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Autonomic control of heart rate: Pharmacological and nonpharmacological modulation

Abstract The evidence of the predictive value of autonomic markers has generated a growing interest for interventions able to influence autonomic control of heart rate. The hypothesis is that an increase in cardiac vagal activity as detected by an increase in heart rate variability (HRV) or baroreflex sensitivity (BRS) may be beneficial in the ischemic heart. Numerous experimental data support the hypothesis that augmenting vagal activity might be protective against lethal ischemic arrhythmias. Among them is the evidence that ventricular fibrillation during acute myocardial ischemia may be largely prevented by electrical stimulation of the right cervical vagus or by pharmacological stimulation of cholinergic receptors with oxotremorine. There is an inherent danger in the so far unwarranted assumption that modification of HRV or BRS translates directly in cardiac protection. This may or may not be the case. It should be remembered that the true target is the improvement in cardiac electrical stability and that BRS or HRV are just markers of autonomic activity. Low dose scopolamine increases HRV in patients with a prior myocardial infarction. This observation, combined with the evidence that elevated cardiac vagal activity during acute myocardial ischemia is antifibrillatory, has generated the hypothesis that scopolamine might be protective after MI. We tested low dose scopolamine in a clinically relevant experimental preparation for sudden death in which other vagomimetic interventions are effective and found that this intervention does indeed increase cardiac vagal markers but has minimal antifibrillatory effects. This is in contrast to exercise training that in the same experimental model had a marked effect on both BRS and HRV and at the same time provided strong protection from ischemic ventricular fibrillation. Thus, based on the current knowledge it seems appropriate to call for caution before attributing excessive importance to changes in „markers“ of vagal activity in the absence of clear-cut evidence for a causal relation with an antifibrillatory effect.

Key words Vagal activity – ventricular fibrillation – myocardial infarction

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Introduction

Experimental and clinical evidence have established and have described the existence of a dose relationship between the autonomic nervous system, acute myocardial ischemia, and occurrence of lethal cardiac arrhythmias (6, 25, 40, 41, 49). Specifically, dominance of sympathetic or vagal reflexes during acute myocardial ischemia markedly increases or decreases, respectively, the risk for developing lethal arrhythmias and sudden death.

Almost two decades ago, our group developed an experimental preparation for sudden death in conscious dogs with a prior myocardial infarction (38). This animal model provided the first experimental evidence that the likelihood of having predominant sympathetic reflexes, and thus a greater risk of dying, or vagal reflexes, and a greater chance of surviving, dur-

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ing acute myocardial ischemia could be predicted by analyzing autonomic control of heart rate prior to the occurrence of the ischemic event. Baroreflex sensitivity (BRS) was used to analyze autonomic control of heart rate and correctly identified a large number of post-myocardial infarction animals at high risk of having arrhythmic death at the time of a new and brief ischemic episode (42). This represented a strong rationale to test the potential of autonomic markers to identify among post-myocardial infarction patients those at higher risk of dying of lethal arrhythmic events. The clinical relevance of this information was initially suggested by some pilot studies (16, 23). More recently the multi-center international trial ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) has prospectively shown in 1284 post-myocardial infarction patients that both BRS and heart rate variability (HRV) have strong and independent predictive value for cardiac mortality (22).

The evidence of the predictive value of autonomic markers has generated a growing interest for interventions able to influence autonomic control of heart rate. The thought underlying this interest is that an increase in cardiac vagal activity as detected by an increase in HRV or BRS may be beneficial in the ischemic heart. As matter of fact the concept that interventions augmenting vagal activity might be protective against lethal ischemic arrhythmias is supported by numerous experimental data (11). Among them, the evidence that ventricular fibrillation during acute myocardial ischemia may be largely prevented by electrical stimulation of the right cervical vagus (48) or by pharmacological stimulation of cholinergic receptors with oxotremorine (9, 10).

There is, however, an inherent danger in the so far unwarranted assumption that modification of HRV or BRS translates directly in cardiac protection.This may or may not be the case. It should be remembered that the true target is the improvement in cardiac electrical stability and that BRS or HRV are just markers of autonomic activity.

Hereafter, a brief summary of experimental and clinical data concerning the predictive value of autonomic markers and the potential mechanisms involved in autonomic derangements in the ischemic heart will be presented. Subsequently, the influences on cardiac electrical stability of pharmacological and nonpharmacological interventions able to modulate autonomic markers will be discussed.

