Adrenaline Versus Isoprenaline for Arrhythmia Induction

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11.1 Adrenaline Versus Isoprenaline for AVNRT Induction

11.1.1 Introduction

AVNRT can be induced in the EP lab by atrial or ventricular stimulation in the basal state or after drug administration. The drug of choice is isoprenaline, but in some European countries, the lack of the drug demands efforts to search for other options.

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To date, there is no study that compares efficacy of isoprenaline versus adrenaline for AVNRT induction in the EP lab. In our study we compared the two drugs in terms of efficacy and side effects. The results shows that both isoprenaline and adrenaline have a high sensibility for AVNRT induction: 81.6% for adrenaline and 90% for isoprenaline. The difference of 8.4% between the two drugs is nonsignificant, although it looks that isoprenaline would have a better profile. A higher number of patients are necessary to confirm the difference between the two drugs.

11.1.2 Hypothesis

In order to compare isoprenaline with adrenaline, we included all patients with AVNRT that received isoprenaline and all patients that received adrenaline. No match was done between the two groups because the number of patients in the two groups was low.

11.1.3 Materials and Method

11.1.3.1 Study Population

We studied a consecutive group of patients with AVNRT ablation and no arrhythmia induced in the basal state. For arrhythmia induction we infused adrenaline in 49 patients and isoprenaline in 20 patients. Every patient had a history of AVNRT with an ECG showing retrograde P wave in inferior leads: D2, D3, avF, or rsR′ in lead V1. The study was retrospective and observational without any action on the study group. We did not select the patients; we did not perform a "match" of the patients in function of the age or sex; we just included all the patients that required isoprenaline or adrenaline treatment in order to obtain data from "real-world" patients.

The isoprenaline group was composed of 20 patients, 18 female and 2 male patients. The adrenaline group was composed of 16 female and 33 male patients.

11.1.3.2 Electrophysiological Study

Electrophysiological study was performed without general anesthesia or sedation. The only anesthetic used was 1% lidocaine subcutaneously at the site of catheter insertion. All patients were in sinus rhythm at the beginning of the electrophysiological study. Catheters were inserted inside the heart chambers using the femoral, subclavian, or jugular vein. The right side was preferred over the left side. For most of the procedures, four catheters were used according to our department protocol: one in the superior right atrium, one in the region of the His bundle, one inside the coronary sinus, and one at the apex of the right ventricle.

We performed atrial and ventricular stimulation to measure the refractory period of the atrium, ventricle, and AV node. We excluded the presence of an accessory pathway by atrial and ventricular stimulation and by demonstrating absence of retrograde conduction to the atrium or when present decremental conduction with the first atrial depolarization at the level of the His bundle. After arrhythmia

induction we used atrial and ventricular entrainment to confirm AVNRT by measuring the post-pacing interval, and we excluded orthodromic reentrant tachycardia or atrial tachycardia. We stimulated the atrium with up to three extrastimuli at the level of high right atrium and coronary sinus on a 600 and 400 imposed rhythm. If the clinical arrhythmia could not be induced with extrastimuli, then burst atrial or ventricular pacing was performed.

When clinical arrhythmia could not be induced, we infused 1 μg/kg/min isoprenaline or infused 0.1 μg/kg/min adrenaline to facilitate arrhythmia induction. The choice between the two drugs was left at the discretion of the interventionist. When adrenaline was infused, an initial dose of 0.05 μg/kg/min was used and increased by 0.05 μg/kg/min every 5 min until the heart rate increased by 50% to at least 100 bpm but not more than 150 bpm (cycle length of 400 ms). The dose of adrenaline that permitted increase of the heart rate was 0.1–0.3 μg/kg/min (Fig. 11.1). When isoprenaline was infused, it was started at a dose of 0.5 μg/kg/min and then increased with 0.5 μg/kg/min every 3 min until the heart rate increased by 50% to at least 100 bpm but not more than 150 bpm. The medium dose of isoprenaline was 5 μg/kg/min. No patients received both drugs in association.

11.1.3.3 Statistical Analysis

Statistical analysis was performed using the 22 SPSS version. For descriptive statistics we used mean and standard deviation in case of normally distributed values. For continuous variables without normal distribution, we used median and interquartile range. For comparison between isoprenaline and adrenaline, we used the chi square test and the Fisher test when appropriate. For comparison of normally distributed variables, we used the student test and in case of abnormal distribution, the Mann-Whitney U test.

