Class I and III antiarrhythmic drugs for prevention of sudden cardiac death and management of postmyocardial infarction arrhythmias. A review

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Background. The aim of the present paper is to review the evolution of concepts regarding the use of Class I and III antiarrhythmic drugs (AADs) in myocardial infarction over the past four decades.

Methods. Results of animal experiments carried out by the authors and papers published between 1970 and 2012 in journals and the PubMed search system were used.

Results. Animal experiments carried out as early as the 1970s showed that Class IB and IC AADs lose their antiarrhythmic effect and electrically destabilize ventricles in the very early phase of myocardial ischemic focus formation. The cause of this is interaction between Class IB and IC AADs as well as Class III AADs with sympathetic neural activation (SNA) of the heart in the early phase of myocardial ischemia. Given the extremely high and uneven distribution of noradrenaline in tissue, SNA results in dispersion of the depolarization and repolarization processes in the ventricles. The clinical sequels of the interaction between the effects of AADs and SNA are as follows: the antiarrhythmic effect of AADs is restored in AMI once SNA has resolved; membrane-destabilization of the ventricles can be restored any time in the presence of randomly occurring SNA not only due to increasing myocardial ischemia but, also, as a result of psychological stress (emotions), and any pre-existing structural heart disease will enhance the pro-fibrillatory effect of a randomly occurring SNA.

Conclusions. Despite the above risks, AADs continue to play an irreplaceable role in suppressing post-myocardial arrhythmias and in preventing sudden cardiac death following ICD placement. The risk of AADs' proarrhythmic effect in SNA can be reduced by combining them with beta-blockers. The last recourse when attempting to suppress malignant ventricular tachyarrhythmias is left sympathetic denervation of the heart.

Key words: antiarrythmics, sympathetic neural activation, sudden cardiac death, postmyocardial arrhythmias

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INTRODUCTION

A review of randomized controlled trials was published in 1993 to summarize the effect of prophylactic therapy with antiarrhythmic drugs (AADs) on mortality in patients with acute myocardial infarction (AMI) (ref.[1]). The analysis revealed that routine use of Class I AADs is associated with increased mortality and beta-blockers have been conclusively shown to reduce mortality. The limited body of available data for amiodarone appear promising while those obtained for calcium-channel blockers disappointing. The same conclusion was reported in 2010 by authors of a paper focused on prevention of sudden cardiac death (SCD) by AADs and implantable cardioverter-defibrillators (ICDs) (ref.[2]). The authors noted that sodium-channel blockers and pure potassium-channel blockers actually increase mortality and, that, "it's only the beta-blockers that had been proven to reduce the incidence of SCD". Another review appearing in 2011 (ref.[3]) observed that Class I AADs can be used in patients with structurally normal heart and are contraindicated in those with structural heart disease. Beta-blockers have

been demonstrated to be beneficial in preventing mortality and malignant tachyarrhythmias in post-AMI patients and patients with ICDs. Amiodarone has a neutral effect on mortality.

In contrast with these disappointing conclusions for membrane-acting AADs, the current relevant literature includes papers referring to their beneficial therapeutic, not preventive use in various forms of ventricular tachyarrhythmias complicating AMI or another structural heart disease[4,5]. The increased interest in AADs is attested to by the testing of the antiarrhythmic efficacy of the known neuroprotective agents ranolazine and riluzole, i.e., agents blocking myocyte membrane-acting sodium channels[6,7]. Prevention and treatment of life-threatening ventricular arrhythmias have recently been improved by ICD placement. Despite this, patients with ICDs may still require adjunctive therapy with AADs - 16-70% of patients who had received ICDs were ultimately treated with AADs (ref.[8]). A literary review suggests that, despite the development of newer therapeutic modalities and serious reservations, AADs cannot be viewed as a "dead" class of drugs[2]; rather, it is critical to demarcate the boundaries

for their *lege artis* use. Therefore, the present paper seeks to provide answers as to when and why the antiarrhythmic effect of Class IB and IC membrane-acting AADs is reversed to a proarrhythmic (membrane-destabilizing) one and to identify the clinical sequels for patients with structural heart diseases treated with these antiarrhythmics. The authors also present a potential solution possibly attenuating the proarrhythmic action of these agents and enhance their safe use.

RESULTS OF EXPERIMENTS CONDUCTED AT THE INSTITUTE FOR CLINICAL AND EXPERIMENTAL MEDICINE (IKEM)

Fejfar et al. tried to define a strategy reducing the risk for SCD by ventricular fibrillation (VF) using first - aid drug administered immediately after onset of AMI to attenuate pain and fear, and to electrically stabilize the heart until professional treatment is provided. The agent should prevent electrical destabilization of cardiac ventricles and development of VF until the physician has arrived[9]. As, in the 1970s, only two agents, lidocaine and beta-blockers, were available for this purpose, the membrane-stabilizing effect of both agents were tested in animal experiments mimicking the patient's heart condition prior to arrival of the physician in the earliest phase of myocardial ischemia.

METHODS

The authors used a canine model of local myocardial ischemia after one-stage ligation of the anterior descending branch of the left coronary artery (LAD.) Acute experiments were performed in anesthesized mongrel dogs and finished by euthanasia (overdosing with pentobarbital). Criteria formulated by the IKEM's Ethic Committee (similar to those developed by the International Animal Care and Use Committee in 1986) were complied with throughout the experiments and in the dogs' living conditions.