The predictive value of autonomic markers

Autonomic markers and risk for ventricular fibrillation

Much information on the mechanisms involved in the genesis of sudden cardiac death had been obtained in an experimental model in which ventricular fibrillation could be reproducibly induced by clinically relevant stimuli (38). This conscious animal preparation, already described in several circumstances, combines three elements highly relevant to the genesis of malignant arrhythmias in man: a healed myocardial infarction, acute myocardial ischemia, and physiologically elevated sympathetic activity. In brief, 30 days after an anterior wall myocardial infarction, chronically instrumented dogs perform a submaximal exercise stress test. When heart rate reaches approximately 210–220 b/min, a 2 minute occlusion of the circumflex coronary artery is performed by means of a pneumatic occluder previously positioned around the vessel. After 1 minute exercise stops while the occlusion continues for another minute. This "exercise and ischemia test" triggers ventricular fibrillation in almost 50 % of the animals. The dogs run with steel paddles ligated to their chest so that an effective defibrillation can be accomplished within seconds from the onset of the lethal arrhythmia. The outcome of the test is highly reproducible over time in the same animal and allows for to the clear separation of two groups: 1) animals that develop ventricular fibrillation and are defined "susceptible" to sudden death; 2) dogs that survive and are defined "resistant". A crit-

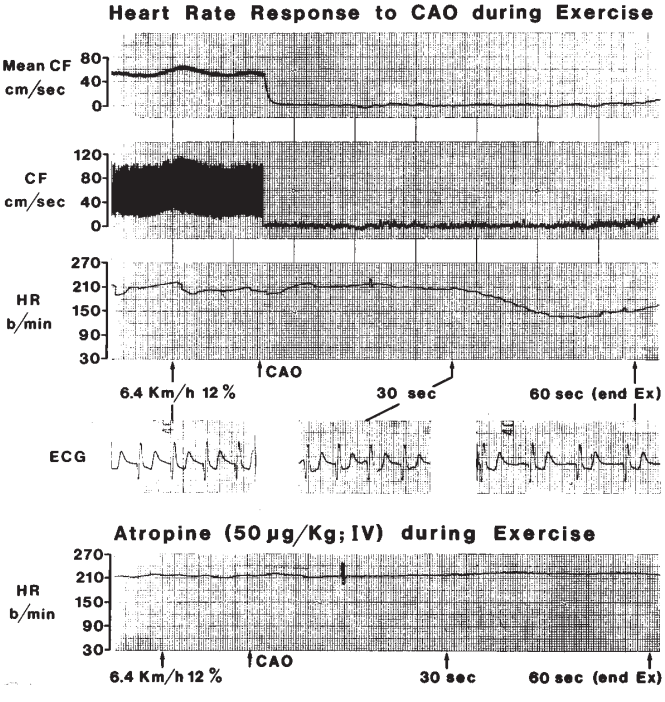

Fig. 1 Heart rate response to acute myocardial ischemia in a dog resistant to ventricular fibrillation. From top to bottom, mean and actual coronary flow (CF), the tachogram, and the electrocardiogram (ECG) before and at 30 and 60 seconds of acute ischemia. Within 30 seconds of ischemia, a marked bradycardia occurs despite the ongoing exercise and the animal is protected from lethal events. Atropine completely prevents the reflex heart rate reduction during ischemia.

ical difference between the two groups of dogs was that "resistant" dogs very often had marked reduction in heart rate during acute myocardial ischemia despite the ongoing exercise, while susceptible dogs had an opposite response, i.e., an increase in heart rate (38). The reflex heart rate increase during ischemia could have been readily explained by the combination of the baroreflex response to the decline in arterial blood pressure and of the excitatory cardio-cardiac sympathetic reflex (28). However, in the susceptible dogs the reflex tachycardia could not be attributed to a greater hemodynamic impairment, since mean blood pressure and dp/dt max just before the occurrence of ventricular fibrillation was not different from that of resistant dogs at the same moment (7). The unexpected heart rate reduction induced by myocardial ischemia in the resistant dogs was clearly dependent on a vagal reflex, as it could be prevented by atropine (Fig. 1; 12).