11.1.4 Results

In the adrenaline group, AVNRT was induced in 40 of 49 patients (81.5%) and in the isoprenaline group 18 of 40 patients (90%). Although the percentage was higher in the isoprenaline group, the statistical test showed a nonsignificant difference between the two groups with a p value of 0.396 (Table 11.1).

11.1.4.1 Side Effects of Isoprenaline and Adrenaline

Adrenaline infusion had to be stopped in 2 of the 49 patients (4%) because of headache at blood pressure values of more than 180/110 mmHg, for infusion rates of more than 0.2 μg/kg/min. Blood pressure was lowered with intravenous enalaprilat. Tremor also appeared at doses >0.1 μg/kg/min. Because tremor was well tolerated by the patients, infusion was not stopped for this side effect.

In the isoprenaline group, the most frequent side effects were agitation and tremor, but they were well tolerated by the patients during the electrophysiological study.

During adrenaline infusion atrial premature beats and ventricular premature beats were rarely seen at doses >0.2 μg/kg/min.

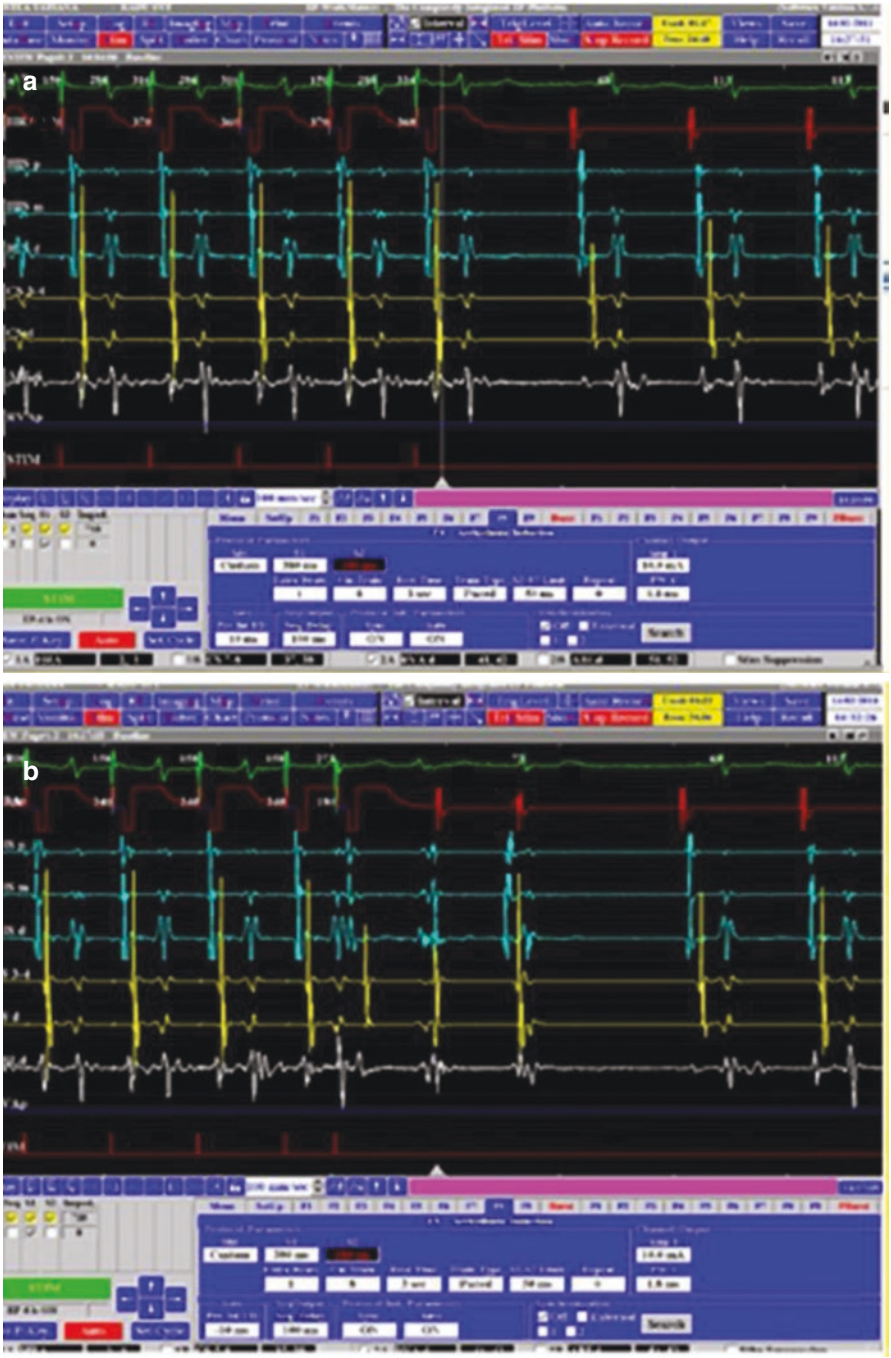

Fig. 11.1 Atrial stimulation for AVNRT induction without and with adrenaline. (**a**) Before adrenaline infusion, programmed atrial stimulation fails to induce atrial echo beats or AVNRT. (**b**) After adrenaline infusion, programmed atrial stimulation induces two atrial extra beats

Table 11.1 Comparison between the two groups: isoprenaline and atropine find no significant difference between them

Independent samples test										
		Levene's test for equality of variances		*t*-Test for equality of means						
									95% confidence interval of the difference	
		F	Sig.	*t*	df	Sig. (2-tailed)	Mean difference	Std. error difference	Lower	Upper
VAR00001	Equal variances assumed	3.341	0.072	−0.853	67	0.396	−0.08367	0.09804	−0.27937	0.11202
	Equal variances not assumed			−0.944	44.638	0.350	−0.08367	0.08866	−0.26228	0.09494

11.1.5 Discussion

11.1.5.1 Result Interpretation

Our study shows that both isoprenaline and adrenaline have a high sensibility for AVNRT induction: 81.6% for adrenaline and 90% for isoprenaline. The difference of 8.4% between the two drugs is nonsignificant, although it looks that isoprenaline would have a better profile. A higher number of patients are necessary to confirm the difference between the two drugs.

Adrenaline was generally well tolerated; the infusion had to be stopped in 4% of the patients (2 out of 49 patients). None of the patients from the isoprenaline group had significant side effects that would require termination of the infusion.

