CORRELATION BETWEEN ELECTROCARDIOGRAPHIC AND HISTOPATHOLOGICAL CHANGES IN ISOPRENALINE-INDUCED MYOCARDIAL INJURY

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ABSTRACT

Myocardial injury was induced in 25 dogs by infusing isoprenaline, 2-4 microgram per kg per minute for the duration of six hours. 10 dogs served as controls which received only physiological saline. Animals receiving isoprenaline 2 microgram per kg per minute were labelled as experimental group A and other receiving microgram per kg per minute as experimental group B. Histopathological observations in experimental groups A & B showed subendocardial haemorrhage in the papillary muscles and apex of left ventricle as early as two-three hours of infusion. Focal lesions characterized by congestion, dilatation and extravasation of blood was observed near necrotic myocardium. Group A animals showed only severe tachycardia while in group B myocardial infarction in 80% and only ischaemic changes in 20% of animals were observed. Out of animals in group B, 37.5% developed myocardial infarction after two hours of infusion while remaining 62.5% developed changes after four hours. Histopathological changes were very well correlated with ECG findings observed in the present study.

INTRODUCTION

Urbanisation and industrialisation have brought in their wake, tension and worries which have led to a steady increase in incidence of myocardial infarction (MI) which has reached epidemic proportions. This is the most killing and disabling disease of modern man in this era. Physicians have come to rely greatly on ECG, though it is well known that there are patients with MI in whom ECG does not show any abnormality. The WHO Expert Committee on Cardiovascular Disease and Hypertension (1954) considered that out of all the investigations available, perhaps none is as helpful as electrocardiography. Myocardial lesions induced by means other than vascular occlusion have been the subject of intensive study during recent years. Chappel, et al (1951) observed that animals receiving doses greater than one fourth the lethal dose of isoproterenol showed severe lesions in the lungs, brain, liver and kidney consistent with the picture of severe shock. These lesions were characterised by pulmonary oedema and haemorrhage and cerebral oedema. In dogs given prolonged infusion of norepinephrine, the lesions consisted of focal myocardial necrosis, accumulation of inflammatory exudate and epicardial hemorrhage. Chappel and associates (1959) studied the comparative cardiac necrotising activity of isoprena-
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Table I. Morphological grading of myocardium after isoprenaline-induced myocardial injury in dogs

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No lesion.</td>
</tr>
<tr>
<td>I</td>
<td>Mottling of the apex and part of left ventricle with dark red streaks.</td>
</tr>
<tr>
<td>II</td>
<td>Focal haemorrhage limited to apex.</td>
</tr>
<tr>
<td>III</td>
<td>Focal subendocardial haemorrhage mainly in papillary muscles and apex and extending to interventricular septum.</td>
</tr>
<tr>
<td>IV</td>
<td>Focal haemorrhages in the papillary muscles of left ventricle and atrioventricular valve cusps, extending to the right ventricle and auricle.</td>
</tr>
</tbody>
</table>

In rats. Cardiotonic action of isoprenaline which induces an infarct-like necrosis, has been of particular interest since standardized doses consistently produce myocardial lesions of reproducible severity (Rona et al., 1954). Rona et al. (1962) from their experimental studies on rats, showed that isoprenaline produced an infarct-like necrosis of ventricular myocardium. Kraikiphanitch et al. (1976) induced myocardial injury in mongrel dogs by infusing epinephrine at the rate of 4 μg/kg/min for six hours at a flow rate of 2 ml per minute. Jennings et al. (1960) reported classical ST-segment elevation in myocardial necrosis in leads I, III and aVF in dogs after occluding the circumflex branch of coronary artery. Norman et al. (1961) studied ECG changes in 10 rats in which left coronary had been ligated. Anterior and apical transmural infarction were found to reliably produce alterations in the ECG consisting of Q wave deformity, increased amplitude of R wave, lengthening of QT interval and QR or QS configuration.

The present study has been aimed to define more clearly the correlation of electrocardiographic and histopathological changes in experimentally-induced myocardial infarction which closely resembles the myocardial infarction in human beings.

**MATERIAL AND METHODS**

This work was conducted on 35 dogs, dividing them into two groups. The control group comprising of 10 dogs received continuous infusion of physiological saline at the rate of 2 millilitres per minute for six hours: The experimental group of 25 dogs, subdivided into experimental group A consisting of five animals (low dose group) received 2 μg/kg/min and experimental group B comprised of 20 dogs (high dose group) received 4 μg/kg/min for the duration of six hours.

After six hours of infusion, or after the death of the animal during the procedure, the animals were sacrificed and hearts were removed and injected with 10% sucrose solution through the aorta. They were cut open and washed with physiological saline and were evaluated morphologically for gross lesions as given in Table I.

![Table II. Microscopic grading of myocardium after isoprenaline-induced myocardial injury in dogs.](image)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>No change.</td>
</tr>
<tr>
<td>Mild</td>
<td>Focal involvement of myocardium showing capillary dilatation and haemorrhage and oedema in the interstitium. Vascular and fatty degeneration, granular disintegration and hyaline necrosis of muscle fibres.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Focal involvement of myocardium showing necrosis and leukocytic infiltrations.</td>
</tr>
<tr>
<td>Severe</td>
<td>Focal changes seen in myocardium. The myocardial fibres showing abnormal staining, capillary dilatation and haemorrhage and oedema.</td>
</tr>
</tbody>
</table>

Samples of myocardium showing massive haemorrhage and necrotic changes were taken for histological study. After dehydration in different grades of alcohol, cleaning was done in cedar wood oil. Paraffin blocks were made and frontal sections of the myocardium were cut and stained with hemotoxyline and eosin. The severity of lesions were graded microscopically as shown in Table II.