Based on this evidence it became rational to try to measure cardiac vagal reflexes to test whether such a measure could identify those individuals more likely to activate the vagus during acute myocardial ischemia and, thus, more likely to survive. A simple approach was to measure BRS specifically looking to the vagally mediated reflex bradycardia consequent to blood pressure rise. The method used was the one described by Sleight's group (43): BRS was measured by the slope of the regression line correlating consecutive R-R intervals with the increasing values of systolic blood pressure due to the bolus injection of phenylephrine. The changes at the sinus node level after injection of phenylephrine reflect primarily vagal reflex activity but are significantly influenced by the concomitant level of sympathetic activity (5, 17). The main finding of this study was that in the 86 dogs resistant to sudden death BRS was markedly and significantly higher than in the 106 dogs at high risk for ventricular fibrillation (17.7 ± 6.0 vs. 9.1 ± 6.5 ms/mmHg $p < 0.001$). This indicated that the capability of reflexly increasing vagal activity was significantly depressed in those dogs that were at higher risk for developing ventricular fibrillation.

The link between altered autonomic control of heart rate and risk for lethal arrhythmias was further described by the use of HRV (18, 47). The predictive value of this marker has been extensively described (46).

Mechanisms of autonomic imbalance after myocardial infarction

The comprehension of the potential factors involved in autonomic imbalance after myocardial infarction is critical for the use of autonomic markers for post-myocardial infarction risk stratification and for the interpretation of the effects of autonomic interventions. Such mechanisms are not yet fully understood, but neural reflexes of cardiac origin are likely involved. Among the various possibilities (40), cardio-cardiac sympatho-vagal reflexes may play an important role (27). The changes in the geometry of a beating heart secondary to the presence of a necrotic and noncontracting segment may quite conceivably increase beyond the normal firing of sympathetic afferent fibers by mechanical distortion of their sensory endings. Such a sympathetic excitation affects and impairs the baroreceptor reflex, i.e., interferes with the physiological increase in the activity of vagal fibers directed to the sinus node (5, 17). This hypothesis is supported by experimental evidence obtained by recording vagal efferent activity prior to and after removal of the left sided afferent and efferent cardiac sympathetic fibers by left stellectomy in anesthetized cats (5). Both tonic and reflex vagal activity (following the rise in blood pressure) were significantly higher after left stellectomy. In 16 anesthetized cats removal of the left stellate ganglion increased resting level of vagal activity from 1.2 ± 0.2 to 2.1 ± 0.3 imp/sec (+ 75 %, $p < 0.01$, Fig. 2). In the same cats, vagal activity during similar blood pressure rises induced by phenylephrine was also higher after left stellectomy (4.7 ± 0.7 vs. 2.2 ± 0.4 imp/sec, $p < 0.001$), with an increment of 134 ± 24 vs. 86 ± 18 % ($p < 0.05$) versus the resting level. These data indicate that the presence of cardiac afferent sympathetic

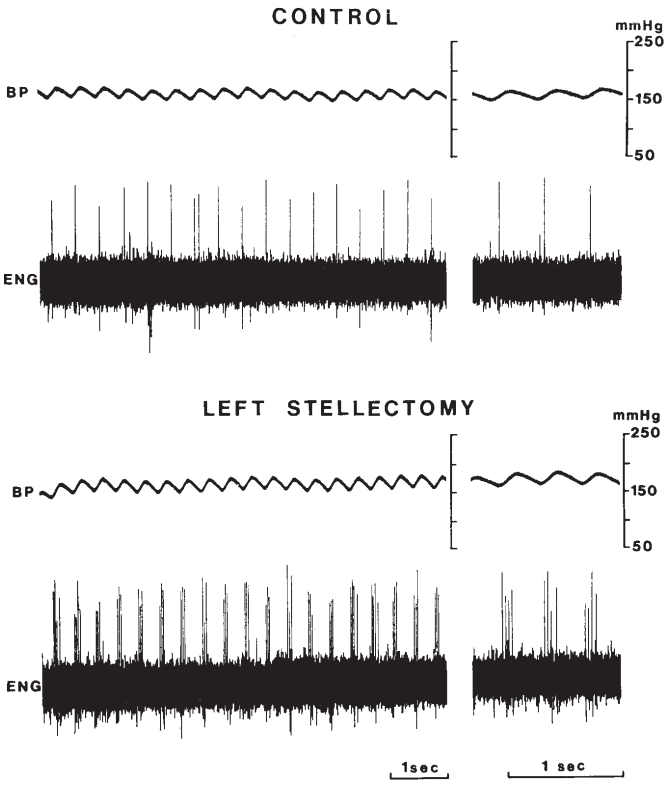

Fig. 2 Tracings showing the activity of a single cardiac vagal efferent fiber at the same blood pressure level before and after (bottom panel) left stellectomy. The fiber shows a pulse-synchronous activity that is clearly increased after left stellectomy.

activity produces a tonic constraint on vagal efferent activity and blunts the reflex increases secondary to blood pressure rises. They also support the hypothesis that the depression in vagal control of heart rate observed often after myocardial infarction may depend largely on an increase in afferent sympathetic traffic of cardiac origin.

