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REVIEW

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On the genesis of myocardial ischemia

Zur Genese der myokardialen Ischämie

Zusammenfassung Etwa drei Viertel der myokardialen Ischämien werden vom autonomen Nervensystem getriggert. Die pathognomonische Konstellation besteht dabei in einer Kombination aus weitgehender Blockierung der tonischen Vagusaktivität in Verbindung mit gesteigerter sympathischer Aktivität. Die Reduktion der tonischen Vagusaktivität, charakteristisch für die ischämische Herzkrankheit, wie auch die akuten Blockaden der vagalen Herzimpulse, die zur Ischämieauslösung führen, stehen in keiner Abhängigkeit von koronaren Gefäßprozessen. In dieser Arbeit werden die pathophysiologischen Schritte diskutiert, die von der sympatho-vagalen Dysbalance in die myokardiale Ischämie führen. Eine hochgradige Steigerung der aeroben Glykolyse im Myokard als Folge der autonomen Dysbalance kommt dabei besondere Bedeutung zu.

Schlüsselwörter
Ischämische Herzkrankheit – Myokardiale Ischämie – Autonomes Nervensystem – Kardiale Vagusaktivität – Herzfrequenz-Variabilität (HRV)

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Summary About three quarters of myocardial ischemic events are triggered by the autonomic nervous system. The pathognomonic constellation is a combination of an almost complete withdrawal of tonic vagal activity with increased sympathetic activity. The reduction of tonic vagal activity, which is characteristic for ischemic heart disease, and the acute withdrawal of vagal drive preceding the onset of ischemia are not dependent on coronary artery disease. In this paper, the pathophysiological steps that lead from sympathetic-parasympathetic imbalance to myocardial ischemia shall be discussed. A considerable increase of aerobic glycolysis within the myocardium as a result of the autonomic imbalance is of special importance in this process.

Key words
Ischemic heart disease – myocardial ischemia – autonomic nervous system – cardiac vagal activity – heart rate variability (HRV)

Introduction

The classic model on the onset of ischemia, the combined severe coronary stenosis and increased myocardial performance, always called for a dynamic-functional addition. The reason therefore is that the occurrence of myocardial ischemia is not categorically bound to a specific increase of myocardial performance in daily life. The assumption that ischemia is provoked by coronary spasms has therefore experienced once again a temporary revival throughout the last few decades. Subsequently, the concept of a dynamic stenosis developed. As a result of the NO research, the significance of free radicals and with that the role of oxidative stress in the genesis of ischemia came into the scope of attention over the last few years.

All of these factors contribute to the onset of ischemia merely over a coronary mechanism. A vascular-independent onset of ischemia is described in this paper. The majority of myocardial ischemic events are triggered by the autonomic nervous system. In these cases, the combination of an acute withdrawal of tonic vagal activity with increased sympathetic activity is pathognomonic. The chronic reduction of efferent vagal influences, which is characteristic for ischemic heart disease, as well as their acute withdrawals are in no way dependent on coronary vascular processes.

Over the last fifteen years, the analysis of heart rate variability (HRV) has enabled us to specify the influences of the autonomic nervous system on the heart to a high degree [135]. Nowadays, it is possible to make clear statements on the behavior of the sympathetic and parasympathetic nervous system in ischemic heart disease and in the process of the onset of ischemia. A method-critical introduction into HRV analysis as well as a description of every single subsequently cited article can be found in the following work [129].

Sympathetic-parasympathetic imbalance in ischemic heart disease

HRV analysis enables the determination of tonic cardiac vagal activity independent from reflex influences. The thereby recorded vagal tone is primarily modulated within the hypothalamus by means of biological rhythms and influences of superior centers within the scope of ergotropic-trophotropic controlling processes.

Ischemic heart disease is accompanied by a significant chronic reduction of vagal tone. Tonic efferent vagal activity is characteristically reduced by approximately a third in ischemic heart disease [1, 15, 24, 25, 61, 63, 69, 89, 96, 107, 108, 114, 134, 137, 145]. In acute phases, like instable angina, one can find further drastic reductions of vagal heart activity, for instance by another third [134].

The HRV analysis provided no basis for an increased sympathetic tone in comparison to healthy people, as generally anticipated for ischemic heart disease. One paper, based on the comparison of three different study populations though, had as a result an impairment of sympathetic tone in ischemic heart disease [15].

The circadian rhythm of HRV is disturbed in ischemic heart disease. Characteristically, the parasympathetic regeneration during nighttime is distinctively impaired [25, 69]. The almost complete loss of its circadian rhythm makes clear that the reduction of vagal tone in ischemic heart disease is due to an impairment of the hypothalamic parasympathetic controlling power. Characteristically, there is a sympathetic-parasympathetic imbalance in ischemic heart disease, represented by predominant sympathetic influences due to diminished vagal activity.

The withdrawal of tonic vagal activity in ischemic heart disease stands in no relation to the coronary-sclerotic process [63, 107, 114, 134]. The vagal dysfunction exists independent from the impairment of coronary flow, independent from established coronary risk factors, as well as independent from the functional condition of the left-ventricular myocardium. A withdrawal of vagal heart activity previous to any manifestation of coronary artery disease proved to be an independent predictor for the onset of cardiac events in the following years [137]. The extent of reduced vagal activity among a collective of persons without any perceptible signs of arteriosclerosis was prospectively in significant correlation to the occurrences of myocardial infarction, sudden cardiac death and bypass operation [89].

