REVIEW

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Sudden Cardiac Death Thirty Years Ago and At Present

The role of autonomic disturbances in acute myocardial infarction revisited

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Short title:

Sudden Cardiac Death

Summary

The most common cause of sudden cardiac death is ventricular fibrillation (VF). In addition to the status, size and location of the ventricular focus, a major pathogenic mechanism triggering VF is autonomic dysbalance (disturbance). This term refers to a wide range of reflex changes in the ratio of sympathetic to vagal ventricular activation over time, occurring immediately after coronary artery occlusion at the onset of acute myocardial infarction (AMI). Another trigger of VF is autonomic disturbance due to emotional stress.

Experimental and clinical research into autonomic disturbances associated with coronary artery occlusion and emotional stress was given considerable attention as early as some 30 years ago when researchers were already searching for ways of inhibiting autonomic disturbances using predominant sympathetic and vagal activation by beta-blockers (BB) and atropine, respectively. The aim of our paper is to compare results obtained 30 years ago with current status of experimental and clinical research into SCD prevention. Another aim is to identify questions that have remained unanswered to date; answers to these outstanding questions could help further reduce the risk of SCD.

Key words

Sudden death, myocardial ischemia, ventricular fibrillation, autonomic disturbances, prevention

Text:
INTRODUCTION

The most common cause of sudden cardiac death (SCD) is ventricular fibrillation (VF). Its sudden onset is due to three pathogenic factors and their interaction. The first factor is an arrhythmogenic myocardium with ischemic cardiomyopathy, left ventricular hypertrophy or post-infarction scar. Another factor is dysbalance of autonomic activation of the heart. The dysbalance "modulates" the vulnerable myocardium and raises the risk for VF in the event of sympathetic activation predominating over vagal activation thus increasing the risk for cardiogenic shock should vagal activation predominate. A dangerous scenario is co-activation of both autonomic systems or chronic prevalence of sympathetic activation of the heart in heart failure. In AMI, the trigger originates directly in the focus of local myocardial ischemia immediately after coronary artery occlusion. Other triggers for VF or cardiogenic shock include intense emotional stress, anxiety or pain. Ventricular electrical stability is determined by myocardial vulnerability together with the current autonomic activation of the heart. In addition, ventricular electrical instability lowers the myocardial resistance to sustained ectopic tachyarrhythmia due to enhanced automaticity (triggered activity). Ventricular electrical stability is defined as an ability to maintain normal conduction of electrical impulses even in the presence of interfering external or internal stimuli. There has been a major decrease in SCD rates over the past 30 years thanks to timely cardiopulmonary resuscitation, percutaneous coronary intervention (PCI), and cardioverter/defibrillator (ICD) implantation. Still, the main factor reducing the incidence of sudden arrhythmic death remains to be modulation of neuroautonomic dysbalance (disorder) with beta-blockers, both with AMI in the presence of an intact heart, and in myocardial infarction survivors suffering from coronary heart disease. A major adjuvant role in decreasing the incidence of SCD is played by

statins, antihypertensive agents, and antiplatelet agents/anticoagulants. A promising approach in the earliest phase of AMI is a combination of opiates with benzodiazepines (analgosedation). The aim of the present paper is to summarize results obtained since the 1960s in research projects into the pathogenesis and prevention of SCD.

AUTONOMIC DISTURBANCES AT THE ONSET OF ACUTE LOCAL MYOCARDIAL ISCHEMIA – EXPERIMENTAL RESULTS

First, it should be remembered that the outcomes of experimental interventions conducted in experimental animals are affected by the type of general anesthesia employed. While pentobarbital-based anesthesia will inhibit vagal activity (Korner *et al.* 1968), the activity will be increased by anesthesia using morphine and sulphate complemented with chloralose (Yoon *et al.* 1977). Current autonomic sinus node activation is determined as the difference between current heart rate (HR) and intrinsic (IHR) (José and Collison 1970). Higher and lower levels of current HR suggest sympathetic and vagal activation, respectively. Current ventricular activation after an experimental intervention reflects the difference between ventricular fibrillation thresholds (VFTs) after and before the intervention. A decrease in VFT suggests an increase in sympathetic activation and vice versa. The first to introduce the technique of VFT measurement to experiment were Wiggers and Wégria as early as 1940 (Wiggers *et al.* 1940). The technique of VFT measurement was subsequently used in experiment by a number of authors. A major advantage of VFT measurement is evidence of a decrease in ventricular electrical stability occurring as early as the first 10 minutes since coronary artery ligation. Another finding is that the risk for life-threatening arrhythmias is highest within the first hour of the onset of local myocardial ischemia in the presence of persistently decreasing ventricular electrical stability.

