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Routine Heart Rate-Based and Novel ECG-Based Biomarkers of Autonomic Nervous System in Sports Medicine

Herzfrequenz-basierte und neue EKG-basierte Biomarker des autonomen Nervensystems in der sportmedizinischen Diagnostik

REVIEW

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Summary

› **In the last years** biomarkers of the autonomic nervous system have been increasingly used in sports medicine to optimize guidance of training intensity and detect training-induced fatigue. Especially heart rate-based biomarkers, including heart rate variability (HRV) and heart rate recovery (HRR) have been tested extensively in these fields for many years. Recently, novel ECG-based biomarkers deceleration capacity (DC) and periodic repolarization dynamics (PRD) have been established and hold promise for future sports research. These markers reflect influences of sympathetic and vagal nervous systems and can be modulated by external and internal factors such as stress, sports, hypobaric/hypoxic states at high altitude or under hyperbaric conditions while diving. Furthermore, these markers are used for risk stratification of sudden cardiac death (SCD) in cardiovascular patients.

› **In this review** we briefly highlight these autonomic biomarkers in sports performance diagnostics and high altitude medicine as well as diving and illustrate their role as predictors of SCD. Due to the extent of the review we focus on the most established and promising parameters: heart rate variability (HRV), heart rate recovery (HRR), periodic repolarization dynamics (PRD) and deceleration capacity (DC). We aim to provide an overview of their current and potential application in sports medicine and discuss current challenges in interpretation.

Zusammenfassung

› **Biomarker des autonomen Nervensystems** wurden in den letzten Jahren vermehrt in der Sportmedizin zur Optimierung der Steuerung der Trainingsintensität und zur Detektion von Trainings-induzierten Erschöpfungszuständen integriert. Hierbei wurden in den letzten Jahren besonders die Herzfrequenz-basierte Biomarker heart rate variability (HRV) und heart rate recovery (HRR) ausführlich validiert. Vor kurzem wurden neue EKG-basierten Biomarker deceleration capacity (DC) und periodic repolarization dynamics (PRD) etabliert. Sie spiegeln den Einfluss des sympathischen und parasympathischen Nervensystems wider und werden durch äußere sowie körpereigene Einflüsse inklusive Stress und Sport, aber auch hypobare/hypoxische Zustände in der Höhe und hyperbare Zustände beim Tauchen moduliert. Diese autonomen Biomarker spielen zudem eine Rolle im Rahmen der Risikostratifizierung bei herzkranken Patienten hinsichtlich plötzlichem Herztod.

› **In diesem Übersichtsartikel** beleuchten wir diese autonomen Biomarker hinsichtlich ihres Einsatzes in der Sportleistungsdiagnostik, Höhenmedizin, beim Tauchen und als Prädiktoren des plötzlichen Herztods. Aufgrund des Umfangs der Arbeit fokussieren wir uns auf die am längsten etablierten und klinisch vielversprechendsten Parameter heart rate variability (HRV), heart rate recovery (HRR), periodic repolarization dynamics (PRD) und deceleration capacity (DC). Wir möchten zudem einen Überblick darüber bieten, wo im Bereich der Sportmedizin die Messung dieser autonomen Biomarker praktikabel und vielversprechend erscheint und gehen auf Probleme bei der Interpretation der Marker ein.

KEY WORDS:
Periodic Repolarization Dynamics, Deceleration Capacity, Training Control, Risk Stratification, Sudden Cardiac Death, Heart Rate Variability

SCHLÜSSELWÖRTER:
Periodic Repolarization Dynamics, Deceleration Capacity, Trainingssteuerung, Risikostratifizierung, plötzlicher Herztod, Herzfrequenzvariabilität

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Introduction

From rest and sleep to work and workouts, our heart has to adapt its activity to meet the demands of the body during the day. The autonomic nervous system (ANS) plays a pivotal role in regulating our heart rate, cardiac contractility and blood pressure. Sympathetic hyperactivity interacts with renin-angiotensin-aldosterone system, increases blood pressure as well cardiac pre- and afterload and worsens heart failure (29, 52). The autonomic nervous system directly affects cardiac electrophysiology modulating the intrinsic heart rate generated by the sinoatrial node, as it changes ion channel currents, their expression and consequently action potential duration (40).

Measurement of resting as well as exercise heart rate has been established throughout decades in team sports and endurance athletes to estimate ANS activity and this has provided vital insights in the connection between the autonomic nervous ›

Table 1

Frequently calculated HRV parameters and their physiological background (13, 16, 39, 56, 61, 68, 69, 72, 73).

