Clinical Research

Time Course of Ventricular Fibrillation and Defibrillation Thresholds Following Amiodarone Intravenous Bolus Administration: An Experimental Study

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Introduction: The aim of the study was to examine the early time course of changes in ventricular fibrillation and defibrillation thresholds after an intravenous bolus of amiodarone in an experimental pig model of transient myocardial ischemia.

Methods: Ventricular fibrillation threshold and relative ventricular refractory period were measured in anesthetized open-chest pigs after 3 min of regional coronary ischemia before (time 0) and 2, 15, 30, 60 and 90 min after the injection of 5mg/kg intravenous bolus of amiodarone in 15 sec (Group I, n=10) or normal saline (Group II, n=5). Defibrillation threshold was also measured by systematically increasing the stored voltage until defibrillation was accomplished. Hemodynamics, acid-base balance and temperature were kept stable throughout the experiments.

Results: Amiodarone caused a steady increase in ventricular fibrillation threshold and relative refractory period. The earliest significant change of the threshold, at a mean value of 50% of control values, was observed at 15 minutes after amiodarone administration (13.7 ± 6.5 mA versus 9.2 ± 4.6 mA, p=0.009) and reached a maximum at 4-fold values of reference value, 60 minutes after infusion (50.3 ± 37.8, p=0.008). In contrast, ventricular defibrillation threshold did not show any change (p=0.342).

Conclusion: In this experimental study, intravenous bolus administration of amiodarone, increased ventricular fibrillation threshold and relative refractory period steadily over time, reaching a plateau 60 minutes after the injection, without any effect on defibrillation threshold.

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Amiodarone is an antiarrhythmic agent particularly effective in the prevention and treatment of a wide spectrum of ventricular and supraventricular arrhythmias. However, the long time interval that is required for the development of the maximum antiarrhythmic activity of oral amiodarone considerately limits its use, particularly when antiarrhythmic action is immediately required. On the contrary, intravenous amiodarone acts rapidly and it often is a life saver in managing drug resistant fatal arrhythmias.

Thus, in non-randomized studies, when administered in in-hospital prolonged cardiac arrest due to ventricular tachycardia or ventricular fibrillation, amiodarone promoted rapid re-establishment of organized electric activity, while in patients with resistant out-of-hospital cardiac arrest, randomized intravenous administration of amiodarone increased the probability of patient’s ad-
mission in hospital\textsuperscript{21}. Finally, in experimental models of spontaneous ventricular fibrillation, resistant to xylocaine and adrenaline in combination with electric defibrillations, intravenous administration of amiodarone contributed favorably in its defibrillation\textsuperscript{22}.

As other antiarrhythmic drugs with prophylactic and therapeutic action against ventricular fibrillation\textsuperscript{23,24}, amiodarone is characterized by the possibility of increase in the experimental ventricular fibrillation threshold\textsuperscript{25-30}. The minimum, however, required time interval for the development of this increase, as well as its change over time have not been studied. The purpose of this study was to estimate the time course of ventricular fibrillation and defibrillation thresholds, after rapid intravenous administration of amiodarone, in an experimental model of acute myocardial ischemia.

**Material and method**

Nineteen pigs, with body weight ranging between 25 and 35 kg were used for this study.

**Anesthesia and animal preparation**

The animals were pre-anesthetized with intramuscular administration of a mixture of ketamine (20mg/kg), atropine (0.5mg) and midazolame (0.5mg/kg). They were intubated with an endotracheal tube of 7.5mm and mechanically ventilated with room air and supplemental oxygen, of a volume of 15ml/kg for each inhalation and frequency of 15 breaths per minute. After intubation, general anesthesia was given with successive administration of thiopental (9mg/kg), fentanyl (500mg) and pentobarbital (4mg). For the maintenance of anesthesia and analgesia during the experiment, continuous intravenous infusion of thiopental in dose of 3mg/kg/hr and fentanyl in dose of 3mg/kg/hr was administered, while for satisfactory myorelaxation, pentobarbital in dose of 2 mg every 30 minutes was given. An arterial line was inserted in the right carotid, while a 7F catheter was inserted through the right external jugular vein for fluid infusion, blood sampling and recording of central venous pressure.

