

# Effects of Aspirin and Indomethacin on Ventricular Arrhythmias Comparative Study

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## Abstract

The effects of aspirin and indomethacin on the ventricular arrhythmias produced by ligation (ischaemia) and unligation (reperfusion) of the circumflex branch of the left coronary vessel were evaluated in fifty male rabbits weighing 1.5 - 2 kg. Pretreatment of animals with aspirin (50 mg/kg i/v) suppressed all arrhythmias during ischaemia. Low dose of aspirin (12.5 mg/kg i/v) produced no mortality. Indomethacin (2.5 mg/kg) was unable to control ischaemia and reperfusion-induced ventricular arrhythmias. However, higher doses of indomethacin (50 mg/kg) suppressed ischaemia-induced arrhythmias to some extent but the mortality rate was increased (37%). Fragment of ventricular fibrillation was zero during ischaemia after treatment with aspirin and indomethacin but reperfusion-induced ventricular fibrillation was not controlled by any of these drugs. Aspirin (12.5 mg/kg, 50 mg/kg) and indomethacin (2.5 mg/kg) significantly suppressed ischaemia - induced tachyarrhythmias while reperfusion induced tachyarrhythmias were suppressed only by aspirin. There was no significant effect on the mean arterial pressure after these drug treatments(JPMA 44:261,1994).

## Introduction

Common ventricular arrhythmias are ventricular extrasystoles, ventricular tachycardia and fibrillation. The common causes include acute or chronic ischaemia, digitalis toxicity, effects of anti-arrhythmic drugs and tricyclic antidepressants. Ischaemia and reperfusion both produce increase in heart rate (tachyarrhythmias) due to the endogenous release of catecholamine. Moreover, ischaemia and reperfusion are potent stimuli for prostaglandin synthesis by heart<sup>1,2</sup>. Prostaglandins are released from ischaemic myocardium and nonsteroidal anti-inflammatory drugs (NSAID) block its release<sup>3</sup>. NSAIDs differ in potency and degree of prostaglandin synthesis inhibition<sup>4</sup>. Studies have shown that thromboxane A<sub>2</sub> is released during ischaemia and reperfusion<sup>5</sup>. Aspirin like drugs are potent inhibitors of thromboxane A<sub>2</sub> (TxA<sub>2</sub>). Antagonists of TxA<sub>2</sub> seem to afford a direct cardio protective effect during occlusion. The protective effect of aspirin may be due to inhibition of synthesis and release of TxA<sub>2</sub> from myocardium<sup>6</sup>. This study attempts to evaluate the effects of aspirin and indomethacin on ventricular arrhythmias produced during ischaemia and reperfusion by ligating the circumflex branch of left coronary artery in male rabbits.

## Materials and Methods

Male rabbits of species, *Oryctolagus cuniculus* weighing 1.5-2 kg were used in our experimental model. Pentobarbitone sodium (30 mg/kg.i/v) was used as anesthetic agent, both for induction and maintenance. Ventilator (volume-operated) was adjusted at 32 strokes/min, 16-20 ml/stroke of air. Mean arterial pressure was recorded by direct cannulation of femoral artery and connecting it to the pressure transducer of harvard oscillograph (speed 50 mm/sec). Parameters recorded included heart rate (HR), mean arterial pressure (MAP) and ECG changes. Animals in which surgical procedure produced arrhythmias or severe fall in mean arterial pressure were discarded. Circumflex branch of left coronary

artery was ligated close to auricle to produce ischaemia and unligated to produce reperfusion<sup>7</sup>. Ischaemia of 15 minutes was produced followed by a period of reperfusion of 30 min. Aspirin 12.5 mg/kg, 50 mg/kg I/V and indomethacin 2.5 mg/kg, 10 mg/kg I/V were given 15 mins prior to the ligation of vessel. Indomethacin infusion 180 µg/kg was maintained throughout the experiment to keep the plasma level constant. The rabbits were divided into five groups, I, II, III, IV, V. Group I (n=20) was selected as control. This group underwent same surgical procedure and was given no drug. Group II (n=6) was given aspirin 12.5 mg/kg i/v slowly before the ligation of Cx branch of left coronary artery (Cx, LCA). Group III (n=7) was given aspirin, 50 mg/kg I/V before ligation of Cx, LCA. Group IV (n=9) was given indomethacin 2.5 mg/kg I/V before ligation of Cx, LCA. Group V (n=8) was given indomethacin 10 mg/kg I/V slowly before ligation of Cx, LCA

### Statistical Analysis.

The results were estimated and expressed as  $X \pm S.E$  ( $X$  = mean S.E. = Standard error). Treatments were estimated at 5% level of significance. Wherever necessary paired or unpaired "t" test was used. Percentages of the ventricular arrhythmias were compared.

### Results

The following results of heart rate, mean arterial pressure and E.C.Gs were observed in **Group I to V**.

