Acute Effects of Anti-Anginal Drugs on Cardiac Pacing Threshold

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SUMMARY

Forty cardiac pacing threshold studies were conducted in 25 patients being temporarily paced prior to permanent pacemaker implantation using the following anti-anginal drugs: Nitroglycerine 0.5 mg (7 patients), nifedipine 10 mg (7 patients) administered sublingually and intravenously administered (IV) oxyfedrine 0.15 mg/kg (6 patients), propranolol 0.1 mg/kg (10 patients), and verapamil 0.15 mg/kg (10 patients). Changes in voltage (volts), current (mA), energy (micro-joules) and resistance (ohms) were measured using a pacemaker system analyser at a constant pulse width (0.6 msec.) and pacing rate.

Nitroglycerine significantly decreased the voltage and current threshold ($p < 0.05$). No significant change was seen in energy and resistance parameters. Nifedipine and propranolol did not have any significant effect on voltage, current, energy or resistance parameters. Oxyfedrine significantly decreased voltage threshold ($p < 0.05$) with no change in other parameters. Verapamil caused a significant increase in the current and energy threshold ($p < 0.05$), without changing the voltage threshold significantly. The resistance values showed a consistently decreasing trend.

The threshold for cardiac pacing is defined as the smallest amount of electrical energy that produces consistent capture outside the refractory period of the heart.[1] Cardiac pacing threshold is not a static entity and is influenced by physical, physiological, pharmacological and metabolic interventions.[2-3] Though there are a few studies evaluating the effect of cardio-active drugs on pacing thresholds, they are confined to anti-arrhythmic agents.[2-4] Anti-anginal agents are commonly used drugs in patients with ischemic heart disease who require cardiac pacing. To the best of our knowledge there is no published data on the effect of these agents on the stimulation thresholds. In the present study we have evaluated the acute effects of some commonly used antianginal agents viz: nitro-glycerine, nifedipine, oxyfedrine, propranolol and verapamil on the voltage, current, impedance and energy thresholds at a constant pulse-width and rate.

MATERIAL & METHODS

Forty studies of cardiac pacing threshold were done in 25 patients (18 males, 7 females) in the age range 24-80 years (mean age 59.5 Years) who were on temporary right ventricular endocardial pacemakers for the following indications: Complete heart block (12), high grade atrio-ventricular block (8), and sick sinus syndrome (5). The criteria for selection of patients and the study protocol has been described previously.[4] All the patients were studied in a wakeful, post absorptive phase in the supine position. Physical activity of any kind or changes

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in posture were restricted throughout the study to avoid alteration in the electrode position. The thresholds were measured using a 6F bipolar pacing catheter connected to a pacemaker system analyser (cardiac pacemaker incorporation, Cardiotest 2200) and a cardiac monitor at a constant pulse width (0.60 msec.). The following parameters were measured (1) voltage in voles, (2) current in milli-amperes, (3) resistance in ohms and (4) energy in micro-joules. The resistance of the lead and the lead-cardiac interface was measured at a fixed output of 5 volts as a direct reading and also by noting the corresponding current delivered at this voltage which gives the resistance by using the ohm's law (Resistance = voltage/current). The energy threshold was calculated using the formula of Davies & Sowton (Energy = voltage x current x Pulse width). Constancy of the basal threshold parameters was ensured for a minimum of 30 minutes. The basal parameters were measured during steady breathing as well as during deep inspiration and expiration.

The study subjects were divided into 5 groups based on the different anti-anginal drugs used: Group I - Nitroglycerine 0.5 mg sublingual (7 patients), Group II - Nifedipine 10 mg sublingual (7 patients), Group III - Oxyfedrine 8 mg IV (6 patients), Group IV - Verapamil 0.15 mg/kg body weight I.V.. (10 patients), and Group V - Propranolol 0.1 mg/kg body weight I.V. (10 patients).