Modulation of autonomic control of heart rate

Nonpharmacological interventions: Exercise training

A physiologic way to achieve an increase in vagal control of heart rate is represented by exercise training. It is a common knowledge that exercise training produces a lower resting and exercising heart rate (37). This typical response has been interpreted as the consequence of a combined effect of exercise training on both limbs of the autonomic nervous system.

The exercise training-induced changes in cardiac vagal activity are the results of several significant modifications on the heart and on the autonomic nervous system. Specifically, clinical and experimental findings indicate that exercise training increases myocardial contractility (44), maximal oxygen uptake (14), and cardiac oxygen consumption. In trained individuals total heart catecholamine content is decreased (13). An attenuated adrenergic, alpha mediated, vasoconstrictor activity on coronary vessels has been observed in trained dogs (24). Surprisingly, there is very little information of the effects of exercise training on autonomic markers. An increase in HRV and BRS after exercise training has been described in normal and in mild hypertensive subjects (1, 32). One of the potential accepted mechanisms for the reduction in cardiac sympathetic activity is the documented reduction in beta-adrenergic receptors density after exercise training (45). The increase in vagal activity could be due to a greater baroreceptorial stimulation consequent to the increase in contractility (50). Independently from the mechanisms involved, the net outcome of these combined effects is that exercise training shifts the autonomic control of heart rate toward a predominance of the vagal component. A critical aspect of this informations is related to the fact that exercise training has been associated with increased health benefits, and specifically with reduced cardiovascular mortality (15, 31, 36).

The availability of the experimental model in conscious dogs where occurrence or prevention of lethal arrhythmias primarily depends upon autonomic reflexes allowed us to investigate the relation between autonomic modifications induced by exercise training and risk for sudden cardiac death. In a first study (2), we observed that 6 weeks of exercise training significantly increased the depressed BRS of 8 dogs with a healed myocardial infarction susceptible to ventricular fibrillation (from 5.4 ± 1.2 to 13.2 ± 4 msec/mmHg). At the same time, another group of susceptible dogs was kept for six weeks in cage rest and did not show any autonomic change. The main finding of the study was that, concomitant with the increase in BRS, all 8 trained dogs became resistant to lethal arrhythmias during the exercise and ischemia test while all but one cage-rested dogs had no change in BRS and had recurrence of ventricular fibrillation. The one dog that behaved differently in this latter group had an increase in its BRS and became resistant to sudden cardiac death. The advantage of the experimental preparation is that, in contrast to clinical trials, by definition no changes in lifestyle other than exercise training occurred in the subjects under study. In this controlled environment this was the first documentation that training could be an independent factor able to concomitantly modify a marker of cardiac vagal activity and to reduce risk for ventricular fibrillation.

Two studies by Hopie and colleagues supports the concept that exercise training increases electrical stability of the ventricle. In the first study (30) it was found that isolated hearts from trained rats had a higher ventricular fibrillation threshold and a lower increase in cAMP in the ischemic area when compared to hearts from untrained rats. In the second study (35), in a similar preparation ventricular fibrillation threshold was higher in rats treated with exercise training after a first myocardial infarction than in untrained rats both prior to and after the onset of a second acute myocardial infarction.

Our initial observation in conscious dogs was interpreted as potentially dependent upon an increased cardiac performance in hearts damaged by the anterior wall myocardial infarction. We recently extended the initial observation to dogs without

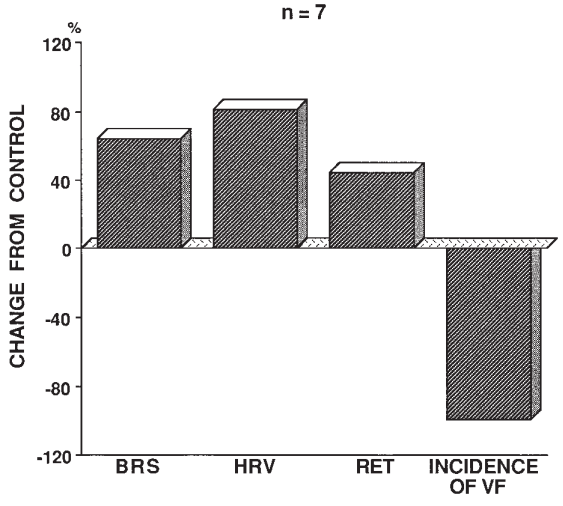

Fig. 3 Effect of exercise training on baroreflex sensitivity (BRS) heart rate variability (HRV), repetitive extrasystole threshold (RET), and on risk for ventricular fibrillation during the exercise and ischemia test.