Sympathetic denervation of the heart, metipranolol and flunitrazepam

The authors studied the degree of both sympathetic sinus node and ventricular activation in the early phase of ischemic focus formation in the left ventricle of dogs under pentobarbital anesthesia (Vrána *et al.* 1978, Fejfar and Vrána 1993). In their pre-experimental series, these authors noted that IHR (José et Collison 1970) unaffected by sympathetic and vagal activation in dogs under pentobarbital anesthesia was 126±14 beats/min (N = 14). When assessing neuroautonomic ventricular activation in the dogs under pentobarbital anesthesia, the authors used the mean VFT measured prior to coronary ligation (2.0±0.2 mA; N = 75). Both mean values, those of IHR and VFT, were then used as standards to evaluate results of their experiments. The first group comprised dogs with preserved sympathetic innervation of the heart (Group S). The other group was made up by dogs with bilateral extirpation of the upper thoracic sympathetic ganglia 2 months before the actual experiment (Group D). Preparation of both groups for the experiment was identical. The dogs were anesthetized with pentobarbital at a dose of 30 mg/kg. Thoracotomy was performed as the first step to fix the stimulation electrode into the apex of the right ventricle and to place a loose ligature around the left anterior descending coronary artery (LAD) 2 cm apart from this origin. The thorax was closed

thereafter and actual measurements of ventricular electrical stability (VFT) did not begin until the dogs had achieved respiratory and circulatory steady state. Results are shown in Tab 1.

The predominant type of sinus node activation in animals assigned to Group S in the early phase of ischemia was neurogenic sympathetic activation (HR > IHR 125 beats/min). The same applies to sympathetic ventricular activation (VFT < 2.0 mV). Four of the eight dogs in the group developed spontaneous VF. Surgical sympathetic denervation of the heart in dogs assigned to Group D abolished both neurogenic sinus node and ventricular activation. One dog developed spontaneous VF while another one, heart failure (two dogs out of 22). In Group D, the rate of ventricular extrasystoles (VESs)/min was lower compared with Group S. Neurogenic vagal activation was not observed in the early phase of ischemia in Group S or Group D inhibited as it was by the effect of pentobarbital anesthesia.

Results similar to those obtained after sympathetic denervation were observed after the administration of the non-selective beta-blocker (BB) metipranolol and the benzodiazepine flunitrazepam (Tab 2). Both agents inhibited neurogenic sympathetic sinus node and ventricular activation in the early phase of ischemia. Compared with the benzodiazepine, the BB increased VFT several times. Timely administration of both agents prevented life-threatening arrhythmias from occurring during the experiments.

Summary and clinical implications: Sinus node and ventricular neurogenic sympathetic activation in the early phase of ischemia in dogs under pentobarbital anesthesia raises HR above standard IHR levels while decreasing ventricular electrical stability below the standard. The predominant type of activation of the heart in the early phase of local myocardial ischemia is sympathetic neurogenic activation, reducing ventricular electrical stability and increasing the risk for VF. Preventive sympathetic denervation of the heart or timely administration of a BB/benzodiazepine will reduce the risk for VF even in the presence of vagal activation inhibited by an anesthetic.

Effect of vagal stimulation, atropine and propranolol

The effect of vagal activation in the earliest phase of ischemia was studied in dogs anesthetized with a combination of morphine and chloralose (Yoon *et al.* 1977). Electrical stimulation was used to maintain HR at 150 beats/min. The authors observed alterations in neuroautonomic activation during short-term, 5-min myocardial ischemia. While electrical stimulation of a decentralized cervical vagus prior to induced myocardial ischemia (LAD ligation) did increase VFT, vagal stimulation failed to raise VFT in incipient myocardial ischemia. A similar result was obtained following vagal inhibition with atropine. Atropine, while decreasing VFT before ligation of the artery, had no effect on the VFT decreased after LAD ligation. Propranolol administered after LAD ligation raised VFT appreciably; however, vagal stimulation failed to achieve a further increase in VFT. Likewise, vagal blockade with atropine had no effect on VFT increased by propranolol. These results indicate that the dominant factor controlling ventricular electrical stability in the earliest phase of myocardial ischemia was sympathetic activation or blockade. Vagal electrical stimulation had no effect whatsoever.

Effect of electrical stimulation of the vagus nerve and stellate ganglia

In cats under general pentobarbital anesthesia, the right and left vagus nerves and both stellate ganglia were isolated, centrally disconnected and prepared for electrical stimulation (Bergamaschi 1978). A ligature was passed around the isolated coronary artery. The model allowed for monitoring of spontaneous HR and assessing the nature of VESs during isolated electrical stimulation of the distal stump of the right vagus nerve, both stellate ganglia, simultaneous stimulation of vagus nerve and stellate ganglia as well as other combinations of vagal or sympathetic stimulation (superimposition and discontinuation of vagal or sympathetic stimulation). This was in fact a most ingenious simple experimental model designed to investigate the effect of neuroautonomic dysbalance at the onset of ischemic lesion formation 10 minutes after coronary artery ligation. Prior to artery ligation, isolated sympathetic stimulation would induce tachycardia, vagal stimulation, bradycardia, with simultaneous sympathetic and vagal stimulation inducing AV block and the appearance of other idioventricular escape rhythms. The effect of ventricular stimulation on arrhythmogenesis changed substantially as early as 10 minutes after coronary artery ligation, that is, in the earliest phase of ischemia. While stimulation of stellate ganglia induced only tachycardia, vagal stimulation resulted in either sinus bradycardia or idioventricular escape rhythm, VT or ventricular arrhythmias. Interruption of vagus nerve stimulation was generally followed by restoration of sinus rhythm. When the vagus nerve and stellate ganglia were stimulated synchronously, nodal rhythm and ventricular premature contraction were observed in the majority of cats.