These results support the use of adrenaline in the EP lab for arrhythmia induction when isoprenaline is unavailable. The disadvantage of adrenaline is the increase in the blood pressure compared to isoprenaline which lowers the blood pressure; therefore some authors use the association of adrenaline with isoprenaline when the last one is unable to induce ventricular tachycardia [1].

We have found a similar efficacy for both isoprenaline and adrenaline. But the result does not mean that both drugs have the same efficacy as the low number of patients is a limitation of our study. For a significant p value and a difference of 5% between both groups, a number of 242 patients for adrenaline and isoprenaline would be mandatory.

11.1.5.2 Prior Studies with Isoprenaline

Hariman et al. [2] demonstrated that isoprenaline is effective for PSVT induction in patients that are non-inducible in the basal state or after atropine injection. Toda et al. [3] found a sensitivity of 50% for isoprenaline for the induction of paroxysmal supraventricular tachycardia in patients that had the arrhythmia during an effort. Huycke et al. [4] found a sensitivity of 67% and a specificity of 100% for PSVT induction in 20 patients with dual nodal pathway without any arrhythmia induced in the basal state. In the same year, Brembilla-Perot et al. [5] published their results with isoprenaline and showed similar results to our study, a sensitivity of 90% for induction of effort-induced PSVT (29 out of 32 patients). In the control group of 37 patients without PSVT, after isoprenaline infusion it was impossible to induce PSVT and allowed the calculation of a 100% specificity for isoprenaline. Stellbrink et al. [6] demonstrated that isoprenaline infusion in patients with AVNRT facilitated induction in 93% of the total of 80 patients. Katz et al. [7] reported a sensitivity of 46% for PSVT induction in patients with ventricular preexcitation. Oral et al. [8] demonstrated a sensitivity of 80% and a specificity of 95% for atrial fibrillation induction after 20 μg/min isoprenaline, in patients with paroxysmal persistent or long-term persistent atrial fibrillation.

11.1.5.3 Prior Studies with Adrenaline

The effect of adrenaline in patients with supraventricular tachycardias is known; it facilitates arrhythmia induction, but studies are made on a low number of patients and give no information on the sensibility of this drug for PSVT induction. Increase

in plasma concentration of adrenaline leads to decrease in atrial refractory period, decrease in refractory period of the AV node, and increase in the conduction velocity through the AV node, facilitating induction of AVNRT or orthodromic reentrant tachycardia in patients with accessory pathways.