Electrical stability/instability of cardiac ventricles were defined using the value of ventricular fibrillation threshold (VFT) in mA. The standard course of changes in VFT after LAD ligation in control experiments without drug administration was as follows: as early as 2 min after LAD ligation, VFT dropped to 20-30% of baseline to remain unchanged for an approx. 1 h, and return to baseline after some 4 h post-ligation. The above validated model was used to test the membrane-stabilizing/destabilizing effect of two Class IB AADs, trimecaine (MESOCAIN, a lidocaine analog, United Pharmaceutical Works, Prague, Czech Republic) and lidocaine (LIDOCAINE, Astra AB, Söderfälje, Sweden) and, also, the Class IC antiarrhythmic moricizine (ETHMOZINE, Cardiology Research Center of the USSR Academy of Medical Sciences, Moscow, USSR). Control drugs included the beta-blocker metipranolol (TRIMEPRANOL, a propranol analog, Research Institute for Pharmacy and Biochemistry, Prague, Czech Republic), propranolol (INDERAL, Imperial Chemical

Industries, Millbank, London, Great Britain), and the benzodiazepines flunitrazepam (ROHYPNOL, United Pharmaceutical Works, Prague, Czech Republic) and midazolam (DORMICUM, Hoffmann-La Roche Ltd, Basel, Switzerland). To compare the effects of the above agent, a group of dogs was used after surgical sympathetic denervation by bilateral removal of the upper thoracic sympathetic ganglia (Th1-Th5). Dogs with sympathetic denervation of the heart had their VFT measured prior to LAD ligation and at pre-defined time intervals thereafter[10].

Statistical analysis

The sum of VFT measurements in each animal before the ligature (A) was compared with the VFT measurements following ligature (B). Student´s t-test was used to compare the results at the level of 5% (A =/= B).

Results - changes in fibrillation threshold

In the early phase of local myocardial ischemia from LAD ligation to the first hour of ischemia, the AADs trimecaine, lidocaine, and moricizine, administered intravenously 2 min before local myocardial ischemia at a dose of 3 mg/kg b.w., failed to prevent the usual decrease in VFT in the early phase of ischemia (P=0.05). The means of VFT differed at the level 5%. The drop in VFT persisted for 30 min after the onset of local myocardial ischemia. Unlike AADs, the non-selective beta-blocker metipranolol, administered at a dose of 0.1 mg/kg prior to LAD ligation, raised VFT under identical experimental conditions as early as minutes 2 to 30 of local myocardial ischemia to 500% of baseline (P=0.05). The decrease in VFT in the early phase of ischemia was also prevented by prior surgical sympathetic denervation of the heart (P=0.05).

Further experiments were designed to monitor the electro-stabilizing effect of trimecaine, lidocaine, metipranol, propranolol, flunitrazepam, and midazolam administered at minute 15 of local myocardial ischemia. There was a significant decrease in VFT at minute 8 post-LAD ligation. The tested agents were administered at minute 15 to monitor VFT changes at minutes 23 and 45 of ischemia. At minutes 23 and 45, trimecaine (3 mg/kg) did not raise VFT value above that measured at minute 8 (NS). By contrast, metipranolol (0.3 mg/kg) and propranolol (1.2 mg/kg) increased VFT at minutes 23 and 45 above the value measured prior to LAD ligation (P<0.01). After a decrease in VFT at minutes 8 following flunitrazepam (0.25 mg/kg) or midazolam administration, VFT returned to baseline prior to local myocardial ischemia at minutes 23 and 45 (P<0.01). A combination of flunitrazepam (0.25 mg/kg) and metipranolol (0.1 mg/kg) raised VFT at minutes 23 and 45 to values virtually identical to those obtained with metipranol at a dose three times as high (0.3 mg/kg). (P<0.01). Flunitrazepam administration resulted in a threefold increase in the electro-stabilizing effect of metipranolol.

Surprisingly, the membrane-stabilizing potential of mesocaine and moricizine was restored in the late phase of ischemia, as documented in the heart not damaged by local myocardial ischemia. Mesocaine administered at 4

and 8 h from the onset of myocardial ischemia increased VFT to 300 - 400% of its baseline value (P=0.05) (ref.[10-13]).

Successful restoration of cardiac rhythm by defibrillation shocks in local myocardial ischemia

We were unable to demonstrate–based on the magnitude of decrease in VFT in the early phase of local myocardial ischemia–whether or not mesocaine, lidocaine, and moricizine decrease the electrical stability of cardiac ventricles to a greater extent than in control groups. To find out, results of experiments with sodium-channel blockers beta-blockers were pooled into a single "canine mortality study" evaluating the success rate of restoring cardiac rhythm by defibrillation shocks. In cases where four transthoracic discharges (200-300 J) failed to terminate ventricular fibrillation, the VF was classified as refractory. In two control series not receiving any AADs (n=43), refractory VF developed in two dogs (4.6%). In the three series (n=32) involving administration of mesocaine, lidocaine, and moricizine prior to LAD ligation, VF occurred in 14 dogs (43.8%). Ventricular fibrillation refractoriness was noted between minutes 2 and 20 following LAD ligation. Ventricular defibrillation was invariably successful after the administration of beta-blockers (metipranolol, propranolol) and, also, in dogs with the upper thoracic sympathetic ganglia removed. Our experiments also showed that refractory VF is not a manifestation of an increased defibrillation threshold but the result of an enormously decreased electrical stability of cardiac ventricles. A shock was always followed by regular cardiac rhythm which, however, quickly returned to VF within several seconds[14].

Our results of VFT measured after LAD ligation using our standard technique and obtained over a period of 15 years were summarized in a publication. Analysis of 143 experiments revealed that the heart rate of dogs after LAD ligation was significantly higher (P<0.001) in 52% of animals experiencing a decrease in baseline VFT by more than 50%. Also, our experiments showed that administration of the beta-blocker metipranolol at minute 15 of ischemia in both groups of dogs resulted not only in a significant increase in VFT but, also, in bradycardia (110 beats/min and below) in 15% of cases. Given the intrinsic heart rate of the dog (135 beats/min), the implication is that sympathetic neurogenic activation of the heart was switched to parasympathetic one by the effect of metipranolol[15].