A middle thoracotomy, dissection of pericardium and suspension of the heart in a pericardial cradle, preparation of left anterior descending coronary artery in its middle section and application of middle-bond tape for temporary vessel occlusions followed. A bipolar J shaped epicardial electrode was anchored on the anterior wall of the right ventricle. Similarly, a pair of flat, unipolar electrodes, with diameter 10mm each, were epicardially positioned, the anodic on the anterior wall of the left ventricle, respectively to the potential ischemic area, while the cathodic on the posterior wall of the left ventricle, distal to the potential ischemic zone. The electrode tips were connected to a continuous voltage dual-channel digital output stimulator. The first output, connected to the right ventricle electrode, was used for heart pacing with electric stimuli of 2 msec duration, while the second output, connected to the left ventricle electrodes was administering electric pulses, of 10msec duration, in order to cause ventricular fibrillation.

The animal was heparinized, with the administration of 1000 IU of heparin after the completion of surgical procedure and then with 500 IU every hour. The animal’s temperature was checked with a rectal thermometer and was maintained within a range of ±0.5 °C of the initial temperature with the use of an electric blanket. Arterial blood gas measurements were performed for the estimation of pH and its maintenance between 7.35 and 7.45 (with proper ventilation parameter adjustments and the administration of bicarbonates when necessary), while adequate fluid administration ensured normal arterial pressure during the experiment.

**Electrophysiological study**

**Diastolic pacing threshold**

The electrophysiological study began with the calculation of diastolic pacing threshold. More specifically, for the bipolar pacing electrode, the intensity of initially given electric stimulus was equal with 0.5mA, and was increased at 0.1mA each time, until constant excitation of heart was achieved. For the pair of unipolar electrodes, the calculation of diastolic threshold was performed starting from intensity value of 1mA, and increasing by 0.5mA each time.

**Relative ventricular refractory period**

The estimation of relative refractory period always preceded the measurement of ventricular fibrillation threshold.

Occlusion of the left anterior descending artery was performed and after 2 minutes, the heart was
paced regularly at 200 beats per minute (S1). Electric stimuli of 10msec duration and intensity equal to the calculated diastolic threshold (S2) were administered in the left ventricle after each tenth pacing stimulus and in progressively increasing time intervals (S1-S2), starting from 150msec and increasing by 1msec each time. The minimum time interval (S1-S2) for which the early-administered electric stimulus (S2) would cause depolarization of ventricular myocardium, was determined as relative refractory period.

**Ventricular fibrillation threshold**

Short after the completion of measurement of relative refractory period and while the ligation of left anterior descending artery was maintained, an electric stimulus (S2) was also administered, with a progressively increasing intensity every 10 pacing beats and in a time interval from the tenth (S1-S2) equal to the calculated relative refractory period. The measurement started with a stimulus of an intensity equal to the diastolic threshold, which was increased by 1mA each time. For each value of stimulus intensity, two attempts were made. The minimum intensity electric stimulus capable of inducing ventricular fibrillation, was considered as ventricular fibrillation threshold for the particular state of the animal.

**Ventricular defibrillation threshold**

The internal defibrillation system of NYHON COHTEN 1500 defibrillator was used for defibrillation of induced ventricular fibrillation, with defibrillation paddles made of stainless steel and with internal junction area of 3.5cm².

The defibrillation attempt began 10 seconds after the onset of ventricular fibrillation, following the release of ligation of the anterior descending artery. A series of defibrillations with increasing intensity (3, 5, 10, 15, 30 and 50 J) were administered, with two attempts performed for each value. The interval between successive defibrillations would be determined by the time required for the determination of maintenance of ventricular fibrillation on the one hand, and by the defibrillator’s charging time on the other. In prolonged ventricular fibrillation (>30sec), the attempt of defibrillation was interrupted for an interval of myocardial compressions, of a duration of 20 to 30 seconds approximately, and was continued with repeated defibrillations with the highest value of intensity at 50 J.