In the study of Cismaru et al. [9], an increase in the plasma concentration of adrenaline facilitated PSVT induction in patients that were non-inducible in the basal state.

11.1.5.4 Limitations

This study has two important limitations: first is a nonrandomized study that considered all the patients that received adrenaline and isoprenaline, even if we found significant differences between the two groups in terms of sex representation. Matching for age and sex between both groups could not be possible because a much lower number of patients would have been obtained. The number of patients in this study was already low and made the comparison between adrenaline and isoprenaline nonsignificant.

11.1.6 Conclusion

Adrenaline and isoprenaline showed a similar efficacy for AVNRT induction in the EP laboratory. Adrenaline can be used when isoprenaline is difficult to obtain. The calculated efficacy for adrenaline was 81.5 and 90% for isoprenaline, without significant statistical difference between them. To obtain a significant difference between the two drugs with a significant p value lower than 0.05, a higher number of patients is required in both groups.

11.2 Adrenaline Versus Isoprenaline for Ischemic VT Induction

11.2.1 Introduction

Ventricular tachycardia in patients with ischemic heart disease has a poor prognosis. In those patients the best option is an ICD implant for the prevention of sudden cardiac death. Catheter ablation is an auxiliary method that is performed in patients implanted with an ICD that received multiple internal electrical shocks. In some Eastern countries, ICDs are not available for all the patients that need it so catheter ablation, when available, can be performed in patients with episodes of VT without ICD protection.

In some patients clinical VT can be induced by stimulating the ventricle at the level of RVOT or RV apex. When VT is non-inducible, drugs are used in the EP lab to facilitate arrhythmia induction. The most used drug is isoprenaline which is considered the gold standard, but in some East European countries, the drug is not available. Therefore other options have been searched. Atropine is not a good option

because its effect is mostly on the sinus node and AV node, with small or almost no effect on the atrial and ventricular myocardium. We tested adrenaline for VT induction, and we compared the results with those existing in the medical literature on isoprenaline.

11.2.2 Hypothesis

In order to compare isoprenaline with adrenaline, we took all the patients with ischemic VT that received adrenaline for VT induction and compared with reported sensibility of isoprenaline for VT induction found in medical literature. The effects of isoprenaline and adrenaline are slightly different as isoprenaline acts on β1 and β2 receptors and adrenaline acts also on α1 and α2 receptors.

11.2.3 Materials and Method

11.2.3.1 Study Group

Ninety-two consecutive patients with ventricular tachycardia were selected for this study, having (1) old myocardial infarction, (2) repeated episodes of ventricular tachycardia, (3) treated with amiodarone, and (4) performing an electrophysiological study. Of the 92 patients, we excluded those with RVOT, LVOT ventricular tachycardia, fascicular VT, patients with right ventricular dysplasia, left ventricular noncompaction, and left ventricular hypertrophy. In the end only 12 patients presented the inclusion criteria for further analysis.

11.2.3.2 Electrophysiological Study

All the patients came to the EP lab in the post-absorptive state. Amiodarone was continued the days before electrophysiological study and the same day because the effect of amiodarone was studied during intervention. The right femoral or right jugular vein was punctured, and one or two catheters were inserted at the level of right ventricular apex and RVOT. Ventricular stimulation was performed with up to three extra beats on an imposed rhythm of 600 and 400 ms. If no sustained arrhythmia was induced, lasting for more than 30 s or with hemodynamic instability, then adrenaline was infused.

11.2.3.3 Adrenaline Infusion

The dose of adrenaline infused was 0.05–0.2 μg/kg/min adjusted to obtain a heart rate over 100 bpm but not more than 150 bpm. During adrenaline infusion, programmed atrial and ventricular stimulation was performed at the apex of the right ventricle and RVOT.

There were no important ischemic side effects like angina or ST significant depression or elevation on 12-lead ECG. The most frequent side effect was tremor, which was well tolerated by the patients. The second encountered side effect was rise in the blood pressure, but after lowering the dose of adrenaline, the blood pressure normalized, but the heart rate remained over 100 bpm.

11.2.3.4 Catheter Mapping and Ablation

For catheter ablation the conventional approach was used with fluoroscopic guidance for the first cases and the three-dimensional mapping using the EnSite NAVX Saint Jude system or the CARTO-Biosense system.