Summary

The tested Class IB and Class IC sodium-channel blockers (mesocaine, lidocaine, and moricizine) decrease, in the early phase of local myocardial ischemia, the electrical stability of the cardiac ventricles and their ability to stop fibrillation. After the early phase of myocardial ischemia, i.e., at hour 4 and 9 since LAD ligation, mesocaine, lidocaine, and ethmozine raised the electrical stability of cardiac ventricles. The beta-blockers metipranolol and propranolol, and surgical denervation of the heart tested under identical experimental conditions increase statistically significantly, in the early phase of local myocardial ischemia, the electrical stability (VFT) of cardiac ventri-

cles. The benzodiazepines flunitrazepam and midazolam prevent a decrease in the electrical stability of cardiac ventricles in the early phase of local myocardial ischemia. If combined with metipranolol, they increase the latter´s electro-stabilizing effect by a factor of three.

RESULTS OF EXPERIMENTS IN INTERNATIONAL LABORATORIES

Results obtained in the laboratories of the Prague-based Institute for Clinical and Experimental Medicine were confirmed in several international laboratories and complemented with additional data. In one, the effect of lidocaine on the VFT following coronary artery occlusion was studied in a canine model. The drop in VFT following acute LAD ligation was neither eliminated, nor even merely diminished by lidocaine administration. Lidocaine failed to reduce the incidence of spontaneous VF after left circumflex coronary artery occlusion[16]. In another laboratory, ventricular reentry and automaticity were assessed after coronary ligation in cats. It was found that lidocaine (2-4 mg/kg) administered after one-stage LAD ligation may accentuate ventricular reentry[17]. Vulnerability to the fibrillatory process induced by coronary occlusion was assessed in the actually ischemic porcine heart. In addition, experimental results showed that lidocaine tends to increase the risk of ischemic VF, fails to control enhanced excitability, and worsens conduction disorders. Use of lidocaine against rhythm disorders in AMI is probably contraindicated[18]. Facilitation of reentry by lidocaine in canine AMI was demonstrated in a group of 11 dogs in whom the distal branches of the left circumflex artery were ligated 35 days prior to study. In this subacute myocardial infarction group, sustained monomorphic ventricular tachycardia (VT) was inducible by programmed electrical extrastimuli as late as 1-4 days after consecutive LAD ligation before lidocaine administration in one, but in seven dogs after lidocaine. The results show that lidocaine (3 mg/kg) has arrhythmogenic/proarrhythmic action probably due to its depressant effect on moderately sick cardiac tissue[19]. The membrane-stabilizing effect of lidocaine and moricizine in the late phase of myocardial ischemia on the canine model of AMI was confirmed in two international laboratories. Lidocaine infusion started simultaneously with one-stage LAD ligation in a group of dogs did not begin to raise a decreased VFT until 2 h of myocardial ischemia[20]. While moricizine administered at hour 2 after LAD ligation increased VFT in only some dogs, the same drug administered at hour 4 of ischemia increased VFT in all dogs in the group[21]. The finding that Class I AADs increase VFT after an interval of several h since coronary artery ligation is consistent with their well-known antiarrhythmic action. In anesthetized dogs, mesocaine decreased, at hours 24 - 48 since coronary artery ligation, the frequency of polytopic ventricular ectopy by 40% (ref.[22]). They were arrhythmias induced by increased catecholamine levels and not by increased sympathetic activation of the heart, and their frequency is not changed by previous surgical denervation of the heart.

Other laboratories tested the effect of AADs on life-threatening arrhythmias (VT, VF), induced by the interaction between acute myocardial ischemia and sympathetic hyperactivity using a cat model of AMI after one-stage LAD occlusion for 2 minutes only[23]. The left stellate ganglion was stimulated for 30 sec at the beginning of the last minute of occlusion and created a condition of very high electrical instability. Ventricular arrhythmias (VT, VF) appear only when the two stimuli, coronary artery occlusion and left stellate ganglion stimulation, are coupled. The authors compared the ability of Class I, II, III and IV AADs to suppress ventricular arrhythmias induced by simultaneous coronary artery occlusion and stellate ganglion stimulation. The Class I AADs lidocaine, mexiletine, and propafenone completely failed to afford protection, and worsening of arrhythmias was observed in several instances. Propranolol (Class II) significantly reduced the incidence of VF and VT and showed efficacy in approximately 80% of the animals. Amiodarone (Class III) and verapamil (Class IV) completely prevented the onset of VT and VF. Sympathetic hyperactivity due to stellate ganglion stimulation could influence the response to lidocaine by bringing the resting potential of partially depolarized fibers back to more negative values as well as by promoting the genesis of lidocaine-insensitive slow action potentials. In another experimental study, the interaction between flecainide (Class IC) and the autonomic nervous system was assessed in cats using a combination of acute myocardial ischemia and sympathetic stimulation[24]. Flecainide does not prevent, and may actually favor the occurrence of sustained VT during myocardial ischemia and enhanced sympathetic activity. By countering the sympathetic activity, propranolol (Class II) prevented and abolished the proarrhythmic effect of flecainide. The exacerbation, whenever a transient ischemic episode is accompanied by elevated sympathetic activity, of the ischemia-induced conduction delay caused by flecainide may in part explain the mortality data of the Cardiac Arrhythmia Suppression Trial (CAST). This assumption has been confirmed in the clinical setting. Increased mortality rates during flecainide therapy associated with enhanced sympathetic activation of the heart were noted in patients one month after AMI following changes in power spectral measures of heart rate variability[25].