The defibrillation that led to re-establishment of sinus rhythm and normal arterial pressure was considered successful. Development of ventricular tachycardia was considered successful, if, ten seconds after its establishment, cardiac frequency was slowed down and arterial pressure began to restore. The re-establishment of sinus rhythm was done automatically or with synchronized defibrillation, if the duration of tachycardia exceeded 30 seconds. In opposite case, defibrillation was considered unsuccessful and a new one was attempted. The minimum electric energy that led to successful defibrillation was considered as ventricular defibrillation threshold for the particular state of the animal.

**Administration of amiodarone and study of its electrophysiological effect over time**

Before each measurement, recording of hemodynamic parameters (arterial and central venous pressure), blood gas sampling and rectal temperature measurement were performed.

The measurement protocol of ventricular fibrillation, defibrillation thresholds and drug administration was as follows:

Before the administration of the drug and for testing the reproducibility of the method, two (or more if needed) reference attempts without ischemia were made. Measurements were accepted provided their difference did not exceed 20% of the highest of the two, and their mean value constituted the reference threshold on acute myocardial ischemia. The minimum time interval that intervened between successive measurements was never less than 15 minutes.

Immediately afterwards, a rapid (within 15 seconds), bolus, intravenous infusion was performed of: a) amiodarone at a dose of 5mg/kg of body weight dissolved in 20cc of normal saline (n=10) or b) 20cc of normal saline (n=5), (control group), in a randomized and blinded way.

The measurements on acute ischemia were repeated at 2, 15, 30, 60 and 90 minutes after the completion of drug infusion.

**Statistical analysis**

The electrophysiological and hemodynamic parameters were expressed as mean values ± standard de-
viation for each group of animals. Mean values at various time points of measurement were compared for each group of animals, using the Repeated Measurement Analysis of Variance. In cases where statistical significance was observed, LSD (Least Significant Difference) test was used in order to compare individual mean values. The differences in treatment response, between the control group and the amiodarone group, were analyzed using values of variance. These values were derived from the calculation of difference between the reference value and the measured value at each time point of treatment administration, for each animal. These variances, calculated in this way, at various times of measurement, were compared between the two groups of animals with a simple t-test.

The difference for which p value was less than 0.05 (p<0.05) was considered statistically significant.

Results
From a total of nineteen animals, fifteen completed the protocol successfully. Ten of these received amiodarone and the remaining five normal saline.

1. Ventricular fibrillation threshold
   a) Reference values
   The mean value of ventricular fibrillation threshold in reference measurements without ischemia was 35.6 ± 9.2mA for all animals (group A and B). Under ischemic conditions, ventricular fibrillation threshold was decreased at 9.2 ± 5.2mA, (p=0.000). The mean value of reference threshold without ischemia, in group A animals that received amiodarone was 33.6 ± 9.7mA versus 39.6 ± 7.5mA for control group B (p=0.222). Ventricular fibrillation thresholds under ischemia showed no difference between the two groups (9.2 ± 4.6mA in group A versus 9.5 ± 6.7mA in group B, p=0.920).

   b) Change of ventricular fibrillation threshold over time, under ischemia for control group (group B)
   No threshold significantly different from the reference value was observed at any time (Figure 1 and Table 1).

   c) Change of ventricular fibrillation threshold over time, under ischemia for animals that received amiodarone (group A)
   In this group of animals, progressive increase of threshold was observed over time, which reached a maximum 60 minutes after drug administration, and stabilized thereafter (Figure 1 and Table 1). At 2 minutes after amiodarone administration, ventricular fibrillation threshold was increased by 24% of the control value (p=0.113), with further increase

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>GROUP A (amiodarone (5 mg/kg))</th>
<th>GROUP B (normal saline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference value</td>
<td>9.2 ± 4.6</td>
<td>9.5 ± 6.7</td>
</tr>
<tr>
<td>2 minutes</td>
<td>11.4 ± 8.4</td>
<td>11.4 ± 9.8</td>
</tr>
<tr>
<td>15 minutes</td>
<td>13.7 ± 6.5*†</td>
<td>9.6 ± 6.1</td>
</tr>
<tr>
<td>30 minutes</td>
<td>34.2 ± 28.7*†</td>
<td>9.4 ± 5.3</td>
</tr>
<tr>
<td>60 minutes</td>
<td>50.3 ± 37.8*†</td>
<td>8.2 ± 6.8</td>
</tr>
<tr>
<td>90 minutes</td>
<td>53.2 ± 38.8*†</td>
<td>9.4 ± 4.2</td>
</tr>
</tbody>
</table>