FREQUENCY-DOMAIN	UNIT	DESCRIPTION	PHYSIOLOGY
ULF power	ms^2	absolute power of the ultra-low-frequency band (≤0.003 Hz)	To date there is no consensus regarding the underlying mechanisms. Circadian modulations, core body temperature, metabolism and RAAS are suggested to be involved in modulation
VLF power	ms^2	absolute power of the very-low-frequency band (0.003-0.04 Hz)	Sugessted to be intrinsically generated by afferent intracardiac neurons. Amplitude and frequency of oscillations modulated by efferent sympathetic activity. Indicates sympatho-vagal balance and is influenced by kydney functioning incl. RAAS.
LF power	ms^2	absolute power of the low-frequency band (0.04-0.15 Hz)	Initially suggested to mirror sympathetic activity. Recent findings state predominantely parasympathetic activity. LF oscillations mirror information about blood pressure control (baroreceptor and modulation of vasomotortone)
HF power	ms^2	absolute power of the high-frequency band (0.15-0.4 Hz)	Mirrors predominantly parasympathetic activity. HF oscillations show respiratory influences on heart rate
LF peak	Hz	peak frequency of the low-frequency band (0.04-0.15 Hz)	Shows peak frequency of LF spectrum
HF peak	Hz	peak frequency of the high-frequency band (0.15-0.4 Hz)	Shows peak frequency of HF spectrum
LF power	%	relative power of the low-frequency band (0.04-0.15 Hz)	(See absolute LF power)
HF power	%	relative power of the high-frequency band (0.15-0.4 Hz)	(See absolute HF power)
LF/HF ratio	%	ratio of LF-to-HF power	Initially described as an index showing balance between sympathetic and parasympathetic nervous system. As LF power is predominantly related to vagal activity and not to sympathetic activity, as heart rate per se, mechanical events and respiration can influence LF/HF ratio independent of ANS activity. There is no clear physiological basis for LF/HF ratio at the moment.

system and fitness, fatigue and performance ability. As these aspects have been recently discussed broadly (15, 67) our review aims to provide information about "calculated" biomarkers heart rate variability (HRV), heart rate recovery (HRR), deceleration capacity (DC) and periodic repolarization dynamics (PRD) as we think these previously obtained results provide an interesting basis for future research in sports diagnostics particularly as evaluation of DC and PRD has only been started recently in this field.

These biomarkers have been established to monitor autonomic nervous function and detection seems increasingly important in competitive and non-competitive athletes due to several reasons: Firstly, exercise training is able to modulate autonomic function. Secondly, biomarkers may guide regulation of training intensity, improve performance and show fatigue states in leisure-time as well as elite sports. Furthermore, biomarkers are suggested to estimate physiological parameters including anaerobic thresholds (AT) (21). Lastly, these biomarkers hold promise to be useful for risk stratification and eligibility for different sports in athletes with known cardiovascular diseases especially as autonomic dysfunction is directly linked to the occurrence of malignant cardiac arrhythmias (36) and sudden cardiac death (SCD)(4).

Autonomic Biomarkers in Sports Diagnostics and their Relation to Exercise Training

Heart Rate Variability (HRV)

HRV has become increasingly interesting in sports research and for training groups as it is easily and non-invasively recordable and captures aspects of both sympathetic and parasympathetic nervous system (8). Heart rate variability is subdivided in different HRV-indices which measure different aspects of HRV. It can be analysed in time and frequency domain (for spectral indices). Standards of measurement and interpretation of values have been proposed by a task force of the European Society of Cardiology and the American Heart Rhythm Society and detailed information can be gained in its statement paper (72): In short, for time domain methods the so-called normal-to-normal(NN) intervals (all intervals between adjacent QRS complexes resulting from sinoatrial node depolarization) are detected and used for further calculation of indices. Spectral analysis assess low frequency (LF) power (0.04–0.15 Hz), high frequency (HF) power (0.15–0.40 Hz) and the LF/HF ratio (46). Regularly calculated time and frequency indices and their physiological influences are shown in Table 1 (13, 16, 39, 56, 61, 68, 69, 72, 73).

Over the last years studies have investigated HRV in sports and cardiovascular medicine and evaluated HRV in performance diagnostics. Here, HRV indices as functional parameters of the autonomic nervous system have been tested under resting, exercise and post-exercise conditions:

Under resting conditions, differences in HRV between trained and untrained persons have already been described decades ago with 24h-parasympathetic activity being greater in trained than untrained ones (28). During exercise, autonomic function changes physiologically as nicely illustrated by Hottenrott et al. who showed changes of beat-to-beat R-R interval variability and HRV power spectra in a male leisure-time cyclist during exercise testing and differences in spectra according to intensity of training (50% and 80% of $\dot{V}O_2max$) (34). The promising value of autonomic parameters in sports diagnostics is further supported as parameters of HRV are directly linked to functional parameters of training exertion: Heart rate variability threshold (HRVt) coincides with lactate threshold (LT) and ventilatory threshold (VT) during graded exercise (41). Anaerobic threshold (AT) was determinable by HRV measurements in swimmers providing a useful tool for training monitoring and guidance in future (21).