The intravenous agents (propranolol, verapamil, oxyfedrine) were administered through a preestablished intravenous line, over a period of 5 minutes. A close watch was kept on the general condition, heart rate and rhythm, blood pressure and respiratory rate. The repeat threshold measurements after intervention were recorded every 5 minutes for 30 minutes every 10 minutes for 1 hour and every 15 minutes for 2 hours, or a period till the values returned to basal level.

The results were subjected to statistical analysis using the student's "t" test for paired data.

RESULTS

GROUP I : Nitroglycerine (Table I) - (Figure I)

The group as a whole showed a significant decrease in the voltage and current threshold ($p < 0.05$). Though the changes in energy threshold showed a decreasing trend, it did not achieve statistical significance. There was no significant change in the resistance of the lead.

The time of maximum change varied from 10-60 min. (mean 24 min). The changes reverted to basal level within 80 minutes in all.

GROUP II : Nifedipine (Table II) - (Figure 2)

There was a variable change in the voltage, current, energy and resistance parameters in this group. None of the changes were, however, statistically significant.

The maximum change occured from 10-90 minutes (mean 41 minutes) and the changes reverted to basal level within 100 minutes in all.

GROUP III : Oxyfedrine (Table III) - (Figure 3)

There was a significant decrease in the voltage threshold ($p < 0.05$). No significant change was seen in current, energy and resistance parameters.

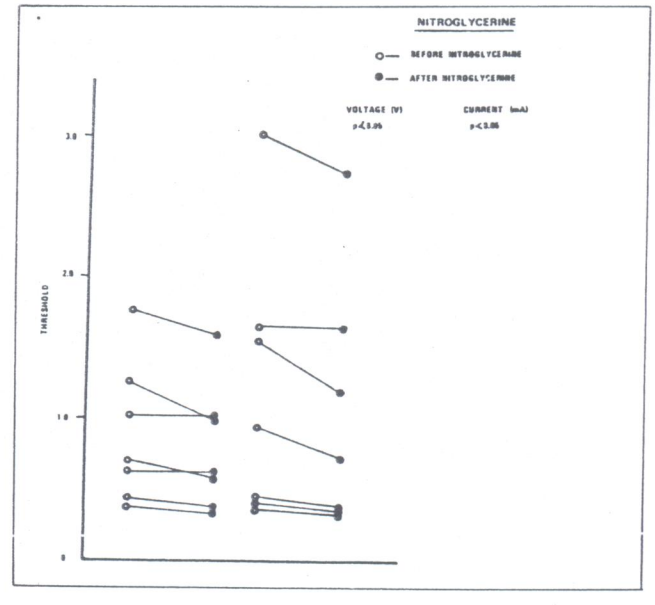

Fig. 1 : Effects of nitroglycerine on the voltage and current threshold.

Table I

EFFECTS OF NITROGLYCERINE

PARAMETER	BASAL (mean)	MAXIMUM CHANGE (mean)	p VALUE
VOLTAGE (V)	0.89 ± 0.506	0.789 ± 0.450	< 0.05
CURRENT (mA)	1.242 ± 0.958	1.086 ± 0.863	< 0.05
RESISTANCE (Ohms)	583.3 ± 117.4	592.1 ± 113.4	NS*
ENERGY (micro joules)	0.911 ± 1.133	0.712 ± 0.914	NS

* NS = Not significant

The maximum change occured from 5-105 minutes (mean 33.3 min). The change reverted to basal level within 120 minutes).

GROUP IV : Verapamil (Table IV) - (Figure 4)

Significant increase in current ($p < 0.05$) and energy ($p < 0.05$) thresholds were observed with verapamil with no statistically significant changes in the voltage threshold. The resistance of the lead and lead cardiac interface decreased in all patients (means 549.2 ± 124:1 to 514 ± 95 ohms) although it did not attain a statistical significance ($p > 0.05$).

The maximal changes occured within 5-30 minutes (mean 25 min) and reverted to basal level within 75 minutes.

GROUP V : Propranolol (Table V) - (Figure 5)

The group showed no significant change in the current, voltage, energy thresholds and resistance parameters ($p > 0.05$) although in one patient an appreciable increase in the current. (30%), energy (71%), and voltage (32%) threshold was observed.