The aim of another study was to test *in vivo* and *in vitro* the effect of adrenergic activation on membrane-action potential (MAP) prolongation by the potassium-channel blocking agent *d*-sotalol (Class III) (ref.[26]). *In vivo* experiments were carried out in dogs with preserved coronary circulation and *in vitro* experiments with isolated guinea pig ventricular myocytes. Under control conditions, sotalol prolonged MAP duration by 19% *in vivo* and by 24% *in vitro*. Adrenergic stimulation by electrical stimulation of the left stellate ganglion *in vivo* or by isoproterenol *in vitro* reduced MAP prolongation produced by sotalol by 40% *in vivo* and by 60% *in vitro*. The authors concluded that sympathetic activation impairs the antifibrillatory effect of sotalol. Therefore, potassium-channel blockers may not offer effective protection from malignant ischemic arrhythmias that occur in the setting of elevated

sympathetic activity. The outcome of the above experiments is invaluable in that it demonstrates the effect of adrenergic stimulation *per se* without tissue ischemia on MAP shortening by suppressing potassium inward current. Sympathetic activation impairs the well-known antifibrillatory effect of sotalol by significantly shortening MAP of cardiomyocytes.

International laboratories also investigated the membrane-stabilizing effect of diazepam. Diazepam administered to dogs with preserved coronary circulation increased the VFT measured using Lown's method[27]. In other experiments, the membrane-stabilizing effect of diazepam was assessed in dogs prior to coronary artery ligation. Diazepam enhanced the latency of onset of coronary fibrillation[28].

Summary of experimental results in international laboratories

In the early phase of myocardial ischemia induced by one-step coronary artery ligation, the sodium-channel blocker lidocaine does not increase VFT, yet it tends to increase the risk of VF. Facilitation of reentry was observed as late as 1-4 days after consecutive two-step coronary artery ligation.

A combination of short coronary artery occlusion and left stellate ganglion stimulation was associated with the development of life-threatening arrhythmias (VT, VF). Administration of Class IB and IC AADs (lidocaine, mexiletine, propafenone, and flecainide) failed to afford protection and worsening of arrhythmias was observed. Propranolol, amiodarone, and verapamil completely prevented the onset of VT and VF. Electrical stimulation of the left stellate ganglion, even without coronary artery occlusion, reduced the MAP prolongation produced by *d*-sotalol administration. Thus, potassium-channel blockers may not offer effective protection from malignant arrhythmias that occurred in the setting of elevated sympathetic activity.

MEMBRANE-ACTING ANTIARRHYTHMIC DRUGS IN CLINICAL TRIALS

Lidocaine

Dysrrhythmias developing within one hour of the onset of symptoms of AMI have been documented in 284 patients. "Ventricular dysrrhythmias were frequent and showed a disappointing response to lignocaine therapy". This was how the effect of lidocaine in the acute out-of-hospital phase of AMI was described in 1971 (ref.[29]). This contrasts with the beneficial results of lidocaine administered to 212 patients in a later phase of AMI, as reported in 1974 (ref.[30]). Lidocaine was administered intravenously as a bolus of 100 mg followed by infusion at 3 mg/min upon admission to the coronary care unit. The results indicate that lidocaine was highly effective in preventing primary VF. The authors themselves point out the favorable results obtained in the coronary care unit may not be consistent with those of patients seen during the earliest pre-hospital phase of AMI.

Intramuscular lidocaine for prevention of lethal arrhythmias in the pre-hospital phase of AMI was recommended and tested in two clinical trials published 1974 and 1985 (ref.[31,32]). Results of both trials documented a beneficial prophylactic antifibrillatory effect of lidocaine in the pre-hospital phase of suspected AMI. Authors of the 1985 trial do concede that the outcome may have been due to the "typical patient and doctor delay". Thus, the very early phase of myocardial ischemia is seldom witnessed and therapy is almost always initiated with a considerably delay. Because of this, the ultimate outcome of a trial is largely dependent on the phase of AMI where lidocaine was actually administered.

In 1976, the "lidocaine wave" reached what was Czechoslovakia then[33]. The first-line physician was supposed to immediately (still before transfer of the patient to hospital) administer the patient experiencing a suspected AMI i.m. MESOCAIN SPOFA at a dose of 200-300 mg. However, the antifibrillatory effect of trimecaine or its potential to decrease the incidence of out-of-hospital SCD have never been assessed. The contradictory results of clinical trials with prophylactic lidocaine administration were critically reviewed by Yadov and Zipes in 2004 (ref.[34]). In their review article, the authors concluded that, based on the information available at that time, lidocaine could not be used prophylactically to treat patients with documented or suspected AMI.

Research into lidocaine use in AMI continued in 2011 focusing on its potential therapeutic use. Results of a large retrospective analysis support the therapeutic use of lidocaine in a bid to suppress life-threatening arrhythmias during in-hospital care[5]. A combined database of the GUSTO IIB and GUSTO III trials was used to identify AMI survivors developing VT (36.8%), VF (48.4%), or both fatal arrhythmias at a time (14.8%). Authors of the analysis hypothesized that therapeutic use of lidocaine and amiodarone in response to post-myocardial ventricular arrhythmia is different from prophylactic administration of lidocaine. The authors were convinced that acute antiarrhythmic therapy has a very different therapeutic goal – to suppress current ventricular arrhythmia during the highest risk period. In lidocaine-treated patients, the 3-h survival rate after the onset of VT/VF was 85% compared with 74.1% among those not receiving lidocaine (HR 0.72; $P<0.001$). A lower risk of death was associated with amiodarone administration (HR 0.39 vs HR 0.72). While, at 30 days, there was no evidence of a higher or lower risk of death in lidocaine-treated patients (HR 1.07), there was evidence of a higher risk of death in those treated with amiodarone (HR 2.71). Patients receiving concomitant amiodarone and beta-blocker therapy were at lower risk of death (HR 1.27). The authors concluded that patients suffering an AMI who develop recurrent sustained VT/VF despite treatment directed toward the underlying ischemia (beta-blockers or revascularization) often require membrane-acting antiarrhythmic drug therapy.

