia and hypoxia to be highly significant (P<0.001, <0.001 and <0.01 respectively). In contrast, the depression of contractions during hypoxia was not significantly different in the control and labetolol groups, confirming the absence of any negative inotropic action by the drug.

**Discussion**

Evidence from acute experiments in anaesthetised dogs that α-adrenoceptor blocking drugs reduced the ventricular arrhythmias precipitated by reperfusion after 35 min occlusion of a coronary artery⁵ raised the possibility that α-adrenoceptor blockade could be of

### TABLE 3  Effects of labetolol (4.1 μmol-litre⁻¹) in hypoxia

#### A Depolarisation

<table>
<thead>
<tr>
<th></th>
<th>Resting potential</th>
<th>Action potential amplitude</th>
<th>Max rate of depolarisation</th>
<th>Conduction velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C (mV)</td>
<td>L (mV) (pre-drug)</td>
<td>C (mV) (pre-drug)</td>
<td>C (mV) (pre-drug)</td>
</tr>
<tr>
<td>Normoxic controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) N₂, SEM</td>
<td>−75.3</td>
<td>−72.1</td>
<td>92.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Difference from normoxic controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2)</td>
<td>Δ% (post drug)</td>
<td>Δ% (post drug)</td>
<td>Δ% (post drug)</td>
<td>Δ% (post drug)</td>
</tr>
<tr>
<td>3) H₁</td>
<td>−2.1</td>
<td>−5.4</td>
<td>−4.4</td>
<td>−9.6</td>
</tr>
<tr>
<td>4) H₂</td>
<td>−1.6</td>
<td>−9.7**</td>
<td>−2.3</td>
<td>−12.7</td>
</tr>
<tr>
<td>5) H₃</td>
<td>−7.15*</td>
<td>−12.1***</td>
<td>−7.9**</td>
<td>−27.2**</td>
</tr>
</tbody>
</table>

#### B Repolarisation

<table>
<thead>
<tr>
<th></th>
<th>APD₂₀</th>
<th>APD₅₀</th>
<th>APD₉₀</th>
<th>Contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C (ms)</td>
<td>L (ms)</td>
<td>C (ms)</td>
<td>L (ms)</td>
</tr>
<tr>
<td>6) Normoxic controls no drug</td>
<td>23.4</td>
<td>31.2</td>
<td>47.8</td>
<td>57.8</td>
</tr>
<tr>
<td>SEM</td>
<td>0.9</td>
<td>1.5</td>
<td>1.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Difference from normoxic controls</td>
<td></td>
<td></td>
<td>Δ%</td>
<td>Δ%</td>
</tr>
<tr>
<td>7)</td>
<td>−0.4</td>
<td>−6.1</td>
<td>+1.5</td>
<td>−18.1*</td>
</tr>
<tr>
<td>8) H₁</td>
<td>−36.6***</td>
<td>−29**</td>
<td>−38.71***</td>
<td>−33.4***</td>
</tr>
<tr>
<td>9) H₂</td>
<td>−35.13***</td>
<td>−34.8**</td>
<td>−39.2***</td>
<td>−36.5***</td>
</tr>
<tr>
<td>10) H₃</td>
<td>−40.6***</td>
<td>−36.0**</td>
<td>−41.4***</td>
<td>−38.4**</td>
</tr>
</tbody>
</table>

Statistical significance of differences as in table 1.
value in the treatment of arrhythmias associated with human ischaemic heart disease. In the dog model the large mass of myocardium suddenly deprived of its blood supply is surrounded by normal tissue, and it is possible that on reperfusion the blood supply may be unevenly distributed, because small regions of \( \alpha \)-adrenoceptor mediated vasoconstriction could juxtapose islands of ischaemia to hyperaemic areas. During occlusion blood flow to the surrounding normal zone is increased substantially (and to a greater extent in the untreated than in the \( \alpha \)-blocked animals); on reperfusion, hyperaemic flow was 2\( \frac{1}{2} \) times the pre-occlusion value.\(^5\) Thus, although phentolamine did not cause any significant shift in the distribution or magnitude of the total hyperaemia, it is possible that arrhythmogenic heterogeneities of perfusion caused by \( \alpha \)-adrenoceptor mediated local vasoconstrictions in the untreated myocardium could have gone undetected.