The maximal changes occured within 5 to 50 minutes (mean 26.5 minute) which reverted to basal levels within 75 minutes.

Table II

EFFECTS OF NIFEDIPINE

PARAMETER	BASAL (mean)	MAXIMUM VALUE (mean)	p VALUE
VOLTAGE (V)	1.186 ± 0.602	1.204 ± 0.654	NS
CURRENT (mA)	1.609 ± 0.862	1.692 ± 0.972	NS
RESISTANCE (Ohms)	543.8 ± 57.9	541.4 ± 52.6	NS
ENERGY (micro joules)	1.410 ± 1.287	1.544 ± 1.505	NS

Table III

EFFECTS OF OXYFEDRINE

PARAMETER	BASAL (mean)	MAXIMUM VALUE (mean)	p VALUE
VOLTAGE (V)	1.395 ± 0.626	1.308 ± 0.558	< 0.05
CURRENT (mA)	1.945 ± 1.01	1.879 ± 0.877	NS
RESISTANCE (Ohms)	550.1 ± 78.9	533.3 ± 49.5	NS
ENERGY (micro joules)	1.938 ± 1.475	1.731 ± 1.259	NS

DISCUSSION

Excitation of a single myocardial cell or a syncitium of cells is a function dependent upon (i) the exciting stimulus, (ii) the resting membrane potential.[5 9] The Pacemaker standard Sub-committee of the Association for the Advancement of Medical Instrumentation defines stimulation threshold as the "minimum stimulation level consistently producing propagated cardiac depolarization".[10] Accurate threshold evaluation requires measurements of voltage, current, pulsewidth and oscilloscopic recordings of the pulse waveform. The threshold depends upon pulse duration and therefore must be measured at specific pulse widths.[11] Althoug current threshold has been very widely used, voltage threshold is the preferable measurement.[11]

The pacing threshold after implantation of a pacemaker is subjected to changes which are dependent on many physiological and electro-biological factors like the diurnal variation,[12] passage of time [1,3,14] the surface area, configu-

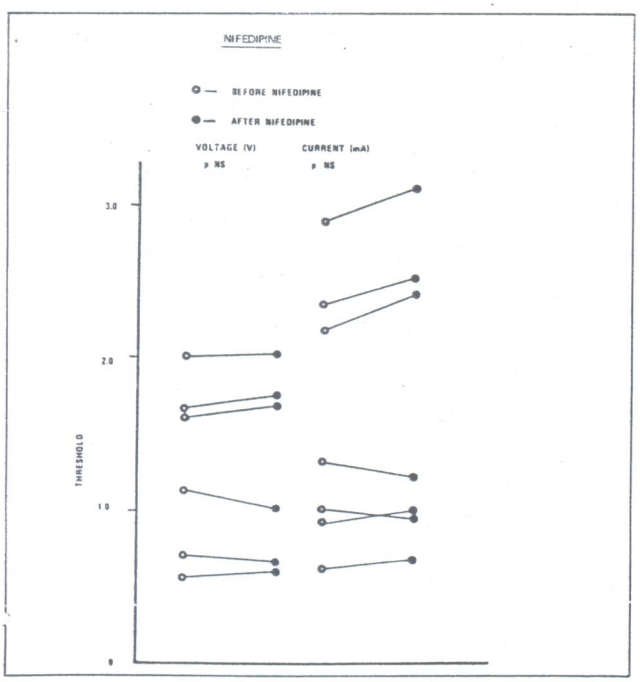

Fig. 2 : Effects of nifedipine on the voltage and current threshold.