Flecainide, encainide, and moricizine

The Cardiac Arrhythmia Suppression Trial (CAST) included AMI survivors experiencing ventricular arrhythmias[35]. Encainide and flecainide accounted for the excess of deaths from arrhythmia by 4.5% vs 1.2% in the placebo group (RR 3.6) and higher total mortality 7.7 vs 3.0%, respectively (RR 2.5). Its authors concluded that neither encainide nor flecainide should be used in the treatment of patients with VT after AMI, even through these drugs may be immediately effective in suppressing VT (ref.[30]). CAST II included patients 4 to 90 days post-AMI experiencing premature ventricular contractions. Compared with placebo, two-week treatment with moricizine resulted in a fivefold increase in cardiac mortality (RR 5.6, $P=0.001$). The number of moricizine-treated patients dying of arrhythmias was also higher. The authors concluded that moricizine-based therapy of AMI survivors is not only ineffective but even dangerous[36]. These findings provided an impetus for a search for explanations for the mortality data obtained in the CAST and CAST II trials. A retrospective analysis of mortality of patients not receiving beta-blockers revealed that the onset of arrhythmic death displayed a bimodal variation with segmental peaks in the morning and late afternoon due to the circadian pattern of sympathovagal neural activity. The results suggest the possibility of a complex interaction among AADs, sympathetic nervous system activation, and AMI (ref.[37]).

Amiodarone

Amiodarone is a generally recognized Class III antiarrhythmic indicated to suppress sustained VTs lasting 30 sec and more within the first 48 h during the acute phase of AMI (ref.[38]). The major effect of amiodarone therapy is inhibition of outward potassium current resulting in a prolongation of action potential duration as well as prolongation of effective refractory period caused by inhibition of outward potassium current. Amiodarone has been shown to be effective for both the termination of ongoing ventricular arrhythmias as well as for the prevention of recurrence VT/VF during electrical storm. Amiodarone has been reported to cause a variety of cardiac and extracardiac side effects. Amiodarone is structurally similar to thyroxine and some adverse events are due to the high content of iodine (37% of weight). Extracardiac adverse effects in per cent of cases are: hypo/hyperthyreoidism 10, pulmonary fibrosis 2-17, corneal microdeposits for longer than 6 months therapy 90, photosensibility 4-9, and abnormal liver function. Cardiac adverse events are: sinus bradycardia, high degree A-V block and torsade de pointes. "Despite the well-understood toxicity, amiodarone remains the most effective and safe in the short time antiarrhythmic drug for ventricular arrhythmias" (ref.[39]). The use of amiodarone in secondary prevention in patients´ recovering from AMI was evaluated in two randomized clinical trials, EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Myocardial Infarct Amiodarone Trial). In both trials, amiodarone therapy was associated with a significant reduction in the risk of arrhythmic cardiac death or resuscitated death. The ECMA project compared, based on an analysis of results of the two above trials, the antiarrhythmic effect of amiodarone monotherapy with that of an amiodarone/beta-blocker combination[40]. The amiodarone-

only group included 657 patients while that treated with an amiodarone and beta-blocker combination was made up by 691 patients. The analysis showed that the relative risk of arrhythmic cardiac death or resuscitated cardiac arrest in the amiodarone-only group was higher (RR 0.85) compared with the group receiving a combination of amiodarone and a beta-blocker (RR 0.39; *P*=0.05 and 0.03). The risk of cardiac arrhythmic death in patients with a higher resting heart rate (80 beats/min and over) treated with the amiodarone/beta-blocker combination was lower (RR 0.23) compared with amiodarone-only-treated patients (RR 0.88).

Results of the analysis suggest that the risk of arrhythmic cardiac death is increased by amiodarone in the presence of higher sympathetic neural activation of the heart while being decreased with the amiodarone/beta-blocker combination. As a result, the authors of the ECMA project suggest patients receiving amiodarone should not discontinue their background beta-blocker therapy. The Czech Society of Cardiology guidelines recommend each patient after an AMI should receive chronic beta-blocker therapy[38]. Management of sustained VTs after an AMI with amiodarone is most often based on recommendations put forth by the authors of the ECMA project[41].

Beta-blockers, benzodiazepines, and sympathetic denervation of the heart

The cornerstone of prophylaxis of arrhythmic SCD in AMI are currently the Class II AADs beta-blockers. This has been documented both by what are now classic studies conducted in the 20th century[42] and recent trials including post-AMI patients without and with chronic heart failure[43,44]. Benzodiazepines suppress sympathetic neural activation of the heart as well as activation of the pituitary-hypothalamo-adrenal axis. In indicated cases, benzodiazepines may serve as agents suppressing sympathetic neural activation of the heart in patients experiencing initial symptoms of AMI in the out-of-hospital setting[45]. Alprazolam blunting sympathetic activation may be beneficial in cardiac disorders where increased sympathetic tone is potentially deleterious[46]. Short-term alprazolam treatment in patients with recent AMI suppresses salivary cortisol secretion and modifies their behavioral and psycho-physiological status[47]. Diazepam lowers stress reaction, mean noradrenaline and adrenaline secretion rates, and malignant arrhythmias within the first 12 h after hospital admission[48]. As agents reducing psychological stress, benzodiazepines should be used to prevent SCD in patients in the earliest pre-hospital phase of AMI (ref.[49]).

Surgical sympathetic denervation of the heart is a novel therapeutic option in clinical practice as a treatment of choice in the management of sustained VTs in patients who have failed to respond to pharmacotherapy. Its availability has improved with the advent of video-assisted thoracoscopic surgery[50]. Sympathetic denervation of the heart has been recently recommended also in patients receiving an ICD in an effort to minimize the number of shocks and to prevent electrical storms induced by defibrillation shocks[51].