myocardial infarction to test whether exercise training prior to an ischemic event could be of benefit at the time of its occurrence (19). Seven healthy dogs that developed ventricular fibrillation during a control exercise and ischemia test were exposed to six weeks of exercise training. After this treatment, the low to high frequency ratio in the spectral analysis of HRV was decreased by 52 % BRS by 69 % from 16 ± 8 to 27 ± 14 msec/mmHg. Electrical threshold for ventricular repetitive responses was increased by 44 %, from 32 ± 6 to 46 ± 4 mA. At the same time, none of the dogs developed again ventricular fibrillation during a second exercise and ischemia test (Fig. 3). A likely mechanism involved in this antifibrillatory effect involves the fact that exercise training increases metabolic efficiency during ischemia. However, the fact that repetitive extrasystole threshold was also significantly increased after training strongly supports the hypothesis that this intervention, by modulating autonomic balance, significantly improves the electrical stability of the ventricles.

In conclusion, exercise training is a very effective tool, able to significantly increase vagal contribution to the autonomic control of heart rate. This results in an improvement of cardiac electrical stability and, ultimately, in a reduced risk for arrhythmic events in the ischemic heart as the consequence of several concomitant actions on ventricular performance, metabolic activity, and cardiac reflexes. Indeed, exercise training seems to be able to specifically act at various sites and on various mechanisms involved in genesis of ischemia-dependent ventricular tachyarrhythmias.

Exercise training appears to be an inexpensive non-pharmacological intervention, available for mass program that can reduce risk for cardiovascular mortality in coronary artery disease patients and may have the potential to significantly influence risk for lethal events even when performed prior to the development of ischemic heart disease.

Pharmacological interventions:
Low dose of muscarinic receptors blocking agents

Low dose of muscarinic receptors blockers may produce a paradoxical increase in vagal efferent activity. Atropine is known to induce bradycardia (as a "paradoxical" vagomimetic effect) at low doses and the expected heart rate increase (as the typical antimuscarinic effect) at higher doses (52). For atropine this effect has been recognized since the beginning of the century (54), but the precise mechanisms have not yet been fully clarified. There has been indeed a proliferation of publications reporting the "positive" effect of a variety of interventions on HRV and BRS (4, 8, 34, 51).

In 1993 four different studies from independent groups reported similar findings using transdermal administration of scopolamine. The main finding common to the four studies was that in patients with a healed myocardial infarction low dose scopolamine was able to significantly increase various measures of HRV both in time and frequency domain. The conclusion derived from the HRV results were also strengthened by the study of BRS performed in three of these four studies (4, 8, 34). BRS was increased by scopolamine by an extent ranging from 42 to 98 %.

In one of these studies (34) the influences of transdermal scopolamine on cardiac electrical properties were also evaluated. Effective refractory periods of right atrium, atrioventricular node, and right ventricle were assessed before and after scopolamine in 20 patients with a recent myocardial infarction. After wearing one patch of transdermal scopolamine for 24 hours, right atrium refractory period decreased from 242 ± 44 to 223 ± 41 msec ($p < 0.01$), atrioventricular node refractory period increased from 320 ± 65 to 357 ± 77 msec ($p < 0.05$) and right ventricle refractory period increased from 224 ± 14 to 235 ± 16 msec ($p < 0.001$) (Fig. 4).