#### Group I

During 15 mins ischaemia ventricular ectopic beats (VEBs) were produced in 10% ventricular tachycardia (VT) in 15% and VF (Ventricular fibrillation) in 15% of the animals. During 30 mins reperfusion, VEBs were produced in 10%, VT in 15% and VF in 30% of the animals (Table I).

**Table I. Effects of drugs on ventricular arrhythmias.**

Groups	Drug and Dose	15 minutes ischaemia				30 minutes reperfusion			
		VEBs	VT	VF	Blocks	VEBs	VT	VF	Blocks
I	Control (n=20)	2 (10%)	3 (15%)	1 (15%)	-	2 (10%)	3 (15%)	6 (30%)	-
II	A1 (n=6)	1 (17%)	-	-	-	-	-	1 (17%)	-
III	A2 (n=7)	-	-	-	-	2 (28%)	1 (14%)	1 (14%)	-
IV	I1 (n=9)	3 (33%)	-	-	1 (11%)	1 (11%)	-	3 (33%)	1 (11%)
V	I2 (n=8)	1 (12%)	1 (12%)	-	-	5 (62%)	4 (50%)	2 (25%)	-

VEB= Ventricular Ectopic Beats

VT=Ventricular Tachycardia

VF=Ventricular Fibrillation

A1=Aspirin 12.5 mg/kg

A2=Aspirin 50mg/kg

I1=Indomethacin 2.5 mg/kg

I2=Indomethacin 10 mg/kg

There was 10% mortality during ischaemia and 15% mortality during reperfusion (Table II).

**Table II. Effects of drugs on mortality.**

Groups	15 minutes ischaemia	30 minutes reperfusion
I Control (n=20)	10%	15%
Aspirin		
II 12.5 mg/kg (n=6)	-	-
III 50 mg/kg (n=7)	14%	-
Indomethacin		
IV 2.5 mg/kg (n=9)	11%	-
V 10 mg/kg (n=8)	12%	37%

During ischaemia heart rate (H.R.) was  $380 \pm 11.40$ /min and mean arterial pressure (MAP) was  $37.16 \pm 87$  mmHg. During reperfusion, H.R. was  $390 \pm 21.09$ /min and MAP was  $40.83 \pm 10.31$  mmHg

(Tables III and IV).

Table III. Effects of drugs on heart rate.

Groups	Drug and Dose	15 minutes ischaemia				30 minutes reperfusion			
		Control(n=6) Group I	Test(n=6)	%Change	P value	Control(n=6) Group I	Test(n=6)	%change	P value
II	A1(n=6)	380±11.40	298±22.1	-21.57	<0.01	390±21.09	310±20.32	- 20.51	<0.001
III	A2(n=6)	380±11.40	386.33±22.01	+1.57	>0.05	390±21.09	406.33±23.82	+4.18	>0.05
IV	I1(n=6)	380±11.40	334±20.32	-12.10	<0.05	390±21.09	388±25.0	- 0.51	>0.05
V	I2(n=6)	380±11.40	395±23.10	+3.94	>0.05	390±21.09	420±14.22	+7.69	>0.05

A1=Aspirin 12.5 mg/kg  
A2=Aspirin 50 mg/kg  
I1=Indomethacin 2.5 mg/kg  
I2=Indomethacin 10 mg/kg

Table IV. Effects of drugs on mean arterial pressure.

Groups	Drug and dose	15 minutes ischaemia				30 minutes reperfusion			
		Control(n=6) (Group I)	Test	%Change	P Value	Control(n=6) (Group I)	Test	%Change	P value
II	A1 (n=6)	37.16±8.71	33.5±5.54	-9.84	>0.05	40.83±10.31	34.16±7.35	- 16.33	>0.05
III	A2 (n=6)	37.16±8.71	50.66±3.99	+36.32	>0.05	40.83±10.31	41.83±4.26	+2.44	>0.05
IV	I1 (n=6)	37.16±8.71	38.33±3.57	+3.14	>0.05	40.83±10.31	43.5±4.92	+6.53	>0.05
V	I2 (n=6)	37.16±8.71	39.33±1.73	+7.18	>0.05	40.83±10.31	35.33±14.36	- 13.47	>0.05

A1=Aspirin 12.5 mg/kg  
A2=Aspirin 50 mg/kg  
I1=Indomethacin 2.5 mg/kg  
I2=Indomethacin 10 mg/kg

## Group II

During 15 mins ischaemia VEBs were produced in 17% of the animals and no VT, VF or Blocks were produced. During reperfusion VF was produced in 17% of the animals and no VEBs VT or Blocks were occurred (Table V).

There was no mortality (Table II). During 15 min ischaemia and 30 min reperfusion heart rate was significantly reduced i.e., 21.57% and 20.51% and MAP was not affected significantly i.e., -9.84% and -16.33% (Tables III and IV).