Diagnostic criteria for defining myocardial ischaemia and infarction based on ECG pattern were taken as alterations in ST-segment, T-wave changes and significant Q wave or development of QS wave complex with ST and T wave changes.

**RESULTS**

Electrocardiogram: No alterations from the standard ECG pattern were noted in the control group, which only received physiological saline infusion. In the experimental group of five animals which were given two microgram isoprenaline infusion per kilogram per minute for six hours, ST and T-wave changes were noted as a result of profound tachycardia (Fig.1) and no specific infarction pattern was observed even after six hours. In exp. group B (high dose group) 16 animals (80%) showed definite changes indicative of myocardial infarction and the remaining four dogs (20%) showed ischaemic changes by means of ST-segment and T-wave alterations. With respect to time course, six animals (37.5%) out of the sixteen dogs developed changes characteristic of infarction within two hours of isoprenaline infusion, whereas the remaining ten dogs (62.5%) developed changes only after four hours. As regards location of infarction, 12 animals (75%) showed changes in ECG indicative of inferior wall infarction (Fig.2) whereas in four animals (25%) infarction was confined to the anterior wall (Fig.3).

Histopathological changes:

Macroscopic: No significant changes were observed in hearts from control animals after six hours of infu-

Table III. Macroscopic picture of the myocardium

<table>
<thead>
<tr>
<th>Grade</th>
<th>Control</th>
<th>Experimental A</th>
<th>Experimental B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I</td>
<td>-</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>-</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>-</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>IV</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
</tbody>
</table>

DISCUSSION

Electrocardiographic Changes: Isoprenaline being a beta-adrenergic stimulant has a positive chronotropic and inotropic effect on the heart. Consistent with this concept, tachycardia was observed in all the animals treated with isoprenaline. Besides this, other electrocardiographic changes were also observed in the experimental group animals. The uniformity of polariza-
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...tion during electrical diastole of ventricles and also the repolarization process appeared to be affected in most of the ECG recordings, as there were ST-segment deviation and T-wave changes similar to those of myocardial ischaemia. The low dose group comprising of five animals only showed marked tachycardia. Sixteen (80%) out of 20 animals in experimental group B showed definite changes indicative of myocardial infarction.

As regards time sequence, six animals (37.5%) showed changes of myocardial necrosis within two hours of isoprenaline infusion and the remaining ten (62.5%) developed changes four hours after infusion. Inferior wall infarction was seen in 12 animals (75%) while four (25%) showed anterior wall infarction. Four animals in experimental group B (high dose group) only showed supraventricular tachycardia with ST segment and T wave changes. Mahajan, et al (1976)\textsuperscript{9} produced myocardial infarction in monkeys by intravenous infusion of noradrenaline at the rate of 20 microgram/kg/minute and observed ST, T changes due to tachycardia in most of the animals. In some animals they observed abnormal Q and QS patterns revealing recent acute myocardial infarct. Hill, et al (1960)\textsuperscript{10} produced electrocardiographic changes characteristic of myocardial ischaemia and focal subendocardial necrosis by isoprenaline administration in rats. Chopra and Nag (1972)\textsuperscript{11} reported myocardial damage in left ventricle of dogs within a few seconds after coronary ligation. Ganguly, et al (1987)\textsuperscript{13} observed in their experimental study that increased norepinephrine levels in plasma is associated with functional, biochemical and ultrastructural alterations in cardiac cells. The extent of the increase in catecholamine levels is now known to be related to the severity of the infarction and to the development of arrhythmias.\textsuperscript{14} Mueller & Thoenen (1971)\textsuperscript{15} observed that isoproterenol-induced myocytolysis in heart muscle is associated with an increased turnover of norepinephrine as a result of increased release of a physiologically active neurotransmitter.

**Histopathology:** Chappel, et al (1951)\textsuperscript{3} reported increase in heart size and weight in rats treated with high dose of isoprenaline (82 mg/kg body weight). Infarct-like myocardial lesions involving the apex, lower part of left ventricle, interventricular septum and occasionally the right ventricle were also observed. Histology revealed hyaline necrosis of myocardial fibres with marked fatty changes, leukocytic reaction and sequestering interstitial oedema. Small doses were not found to produce gross lesions in the heart. Subendocardial haemorrhage and fuchsinophilic degeneration of conductive tissue were reported by Szakacs and Mehlman (1960)\textsuperscript{12} in dogs treated with norepinephrine at a rate of 1 microgram per kg body weight per minute.
for 10 hours. Ganguly, et al (1989) and Rossi & Carillo (1985) observed the enlargement of the myocardial muscle mass and cardiac hypertrophy in patients when the catecholamine activity increases. Macroscopic appearance of the myocardium in experimental dogs in the present study suggested endocardial haemorrhage in papillary muscles, which was confirmed by the microscopic picture of focal subendocardial haemorrhage. Capillary haemorrhage, especially in the subendocardium seen in the present series could be explained on the basis of the profound and prolonged ventricular tachycardia which was observed in the experimental animals in the present study. The tachycardia prevents capillary blood flow in the subendocardial area where the pressure gradient is the highest. Under the stress of mounting oxygen debt, the walls of the blood vessels in the capillary muscles become permeable and allow blood to escape into the surrounding tissues. In the end it could be stated that appearance of subendocardial haemorrhage and other histological changes in the cardiac tissue, and the electrocardiographic events are a train of events initiated by tachycardia and set in motion by hypoxia and end in a well-defined myocardial necrosis simulating human myocardial infarction.

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REFERENCES