When the conventional approach was used, a coronary sinus catheter was placed inside the coronary sinus to locate the mitral valve plane. The ablation catheter inside the left ventricle was an irrigated 4 mm tip one.

In every patient, attempts were made to induce ventricular tachycardia and to map the left ventricle during VT. If no VT could be induced during standard atrial and ventricular stimulation, then adrenaline was infused to facilitate induction. When VT was associated with hemodynamic instability, points of activation were taken during VT and points of voltage during sinus rhythm to make an idea about the reentry circuit.

Both antegrade and retrograde approaches were used to reach the left ventricle. Patients received i.v. heparin in dose of 70 U/kg and further doses to maintain an ACT of 250–350 ms. We did not use the classical approach with entrainment mapping because we believe it can change the cycle length of the tachycardia and change the activation pattern. So the value of the post-pacing interval was not useful in our patients. On the other hand, we used activation mapping to search for the reentry circuit and ablate at the level of the reentrant isthmus.

Catheter ablation was performed inside the left ventricle with 35–45 W and a cutoff temperature of 55 °C for irrigated catheters. Rarely non-irrigated catheters were used for the first cases of VT ablation.

11.2.3.5 Statistical Analysis

For statistical analysis the SPSS program was used. Normal distribution was tested using the Shapiro-Wilk test. In case of normal distributed values, the student test was used for comparison and in case on non-normal distributed values the Mann-Whitney U test.

11.2.4 Results

The studied population consisted in 12 patients with a mean age of 55 years old of which 85.7% were males. All patients had a history of myocardial infarction. In none of the 12 patients, ventricular tachycardia could be induced during programmed ventricular stimulation because patients were treated and protected by amiodarone (Figs. 11.2 and 11.3).

After adrenaline infusion in 6 of the 12 patients, ventricular tachycardia could be induced. The duration of the VT was either >30 s, or it associated hemodynamic instability so it was called sustained VT (Fig. 11.4). The mean cycle length of the VT was 315 ms with a minimum of 210 and a maximum of 400 ms. In six patients despite adrenaline, VT could not be induced as they were protected by amiodarone. Of the six patients, three had an old inferior myocardial infarction, and three had an old anterior myocardial infarction. The mean age in the group of patients with inducible VT was 56 years, and the mean age was 54 years in the group without induced VT under adrenaline (nonsignificant p value).

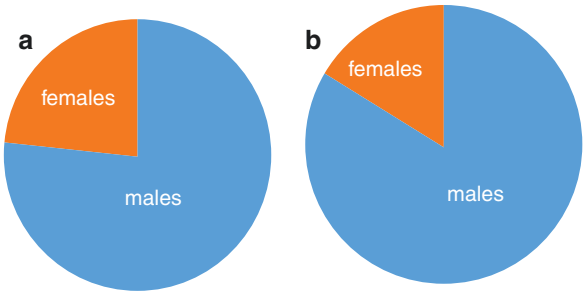

Fig. 11.2 Sex distribution in the (**a**) control group and (**b**) adrenaline group

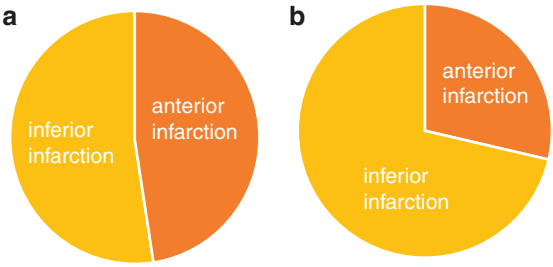

Fig. 11.3 Distribution of myocardial infarction in the two groups: (**a**) control group and (**b**) adrenaline group