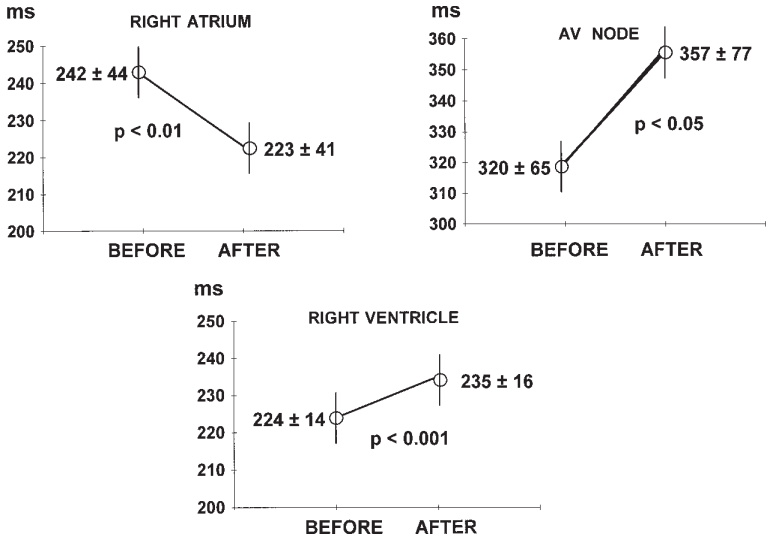

Fig. 4 Effect of low dose scopolamine on refractoriness in the right atrium and ventricle and on the atrioventricular node (av node). The increase in cardiac vagal activity after scopolamine results in an increased refractoriness of the av node and of the right ventricle and in reduced refractoriness at the atrial level.

More recently attention has been devoted to pirenzepine, an antimuscarinic agent widely used for peptic ulcer therapy. Low doses of intravenous pirenzepine have been found to increase the standard deviation of the RR intervals by 58 % in 6 normal volunteers (52). Pirenzepine in contrast to scopolamine does not have central action, and more importantly can be used orally for long time with minimal side effects. As matter of fact preliminary attempts of chronic therapy with transdermal scopolamine had failed because of a large incidence of side effects. Recently, at our institution, a study aimed to assess efficacy and safety of transdermal scopolamine after MI on a middle-term treatment was interrupted owing to the high incidence of adverse effects (RFE Pedretti unpublished data). Of five patients randomized to transdermal scopolamine, four (80 %) had to withdraw the therapy within the first month of treatment. Two patients developed an intractable cutaneous erythema at the site of patch application, and the two other complained of blurred vision and drowsiness.

In a single-blind, placebo-controlled crossover trial (33), 20 patients underwent evaluation of short-term HRV and BRS 19 ± 6 days after the infarction. Analysis was performed under control conditions and during placebo, oral pirenzepine, and transdermal scopolamine administration. In an initial dose-response study 5 of 8 post-myocardial infarction patients showed a significant increase in BRS and were considered responders to pirenzepine. BRS was reassessed after 2 days of therapy for each oral dose tested. If a BRS increase > 4 ms/mmHg occurred, the patient was considered responder to pirenzepine and that dose was defined effective. All responder patients underwent treatment with a higher dose to assess the possibility of a further increase of vagal activity. In all responder patients administration of a pirenzepine dose higher than the effective one did not induce a further increase in BRS value.

During treatment with 25 mg b.i.d., pirenzepine increased BRS by 58 % (9.16 ± 3.96 vs. 5.71 ± 3.74 msec/mmHg in control condition, p = 0.007). Compared with placebo, at the dose of 25 mg b.i.d. pirenzepine significantly increased all time and frequency domain measures of HRV and augmented by 60 % BRS (10.37 ± 6.82 vs. 6.47 ± 3.22 msec/mmHg, p = 0.0025). Pirenzepine showed a vagomimetic effect that was comparable with that observed with scopolamine; nevertheless, the overall incidence of adverse effects was significantly lower during pirenzepine than during scopolamine condition (1 [5 %] of 20 vs. 10 [50 %] of 20). Thus, oral pirenzepine appeared to have a greater therapeutic potential for the long term treatment of post-myocardial infarction patients than what observed with scopolamine.

Marracini et al. recently found that intravenous pirenzepine may significantly increase exercise tolerance in patients with effort myocardial ischemia compared with saline (26). Time to ischemia and rate-pressure product of ischemia were significantly improved by pirenzepine and the antiischemic effect of pirenzepine was similar to that induced by intravenous isosorbide dinitrate, the reference drug used in the study. Whether the oral dose of pirenzepine used to modulate the cardiac autonomic function could also induce an antiischemic effect still has to be demonstrated.

Overall these data combined with the experimental evidence of the antifibrillatory effect of vagal stimulation fostered the idea that low dose scopolamine could have been an effective tool to reduce arrhythmic risk after myocardial infarction. However, confirmatory data were necessary to prove that such a change in autonomic markers would indeed result in a significant increase in the electrical stability of the ischemic heart.

Experimental evidence: The effect of scopolamine on autonomic markers and on ventricular fibrillation

In order to investigate whether a relation exists between changes in markers of cardiac vagal activity and changes in cardiac electrical stability an experimental study was designed with the specific goal to verify if an intervention known for its ability to increase HRV and BRS would, at the same time, be effective in reducing the incidence of ischemia-induced ventricular fibrillation in the clinically relevant animal preparation (38) in which the capability of BRS and, later, of HRV of predicting risk for arrhythmic death was first described (see above). The effects of low dose scopolamine i.v. on HRV and cardiac electrical stability were studied in dogs with a prior MI that had or did not have ventricular fibrillation during an exercise and ischemia test (20).