Several conclusions could be drawn from the above results: arrhythmias were present in a higher percentage of cats when vagal stimulation was superimposed on preexisting sympathetic activation. Arrhythmias persisted when sympathetic stimulation was stopped while vagal stimulation continued. The high concentration of neuroadrenergic transmitters at the sympathetic nerve terminals supplied by the previous sympathetic discharge could further enhance the automaticity of the hypoxic myocardium. In an identically designed experiment, propranolol completely prevented the development of ventricular arrhythmias during simultaneous vagal and sympathetic stimulation. Sympathetic stimulation is devoid of any hemodynamic effect, but subsequent stimulation of the right vagus nerve will result in decreases in HR as well as BP. Bradycardia during vagal stimulation clearly facilitates the formation of ectopic beats and arrhythmias, as long as there is simultaneous ventricular sympathetic stimulation, with VF induction as a potential risk. Once the sympathetic effect has been abolished, vagal stimulation will only lead to extreme bradycardia and hypotension, with the development of cardiogenic shock as a potential risk. One can only agree with the author's conclusion that simultaneous electrical stimulation of both sympathetic and parasympathetic cardiac nerves always produced cardiac arrhythmias including VF.

PSYCHOLOGICAL STRESS IN CONSCIOUS ANIMALS AT THE ONSET OF LOCAL MYOCARDIAL ISCHEMIA

Stimuli generating in unmyelinated fibers in ischemic cardiac tissue elicit, in the cerebral cortex, a sensation of pain and, subsequently, emotions, that is, fear and anxiety. Strong emotions may ultimately lead to emotional stress whereby impulses come direct from the hyperactive region of the cerebral cortex to the

subcortical layers to activate the cerebral sympathoadrenergic system, the hypothalamo-pituitary-adrenal axis, and the parasympathetic vagal bulbar system. Strong emotional stress per se may induce neuroautonomic dysbalance or significantly augment it increasing the risk for life-threatening cardiac arrhythmias (Matta *et al.* 1976, Lown and Verrier 1978). The relevance of stimuli arising from the cerebral cortex and induced by a painful stimulus in local myocardial ischemia is clearly documented by experiments in conscious dogs and pigs.

Awake dogs with preserved sympathetic innervation of the heart and after sympathetic denervation of the heart

Obelienius *et al.* (1981) designed an experimental model of local myocardial ischemia in awake dogs. The aim was to eliminate the effect of general anesthesia on the neuroautonomic activation of the heart to make the experiment resemble the clinical setting as much as possible. Dogs were perfectly adapted to the laboratory setting and considered the laboratory assistant their "master". A month before the experiment, the dogs, under general anesthesia, had thoracotomy with a loose ligature placed around the LAD. Both ends of the ligature were fixed in a tourniquet in the subcutaneous layer of the neck. On pressing the tourniquet button (through the neck skin), a precoiled spring within the tourniquet tightened the ligature placed loosely on the coronary artery producing local myocardial ischemia. The same procedure was used in another group of dogs, with the difference being that the animals had additionally their superior thoracic ganglia from Th1 to Th5 removed. The experiments did not begin until 4 weeks post-procedurally after the animals had recovered completely. During experiments, we assessed the behavior of the animals as well as made telemetric recordings of the thoracic ECG leads. Results are shown in Tab 3. The coronary artery ligature was tightened unexpectedly for the dog, at a time when the laboratory assistant was "playing" with the dog as usual. The response of dogs with preserved sympathetic innervation was immediate. They became restless, running about the laboratory, with some howling softly or seeking help with their master. Some 15 minutes later, the dogs were lying on their side to rise after about an hour and start moving slowly about the laboratory. Several minutes after the onset of myocardial ischemia, there was sympathetic sinus node activation with HR exceeding IHR (145 beats/min in the awake dog). The activation lasted about 15 minutes turning into vagal activation thereafter. However, none of the animals developed significant bradycardia. Immediately after the onset of myocardial ischemia, the electrocardiogram showed marked ST-segment elevation. Within an hour of the onset of ischemia, all dogs developed isolated VESs, with two dogs showing paired VESs and VT. None of the animals developed VF or cardiogenic shock. Six to 18 hours after LAD ligature, the animals were calm. HR was markedly higher than IHR, with the rate of VESs per minute also increasing. They were polytopic ventricular rhythms and long VT runs which, however, never turned into VF.

A similar procedure was used in the experiment with the group of dogs with sympathetic denervation of the heart. The dogs did not respond to ligature tightening and walked apparently undisturbed about the laboratory. Vagal activation of the sinus node persisted after ligature tightening. ST-segment elevation was documented by ECG also in dogs with sympathetic denervation. All dogs in the group developed only

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isolated VESs within the first hour of ischemia. Between hours 6 and 18, HR was higher than IHR, with newly occurring polytopic VESs, paired VESs and short VT runs.

Summary – sympathetic denervation of the heart will inhibit, after the onset of local myocardial ischemia, manifestations of emotional stress and short-term sympathetic sinus node activation. Dogs with preserved sympathetic innervation of the heart develop more frequent and malignant VESs within the first hour. In the later phase of ischemia, both groups of dogs show marked increases in HR and the rate of VESs.