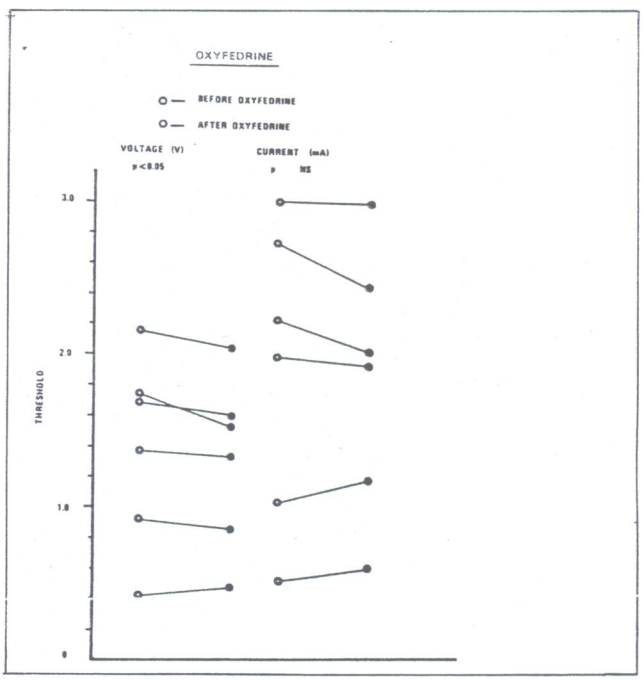

Fig. 3 : Effects of oxyfedrine on the voltage and current threshold.

Table IV

EFFECTS OF PROPRANOLOL

PARAMETER	BASAL (mean)	MAXIMUM VALUE (mean)	p VALUE
VOLTAGE (V)	1.416 ± 1.392	1.617 ± 1.601	> 0.05
CURRENT (mA)	1.85 ± 1.415	2.081 ± 1.671	> 0.05
RESISTANCE (Ohms)	592.4 ± 146	607 ± 148.2	> 0.05
ENERGY (micro joules)	2.613 ± 4.542	3.414 ± 5.649	> 0.05

ration of the electrode,[15] the polarization effect,[16] and the responsiveness of the excitable tissues.[16] Pharamacological interventions which increase the cardiac pacing threshold will have a deleterious effect especially in patients who are totally pacemaker dependent and where the safety margin of stimulation threshols is low.

In a recent study, we have demonstrated the deleterioius effects of anti-arrhythmic agents on the stimulation threshold parameters[4]. Anti-anginal agents are frequently administered to patients on temporary and permanent pacemamers. Except for the studies of Preston et al[2,3] who reported the effect of propranolol on the total energy threshold, there are no other studies assessing these agents on different threshold parameters.

In our study, nitroglycerine decreased the voltage and current threshold significantly. A decreasing trend was shown in energy threshold but it did not achieve statistical significance. No significant change was seen in the resistance parameters. The possible mechanism for this change seems to be due to increased sympathetic activity possibly reflexly mediated, secondary to peripheral vasodilation.

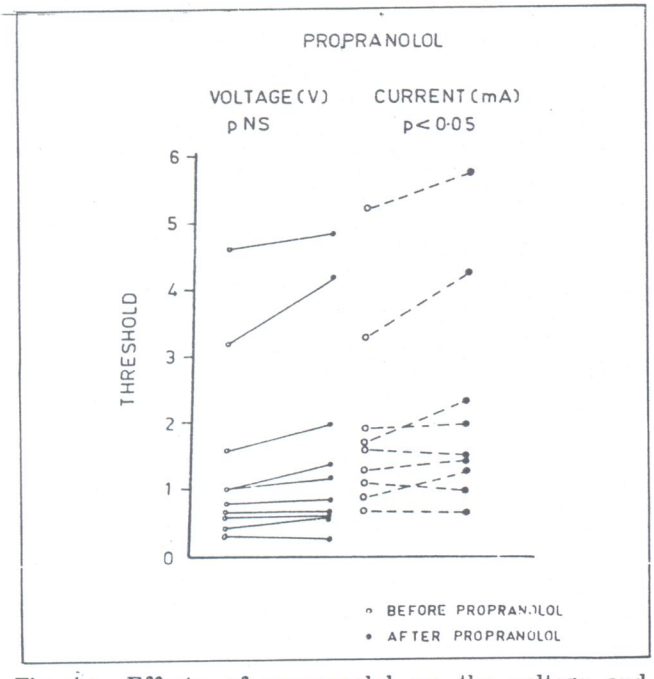

Fig. 4 : Effects of propranolol on the voltage and current threshold.