Prior to scopolamine, susceptible animals had an average StD of the mean R-R interval lower than that of the resistant ones (136 ± 30 vs. 224 ± 33 msec, – 65 %, $p < 0.01$). This difference was progressively reduced by increasing doses of scopolamine and at 1 and 3 µg/kg the values among the two groups became similar: 322 ± 35 vs. 223 ± 31 msec (NS). At higher dose, 10 µg/kg, StD decreased. The coefficient of variance (i.e., the StD of RR interval corrected for heart rate)

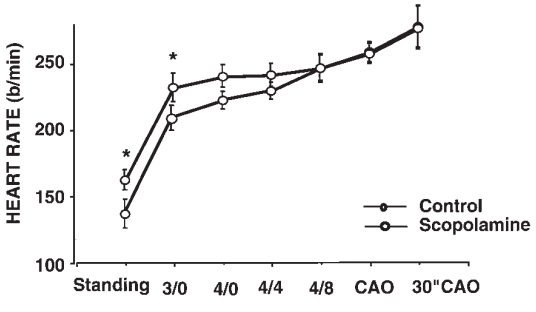

Fig. 5 Heart rate response to exercise and acute myocardial ischemia in control conditions and after scopolamine.

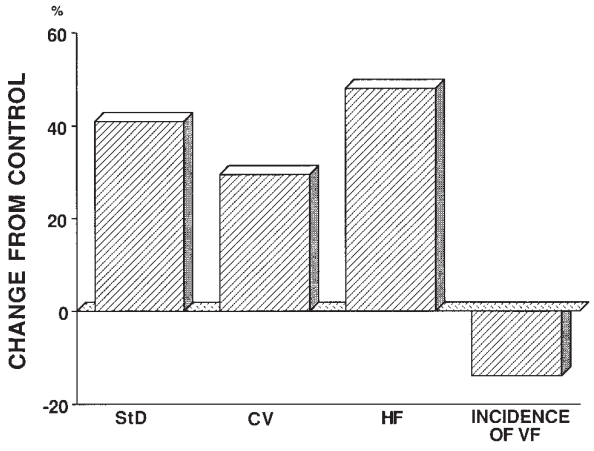

Fig. 6 Effect of low dose scopolamine on different measures of heart rate variability and on risk for ventricular fibrillation during the exercise and ischemia test. Std = standard deviation of RR intervals; CV = coefficient of variance; HF = power in the high frequency band of spectral analysis of heart rate variability.

showed the same pattern observed for the StD. Prior to scopolamine, it was lower by 45 % in the susceptible dogs when compared with the resistant dogs (203 ± 40 vs. 294 ± 33, $P < 0.01$). This difference was reduced to 2 % after administration of 3 µg/kg of scopolamine (224 ± 23 vs. 198 ± 43; NS).

Thus, the effect of scopolamine in autonomic markers in this experimental study paralleled the clinical findings observed in the 4 studies in post-myocardial infarction patients. Additionally, 3.0 µg/kg of scopolamine reduced heart rate at rest and during the lower levels of exercise and ischemia test. However, the chronotropic effect of scopolamine disappeared at higher levels of exercise. During the exercise and ischemia test just prior to the occlusion of the circumflex coronary artery, heart rate was 227 ± 8 b/min in the control test and 226 ± 7 b/min with scopolamine. The reflex response to acute myocardial ischemia was also, in this setting, unaffected by scopolamine. Heart rate at 30 seconds of ischemia was 245 ± 15 b/min in the control tests and 244 ± 15 b/min with scopolamine (Fig. 5).

The critical finding of the study was that scopolamine had minimal antifibrillatory effect. Ventricular fibrillation was indeed prevented in only 1 (14 %) of the 7 susceptible dogs in which it was tested (Fig. 6).

Mechanisms of action of low dose muscarinic receptors blockers and possible explanation of the observed failure

Low dose atropine increases neural activity directly recorded in the vagus (21). Acetylcholine mediates the effects of inhibitory fibers projecting from the ventrolateral respiratory reticular formation on the vagal motoneurons (29). Specifically, during inspiration acetylcholine released from these fibers causes a hyperpolarization of vagal motoneurons and, consequently, a reduction in their firing rate. Atropine, by blocking these inhibitory mechanisms may increase the activity of vagal motoneurons. This hypothesis is supported by the fact that iontophoretic administration of atropine in the area of the nucleus ambiguous increases the activity of vagal-cardiac motoneurons (29). In addition to central actions, peripheral mechanisms, notably blockade of the presynaptic muscarinic modulation of acetylcholine release (53), may contribute to the effect of low dose scopolamine on HRV. This is suggested by the evidence that pirenzepine, the analog of scopolamine that does not seem to have central actions, increases HRV (33).