Awake pigs and cryogenic blockade of the thalamo-cortical pathway

The authors (Skinner and Reed 1978) carried out their experiments in conscious pigs. In the pre-experimental period, piglets under general anesthesia were implanted a loose occluder in the left circumflex coronary artery and two cryoprobes in the subcortical layer at sites crossed by the bidirectional pathway connecting cerebral cortex with the thalamus (thalamo-cortical pathway). After recovery, the coronary arteries of conscious piglets were closed with the occluder to determine the time to VF abolished with a defibrillation discharge. In control experiments, VF developed at an average 5-10 minutes. Bilateral cryogenic blockade of the thalamo-cortical pathway prolonged the time to VF to 35 minutes. VF was able to completely preclude restoration of coronary blood flow at 25 minutes of cryoblockade of the thalamo-cortical pathway and subsequent discontinuation of thalamo-cortical pathway blockade at 35 minutes since myocardial ischemia. The authors' explanation of their results was that impulses coming from the ischemic myocardium to the cerebral cortex via the thalamo-cortical pathway and back to the heart were blocked by cerebral tissue cooling. Blockade of impulses coming from the cerebral cortex to the heart can thus be used to reduce myocardial vulnerability to ischemia.

Suppressing emotions with benzodiazepines

Efforts to suppress emotions and the risk of emotional stress when experiencing chest pain with benzodiazepines date back to the 1970s. Benzodiazepines amplify the activity of gamma-aminobutyric acid (GABA), the main inhibitory system in the central nervous system, by acting as agonists at specific GABA receptors. Receptors for benzodiazepines are located throughout the central nervous system. At the same time, benzodiazepines activate GABA receptors in the cerebral cortex and limbic system, triggering an anxiolytic effect and breaking the pain-anxiety-pain cycle. In awake dogs, suppression of emotional stress with the benzodiazepine diazepam prolonged the interval between coronary artery ligation and spontaneous VF (Hoffmann 1978).

AUTONOMIC DISTURBANCES AT THE ONSET OF ACUTE MYOCARDIAL INFARCTION

Clinical results

For the sake of comparison with experimental data, we selected papers focusing on the hitherto ignored earliest phase of myocardial ischemia developing within one hour of the onset of focus formation.

Pantridge (1978) studied a group of 240 patients over a period of one hour since of the onset of

clinical symptoms of AMI. Of the above number, 89 were followed already during the first 30 minutes. To assess autonomic disturbances in an unbiased manner, it was first necessary to define the criteria of autonomic disturbances. In Pantridge's study, sympathetic overactivity was defined as tachycardia higher than 100 beats/min and BP higher than 160/100 mmHg with or without tachycardia. Similarly, parasympathetic overactivity was defined as sinus bradycardia of 50 beats/min or AV block and systolic BP lower than 100 mmHg.

In the group of 89 patients followed within 30 minutes of the onset of initial symptoms of AMI, normal values of HR and BP were seen in only 17% of patients. One in three patients showed sympathetic overactivity, with parasympathetic overactivity present in half. Eight percent of patients had AV block. Autonomic disturbance (sympathetic or parasympathetic autonomic overactivity) occurred within the first 30 minutes in a total of 83% of patients. This was in contrast with only 56% of the 151 patients followed in the other 30 minutes since the onset of symptoms and showing sympathetic autonomic disturbance. Another major finding was that parasympathetic overactivity is more common with inferior compared with anterior AMI.

Several major conclusions could be drawn based on the study results. VF poses a risk to the patient when spontaneously raising HR, i. e., when vagal activation switches to sympathetic activation. A most noteworthy finding is that immediate correction of the autonomic disturbance and pain relief in the group of 240 patients resulted in a total mortality rate below 10%. This was a particularly remarkable outcome compared with that of a contemporary study not designed to correct autonomic disturbance and reporting a 25% pre-hospital mortality rate.

Thirty years ago, correction of autonomic dysbalance in incipient AMI was based on inhibition of vagotonia and sympathicotonia putting the patient at risk of developing cardiogenic shock.

Epstein et al. (1972) investigated the options to prevent life-threatening arrhythmias associated with bradycardia. Clinical studies have shown bradycardia (HR below 60/min) develops in 40% of patients and is associated with malignant premature ectopic ventricular beats preceding the onset of VF. In an effort to suppress bradycardia in incipient AMI, Epstein suggested patients awaiting medical aid should use self-administration of atropine.

Fejfar et al. (1980) sought to suppress increased sympathetic activity in incipient AMI with a BB. They suggested self-administration of an oral low-dose non-selective BB (metipranolol 10 mg) once the first symptoms of AMI have appeared. Later, these authors added a benzodiazepine and an analgesic to the BB. The effects of self-administration were investigated in a clinical trial involving 246 patients. No side effects were observed in 26 individuals with drug self-administration. Likewise, there was no case of SCD in these patients even if experiencing a reinfarction. Despite the favorable outcome, drug self-administration was not further tested in a larger clinical trial.

Nevertheless, a pilot field study with self-administration provided a most valuable finding in terms of improved psychological status and behavior of patients at risk of reinfarction. The possibility of self-administration gave patients peace of mind and reassurance in their daily lives. The fact that patients received detailed instruction as to what steps to take in the event of AMI recurrence had an additional

beneficial impact. Patients experiencing recurrent AMI called emergency medical service (EMS) earlier and also paid more attention to their good health. They had regular medical checkups, were taking antiplatelet drugs, and only 13 of them continued to smoke.