In humans resuscitated from ventricular fibrillation only 16% had a proven myocardial infarction,\(^1\) and it is possible that \( \alpha \)-ischaemic areas, insufficient to cause gross loss of enzymes or detectable S-T segment changes, are more dangerous from the arrhythmogenic point of view than a larger, but more compact, loss of tissue.\(^1\) Thus the possibility remains that the site of the \( \alpha \)-adrenoceptors responsible for exacerbating reperfusion arrhythmias could be on blood vessels rather than myocardial cells.

The chronotropic and inotropic responses of the heart to sympathetic activation are mediated by \( \beta \)-adrenoceptors, but there is ample evidence for the existence of \( \alpha \)-adrenoceptors in the myocardium, although their physiological significance is uncertain. Govier et al\(^6\) demonstrated that adrenaline and noradrenaline were more potent than isoprenaline in increasing refractory period (RP), an effect blocked by phenoxybenzamine; and that isoprenaline was more potent than adrenaline and noradrenaline in decreasing RP, an effect blocked by propranolol. Giotti et al\(^7\) showed that in sheep Purkinje fibres isoprenaline shortened action potential duration, an effect blocked by propranolol, whereas noradrenaline lengthened APD (especially in the presence of a beta-blocker), an effect blocked by phentolamine. More recently Kass and Wiegert\(^8\) observed that in calf Purkinje fibres low concentrations of noradrenaline lengthened APD, but at concentrations >0.5 \( \mu \text{mol-litre}^{-1} \) APD was shortened. From voltage-clamp studies they concluded that noradrenaline increased both slow inward current and outward repolarising current, but did not investigate the possibility that these effects might be differently mediated by \( \alpha \) - and \( \beta \)-adrenoceptors.

A lengthening of APD, or a reduction of the shortening of APD induced by ischaemia, could be responsible for an antiarrhythmic action (Class 3), but from the evidence of Govier, and of Giotti et al, \( \alpha \)-adrenoceptor blockade in the presence of adrenergic excitation would have the opposite effect, ie would shorten APD.

It is possible, therefore, that blockade of myocardial \( \alpha \)-adrenoceptors is not responsible for the protection afforded by phentolamine against reperfusion arrhythmias. It has recently been shown that cibenzoline, a new antiarrhythmic drug with a rather selective Class 1 action on atrial and ventricular muscle (and devoid of adrenoceptor-blocking activity), greatly diminishes hypoxia-induced shortening of APD.\(^21\) Phentolamine also is known to have a direct action on cardiac membranes in addition to its effect on adrenergic receptors.\(^22\)\(^23\) Thus it is important to know what other actions any adrenoceptor-blocking drug may have before the contribution of its antisympathetic properties can be fully assessed. It has been found that labetolol possessed twice the potency of propranol as a local anaesthetic on frog nerve, and had substantial Class 1 activity on atrial and ventricular tissues, implying restriction of fast inward current. In atrial muscle the plateau (APD\(_{50}\)) was significantly shortened (an effect reversed on wash-out), which would be consistent with blockade of an \( \alpha \)-adrenoceptor mediated APD-lengthening by a low concentration of spontaneously released sympathetic transmitter. In hypoxia, however, labetolol slightly but significantly attenuated the shortening of APD in atrial muscle. In the ventricle, in contrast to the effect on the atrium, labetolol lengthened APD\(_{50}\) significantly in normoxic Purkinje cells and papillary muscle (Class 3 action), but not in the bundle of His. Labetolol had no significant negative inotropic effect on atrial or ventricular contractions, nor did it delay conduction through the A-V node, since the overall prolongation of A-H conduction time could be attributed to restriction of fast inward current in atrial muscle proximal to, and in His cells distal to, the A-V node itself. Thus it was unlikely to have caused any restriction of slow inward current.

It was concluded, therefore, that labetolol could have useful direct antiarrhythmic actions, in addition to any protective effect against coronary occlusion- or reperfusion-induced arrhythmias which might be attributed to blockade of adrenoceptors.

References

4. Govier WC, Mosal NC, Whittington P, Broom H. Myocardial alpha and beta adrenergic receptors as demonstrated by
Electrophysiological effects of labetolol