*p<0.05 versus reference values
†p<0.05 versus control values.
at 15 minutes, reaching 50% of the control value, (p=0.009). At 30 minutes following amiodarone infusion, ventricular fibrillation threshold had quadrupled (p=0.03), reaching its maximum value at 60 minutes (p=0.008). It remained in these levels until the end of the experiment.

d) Comparison of respective ventricular fibrillation thresholds between the two groups

The difference in values of change between the amiodarone group and the control group, expressed as Δ, confirms the above-mentioned results. Thus, Δ value was considerably higher for the amiodarone group 15 minutes after infusion (p=0.016) and was further increased at 30 minutes (p=0.026). This difference was maximized at 60 minutes (p=0.06) and remained at respective levels up to the end of the experiment (p=0.01).

2. Ventricular defibrillation threshold

a) Reference values

The mean value of ventricular defibrillation threshold in reference measurements was 5.2 ± 4.3 J for all animals (group A and B) and after transient ischemia, reference threshold was increased at 13.2 ± 12.5 J (p = 0.056). Ventricular defibrillation thresholds, after transient ischemia, were similar in both groups (14.4 ± 15.2 J in group A versus 11 ± 5.7 J in group B, p=0.545).

b) Change of ventricular defibrillation threshold over time, under ischemia for control group (group B)

Ventricular defibrillation threshold, after transient ischemia, in group B was almost unchanged during the duration of the experiment (repeated measures ANOVA, p=0.673), (Figure 2 and Table 2).

c) Change of ventricular defibrillation threshold over time, under ischemia for animals that received amiodarone (group A)

Ventricular defibrillation threshold in group A, after transient ischemia, remained stable during the experimental period (repeated measures ANOVA, p=0.342), (Figure 2 and Table 2).

3. Relative ventricular refractory period

a) Relative refractory period prior to drug administration

The mean value of relative refractory period in reference measurements was 205 ± 21 msec. This value remained unchanged when measurements were repeated under ischemic conditions (204 ± 24 msec, p=0.872).

b) Change of relative refractory period of left ventricle over time

In control group (group B), the relative refractory period, after the 30th minute of the experiment,
showed progressive reduction, which became significant at 90 minutes from the administration of normal saline (p=0.041) (Figure 3, Table 3).

In amiodarone group (group A), relative refractory period showed progressive increase over time (repeated measures ANOVA, p=0.003) (Figure 3, Table 3). At 2 minutes following drug administration it was increased by an average of 6 msec (p=0.074), at 30 minutes the difference became statistically significant (p=0.037) and it reached its maximum at 90 minutes (mean increase 29 msec, p=0.008). The increase of relative refractory period caused by amiodarone is confirmed by its comparison to the control group where it is observed that 30 minutes after drug administration, relative refractory period in group A is increased while in group B is decreased. At 60 minutes from drug administration, an increase (↑ 22±14 msec) occurred in group A and a reduction (↓ 18 ± 22 msec) in group B, p=0.001, while at 90 minutes the corresponding changes were an increase of 29 ± 25 msec versus a reduction of 26 ± 20 msec, p = 0.001.

4. Hemodynamic effects

Mean arterial pressure prior to drug administration was similar in both groups (83.4 ± 13.6mmHg for group A, versus 90.6 ± 9.8mmHg for group B, p= =0.316). In the group of animals that received amiodarone, two minutes after its rapid bolus intravenous administration, the mean arterial pressure showed significant reduction (68.8 ± 15, p=0.000) and was maintained at approximately the same levels up to the end of the experiment (repeated measurement ANOVA, p=0.951). Following drug administration, mean arterial pressure in group A was considerably lower than that of group B, during the experiment.

Discussion

In this experimental study, rapid bolus intravenous administration of amiodarone, at a dose of 5 mg/kg of body weight, caused constant increase of ventricular fibrillation threshold and relative refractory period of left ventricle over time without influencing the ventricular defibrillation threshold.