Sympathetic-parasympathetic imbalance in the onset of ischemia

According to the data on hand, the autonomic nervous system plays an eminent part in the onset of myocardial ischemia [12, 21, 38, 55, 77, 78, 81, 113, 127, 134, 139, 140]. About 80% of ischemic events occurring in daily life are triggered by drastic decreases of cardiac vagal activity [78, 127]. As one can see in Figure 1, a continuous decrease of vagal cardiac activity (hf-HRV) in the last 60 min prior to the onset of ischemia can be found as the fundamental pattern for the onset of myocardial ischemia under daily life conditions. The increasing withdrawal of efferent vagal cardiac activity becomes clearly more and more critical over the last 2–4 min. During the onset of the ischemic event, vagal activity is withdrawn to a large extent to be regenerated after the event [81].

The "HF component" in the HRV spectrum is a clinically proven marker of tonic cardiac vagal activity. Pressoreceptoric reflex influences of both the sympathetic as well as parasympathetic nervous system lead to increases of the "LF component". According to this examination (Fig. 1), such influences are not given before the onset of ischemia. Sympathetic activity increases are identifiable by means of relative increases of LF power compared to HF power. The more or less parallel course of lf-HRV and hf-HRV, the absence of pre-ischemic relative in-

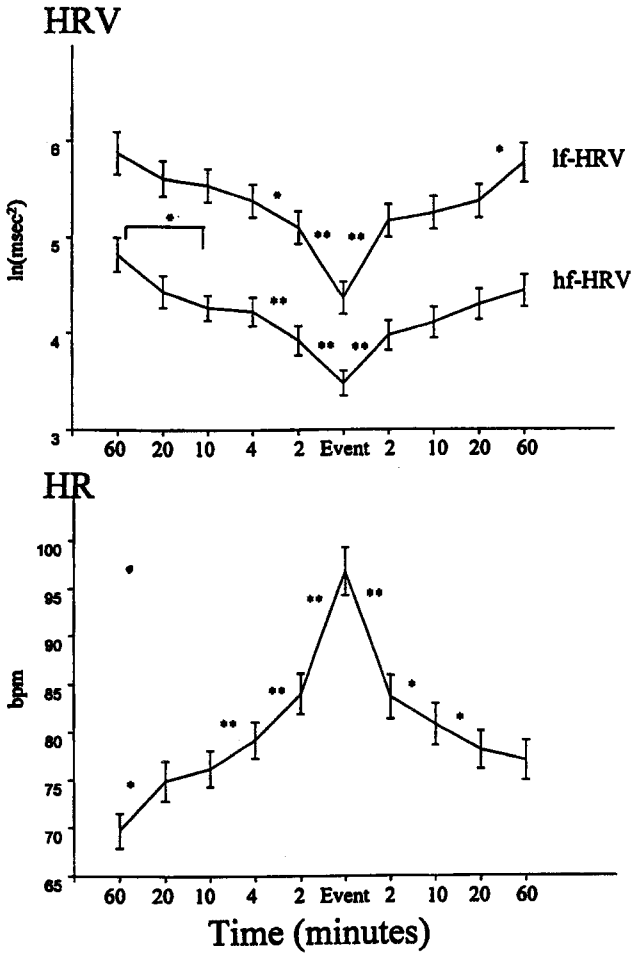

Fig. 1 The behavior of HRV and HR before and after 68 ischemic events among patients with stable coronary artery disease under daily life conditions [81]. Hf-HRV is the marker for vagal activity. The course of lf-HRV compared to hf-HRV provides information on sympathetic activity changes

creases of the LF component in comparison to the HF component implies that generally no immediate increases of sympathetic activity precede ischemic episodes during everyday life.

The pre-ischemic course of vagal activity is exemplarily illustrated in Figure 2 [127]. For our examination, we developed the "wMSD" as an index of HRV, which is based on the grade of the respiratory sinus arrhythmia for the average time period of a respiratory cycle. By this means it was possible to register the course of tonic vagal activity in small steps. The undulating course of vagal activity becomes visible with this method. In Figure 2, such an undulating decrease leads to an onset of myocardial ischemia at the end of the extract.

Figure 3 [127] shows that the final decrease of vagal activity (wMSD) sets in approximately 2 min prior to the onset of ischemia. During the ischemic event the vagal activity remains withdrawn to a high

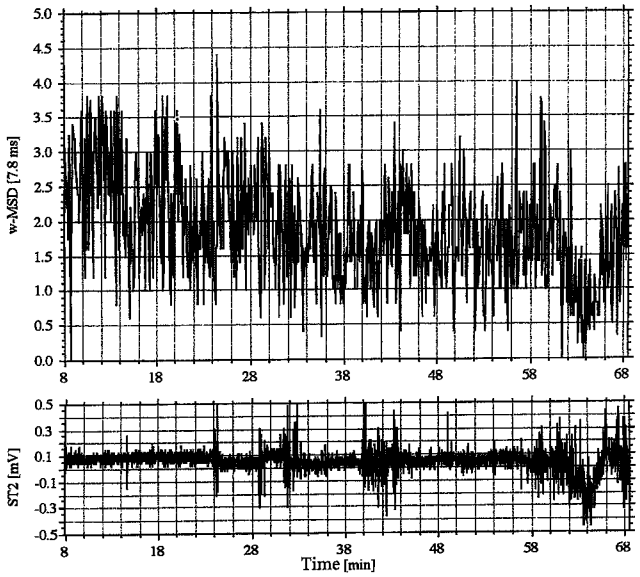

Fig. 2 Course of wMSD and ST in a coronary artery disease patient during an early morning hour (05:08–06:08). wMSD as an indicator of vagal tone gradually decreases with an undulating course. The severe decrease at the end of the extract leads to the onset of ischemia [127]

degree. The recurrence of the vagal activity initiates the end of the ischemia. It became obvious in our examination that a drop below a specific individual threshold value of the HRV for a time period of approximately 1–2 min leads to an onset of myocardial ischemia [127].