Preventing SCD with chronic daily administration of a BB

In the early 1980s, the results of two studies were published with patients after a previous AMI given a non-selective BB on a daily basis. In the Norwegian Multicenter Study (1981), patients were receiving the non-selective BB timolol. The follow-up time was 12-33 months. Total mortality of 13.9% seen in the placebo-treated group declined to 7.7% in the active-treatment group (down by 44.6%). During follow-up, there was also a decrease in the reinfarction rate from 20.1% in the placebo group to 14.4% in the timolol-treated group. Results of the study have shown maintaining a constant level of a BB reduces cardiovascular risk of patients after a previous AMI.

The other study, Beta-Blocker Heart Attack Trial (BHAT 1982), enrolled patients at 21 days after an AMI. Patients were treated with the non-selective BB propranolol. After a follow-up period of 25 months, total mortality rates were 7.2% and 9.8 % in the active-treatment and placebo groups, respectively. BB treatment also reduced the rates of non-fatal AMI from 13% in the placebo group to 10% in the propranol-treated group. The rate of SDC declined from 4.6% in the placebo group to 3.3% in the propranolol-treated group.

Summary: Maintaining constant levels of a BB in AMI patients has generally a cardioprotective effect while specifically reducing the risk for SCD.

Clinical experience with diazepam in the coronary care unit

A study investigating the potential for modulation of emotions and neuroautonomic reactions during AMI within the first 24 hours of first clinical symptoms was conducted by Melsom *et al.* (1976). Patients admitted to the coronary care unit were given diazepam i.v. at a dose of 10 mg followed by oral diazepam at a dose of 15 mg every 8 hours for 3 days. A control group was made up by patients receiving conventional therapy. The mental state was better in the treated group in comparison with the control group. Daily need for analgesics was lower in the diazepam group. Diazepam reduced signs of unrest and anxiety. Malignant arrhythmias were seen only in the control group because the administration of diazepam produced a striking effect on the urinary excretion of catecholamines ($p = 0.001$). The authors conclude that the serious anxiety reactions seen during the initial phase of AMI can be controlled safely by means of diazepam. In addition, administration of diazepam might reduce the incidence of malignant arrhythmias as well as hormonal imbalance during AMI.

AUTONOMIC DISTURBANCES AT THE ONSET OF ACUTE MYOCARDIAL ISCHEMIA – EXPERIMENTAL RESULTS AT PRESENT

A number of papers explaining and providing a further insight into the pathogenesis of life-threatening arrhythmias in incipient local myocardial ischemia have been published since 1990.

Reflex stimulation of sympathetic nerve activity during the local myocardial ischemia

The reflex increase in cardiac sympathetic nerve activity that is induced by pain, anxiety and a fall in cardiac output is accompanied by local exocytotic release of noradrenaline from sympathetic nerve endings of the heart. During the first minutes of ischemia, adenosine accumulating in the ischemic myocardium effectively suppresses noradrenaline release. As ischemia progresses, noradrenaline is transported across the axolemma to the interstitial space of myocardium. As a consequence of this nonexocytotic local metabolic release, extracellular noradrenaline reaches 100 to 1 000 times its normal plasma concentrations within 30 minutes of ischemia. A concentration of this magnitude is capable of producing myocardial necrosis even in a nonischemic heart. The high noradrenaline accumulation has two consequences. The first few minutes of myocardial ischemia are associated with temporary supersensitivity of the myocytes to catecholamines, due to an increase of alpha-1 and beta adrenergic receptors number at the cell surface. Next, the inhomogeneous distribution of catecholamine excess within the heart contributes to the formation of an isolated circuit of microreentry and VF. Activation of the sympathetic nervous system in the early phase of myocardial ischemia is associated with an increased plasma noradrenaline concentration five times that of their normal level. This rise of plasma noradrenaline concentration reflects enhanced activity of the whole sympathetic nervous system rather than local activity in the heart. The direct effect of increased plasma catecholamines on malignant ventricular arrhythmias cannot be assumed to be very important (Schömig 1991, Han *et al.* 1964*).

It follows from the above that the main pathogenic mechanism of life-threatening arrhythmias in the presence of incipient local myocardial ischemia is reflex sympathetic neurogenic activation of the heart. Reflex sympathetic humoral activation has no major effect on arrhythmia genesis.

Sympathetic and vagal co-activation of the heart at the beginning of local myocardial ischemia - the baroreflex sensitivity

Local myocardial ischemia results in VF is about half of experimental animals (Cerati and Schwartz 1991, Schwartz *et al.* 1992). Animals developing VF (susceptible animals) differ from the surviving ones (resistant animals) in that they show decreased baroreflex sensitivity. In resistant animals, the vagal efferent activity in phenylephrine-induced hypertension was increased by 246% as against only 80% in susceptible animals. At the same time, tonic vagal activity was identical in both groups of animals prior to phenylephrine administration. While left stellectomy increased tonic vagal efferent activity by 75 %, efferent vagal activity rose from 2.2 to 4.7 impulses/sec following phenylephrine administration. The study demonstrates that those animals responding spontaneously to myocardial ischemia with stronger vagal discharges are much less likely to develop VF.

Local myocardial ischemia would augment sympathetic afferent traffic and could reduce vagal efferent activity. Direct neural recording has fully confirmed conclusions on the relation between vagal activity and risk for SCD, based on the use of markers such as baroreflex sensitivity and heart rate variability. A retrospective study published in 1993 summarized results obtained in dogs under pentobarbital

anesthesia when measuring VFT at 8 minutes after inducing local myocardial ischemia. A critical fall in VFT occurred in 75 out of 143 dogs, i.e., in 52.4% (p < 0.001) (Fejfar and Vrána 1993). The finding confirmed earlier reports suggesting there are dogs at high or low risk of VF.