Effect of intravenous amiodarone on ventricular fibrillation threshold

Rapid intravenous administration of amiodarone, at a dose of 5 mg/kg of body weight, caused progressive increase of ventricular fibrillation threshold in expe-
rimental model of acute myocardial ischemia. The earliest significant increase in the fibrillation threshold was observed at 15 minutes from the completion of infusion, and was on average 50% higher than control values. This increase was strengthened considerably over time and at 60 minutes after drug administration, it became approximately five times the reference value. No respective change was observed in the control group, in which ventricular fibrillation threshold remained substantially unchanged.

The ability of intravenous amiodarone to increase the ventricular fibrillation threshold has been established in various experimental models\(^{23-30}\). The doses that were used ranged from 2 to 30 mg/kg of body weight, with various ways of infusion and with evaluation of threshold at various times after the completion of administration. However, the minimum time required for threshold increase and its change over time have not been studied.

In this study, no statistically significant early (2 minutes from administration) increase of ventricular fibrillation threshold was found. Ventricular fibrillation threshold was considerably increased between 2 and 15 minutes from the administration of amiodarone. Similar results were also reported by Chen et al\(^{30}\), who did not observe any significant early (2 to 9 minutes from administration) increase of ventricular fibrillation threshold, after the administration of amiodarone at doses of 2 and 5mg/kg of body weight in an experimental model of cardio-pulmonary resuscitation in pigs. The threshold was found to be increased, after 5mg/kg, at 40 minutes following drug administration.

The weakness of amiodarone that was observed in these studies to increase the ventricular fibrillation threshold early is likely to be related to the administered dosage. Given the dose-dependent nature of the drug’s electrophysiological effects\(^{30-32}\), it is possible that higher doses of administration will lead to a more rapid onset of anti-fibrillating action. Indeed, in an experimental model of refractory automatic ventricular fibrillation on acute myocardial infarction, rapid intravenous administration of amiodarone, at a dosage of 10mg/kg of body weight, promoted electric defibrillation of refractory ventricular fibrillation\(^{22}\). Similarly, Lubbe et al\(^{23}\), in isolated hearts of mice, which had been removed 2 minutes after the administration of amiodarone, observed significant increase of ventricular fibrillation threshold for amiodarone doses ranging from 15 to 30mg/kg of body weight.

At clinical level, the time of amiodarone’s onset of action, following rapid intravenous administration, is not fully clarified. There are individual reports concerning the administration of amiodarone during prolonged resuscitation from refractory ventricular tachycardia or ventricular fibrillation where the time of response to treatment was different in various patients. In a series of 14 patients with resistant ventricular tachycardia or ventricular fibrillation\(^{17}\), in whom amiodarone was administered at an initial bolus dosage that ranged from 150 to 600mg, 4 out of the 11 patients that survived were defibrillated with the first electric discharge, while the remaining 7 required more time and additional doses of amiodarone until electrically stabilized. From the total of 11 patients that survived those who received initially higher doses of amiodarone (600, 500 and 350mg) were defibrillated without requiring additional dose.

The dose of 5mg/kg of body weight that was used in the present study, is considered the highest bolus dose with therapeutic action and acceptable level of side-effects\(^{33}\); it is also approximately the same dose with the one used in the Amiodarone for Resuscitation After Out of Hospital Cardiac Arrest Due to Ventricular Fibrillation\(^{21}\) study. The higher percentages of positive results in the female population, which were observed in this study, may be attributed to the higher dose of amiodarone per kilogram of body weight for the women.

The ventricular fibrillation threshold was significantly increased over time. Thus, the threshold was quadrupled at half hour after administration, while maximum increase was observed at 60 minutes, with values 5 times the reference values. This high efficacy was maintained up to the end of the experiment, i.e. 90 minutes following the administration of amiodarone. This increase of ventricular fibrillation threshold over time does not follow the proposed pharmakokinetic models for rapid bolus intravenous administration of amiodarone. Recent studies describe high concentrations of amiodarone in the myocardial tissue, already from 2 to 5 minutes following administration\(^{34,35}\), while in an older study Latini et al\(^{36}\) report maximum concentrations in the myocardium at 10 to 30 minutes after administration. At the time of the drug’s high concentrations in the myocardium, ventricular fibrillation threshold was moderately increased, while further increase was observed when the myocardial concentration of amiodarone was expected to start decreasing.
Regarding the correlation of electrophysiological changes with the concentration of amiodarone in the myocardium, the existing data present significant diversity. Nanas and Mason describe significant correlation between the degree of reduction of conduction velocity and the concentration of amiodarone in the myocardium after continuous intracoronary infusion, without however important changes in repolarization time. Similar myocardial concentrations after long-term treatment with oral amiodarone cause prolongation of action potential, refractory period and QT interval.