Acute increases of sympathetic activity are mostly of no significance for the onset of ischemia, as one can obtain from Figure 1 [81]. Nevertheless, the parasympathetic nervous system does not act freely but always on the basis of sympathetic-parasympathetic balance. Severe withdrawals of vagal activity only induce ischemia in combination with an increased sympathetic activity. Differentiated into day- and night-episodes, it can be shown that myocardial ischemic events during daytime are triggered by a combination of withdrawn vagal activity with enhanced daytime sympathetic tone. In comparison to its base values during nighttime, the distinctly raised sympathetic tone during the course of the day does not require any additional enhancements of sympathetic drive for an onset of ischemia. The nighttime depressions of vagal activity occurring out of the sleep are at times especially impressive; see Figure 4 [128]. At night, severe vagal reductions combine with regular increases of sympathetic activity [78, 101].

In conformity with the examinations on hand, the typical increase of the heart rate prior to an onset of ischemia and in the starting phase of ischemia can be primarily attributed to the withdrawal of vagal

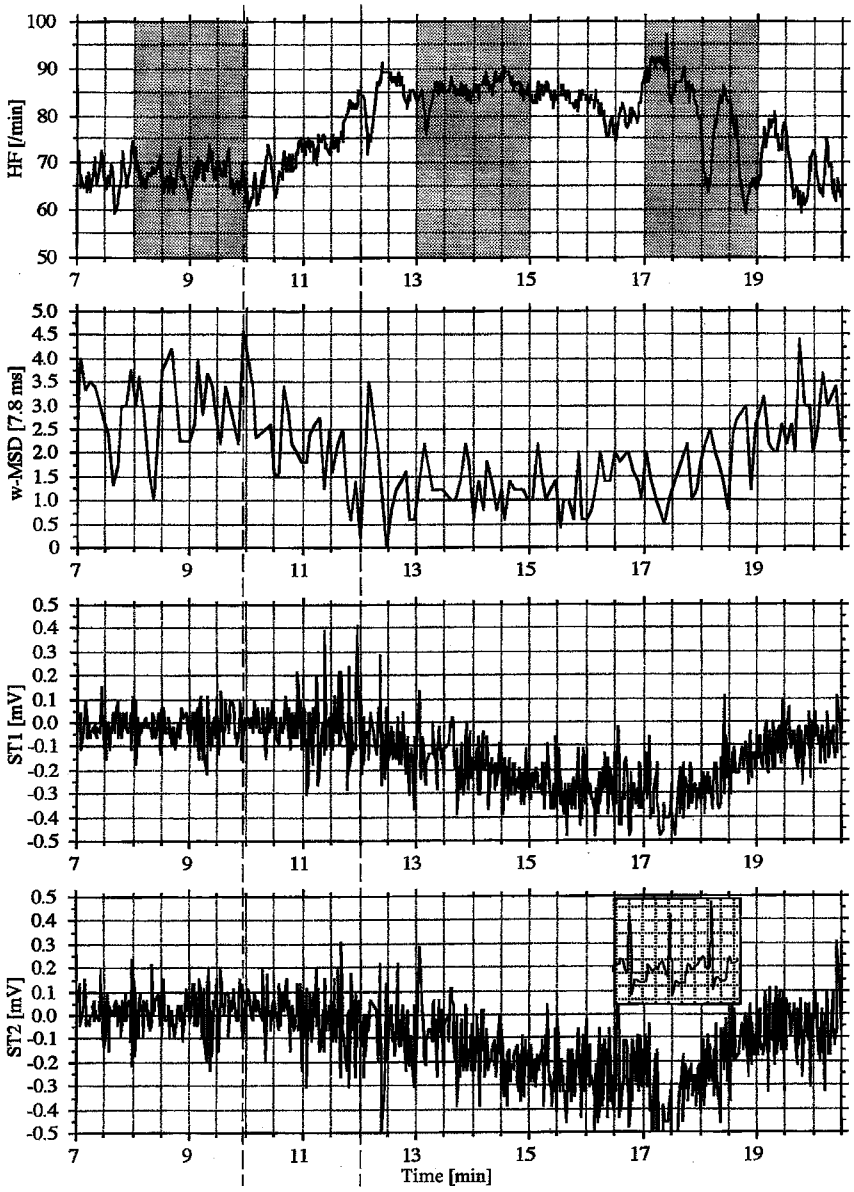

Fig. 3 Example for the course of heart rate (HR) and wMSD as a marker of vagal activity before and during an ischemia with ST depression (ST1 on point J, ST2 80 ms afterwards). The trough-shaped depression of the wMSD precedes a similarly structured course of ischemia by approximately 2 min. The increase of the heart rate after the 17th min enhances the ischemia [127]

activity. Ischemia occurring in daily life shows an average heart rate of about 90 beats per minute at the time of the onset of ischemia [78, 81, 127]. Increases of heart rate in this dimension without a simultaneous reduction of HRV do not lead to an onset of ischemia [127].

According to the present state of knowledge provided by HRV analysis, roughly three-quarters of myocardial ischemic events are triggered by the autonomic nervous system. A temporary extensive withdrawal of vagal heart drive combined with a simultaneously increased sympathetic activity is pathognomonic. Experimental results are still to be expected.

Sympathetic-parasympathetic imbalance in myocardial infarction

One can find drastic reductions of cardiac vagal activity in instable angina [67, 68, 84, 93, 134]. These occur independently from occlusive vascular processes [2]. The extent of vagal withdrawal in instable angina proved to be a prognostic marker in a study: continuous vagal withdrawals came along with persistent recurrent ischemic events, and increases of tonic vagal activity along with improvements [68].

The severe withdrawals of vagal activity in the pre-infarction phase can still be found in the same distinctness 1–2 weeks after an acute infarction.