## Group III

During 15 mins ischaemia there was no ventricular arrhythmia. But during 30 min reperfusion VEBs occurred in 28%, VT in 14% and VF in 14% (Table I). There was 14% mortality (Table II). During 15 mins ischaemia and 30 mins reperfusion HR was not significantly affected i.e., +1.57% and +4.18% and similarly in MAP there was 36.32% and 2.44% positive change (Tables III, IV).

## Group IV

During 15 mins ischaemia VEBs occurred in 33% and atrioventricular block (AV block) in 11%. During 30 min reperfusion VEB, VF and AV block occurred in 11%, 33% and 11% of the animals (Table I). There was 11% mortality during ischaemia (Table II). During 15 min ischaemia H.R. and MAP were changed -12.10% (P<0.05) and +3.14% respectively. During 30 min reperfusion H.R and MAP were not affected significantly i.e., 0.51% and +6.53% respectively (Tables III, IV).

## Group V

During 15 mins ischaemia only VEBs occurred in 12% of the animals. During 30 mins reperfusion VEB, VT and VF occurred in 62%, 50% and 25% of the animals respectively (Table I). There was 12% mortality during ischaemia and 37% during reperfusion (Table II). Heart rate during ischaemia and reperfusion were not significantly changed i.e., +3.94% and +7.69% respectively (Table III). Mean arterial pressure was changed +7.18% and -13.47% during ischaemia and reperfusion respectively (Table IV). These changes were not statistically significant (P>0.05).

## Discussion

This study was undertaken to see the effects of various nonsteroidal anti-inflammatory drugs (NSAIDs)

on the ventricular arrhythmias. Ventricular arrhythmias are produced as a result of increased irritability of myocardium. These may be produced due to abnormal automaticity or due to abnormal conduction, especially re-entry. Useful antiarrhythmic drugs are usually depressant of cardiac functions, a factor of considerable importance in the patient of impaired cardiac functions. Ventricular arrhythmias particularly reperfusion induced arrhythmias are very resistant to most of conventional anti-arrhythmic drugs<sup>6</sup>. Salicylates<sup>6</sup> have no significant effects on the normal haemodynamic parameters<sup>8</sup>. Certain similarities between acute myocardial infarction and acute inflammatory reactions have led to the notion that steroids and non-steroidal anti-inflammatory agents might protect ischaemic myocardium<sup>9,10</sup>. It is also reported that calcium ions are released during ischaemia and reperfusion<sup>11</sup>. In any inflammatory reaction prostaglandins are produced and lysosomal enzymes are liberated. Thromboxane is also released due to tissue damage. Thromboxane A2 is potent agent for platelet aggregation. It means several factors act for the genesis of irritability of the myocardium after ischaemia and reperfusion. Aspirin has been found to decrease the intensity of tachyarrhythmias during occlusion and reperfusion. The protective effect may be due to inhibition of synthesis and release of thromboxane A2 from myocardium<sup>4</sup>. Salicylates like calcium channel blockers depress the slow inward current in both SA nodes cells and atrial muscle fiber of rabbit heart<sup>12,13</sup>. Although nonsteroidal anti-inflammatory agents appear to act by inhibition of prostaglandin biosynthesis, these differ in anti-inflammatory potency and degree of prostaglandin synthesis inhibition<sup>14</sup>. Indomethacin (2.5 mg/kg) is unable to control ischaemia induced and reperfusion induced arrhythmias. Higher doses (10 mg/kg) though control ischaemia induced arrhythmias to some extent but mortality rate is increased. Large doses of indomethacin (50 mg/kg) produced unwanted effects i.e., increased ventricular arrhythmias and this may be due to lysis of lysosomes as large doses of NSAIDs have been reported to produce lysis of lysosomes<sup>15,16</sup>. Both ischaemia and reperfusion act as stimuli for the genesis of ventricular arrhythmias. Most severe arrhythmias that occur after occlusion period of 5-15 min are 50-56% ventricular fibrillation. Reperfusion ventricular fibrillation occurs much less commonly when reperfusion was delayed from 30-60 minutes<sup>6</sup>. Ventricular fibrillation is the worst type of ventricular arrhythmia. Its control is important to protect the animal from death. Previous experimental studies have shown that most of the conventional anti-arrhythmic drugs fail to suppress reperfusion ventricular fibrillation<sup>17</sup>. NSAIDs have also failed to suppress ventricular fibrillation. Non-steroidal anti-inflammatory drugs especially aspirin (12.5 mg/kg) controls ischaemia induced ventricular arrhythmias and supra ventricular tachyarrhythmias without affecting haemodynamic parameter significantly and there is no mortality. On the other hand low dose of indomethacin (2.5 mg/kg) controls supra ventricular tachyarrhythmias but fails to suppress ventricular arrhythmias. When we used large dose of indomethacin (10 mg/kg) ventricular arrhythmias were suppressed but mortality rate increased and moreover supra ventricular tachyarrhythmias were not affected significantly.

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