Therefore, the concentration of amiodarone in the myocardial tissue is not by itself a decisive factor of all the electrophysiological events. Other factors are likely to play important role. More specifically, for the ventricular fibrillation threshold measured in this study, the time lapse since drug administration appears to play a decisive role.

**Effect of intravenous amiodarone on the relative refractory period**

The change of relative refractory period over time was similar to the change of the ventricular fibrillation threshold. Thus, fifteen minutes after the administration of amiodarone, the relative refractory period was increased by 12msec with maximum increase (20 to 22msec) at 60 minutes. This parallel increase suggests a possible correlation between the effect of the drug in the relative refractory period and in the ventricular fibrillation threshold. However, since these increases are not proportional, it is obvious that apart from the prolongation of refractory period, other factors are also likely to be related with the development, but also with the lapse of time, increase of anti-fibrillating action of the medicine.

Indeed, the anti-fibrillating action of intravenous amiodarone is attributed to the reduction of the speed of conduction that is caused rather than in the prolongation of repolarization. Besides, the antisymptomatic effect via the non-competitive α and β blocking action and via the direct sympatholytic action, the inhibition of L calcium channels, the suppression of pathological automation, as well as the vasodilatory effect in coronary vessels, constitute, among others, known actions of amiodarone that may be related to the observed anti-fibrillating action following intravenous administration.

**Effect of intravenous amiodarone on ventricular defibrillation threshold**

The rapid intravenous administration of amiodarone at a dosage of 5mg/kg of body weight did not influence the ventricular defibrillation threshold in the experimental model of acute ischemia and revascularization of myocardium. The attempt of defibrillation began 10 seconds after the development of ventricular fibrillation and following the release of ligation of left anterior descending artery. Important differences in the mean time of preceding ischemia and in the mean time required for defibrillation, were not observed. Ventricular defibrillation threshold did not differ from the reference threshold or the respective threshold of the control group at any time.

Frame et al reported similar results, when they measured the ventricular defibrillation threshold in anesthetized dogs with implanted electrodes in the left ventricle. After rapid intravenous administration of amiodarone, at a dosage of 5mg/kg of body weight, and two hours following this administration, no threshold change was observed.

The dosage of 5mg/kg of body weight of amiodarone, that was studied in the present study, did not appear to influence ventricular defibrillation threshold at any way.

**Clinical applications**

The rapid intravenous administration of amiodarone at a dose of 300mg is proposed today by the American Heart Association as drug of choice for the management of refractory ventricular fibrillation. Indeed in the present study, similar doses of amiodarone (5mg/kg) led to multiple increase of ventricular fibrillation threshold, without at the same time increasing the ventricular defibrillation threshold. However, this small delay in the development of anti-fibrillating action that was observed, raises some questions regarding the efficacy of the proposed dose, and also renders essential the support of the patient during the first minutes of amiodarone administration with persisting and effective cardio-pulmonary resuscitation until the drug stabilizes the myocardium.

Apart from the treatment of refractory ventricular fibrillation, the antiarrhythmic protection of the heart, which is caused by the bolus intravenous administration of amiodarone, may lead to significant decrease in arrhythmic events to patients with
acute myocardial infarction, without the appearance of side effects. The use of intravenous amiodarone on acute myocardial infarction, during the transfer of the patient to the hospital, by decreasing the arrhythmic events, may also decrease the mortality of these patients. Similarly, amiodarone in doses of 5mg/kg of body weight, one hour before the performance of percutaneous transluminal coronary angioplasty, in patients at high risk for arrhythmic events, may turn out beneficial for their prevention.

References