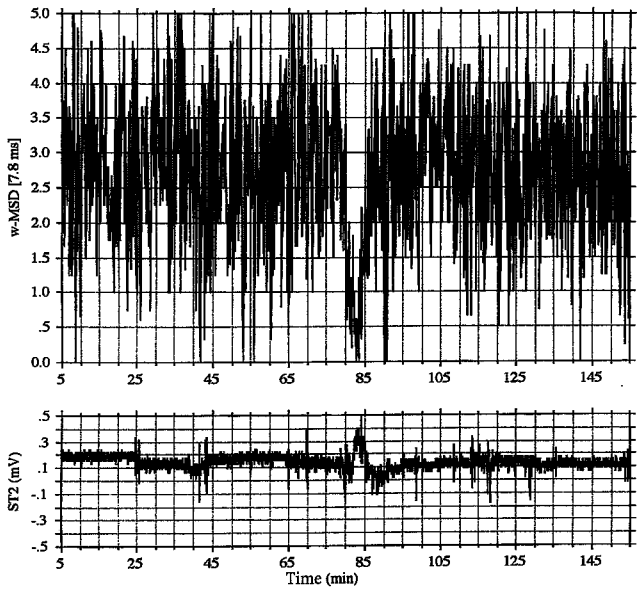

Fig. 4 Example for the drastic decrease of wMSD occurring during sleep that induces an ischemia with ST elevation [128]

After the reflex activation of both branches of the autonomic nervous system has subsided, which occurs during the first days following an acute infarction, the withdrawal of cardiac vagal activity exactly matches the vagal withdrawal during instable angina [67, 68].

As a result of numerous examinations, the extent of vagal withdrawal within the early post-infarction phase proved to be the strongest predictor for the risk of cardiac death within the following years [11, 14, 32, 41, 60, 76, 109, 155]. Reduced vagal activity has a strong association with ventricular arrhythmia and sudden cardiac death. Whenever there is a differentiation between "arrhythmic" and "non-arrhythmic" cardiac death, one can also find a highly significant correlation between reduced HRV after an acute infarction and the non-arrhythmic cardiac causes of death, primarily the cases of death due to re-infarction [60].

Parasympathetic nervous system and ventricular myocardium

In concordance with the present state of knowledge, one has to proceed on the assumption that a majority of myocardial ischemic events are triggered by an autonomic imbalance, which is characterized through a severe withdrawal of vagal drive and synchronously increased sympathetic activity. The basics of the influence of the parasympathetic nervous system on the ventricular myocardium are roughly sketched out in the following sections.

Anatomic fundamentals

Until around 30 years ago, the medical profession worked on the principle that vagal innervation of the mammal heart is limited to the atrium. This view has since then been revised. Vagal fibers, afferent as well as efferent, pass through the AV groove and spread primarily subendocardial within the ventricle in order to supply from there the entire ventricular myocardium with branches. The efferent ventricular vagal fibers are postganglionic with their neurons located in the atrium [16, 154].

The vagal innervation of the atrium is significantly higher than in the ventricle. The density of the cholinergic innervation of the ventricle is assumed to be approximately one fifth in comparison to the atrium [91]. A striking characteristic of the parasympathetic cardiac innervation lies in the neuroeffectoric junction between the cholinergic fiber and the myocardial cell. In this case, they are no typical synapses but the terminal cholinergic fibers form varicosities that release acetylcholine (ACh) into the interstice. ACh diffuses spontaneously over distances of up to many tens of micrometers and thus reaches effector cells within a relatively large area. These facts were described for the first time in 1958 [42] and are now proven [91]. Due to this special neuroeffectoric junction, the parasympathetic nervous system reaches, despite its low postganglionic fiber density, all myocardial cells whose cholinergic receptors are randomly distributed over the entire cellular surface [91].

Physiological fundamentals

Cholinergic receptors in the ventricular myocardium were described for the first time in the 1970s [43] as well as the existence of autonomic nerve fibers in the ventricular myocardium that contain ACh, AChE (acetylcholinesterase), and ChAT (choline acetyltransferase) [22, 75, 118]. Over the last few years, the substantial content of ACh in the mammal's ventricular myocardium has been repeatedly demonstrated in vivo [3, 74].

Intra-coronary infusions of ACh block the positive inotropic effect of catecholamines [65]. Stimulation of the vagal nerves reduces ventricular contractility [35]. During the course of research following these papers, the principle of "accentuated antagonism" became clear soon. Vagal stimulation without

adrenergic stimulation only has a small negative inotropic effect, whereas the same vagal stimulation combined with an increased sympathetic activity shows a remarkable negative inotropic effect [87, 88].

The same applies to the myocardial metabolism. ACh has only a minor influence on the basic glycogenolysis rate. On the contrary, adrenergically enhanced glycogenolysis is inhibited in its activity by two thirds due to addition of ACh [17].

According to the principle of "accentuated antagonism", the enhanced activity on the one hand is firmly bound to an enhanced inhibiting effect due to the antagonistic influence. This principle serves to prevent excessive amplitudes towards one direction. The compensatory control of non-physiological deviations is a basic principle of antagonistic balancing processes.

Adrenergic-cholinergic cooperation in the myocardial cell

Beta-adrenergic stimulation within the myocardial cell leads to an activation of adenylate cyclase, which catalyses the development of cAMP. cAMP, the "second messenger" of the sympathetic nervous system, activates cAMP-dependent protein kinases that once again control the contractile function and the metabolism of the myocardial cell in the sense of sympathetic activation. In complete analogy, cholinergic stimulation leads to an activation of the guanylate cyclase, to the development of cGMP with a consecutive activation of cGMP-dependent protein kinases within the myocardial cell.