Role of antiarrhythmic drugs in patients with ICDs

The implantable cardioverter-defibrillator is currently the most effective tool for preventing SCD in at-risk patients. However, AADs need to be initiated in up to 70% of patients in order to decrease the frequency of defibrillation shocks or terminate ventricular arrhythmias along with antitachyarrhythmic pacing[52].

An effort to decrease the frequency of defibrillation shocks is necessary because ICD shocks are emotionally and physically debilitating, even for patients with chronic heart failure or ischemic cardiomyopathy[53]. To reduce the "shock burden", the following adjuvant drugs have been clinically tested. First, they are beta-blockers, which have proved effective as "basic therapy" - both in classic and more recent studies addressing SCD prevention[39]. The OPTIC trial demonstrated the efficacy of a combination of a beta-blocker and amiodarone[54]. During one-year follow-up, shocks occurred in 38.5% patients assigned to a beta-blocker alone but in 10.3% assigned to amiodarone plus a beta-blocker. This combination significantly reduced the risk of any shock compared with a beta-blocker alone (HR 0.27). Another clinical trial documented a decrease in the frequency of defibrillation shocks in patients with an ICD and recurrent VT and VF receiving adjuvant therapy with dofetilide. Dofetilide decreases the frequency of VT/VF and ICD shocks even when other AADs including amiodarone have failed[55]. There is yet another good reason for the effort to minimize the frequency of ventricular ectopy at the time of ICD placement. A high frequency of ventricular ectopy induces, via a reflex mechanism, SNA of the heart which in turn further raises the frequency of ectopy and eventually the number of defibrillation shocks.

ICDs may be arrhythmogenic due to shock-associated sympathetic stimulation, resulting in initiation of more shocks and electrical storms. Hence the recommendation to treat all ICD recipients with structural heart disease with beta-blockers at the time of ICD implant. Should the patient experience recurrent VT or VF with symptoms or shocks, addition of amiodarone to beta-blockers should be considered[39].

Antiarrhythmic drugs and defibrillation capacity

Adjuvant administration of AADs to patients who have received ICDs has an effect on defibrillation threshold (DFT). Evidence from clinical studies indicates that amiodarone, lidocaine, moricizine, mexiletine, verapamil, and venlafaxine may increase DFT. In contrast, sotalol, dofetilide, and beta-blockers may reduce DFT (ref.[56]). Adrenaline and noradrenaline not only facilitate the induction of sustained ventricular arrhythmias, they rather elevate DFT. After adrenaline infusion, 25% of patients failed to convert after the first shock and required two or more shocks at 30 J to convert[57]. The impact of carvedilol on DFT was studied in patients during 7-min infusions of noradrenaline, adrenaline, and placebo. No differences in intra-group DFT were observed among the carvedilol-treated patients indicating that carvedilol prevents the DFT alteration produced by stress levels of catecholamines[58].

Arrhythmic (electrical) storms

Quite typically, AADs (including beta-blockers!) failed in the treatment of malignant tachyarrhythmias (electrical storms). In one study, sympathetic (left stellate ganglion) blockade with esmolol, propranolol, compared with lidocaine and propafenone, in patients with recent AMI and recurrent multiple VF episodes, reduced one-week mortality from 82% to 22%, and annual mortality from 67% to 5% (ref.[59]). The outcome of this study was confirmed by yet another one. In patients with structural heart disease and recurrent VTs who had failed to respond to "maximal medical therapy" (AADs and beta-blockers), the frequency of electrical storms was only reduced by surgical left-side sympathetic denervation of the heart using removal of the upper thoracic sympathetic ganglia or their blockade by thoracic epidural anesthesia[60]. The efficacy of surgical sympathetic denervation of the heart documents that the membrane-stabilizing effect of all previously used AADs had been suppressed by the enormously high levels of catecholamines in the heart. Of note, successful management of paroxysmal tachycardia by bilateral anesthesia of the stellate ganglion was performed as early as 1949 by Dr. Vilo Jurkovič (lecture presented at the scientific meeting of the Department of Medicine I – then headed by Prof. Weber – at Na Bulovce Hospital in Prague, on 11 November 1949). Deep sedation is another way how to suppress high level of catecholamines in the heart during the arrhythmic storm. The combination of sufentanil or midazolam with propofol reduces sympathetic hormonal activation and lowers adrenaline, noradrenaline and renin-angiotensin concentrations in the blood. Metabolic and endocrine response stop in some cases the arrhythmic storm. Deep sedation should be further tested in clinical studies.

Summary

Lidocaine administered within one hour of the onset of symptoms of AMI is not suitable for prophylaxis of life-threatening arrhythmias. By contrast, lidocaine administered at an interval of several h of the onset of symptoms of AMI did reduce the frequency of sudden arrhythmic death. The antifibrillatory effect of lidocaine is no doubt related to the time elapsed between its administration and initial symptoms of AMI. This makes evaluation of results of clinical trials not reporting the interval between initial symptoms of AMI and institution of therapy most difficult. Lidocaine therapy in suddenly occurring life-threatening arrhythmias (VT/VF) in the late phase of ischemia was successful.

Class IC antiarrhythmics (flecainide, encainide, and moricizine) raise the arrhythmic and overall mortality rates both in the early and late phases of AMI and are thus *de facto* contraindicated in the treatment of AMI. The frequency of SCD was higher in circadian sympathetic activation of the heart.

The Class III antiarrhythmic amiodarone is indicated for the management of life-threatening arrhythmias (VT/VF) and ectopies at an interval of approx. 48 h since the onset of AMI. Its prophylactic use in AMI is virtually out of question in the era of ICDs. When combined with beta-blockers, amiodarone reduces the incidence of arrhythmic cardiac deaths and the number of defibrillation shocks following ICD placement.