Baroreflex sensitivity is not only an important marker for low or high risk of VF; we found a possibility to enhance baroreflex sensitivity by the pharmacological modulation. In acute local myocardial ischemia produced in dogs, baroreflex sensitivity decreases as electrical instability of cardiac ventricles increases. Simultaneous administration of a benzodiazepine (midazolam) and a powerful analgesic (fentanyl) augmented both baroreflex sensitivity and VFT. So, modulation of neuroautonomic activation of the heart by drugs in the early stage of ischemia holds promise as a potential technique of SCD prevention (Vrána *et al.* 1992). This finding now plays a most important role in the earliest phase of management of AMI by the first-line physician (see below).

Intrinsic cardiac nervous system and cardiac autonomic control

The intrinsic cardiac nervous system involves afferent neurones, local circuit neurones (interconnecting neurones) as well as both sympathetic and parasympathetic efferent postganglionic neurones. In such a concept, the intrinsic cardiac nervous system acts as a distributive processor, integrating parasympathetic and sympathetic efferent centrifugal information to the heart in addition to centripetal information arising from cardiac sensory neurones (Armour 1999, Armour 2008). Papers have been published which report the activity of the intrinsic cardiac nervous system in various settings. An example of this is regulation of tachycardia in heart failure and, also, revision of views regarding vago-sympathetic interactions in the diving response, oculocardiac reflex, defense response, startle reflex and somatic nociception. Another interesting example is what is referred to as "vagally mediated tachycardia", and the cluster of mechanisms involved in its development (Arora *et al*. 2003, Paton *et al.* 2005). Regrettably, none of the papers published to date has tested the feasibility of suppressing life-threatening arrhythmias through direct intervention into defined structures of the intrinsic cardiac nervous system, primarily in the setting of its injury by an ischemic focus.

AUTONOMIC DISTURBANCES AT THE ONSET OF ACUTE MYOCARDIAL INFARCTION – CLINICAL RESULTS

Introduction

Experimental and clinical outcomes regarding neuroautonomic dysbalance in AMI have been translated into clinical practice and have become an integral part of the Czech Society of Cardiology (Widimský *et al.* 2009) and the European Society of Cardiology guidelines (Werf *et al.* 2008). According to both guidelines, the physician should correct tachycardia (hypertension) and bradycardia (hypotension) with an i.v. BB and i.v. atropine, respectively. Restless patients may be given an oral tranquilizer as needed. Using the European and Czech guidelines, pain should be controlled by morphine and fentanyl or morphine, respectively. Current guidelines suggest the most effective early in-hospital treatment of AMI is primary

PCI. Early recanalization of the coronary bed will restore coronary blood flow in up to 90% of cases and will prevent further development of the ischemic focus. Data from randomized studies have shown introduction of PCI reduced mortality rates by 20-25% compared with thrombolysis.

Neuroautonomic dysbalance during early in-hospital care

The results of the experimental study by Bergamaschi (1978) have been recently supported by a clinical trial investigating, in patients at high risk of SCD, the switch from sympathetic activation of the heart to vagal activation and vice versa. Neuroautonomic changes were assessed by the authors using spectral analysis of R-R intervals obtained from Holter electrocardiograms. A sudden switch from parasympathetic activation into sympathetic activation resulted in AMI or VF in 22 of 34 patients whereas nine patients developed AV block during a switch from sympathetic to parasympathetic activation (Osaka *et al.* 2010).

Recently, neuroautonomic dysbalance has been shown to persist for several days after hospitalization and to be individualized. This finding was reported in the COMMIT/CCS -2 trial (2005) enrolling patients who presented with ST elevation, left bundle branch block or ST depression within 24 hours of the onset of the symptoms of suspected AMI. The metoprolol-treated group included 22 929 patients with 22 923 patients in the placebo group. The outcome was evaluated after 28 days of hospital stay. Compared with the placebo group, mortality due to arrhythmias declined by 22% in the metoprolol-treated group whereas mortality due to cardiogenic shock rose by 29%. Metoprolol was capable of primarily reducing the risk for VF by 17% and, also, the risk of reinfarction. By contrast, it significantly increased the risk of cardiogenic shock. Compared with placebo-treated patients, a significantly higher number of patients receiving metoprolol had persisting hypotension and bradycardia. The authors of the study concluded that immediate intravenous BB therapy in AMI cannot be recommended routinely.

EMOTIONAL STRESS AND AUTONOMIC DISTURBANCES AT THE ONSET OF ACUTE MYOCARDIAL INFARCTION

Surprisingly, the European (Werf *et al.* 2008) and Czech (Widimsky *et al.* 2009) guidelines for the management of AMI with ST segment elevation ignore the issue of neuroautonomic dysbalance occurring immediately after the onset of AMI, at a time when the patient is left without professional medical care. Under the scenarios contained both in the European and Czech guidelines for the management of AMI with ST-segment elevation, the physician is expected to arrive within 15 minutes. However, the reality is quite different. The patient takes some time before calling EMS so medical aid may not arrive before an average 2 hours since the first symptoms of AMI, that is, at a time when the most dramatic changes in neuroautonomic activation of the heart have already occurred. Efforts to appreciably shorten the time to arrival of medical aid made since the 1980s have failed. This is due to the psychological defensive mechanism referred to as "denial" in psychiatry; subconscious transposition of reality into a situation that the individual would like to see themselves: "Well, this will go away, it's nothing serious. I will not call the doctor" (Honzák *et al.* 2009). Results of a clinical trial (Whitehead *et al.* 2005) showed that the initial symptoms of AMI are associated