Since the 1970s, it is known that the application of ACh on the mammal's ventricular myocardium leads to distinct increases in cGMP content [45, 83, 85, 141], which is induced by activation of muscarine receptors in the myocardial cell [85]. ACh has a negative inotropic effect on the ventricular myocardium, which is triggered by an immediate increase of the cGMP content in combination with a decrease of cAMP [46]. The inhibiting influence of the parasympathetic nervous system on the adrenergically enhanced metabolic activity of the heart is also regulated by an immediate increase of cGMP combined with a decrease of the cAMP content [44].

The various effects of cGMP within the myocardial cell are recorded more and more precisely by contemporary research. It has also been shown on isolated ventricular myocytes that the application of ACh enhances the intracellular content of cGMP and drastically reduces cAMP and oxygen consumption at the same time [53]. On the isolated myocardial cell as well as on the left ventricular free wall, a stimulation of the guanylate cyclase led to significant reductions of contractility and oxygen consumption via an increase of cGMP [40, 133, 143]. The negative functional and metabolic effects of cGMP are more pronounced the more enhanced the myocardial metabolism is [52].

The myocardial cell's function and metabolism are regulated by a highly complex cooperation of cAMP and cGMP. The denervated beating heart consumes ATP; the following increase of ADP stimulates the metabolism. Function and metabolism are regulated separately under autonomic control. A multitude of influences serve to adjust the metabolic activities to the functional requirements.

The interactions between each other play an important role in the concurrence of cAMP and cGMP. Phosphodiesterases (PDE's) regulate the hydrolysis of the cyclic nucleotides. The phosphodiesterases are classified into four major families (I–IV) on the basis of their protein sequence. A cGMP-stimulated PDE II decreases the cell's content of cAMP, a cGMP-inhibited PDE III results in an increase of cAMP within the myocardial cell [125]. With the help of these PDEs, cGMP modulates the cAMP-induced adrenergic activity in the myocardium.

The principle of accentuated antagonism could also be verified on the isolated cardiac myocyte. Increasing cGMP reduced the myocyte function more severely with an increased rather than with a base content of cAMP [144]. This emphasizes the important role of the cGMP-stimulated PDE within the cardiomyocyte [86, 104].

With the help of this antagonistic enzymatic instrument, the effects triggered by cGMP restrict increases of adrenergic activity in the myocardial cell (accentuated antagonism). At the same time, correcting stimulation takes place whenever adrenergic activity severely decreases (reciprocal antagonists stimulation). Both principles together secure the balance of the adrenergic-cholinergic controlling process. The cooperation of the cyclic nucleotides in the myocardial cell follows the dynamics of Yin and Yang [49].

Sympathetic-parasympathetic imbalance and the myocardial cell

HRV analysis has made it obvious that myocardial ischemic events are mostly triggered by an autonomic imbalance characterized through a concurrence of withdrawn vagal activity with increased sympathetic activity. Severe withdrawals of cholinergic activity in the myocardium for a time period of

1–2 min lead to an onset of ischemia in the case of increased sympathetic tone during the daytime or, respectively, in combination with an increase in sympathetic drive during the night.

Cholinergic activity regulates the myocardial content of cGMP. Chronically reduced cholinergic activity, as for instance in ischemic heart disease, results in chronic cGMP reductions in the myocardial cell. The acute withdrawals of cholinergic activity immediately preceding the onset of ischemia induce a temporary severe cGMP impoverishment in the myocardial cell.

According to the principle of accentuated antagonism, even a reduced cGMP level will be sufficient to compensate distinct cAMP increases with all its resulting functional and metabolic effects. However, the sympathetic-parasympathetic balance in the myocardial cell collapses whenever the cholinergic activity drops below a certain threshold for a specific time period.

Following the principle of accentuated antagonism, adrenergic stimulation of the myocardial cell is restricted by cholinergic impulses. The cholinergic inhibiting effect therefore becomes more distinct the stronger the adrenergic stimulation is. In case this inhibiting effect completely stops at a specific point of time, a catapult-like increase of adrenergic activity to a multitude of the initial value results. The adrenergic-cholinergic balance is temporarily annulled. The dropout of the antagonist leads to an uninhibited activation of cAMP-dependent processes.

Epinephrine and myocardium

In order to estimate the consequences of uninhibited adrenergic activity in the myocardial cell, it is sensible to study the effects of epinephrine on the isolated heart.

Fundamental work on the metabolic effects of epinephrine on the isolated heart comes from Williamson (1964). Here it is revealed that epinephrine carries out a two-stage effect on the isolated heart: An immediate strong stimulation of glycogenolysis accompanied by a severe formation of lactate, followed by a long-term increase of the oxidative metabolism as a consequence of an increased performance. The production of lactate is increased eight times. Measurements of the pO_2 within the tissue showed adequate oxygenation of the myocardium under both small and large doses of epinephrine [147]. The extreme lactate production was therefore a result of a severely increased aerobic glycolysis.

An older research paper came to very similar results [51]. Epinephrine immediately increased the performance in the heart-lung preparation and resulted in an instant coronary-venously recordable increase of lactate production in combination with a persisting drop of the coronary-venous pH. An increase of the myocardial O2-consumption only set in with delay.

Glucose is not the first choice substrate of the heart under physiological conditions. Glucose metabolism is inhibited by the presence of fatty acids and ketone bodies. Adrenergic stimulation induces the isolated beating heart to increase glucose utilization due to an enhancement of glucose transport, glycogenolysis, glycolysis and glucose oxidation [36]. The additional energy required for the adrenergically increased performance is provided within the myocardial cell primarily via the glucose metabolism, which is controlled by cAMP.

The application of epinephrine on the isolated spontaneously beating heart perfused with physiologically relevant concentrations of fatty acids led to the following results: extreme increase of glycolysis and glucose oxidation, the oxidation of the fatty acids only increased minimally. Epinephrine induced a decoupling between glycolysis and glucose oxidation in these physiologically perfused hearts. The increase in glycolytic rate was a lot higher than the increase in the glucose oxidation rate with the result of a dramatic increase of the myocardial H^+ production [30]. Therefore, also here we find an increased aerobic glycolysis with the consequence of metabolic acidosis due to adrenergic stimulation.