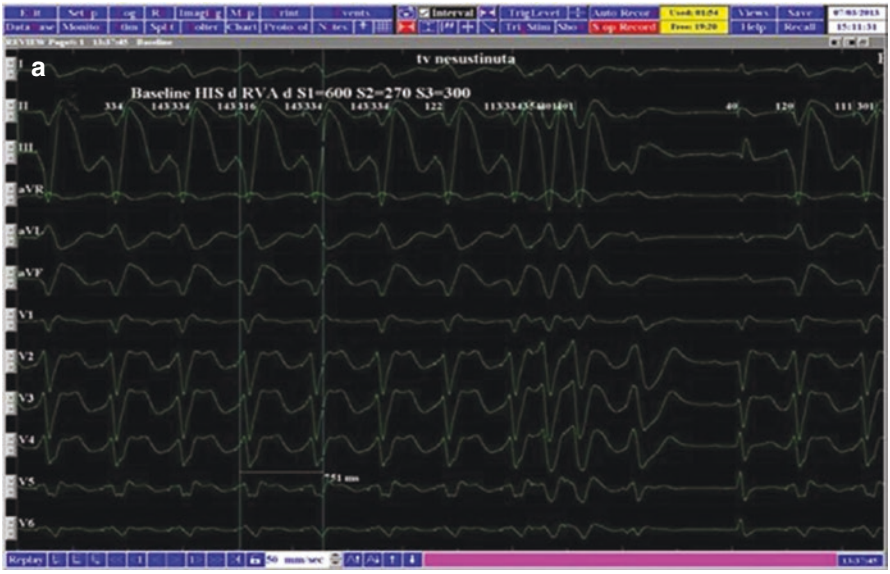

Fig. 11.4 Induction of ventricular tachycardia in a patient treated with amiodarone: (**a**) before adrenaline infusion the patient is protected by amiodarone, and no VT can be induced with programmed ventricular stimulation. (**b**) After adrenaline infusion in dose of 0.1 μg/kg/min, monomorphic VT is induced

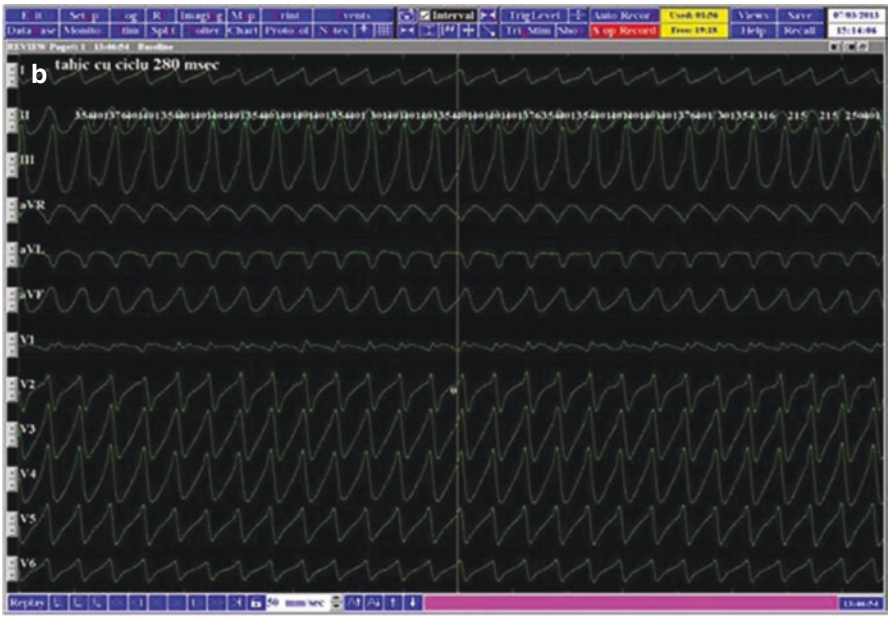

Fig. 11.4 (continued)

Of the five patients with inducible VT, mapping and ablation were performed using the CARTO 3 Biosense Webster system in two patients, the EnSite NAVX system in one patient and the conventional radioscopic system in one patient. For the last patient, as he presented monomorphic VT with hemodynamic instability, substrate ablation was performed with ICD implantation.

Adrenaline was infused in dose of 0.05–0.3 μg/kg/min with tremor as the only side effect during infusion. It was present in three patients but was well tolerated, and the infusion was continued despite this side effect.

No patient presented ST elevation on the 12-lead ECG. In the control group, there were 21 patients with the mean age of 60.7, males 76.2% that were treated with amiodarone and did not receive adrenaline for VT induction. Of the 21 patients, 11 had an old inferior myocardial infarction and 10 an old anterior myocardial infarction. The mean tachycardia cycle length was 275 ms.

Between the two groups, there were no differences in terms of localization of the myocardial infarction: anterior or inferior, ejection fraction, left ventricular dimensions, and tachycardia cycle length. The only difference was the inducibility of VT which was 50% in the adrenaline group and 100% in the amiodarone group (Fig. 11.5). The selection of patients was made to have all the patients inducible in the amiodarone group, without receiving adrenaline infusion.