with distress and fear of dying. Severe psychological symptoms were reported by 22% of patients. Milder presentations of stress and fear of dying were reported in 52% of patients. A prognostically relevant finding is the fact that acute distress and fear of dying experienced during incipient AMI may trigger subsequent depression and anxiety lasting for 3 months after hospital admission. The distress and fear of dying on the first symptoms of incipient AMI were also reported retrospectively by our patients (n = 65) examined at an interval of some 2 months after a myocardial infarction (Fejfar *et al.* 1994). In addition, most of them reported a feeling of helplessness while awaiting the arrival of EMS. This feeling of helplessness was dominated by the idea: "I can do nothing at the moment to save my life, all I can do now is to wait!"

Pharmacological modulation of AMI-related emotional stress

A short-acting benzodiazepine interfering effectively with sympathovagal balance has recently become available. Alprazolam inhibits the activation of the hypothalamo-pituitary-adrenal axis and metabolic stress. Some patients discharged after a previous AMI to receive home care experience anxiety disorders. Alprazolam at a dose of 0.25 mg b.i.d. significantly reduced the scores for free-floating anxiety, phobic anxiety, and somatic complaints in these patients (Prunetti *et al.* 2002).

The availability of a suitable and well tolerated benzodiazepine paves the road to pain relief while reducing emotional stress and anxiety immediately on the first symptoms of AMI through self-administration of a relief drug. Regrettably, this approach continues to be dismissed by cardiologists wrongly believing that the psychological suffering experienced by the patient together with physical suffering on the early symptoms of AMI will make them call EMS promptly. The fact that this misconception has survived for years and the time to calling EMS has not become shorter shows the opposite is true. This makes us believe the self-administered drug should again receive some attention and be tested in smaller clinical trials.

In our current clinical experience, each patient (AMI survivor) should have on hand the following agents for self-administration:

1. Oral alprazolam at a dose of 0.25–1.0 mg, ideally a medication capable of quick buccal resorption upon administration. The above doses are safe, have no adverse effects on the circulation, and are commonly used even by general practitioners. Melsom *et al.* (1976) administered parenteral diazepam to AMI survivors at doses considered very high by current standards. Despite this, patients tolerated the therapy well without developing circulatory instability. Benzodiazepines and opioids can be readily combined and, when administered at low doses, their side effects should presumably not summate. At the above therapeutic range, alprazolam was administered with success to patients diagnosed to have acute coronary syndrome at the Emergency Department of the University Hospital in Motol.

2. Selected at-risk patients should not be denied fentanyl currently available also as spray. Fentanyl has been used for decades and, in fact, at considerably high doses, to induce anesthesia in patients at highest risk scheduled for cardiac surgical procedures. Fentanyl is an opioid with very mild effects on the circulation.

All patients given a drug intended for self-administration should receive appropriate instructions

including psychotherapy and a test for their tolerability of the above dose range. According to current guidelines, the first-line physician will administer an opioid to the individual experiencing an AMI. With respect to experimental data, it would be appropriate to add a benzodiazepine to the opioid. Such a policy would increase baroreflex sensitivity decreasing the risk of SCD in the ensuing course (Vrána *et al. 1992,* La Rovere *et al. 1998).*

Preventing SCD with chronic daily administration of a BB

As shown by classic studies published in the early 1980s (Norwegian Multicenter Study 1981, BHAT study 1982), the drugs of choice for electrical stabilization of the vulnerable myocardium after a previous AMI are BBs. In addition to reducing total mortality, BBs reduce the proportion of those dying suddenly. The 2009 Czech Society of Cardiology guidelines provide a list of BBs to be routinely given to AMI survivors (Vítovec and Špinar 2009). These are propranolol, metoprolol, timolol, acebutol, and carvedilol. There is no doubt that adequate BB levels already before incipient AMI have beneficial effects on myocardial electrical stability in addition to exerting an antifibrillatory action**.** Unlike i.v. or high-dose BBs, preventive chronic administration of low-dose oral BB will not result (as in COMMIT 2005) in the development of bradycardia or cardiogenic shock. Experiments with dogs under general pentobarbital anesthesia have shown that administration of the non-selective BB metipranolol at a dose of 0.1 mg/bw prior to coronary artery ligation will increase VFT about six times at minutes 2-30 of local myocardial ischemia (Vrána *et al.* 1978). Experiments have also shown that preventive maintenance of adequate BB levels before the onset of AMI may possibly reduce the risk for SCD.