Thesis on the onset of ischemia

After these preparing thoughts, a thesis on the onset of ischemia as a consequence of a disturbed adrenergic-cholinergic balance can be defined. The almost complete withdrawal of cholinergic activity preceding the onset of ischemia results in a cellular cGMP impoverishment, which leads to an uninhibited adrenergic stimulation of the myocardial cell once it drops below a certain threshold. The consequences of this are increased aerobic glycolysis with consecutive metabolic acidosis as a result of an increased lactate production.

The electromechanic coupling in the myocardial cell is pH dependent. Acidosis blocks the ability of calcium ions to activate contraction [71]. As a result, muscle tension and contractility decrease [59, 71, 94, 126]. The consequent stretching of the myocardial wall leads to an increase of tissue pressure, which results in an impairment of the arterial supply [7]. This process takes place first in areas of the heart muscle that are under the most pressure, thus

mainly the wall of the left ventricle and its inner layers. The contractile dysfunction as result of the acidosis leads to ischemia. The impaired blood flow of a defined muscle area also stimulates glycolysis due to increasingly anaerobic conditions and enhances therefore the acidotic process. In this way, the collapsed adrenergic-cholinergic balance triggers the onset of myocardial ischemia, starting in the subendothelial layers of the left ventricle.

As a result, the heart muscle increases the production of ACh in the ischemic areas by about 20 times. Simultaneously, afferent vagal fibers induce a reflex withdrawal of norepinephrine production, which is also enhanced by ischemia [72, 73]. These measures have the purpose of reestablishing the adrenergic-cholinergic balancing process and therefore have a causal anti-ischemic effect.

A cGMP impoverishment of the myocardial cell can only occur when the axis of NO and cGMP is blocked. As it is generally known, NO is produced in the endothelial cells of the heart. Under physiological conditions, NO diffuses towards the lumen and into the vascular wall with a wide spectrum of effects. Released by the endothelial cells of capillaries, NO diffuses to the myocardial cells and reacts with a soluble form of guanylate cyclase within the myocardial cell. NO and cholinergic stimulation act synergistically on the myocardium via an increase of the myocardial cell's content of cGMP.

On behalf of the phenomenon of a paradox vasoconstriction due to ACh as well as to physiological adrenergic stimulants, it has become clear that NO produced by the endothelium is blocked already in early stages of the arteriosclerotic process [95, 99, 152]. Modern lifestyle causes a significant metabolic strain with the consequence of an excessive production of oxygen radicals in the endothelial cells. NO, a radical itself, reacts rapidly with superoxide radicals with formation of instable peroxynitrite. In this reaction NO disappears. The industrial lifestyle, the strain due to the most various environmental poisons and the denatured nutrition in general as well as the chronic inflammatory arteriosclerotic process in particular are the source of this excessive production of oxygen radicals within the endothelial cells, which results in the blocking of the NO-cGMP axis.

Verification of the thesis

To what extent can the described concept on the onset of ischemia be verified? In the 1960s and 1970s, the metabolic effects of myocardial ischemia were intensively examined. Three methods to set off ischemia came to practice: physical strain, the application of catecholamines and tachycardia induced by atrial stimulation. The most diverse circulatory parameters are influenced by both ergometric strain and catecholamine infusions so that research has after all concentrated on pacing-induced tachycardia because this form of induced strain generally only alters one parameter, the heart rate.

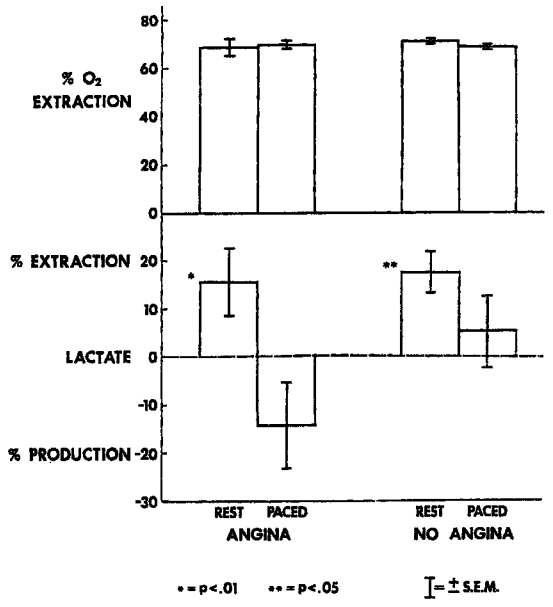

Fig. 5 Changes in oxygen and lactate metabolism induced by right atrial pacing. No changes in O_2 extraction occurred in either the angina or nonangina group with atrial pacing. However, significant changes in lactate metabolism occurred in both groups [64]

As the most essential result of this research, it became evident that the occurrence of myocardial ischemia is usually bound to a significant decline of the myocardial lactate extraction or, respectively, to a lactate production, whereas the oxygen extraction of the myocardium shows no deviations [28, 33, 64, 105, 111]. These correlations can be exemplarily concluded from Figure 5 [54, 64]. In this case, there are 41 patients with coronary artery disease showing a comparable severity of the disease in both groups. Pacing up to the onset of angina was associated with an increase of lactate production without any recordable signs of a lack of oxygen. Even without an onset of ischemia, maximal pacing among patients with ischemic heart disease was combined with lactate abnormalities under unimpaired oxygen supply.