PATHOGENESIS OF ELECTRICAL DESTABILIZATION OF CARDIAC VENTRICLES ON INTERACTION OF AADS WITH SYMPATHETIC NEURAL ACTIVATION OF THE HEART

Results of experiments and clinical trials have shown that sympathetic neural activation (SNA) is a major pathogenic mechanism underlying the development of ventricular arrhythmias and tachyarrhythmias. Sympathetic neural activation occurs in the presence of local myocardial ischemia via Malliani's sympathetic cardio-cardiac reflex[61]. Stimuli from ischemic tissue conducted by afferent pathways to the spinal cord and brain return by efferent pathways via the thoracic sympathetic ganglia to the heart. Sympathetic neural activation also occurs in psychological stress. The stimulus develops directly in the cerebral cortex to be conducted by efferent pathways right to the heart[62]. An increase in SNA can be also observed in high-frequency ventricular ectopy[63] and a circadian pattern of sympathetic predominance[64], virtually whenever there is dysbalance of the neurovegetative system in favor of the sympathetic system. It follows from the above that SNA can be encountered in a variety of clinical settings and its effect on AAD-based pharmacotherapy should therefore be considered.

Sympathetic neural activation is associated with the release of large amounts of noradrenaline from the sympathetic neural endings to the myocardium. Extracellular noradrenaline levels in the myocardium are hundred to thousand times higher than plasma noradrenaline levels during hormonal sympathetic activation mediated by noradrenaline release from the adrenals[65]. In addition, in SNA, foci of high noradrenaline levels in cardiac tissue are distributed unevenly in the vicinity of sympathetic neural endings. Together with its uneven distribution in tissue, the high noradrenaline levels manifest themselves by "dispersion" of the course of depolarization and repolarization of cardiac cell membranes. In this process, microreentry circuits begin to close to eventually be in contact with each other resulting in VF (ref.[66]). Sympathetic neural activation is also associated with expression of adrenergic alpha and beta receptors, manifesting itself by enhanced cardiac tissue sensitivity to catecholamines[65]. A fatal combination of unevenly increased noradrenaline levels in cardiac ventricles and myocyte "supersensitivity" to catecholamines triggers malignant tachyarrhythmias and is the cause of decreased electrical stability of cardiac ventricles. Beta-blockers mitigate the effect of catecholamines on myocytes while also blunting the central sympathetic system activity. As a result, they are the cornerstone of

prevention of high-frequency ventricular ectopy (VT/VF) and SCD.

Because of the presentations of SNA in the myocardium, Class IB and IC AADs lose their membrane-stabilizing effect to paradoxically assume a profibrillatory activity. The high noradrenaline levels in cardiac tissue "modulates" the effect of AADs turning them into drugs with an arrhythmogenic effect[67]. Modulation of the Class IB and IC AADs due to the high noradrenaline levels in cardiac tissue manifested itself in animal experiments by a high degree of electrical destabilization of cardiac ventricles demonstrable by a decrease in VFT (ref.[10]), altered course of membrane-action potentials, and an increased tendency toward reentry circuit closure[19].

Sympathetic neural activation can be induced not only by Malliani's reflex but, also, by psychological (emotional) stress, which is why the SNA-mediated "modulation" of the effect of AADs should also be taken into account in psychological stress, as documented in animal experiments. In rhesus monkeys (macaca mulatta) subjected previously to coronary occlusion, the classic aversive and appetitive Pavlovian conditioning evoked tachycardia, hypertension, and cardiac arrhythmias. Administration of propranolol (0.5 mg/kg) eliminated the conditional increase in VTs that otherwise occurred[68]. Animal experiments suggest that negative emotional stress (fear) as well as positive emotional stress (happiness) induce sympathetic activation of blood circulation including ventricular dysrhythmias. However, the latter occurs only in experimental animals with a previously created focus of local myocardial ischemia or if cardiac ventricles contain foci of hibernating (vulnerable) myocardium. This is tissue chronically adapted to ischemia and vulnerable to VF during SNA (ref.[69]). Results of animal experiments are consistent with clinical observations. There have been reports of strong emotional stress resulting in sudden death during earthquakes[70]. Viewing a stressful soccer match more than doubled the risk of acute cardiovascular event, particularly in men with known coronary heart disease[71]. Anger, physical activity, and psychological trauma associated with burial can trigger ventricular tachyarrhythmias in patients with ICDs (ref.[34,72,73]). Epidemiological studies have demonstrated that the incidence of SCD increases in the morning h, i.e., at a period of time when sympathetic tone of the heart prevails over vagal tone. As a result, the risk of a fatal event in patients treated with Class IB and IC AADs exposed to psychological stress will no doubt be significantly higher.

In emergency care, SNA induced by psychological stress could be theoretically prevented by benzodiazepines alone or in combination with beta-blockers[49,74]. As documented in experiments and clinical trials, benzodiazepines decrease SNA right in the brain centers and provide for electrical stabilization of the heart, although their effect is much weaker compared with that of beta-blockers. The fact that benzodiazepines augment the electro-stabilizing effect of beta-blockers suggests a similar mechanism suppressing the effect of SNA on the myocardium[15,74].

CONCLUSIONS

The following clinical and pathophysiological consequences ensue form presented facts:

Prevention of arrhythmogenic SCD in patients in the earliest phase of AMI with Class IB and IC antiarrhythmics and sodium-channel blockers is definitely not recommended. Class IB antiarrhythmics do not prevent the decrease in electrical stability of ischemic tissue on interaction with SNA. On interaction with SNA, Class IC AADs induce malignant ventricular tachyarrhythmias making these drugs contraindicated in AMI, not only in the early but, also, late phase of its development. Sympathetic neural activity also exerts an unfavorable effect of the membrane-stabilizing action of Class III AADs. Sympathetic neural activity (even without local myocardial ischemia) counteracts the effects of potassium-channel blockers on the duration of repolarization and may impair its antifibrillatory mechanism. Potassium-channel blockers may not offer fully effective protection from malignant ischemic arrhythmias. This is attested to by the fact that their antifibrillatory effect is enhanced when combined with beta-blockers.