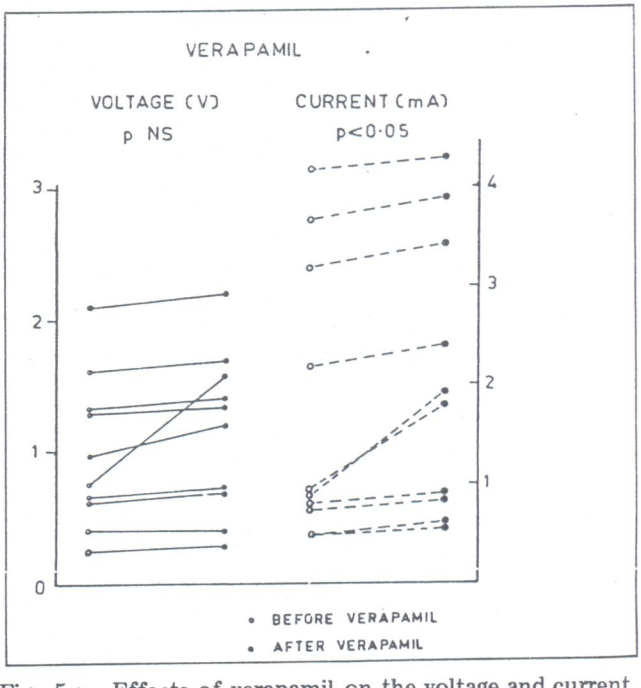

Fig. 5 : Effects of verapamil on the voltage and current threshold.

Table V

EFFECTS OF VERAPAMIL

PARAMETER	BASAL (mean)	MAXIMUM VALUE (mean)	p VALUE
VOLTAGE (V)	0.999 ± 0.580	1.152 ± 0.614	>0.05
CURRENT (mA)	1.763 ± 1.438	2.06 ± 1.399	<0.05
RESISTANCE (Ohms)	549.2 ± 124.1	514 ± 95	>0.05
ENERGY (micro joules)	1.482 ± 1.791	1.847 ± 1.860	<0.05

Calcium entry blocker nifedipine did not produce a significant change in any of the threshold parameters. By virtue of its potent vasodilatory effect leading to increased sympathetic activity, nifedipine should not depress the excitability of cardiac tissue, thus accounting for its lack of effect on the threshold values seen by us. Verapamil on the contrary produced significant increase in current and energy levels delivered at the stimulation site without affecting the voltage threshold significantly. The resistance level however showed a decreasing trend without attaining statistical significance. Since the resistance of the lead in acute experiments is constant, the impedence variation represents changes at the tissue electrode interface suggesting that verapamil has the property of decreased polarisation or overvoltage effect leading to no significant change in voltage inspite of an increased current and energy threshold levels. This interesting property of verapamil has not been reported earlier.

Oxyfedrine significantly decreased the voltage threshold without changing the other parameters. This is probably due to its reported direct sympathomatic effect on the cardiac conduction system as reported by one of us previously. [17]

Propranolol did not result in significant alteration in the voltage, current and energy thresholds. Preston and Judge (1969) reported a minor increase in the stimulation threshold with propranolol in a few subjects and suggested that the change was secondary to a heightened basal sympathetic tone. Similar results were seen by us in one patient. The reason for this is not clear, although the possibility of a basal heightened sympathetic tone (resulting in decreased pacing threshold) which gets cut off by propranolol in our actue study cannot be ruled out.

On the basis of this study, despite the limitations of an acute study, we conclude that the myocardial pacing threshold is not adversely affected by most of the anti-anginal agents. In fact, nitro-glycerine by decreasing the voltage and current thresholds and oxyfedrine by reducing the voltage threshold significantly, could prove to be useful in the setting of pacemaker exit blocks. The safety of verapamil and propranolol in this regard has previously been demonstrated by us.[4]

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