These repeatedly reconfirmed results do not give any evidence that hemodynamically effective coronary stenoses can act as a trigger of ischemia under maximal strain via myocardial hypoxia. The interpretation of these results referred to mixing problems in the coronary sinus, whereupon it should be more likely to register deviations of the lactate meta-

Table 1 Changes in the regional and global myocardial metabolism under maximal atrial stimulation among 7 patients with severe stenoses (≥75%) of multiple coronary arteries including LAD-stenosis [27]

	Preop R	Preop MPR
R%L	+7±1.4	−49±26
G%L	+19±4.8	−22±12
AIV pO_2 (mmHg)	18±1.7	19±1.7
AIV O_2 Sat (%)	30±2.7	33±3.0
CS pO_2 (mmHg)	19±1.3	19±1.8
CS O_2 Sat (%)	32±1.8	33±3.0
Hb (g%)	14.5±0.41	14.5±0.41
ART-AIV O_2 Content (ml%)	13.0±0.28	12.1±0.31
ART-CS O_2 Content (ml%)	12.7±0.34	12.1±0.30
CSBF (ml/min)	136±24	261±40
Global O_2D (ml/min)	25.0±4.4	49.5±8.1
MVO_2 (ml/min)	17.3±2.7	31.8±4.7

R at rest; *CS* coronary sinus; *MRP* at maximum pacing rate; *Hb* hemoglobin; *R%L* anterior wall lactate extraction; *ART* arterial; *G%L* global lactate extraction; O_2D oxygen delivery; *AIV* anterior interventricular vein; *CSBF* coronary sinus blood flow; MVO_2 myocardial oxygen consumption

bolism than those in the O_2 extraction [54]. However, it was clearly documented in animals that coronary flow impairments are first noticeable by a significant increase of O_2 extraction with a subsequent occurrence of lactate production [117, 122].

Lactate production in combination with unchanged oxygen extraction indicates increased aerobic glycolysis and is in keeping with the described thesis on the onset of ischemia. Significant drops of the lactate extraction without any signs of ischemia and lactate production in the case of ischemia are compatible with the assumption that an increasing metabolic acidosis due to increased aerobic glycolysis can act as a trigger of ischemia.

In the following study, one tried to bypass the mixing problems in the coronary sinus. Under maximal pacing-induced tachycardia up to the onset of angina, blood samples were drawn not only from the coronary sinus but also from the anterior interventricular vein (AIV) from 7 patients with multiple significant coronary stenoses (≥75%), always including LAD-stenosis [27]. This vein drains the area that is supplied by the LAD. In this study pre- and postoperative measurements were performed before and after a bypass operation. The preoperative results are listed in Table 1.

These results disprove the mixing argument. The reason therefore is that one can find a distinct lactate production along with completely normal oxygen values in both the local vein as well as in the coronary sinus under maximal pacing rate. This leads to the conclusion that the ≥75% stenoses of the LAD were entirely collaterally compensated during the tachycardiac strain up to the point of the onset of ischemia. A regional hypoxia as the reason for ischemia can be excluded. What is found is an increased aerobic glycolysis with maximally stimulated lactate production. The following metabolic acidosis is suitable to explain the occurrence of ischemia.

The presence of enhanced aerobic glycolysis in ischemic heart disease can also be verified on the basis of the glucose metabolism. Glycolysis as well as the entire glucose metabolism are adrenergic-cholinergically regulated. It has been shown on the beating heart as well as on isolated myocytes that cGMP inhibits the uptake of glucose into the myocardial cell and also the glycolysis rate of the myocardium [9, 37]. By doing so, the cholinergic impulses put up resistance to excessive adrenergic stimulation.

On the contrary, it has also been shown that a withdrawal of cGMP results in a significant stimulation of the glucose metabolism under aerobic conditions in both the myocardial cell as well as the isolated beating heart [9, 37]. A withdrawal of cholinergic impulses induces an enhanced aerobic glycolysis in the myocardium.

Using PET, a study on patients with chronic stable angina showed no differences in the regional myocardial glucose metabolism at rest compared to healthy control persons. In the recreational phase following a strain-induced ischemia, increased glucose utilization was found in those areas that had shown an abnormal perfusion during the stress test. The increased glucose metabolism persisted after all other parameters that had changed during strain, including myocardial perfusion, had normalized [26].

In the same study, the regional and also the global myocardial glucose metabolism were already increased at rest without any symptoms or signs of ischemia among patients with instable angina characterized by repetitive occurrence of spontaneous ST-depressions [26]. Subsequently, both patient groups showed signs of increased aerobic glycolysis. One has to assume a reduced cholinergic activity among both patient groups, more so though with instable than with chronic stable angina.

Coronary consequences

Autonomically triggered myocardial ischemic events are principally reversible. As one can obtain from the Holter records, vagal withdrawals resolve again after an average time period of 5–10 min. Counterregulating, protective processes like the intramural ACh release are known. In how far these ischemic events in case of a longer duration can result in a "non-Q-wave" infarction, is still to be clarified.

Autonomically triggered ischemic events are not strain-dependent, they do not develop during hemodynamic rest and they are also not dependent on coronary vascular processes. However, as a result of such an ischemia, secondary vascular lesions in the coronary-arterial system can occur. The sudden increase of the peripheral vascular resistance accompanying the onset of myocardial ischemia results in abrupt pressure increases within the supplying artery. In this case, tears in the intima and ruptures of plaques can occur, which then themselves can possibly trigger thrombotic-occlusive vascular processes.

It has been known since the 1980s that acute thrombotic occlusions of low-grade stenoses are significantly associated with the occurrence of myocardial infarctions. In the publication of Ambrose et al. (1988), patients with a "Q-wave" infarction showed a stenosis of an average of 34% in the supplying artery during a previous angiography. In no case was the stenosis previously larger than 70%. In a third of all cases, no vascular lesions were found in the artery that led to the infarction. In this study, intima tears of smooth vascular surfaces or plaque ruptures of insignificant stenoses were the starting point for acute thrombotic-occlusive processes in all cases of transmural infarctions. These statements have repeatedly been confirmed [23, 90]. They indicate that severe, over 70% stenoses are generally well compensated by collaterals.