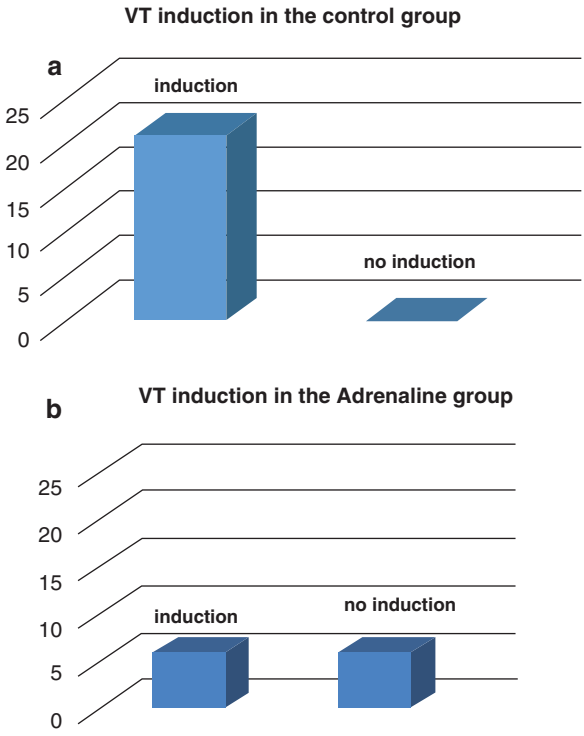

Fig. 11.5 VT induction in the control group and adrenaline group. (**a**) In the control group, VT was inducible in the basal state. (**b**) In the adrenaline group, VT was non-inducible in the basal state, and after adrenaline infusion, only 50% of the patients presented VT

11.2.5 Discussion

11.2.5.1 Main Findings

This study shows that adrenaline can be used in the EP lab for VT induction in patients that are already treated with amiodarone when VT is not inducible in basal conditions. Ischemic VT is the most frequent form of VT in patients with structural heart disease. Most of the time, these patients would be treated with amiodarone as they have a relative contraindication to class I antiarrhythmic drugs. In our patient population, the inducibility rate with adrenaline was 50%.

11.2.5.2 Other Studies with Adrenaline

Morady et al. verified inducibility of ventricular tachycardia in patients treated with adrenaline. They studied 21 patients with ischemic monomorphic ventricular tachycardia treated with quinidine. The infusion rate for adrenaline was 0.025 or 0.05 μg/kg/min. Of the 21 patients treated with quinidine, only 12 were "protected" by quinidine treatment and were uninducible during programed ventricular stimulation. After adrenaline infusion 2 of the 12 patients became inducible. Therefore the inducibility rate under adrenaline was 17%.

Calkins et al. compared the antiarrhythmic effects of quinidine and amiodarone in patients with ventricular tachycardia. The infusion rate for adrenaline was 0.025 μg/kg/min and 0.05 μg/kg/min. Five patients who received amiodarone were

uninducible during programmed ventricular stimulation. After adrenaline infusion none of the five patients became inducible. The inducibility rate under adrenaline in this study was 0% [10].

11.2.5.3 Adrenaline Versus Isoprenaline

We compared studies with adrenaline and isoprenaline in terms of inducibility rate of VT.

Jasayeri et al. reported an induction rate of 59% in patients treated with class I antiarrhythmic drugs that received isoprenaline for VT induction. Patients in this study had coronary artery disease, dilated cardiomyopathy, or no structural heart disease [11].

In accordance, Markel et al. infused isoprenaline 0.03 μg/kg/min in five patients with ventricular tachycardia treated with procainamide, quinidine, propafenone, mexiletine, and lidocaine. Those antiarrhythmic drugs prolonged the cycle length of ventricular tachycardia, and isoprenaline infusion brought the cycle length to the initial value [12].

Compared to isoprenaline, adrenaline had a lower inducibility rate both in the studies of Morady and Calkins. In our study we found an inducibility rate of 50% which is also lower than the percentage found for isoprenaline. Therefore the best option for VT induction remains isoprenaline. Adrenaline should be reserved for cases where isoprenaline is unavailable. Another option like atropine is not a good alternative as the effect on the ventricles is very low with improbable induction of VT.

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