Patients after a previous AMI are on long term beta-blocker therapy to prevent SCD. In those developing ventricular ectopy or sustained VT, beta-blocker therapy is complemented with amiodarone. At present, the only evidence-based option in primary prevention of SCD is beta-blocker therapy, even in patients with chronic heart failure. Beta-blockers increase electrical stability of the heart, decrease irritability of ischemic cardiac tissue, and provide pathogenetically-oriented protection against SNA. Similar to membrane-acting antiarrhythmics, the effect of neurovegetative dysbalance should be considered when prescribing beta-blockers in the early phase of AMI. Interaction between beta-blockers with and neurogenic parasympathetic activation is associated with the risk of cardiogenic shock[15,75,76].

In the pre-hospital phase of AMI, SNA can be blunted by timely administration of benzodiazepines. Another option in effective SCD prevention, in addition to pharmacotherapy with beta-blockers, is sympathetic denervation of the heart, which has proved effective in prevention and management of electrical storms in clinical practice. Presented pathophysiological aspects on prevention of arrhythmias in patients in the earliest and sub acute phase of AMI as well as patients after a previous AMI agree with guidelines of Czech Society of Cardiology[38] or guidelines of European Society of Cardiology[77]. Two AADs, beta-blockers (level of evidence IIa B) and amiodarone (level IC) are recommended only. In the next future some new antiarrhythmic drugs may be recommended[78].

Treatment of ventricular ectopies as well as life-threatening arrhythmias occurring in the late phase of AMI with Class IB and III AADs is clinically necessary. Not only does it reduce the frequency of ventricular ectopies but, also, that of sustained ventricular tachyarrhythmias. It becomes even more important in frequent use of coronary recanalization by PCI associated with post-reperfusion ventricular rhythm disturbances. The fact cannot be

ignored that SNA may occur suddenly even in the late phase of AMI due to occlusion of another coronary artery or due to psychological (emotional) stress modulating the effect of an antiarrythmic agent. So, combination of antiarrhythmic drugs with beta-blockers may blunt the unexpected deleterious effect of SNA in the late phase of AMI.

Adjuvant therapy with AADs is necessary in a large proportion of patients with prophylactic ICD placement. This strategy reduces the number of defibrillation shocks while protecting the myocardium against damage caused by defibrillation shocks which may - under certain circumstances - paradoxically increase the frequency of ventricular ectopies and trigger electrical storms. Besides, decreasing the frequency of shocks has been shown to improve the quality of life of patients. The basic time-proven adjuvant therapy following ICD implantation is administration of beta-blockers alone or in combination with amiodarone[39]. Despite the good results with the combination beta-blockers/amiodarone new drugs for compelling beta-blocker medication after the ICD implantation are in search. Dronedarone, dofetilide and azimilide may better protect myocardium than amiodarone. Ranolazine - a cardioprotective and antiarrhythmic drug class III - is a new promising late sodium current blocker. In combination with beta-blockers (metoprolol, carvedilol) and antiarrhythmic drugs class III (amiodarone, sotalol) proved effective in reducing VT burden and ICD shocks in patients with AADs refractory VT (ref.[79]). Beta-blockers, sotalol, and dofetilide decrease the DFT of cardiac ventricles and raise the chances of an effective defibrillation shock.

What are the lessons learned from experimental and clinical data for the development of new antiarrhythmics? Novel antiarrhythmics are being tested in various animal models as well as in vitro. Regrettably, the effect of SNA on modulating their effects is often disregarded in these tests. Therefore, we think it is appropriate for each novel antiarrhythmic drug to undergo pre-clinical experimental testing to determine whether and how its efficacy is altered in SNA induced by myocardial ischemia, electrical stimulation of sympathetic thoracic ganglia, or psychological (emotional) stress. It is only this experimental screening that can define the area of indications of novel AADs in further trials and use in practice. The "malignant" modulation of the effect of membrane-acting antiarrhythmics by SNA was demonstrated in experiment 15 years before the failed CAST trial. Therefore, it would be reasonable to consider experimental results still before designing clinical trials.

ABBREVIATIONS

AADs, Antiarrhythmic drugs; AMI, Acute myocardial infarction; DFT, Defibrillation threshold; H, Hours; HR, Hazard ratio; ICDs, Implantable cardioverter-defibrillators; IKEM, The Institute for Clinical and Experimental Medicine; LAD, Left anterior descending coronary artery; MAP, Membrane-action potential; PCI, Percutaneous coronary intervention; RR, Relative risk; SCD, Sudden cardiac death; SNA, Sympathetic neural activation; VF, Ventricular fibrillation; VFT, Ventricular fibrillation threshold; VT, Ventricular tachycardia.

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CONFLICT OF INTEREST STATEMENT

Conflict of Interest Statement: *None declared.*

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APENDIX

Drugs mentioned in this review available on the Czech market:

Antiarrhythmics - lidocaine inj, mesocaine inj, propafenon cps, bisoprolol tbl, metoprolol tbl, carvedilol tbl, alprenolol tbl, amiodarone tbl, inj, sotalol tbl, inj, dronedarone tbl, ranolazine tbl.

Benzodiazepines and analgesics - alprazolam tbl, midazolam inj, tbl, diazepam inj, tbl, sufentanil inj, propofol inj.

Two liposoluble non-selective beta-blockers propranolol (INDERAL), metipranolol (TRIMEPRANOL) and mexiletine (MEXITIL) are not available on the Czech market. All these drugs has had high electrostabilizing effect in the earliest phase of AMI.