The occurrence of myocardial ischemia as a result of a collapsed sympathetic-parasympathetic balance is without doubt a vast stressor for the respective vascular surfaces due to the therewith triggered pressure increases. This becomes critical whenever endothelial lesions occur in vascular areas that are not sufficiently collaterally compensated, like ruptures of insignificant stenoses or tears of previously unimpaired vascular surfaces. In case of repeatedly occurring ischemic events, the thereby triggered occlusive vascular process can be stimulated by repeated tears of the vascular surface. It is therefore imaginable that the autonomically triggered ischemia results in a transmural infarction.

Variation of vagal activity

The essential variable that leads to the onset of ischemia due to a sympathetic-parasympathetic imbalance is the tonic cardiac vagal activity. The modulation of tonic vagal activity takes place centrally and can be indirectly determined from the variation of respiratory sinus arrhythmia (RSA). The fundamental factors that vary tonic vagal activity during the course of life have been determined by means of the HRV analysis.

The first data on a genetic influence on HRV have been submitted [123]. Age and sex have a strong effect on HRV. The RSA shows an approximately linear decline between the ages of 20 and 80 [120, 121, 150]. The tonic vagal activity is more strongly developed among women than men, especially before menopause [148]. The female cycle stimulates the central autonomic dynamics in periodical rhythm [119].

Natural rhythms influence lastingly the central autonomic controlling forces. Nighttime and sleep are fundamental regenerators of tonic vagal activity. Regarding the change of seasons and the influence of climate, it is so far known that HRV is lower during the winter than during the summer [82].

Physical and mental strain is accompanied by decreases of cardiac vagal activity that correlate with the degree of strain [6, 19, 103, 124, 138, 149]. Physical exercise increases whereas a sedentary lifestyle decreases the vagal tone [18, 39, 50, 97, 115, 130]. Severe smoking decreases the HRV [62, 100, 131, 151].

Tonic vagal activity is reduced in essential hypertension [5, 70, 79, 80]. Also without autonomic neuropathy (ADN), diabetes mellitus is accompanied with a decrease in HRV [10, 57, 102]. In the same way as in ischemic heart disease, one has to therefore proceed on the assumption of a decrease of the central parasympathetic controlling power in hypertension and diabetes. The neuropathy of the sympathetic and parasympathetic myocardial fibers in ADN directly impairs the autonomic control of the myocardial cells.

Especially during childhood, HRV analyses have made it clear that a vivid emotional and relational life is of crucial importance for the development of tonic vagal activity. Permitting feelings, emotional expressiveness and the ability to relate strengthen the vagal tone. The suppression of feelings and affects as well as a lacking ability to relate weaken cardiac vagal activity already during childhood [8, 29, 34, 47, 56, 112, 132]. Touch [58], sex [20] and love [98] stimulate cardiac vagal activity.

Psychological processes apparently influence the central parasympathetic power to a large extent. By means of HRV analysis, it is proven today that the tonic vagal activity is an integral part of the socio-emotional development of a human being [129]. The liveliness of the emotionality on the basis of a stable emotional controlling ability is a decisive force for the development of vagal tone and vagal reactivity. Chronic suppression of the expression of feelings weakens the vagal tone [66]. A lack of relations, the loss of social support and social isolation inhibit cardiac vagal activity [66]. Depression in general and especially after a myocardial infarction coincides in most cases with an obvious reduction of vagal activity, as it has been documented in numerous studies.

The variable "tonic cardiac vagal activity" underlies the most different influences. The socio-emotional development during childhood seems to be of imprinting influence on the basal vagal tone in later life. Older age has the consequence of a substantial loss of tonic vagal activity. The modern lifestyle with its various strains, the loss of natural rhythms, sedentary lifestyle and further harmful behavior predisposes to a chronic withdrawal of vagal activity. Exhausting strains that do not lead to the desired recognition but to frustration and offence can dangerously withdraw the cardiac vagal activity if the regarding emotions are rigidly suppressed. This applies similarly to the loss of a beloved person when the affected reacts with social withdrawal. In those phases, commonplace strains, anger that does not find an outlet, unwanted reactivations of disappointments and insults going back as far as childhood, which are immediately suppressed again, can completely withdraw the vagal activity. The resulting loss of the adrenergic-cholinergic balance in the myocardium leads to a disinhibition of adrenergic activity with a consecutive onset of ischemia.

Obviously, cardiac vagal activity can also be therapeutically influenced. Beta-blockers and ACE inhibitors result in an increase of tonic vagal activity [31, 92, 106, 153]. It has been shown that the anti-ischemic effect of beta-blockers correlates with an increase of vagal tone [142]. Scopolamine enhances the cardiac vagal tone in shortest time. An anti-ischemic effect of scopolamine transdermal patches on coronary artery disease patients has been described [77].

Ouabain (g-strophantine) leads to a release of ACh in the myocardium [116, 136]. Manganese ions stimulate guanylate cyclase in the myocardium [48]. One can expect anti-ischemic effects of these pharmaceutics. The acute ischemia-resolving effect of glyeroltrinitrate should not only be based on its vasodilative effect but also on the fact that NO boosts the blocked production of cGMP within the myocardial cell with the result that the annulled balancing process of cAMP and cGMP is taken up again.

Therapies targeting for autonomic balance, such as relaxation, breathing exercise, meditation, yoga, qigong and our traditional European natural therapies are suitable to increase vagal tone. Connected with group work in order to "open up the heart" [110], there is an enormous so far almost unutilized potential for the increase and stabilization of tonic vagal activity and thereby for the prevention of cardiac ischemic events.

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