The chronotropic effects of scopolamine progressively decreased with exercise and were largely lost at the highest workload of the submaximal test. The reflex response to acute myocardial ischemia was also unaffected by scopolamine. Overall, the vagal antagonism of the detrimental electrophysiologic effects of adrenergic activation (22) was absent when mostly needed. Based on these findings, the failure of scopolamine in preventing ventricular fibrillation is no longer surprising, particularly in a preparation in which sympathetic reflexes are major contributors to the occurrence of lethal arrhythmias.

The dose of scopolamine may represent a possible mechanism involved in the apparent discrepancy between effects on autonomic markers and effects on lethal arrhythmias. At doses higher than 3 µg/kg it produces two opposite effects, as it markedly increases efferent vagal activity, while simultaneously blocking the vagal effects on heart rate. Thus, the prevalence of the cardiac post-synaptic vagolytic effect of scopolamine at higher doses limits its use to doses probably inadequate to counteract the elevated adrenergic activation due to exercise and ischemia-dependent reflexes.

Clinical implications

The clinical implications of the present data are that low dose of muscarinic receptors blockers have a positive effect on autonomic markers but seems to be of little effect in reducing risk for lethal events in the acutely ischemic heart specifically at a time when sympathetic activity is elevated. This is in sharp contrast to what has been observed with exercise training, which by affecting several aspects of the cardiovascular system and regulation significantly increases autonomic markers and also provides a striking protection from ventricular fibrillation.

On the other hand the potential importance of a chronic (as with exercise training) versus an acute (as with scopolamine) modulation of the autonomic activity shold not be underestimated. From this prospective the use of pirenzepine, a muscarinic antagonist, that as just described increases autonomic

markers and can be chronically used may open the prospective of long term treatment. The possibility of a chronic modulation of cardiac vagal activity in high risk post-myocardial infarction patients deserves attention. A multicenter pilot study involving the Fondazione Maugeri and the University of Pavia is currently ongoing in Italy. This study is aimed at testing the effects of long term therapy with oral pirenzepine in post-myocardial infarction patients with a depressed left ventricular function and markers suggestive of a depressed cardiac vagal activity. The two main issues to be addressed are the persistence over time of the autonomic effects of pirenzepine and its tolerability. If a chronic modulation of cardiac vagal activity appears feasible, this will open the prospective of testing such an intervention in a large post-myocardial infarction population. The experimental evidence that acute administration of these compounds does not reduce risk for ventricular fibrillation in the setting of a new acute ischemic episode after a recent myocardial infarction does not exclude the possibility that chronic vagal stimulation may favorably influence the recovery from a myocardial infarction and ultimately reduce the risk for lethal events.

Conclusions

The rationale for the attempts to increase autonomic markers in post-myocardial infarction patients rests on the multiple evidende that the risk for cardiac mortality and sudden death is higher among individuals with signs of decreased vagal activity. Contrasting scatter data exists about the effects of beta-blockers, which so far represent one of the most effective treatment after myocardial infarction, on autonomic markers (39). ACE inhibitors, which are also effective in reducing mortality after myocardial infarction, probably exert an useful action on sympathovagal balance (3).

A major limitation to the use of autonomic markers to predict efficacy is represented by the fact the degree of increase in vagal activity that may produce antifibillatory effects is still unknown. Exercise training acts on several aspects of cardiovascular regulation and function, shifts the autonomic balance toward a vagal dominance, and significantly increases cardiac electrical stability. On the other hand, low dose of muscarinic antagonists, while positively affecting autonomic markers, seem to have little effect on cardiac electrical stability specifically in condition of elevated sympathetic activity. A possible explanation for this failure is that acute administrations of these compounds looses efficacy when mostly needed, i.e., in the condition of elevated sympathetic activity. The possibility that chronic treatment with low dose muscarinic antagonists may be beneficial deserves further investigation. However, based on the current knowledge it seems appropriate to call for caution before attributing excessive importance to changes in “markers” of vagal activity in the absence of clearcut evidence for a causal relation with an antifibrillatory effect.

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