Chronic preventive BB administration can be considered a most effective strategy of reducing SCD due to VF immediately on the first symptoms until the arrival of medical aid. According to the above BHAT trial, prevention with propranolol led to a 28% decrease in SCD at 2 years. A still more remarkable antiarrhythmic effect was obtained using chronic prevention with carvedilol in the CAPRICORN trial (Fonarow *et al.* 2007). Enrolled into the study were AMI survivors with impaired left ventricular function. Patients were given carvedilol, an ACE inhibitor, and aspirin. Half of them were treated by thrombolysis or PCI upon their admission. Compared with the placebo group, carvedilol-based prevention reduced the incidence of life-threatening arrhythmias by 76%. At the same time, the incidence of supraventricular arrhythmias was decreased by 52%. Results of another clinical trial, COMET (Torp-Pedersen *et al.* 2005), showed that the decreases in cardiovascular mortality and incidence of SCD by carvedilol were significantly greater compared with metoprolol. Carvedilol, a non-selective BB inhibiting also the alpha receptor and having additional antioxidant activity, could thus become another effective agent whose chronic administration would prevent a fatal event in the earliest phase of incipient AMI through its antifibrillatory effect (El-Sherif and Turitto 2005, Kopecky 2006). Consistent with the above mentioned studies are statements by two Czech opinion leaders in cardiology: "Effective treatment of heart failure and myocardial tissue protection against sympathetic-adrenal reaction with BBs since the earliest stage of AMI play an important role", (Bytešník 2010) and "It is only the BBs that have been proven to reduce the incidence of SCD" (Táborský *et al.* 2010).

Results of epidemiological studies demonstrate encouraging declines in community death rates due to coronary heart disease and AMI. However, the declines in annual death rates between 1990-2001 attributed to patients dying from AMI in the out-of-hospital setting (1.9%) were lower than in the hospital setting (4.8%). These data suggest that, in order to sustain the observed community decline, greater emphasis on prevention of SCD and rapid field treatment of patients experiencing an acute coronary event is needed (Goldberg *et al.* 2006). The risk of sudden death following AMI in community practice has declined significantly over past the 30 years. The difference in mortality over the 1979-87 period compared with the 1988-1996 period is 20%. A further decrease by 35% was observed over the 1997-2005 period. A significant role in the decrease in in-hospital mortality is played, among other things, by timely PCI (HR 0.39; p < 0.001) (Adabag *et al.* 2008). Mention should also be made of ICDs contributing to the decrease in mortality in AMI survivors with CAD as comorbidity. Results of the MADITT II trial showed the mortality of AMI survivors declined significantly at 20 months from 19.8% in the group receiving conventional therapy to 14.2% in the ICD-treated group. (Goldberg *et al.* 2010).

CONCLUSIONS AND CLINICAL IMPLICATIONS

- Autonomic dysbalance poses a threat to the patient and raises the risk for SCD.
- The patient should receive a self-administration drug to stabilize their psychological status immediately after the first symptoms of incipient AMI while awaiting the physician. Psychotherapy and educational programs aimed at at-risk individuals are of paramount importance.
- During transfer to hospital and upon arrival to the emergency department, it is critical to treat the patient as recommended by the Czech and European Societies of Cardiology guidelines – stabilizing autonomic dysbalance by normalization of HR and BP with a BB and atropine. We suggest that opioid-based analgesia be complemented with benzodiazepines to enhance baroreflex sensitivity.
- Upon discharge from hospital, it may be reasonable to start chronic preventive use of BBs to reduce the risk for SCD on incipient AMI. The greater antifibrillatory potential of new-generation BBs should be documented in animal experiments and future clinical trials in humans.

Conflict of Interest

There is no conflict of interest.

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Tab 1

Dogs under pentobarbital anesthesia – sympathetic denervation of the heart

Time (min)		C	0-15	15-30	45-60
HR (bpm)	S	160±18	167±17	170±20	175±15
	D	113±18	119±20	121±19	125±22
VFT (mAmps)	S	2.5±0.9	0.5±0.7	1.3±1.1	1.3±0.7
	D	5.4±2.7	3.9±2.5	3.2±20	3.2±15
VES/min	S	0	19	24	22
	D	0	2	2	0

p = 0.01

S – sympathetic innervation preserved, group of 8 dogs

D – surgical sympathetic denervation, group of 23 dogs

C – control values

Tab 2

Dogs under pentobarbital anesthesia – a beta-blocker and a benzodiazepine

	Drug	n	C	min 8 A	min 23	min 45
VFT	metipranolol	14	1.8	0.4	15.0 **	20 ***
(mA)	flunitrazepam	18	2.0	0.5	2.2 **	2.7 **
HR	metipranolol	14	172	172	126 ***	126 ***
(bpm)	flunitrazepam	18	161	166	140 ***	135 ***
MAP	metipranolol	14	109	107	91 **	105
(mmHg)	flunitrazepam	18	115	111	93 **	102

n - number of dogs

C - control values and changes in VFT, HR and MAP at minutes 8, 23, and 45 of ischemia

A - drugs were administered intravenously at minute 15 of ischemia (metipranolol 0.3 mg/kg, flunitrazepam 0.25 mg/kg)

Statistical significance of differences between VFT, HR and MAP values during follow-up and at minute 23 (45): ** p = 0.01, ***p = 0.001.

Tab 3

Awake dogs in chronic setting – local myocardial ischemia

Time (min)		C	0-15	15-30	45-60	6h	18h
	S	83±21	170±24	121±31	107±18	166±48	220±57
HR (bpm)							
	D	75±15	105±24	99±25	72±14	127±40	150±54
	S	0	1.5	2.0	20	95	104
VESs/min							$p = 0.05$
	D	0	0	0.2	1.3	28	45

C – control values

S - sympathetic denervation of the heart preserved, group of 8 dogs

D - surgical sympathetic denervation of the heart, group of 23 dogs