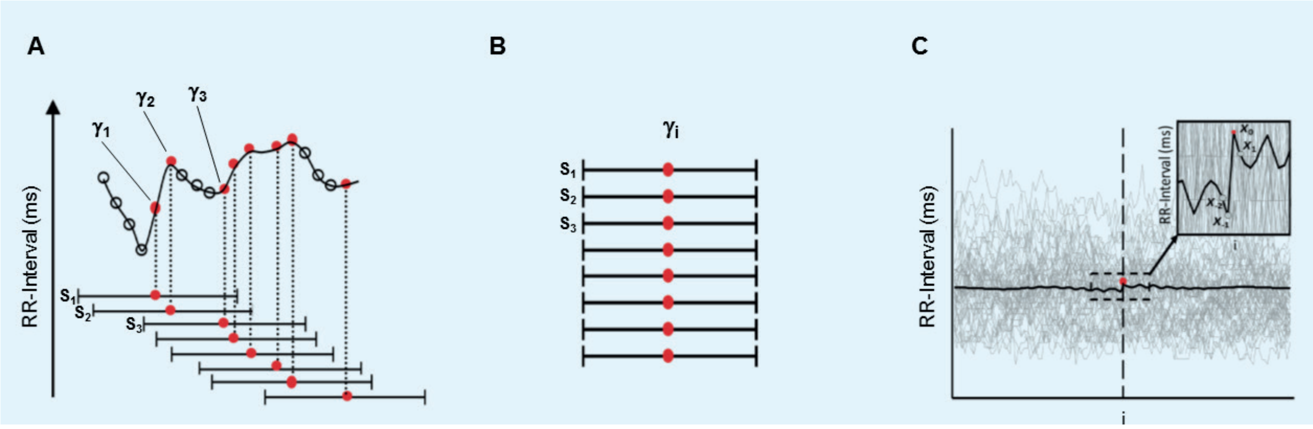

Figure 1

Assessment of DC: A=Definition of anchors. Heartbeat intervals longer than the preceding interval are identified as anchors (red spots; γ1, γ2, γ3,…). Segments of interval data around the anchors (S1, S2, S3,…) are selected. B=Phase rectification. Segments are aligned. C=Phase-rectified signal averaging (PRSA). The PRSA signal X(i) is obtained by averaging the signals within the aligned segments. DC is quantified by wavelet analysis. DC=deceleration capacity. Adapted from (5).

Consequently, as HRV changes during the different stages of exercise and recovery and as they are linked to physiological performance parameters, research groups have tested the value of HRV indices in the context of training surveillance, performance and diagnosis of fatigue and overreaching. Vesterinen et al. found HRV-guided training to significantly improve 3000m running performance compared to a standardized non-guided training group (74). Changes in indices of HRV were found to indicate negative and positive adaptations in response to endurance training and recording HRV indices has therefore been tested for monitoring athletes training adaptation to optimize performance and avoid non-functional overreaching (7, 18, 54): Here, to the current knowledge assessment of 5 min of supine resting HRV capturing vagal activity as well as assessment of submaximal exercise heart rate seem to be most promising as it does not show large day-to-day variabilities compared to assessment of HRV indices during exercise (16). Especially the natural logarithm of the square root of the mean sum of the squared differences between R–R intervals (lnrMSSD) has become an important tool to monitor athlete's adaptation to training as it can be reliably recorded in ultra-short-term ECG segments (24) and is only little influenced by breathing patterns (16). Plews et al. suggest longitudinal monitoring to trace each athlete's HRV fingerprint and found increasing HRV values in elite athletes to be a sign of positive adaptation approaching competitions and coping with training load whereas reductions in HRV shortly before pinnacle events may represent an increasing ability to perform. Especially increases in vagal-related indices of resting and post-exercise correlate with positive adaptation to training and allow increases in performance. Noteworthy, increases in HRV were also found in response to overreaching while HR acceleration was found to decrease in response to overreaching training and could therefore be a potential indicator of training-induced fatigue (7). Daily measurements of resting morning lnrMSSD and computing the lnrMSSD/R-R ratio is promising to distinguish between an enhanced readiness to perform (positive adaptation to training) and maladaptation to training with fatigue, especially in endurance athletes (16). Nevertheless results have to be still taken with care: to date there is still no clear HRV profile indicating overreaching as some study groups found increased, decreased or stable modulation (18). This might be due to different assessment methods, day-to-day variation in HRV indices or differences in training protocols as well as due to a lack of large randomized trials. Correct interpretation of HRV indices thus is challenging and training phase, training load, typical errors of variables as well as other measures of fatigue and performance including psychometric and neuromuscular markers have to be included in analysis in order to distribute training intensity (16).

As sports modulates autonomic function and intensive exercise training can improve autonomic function with significant increases in indices of HRV promoting parasympathetic dominance (55), exercise training is a promising tool to improve autonomic dysfunction in patients with underlying heart diseases. Therefore studies evaluated HRV-guided training in these patients: For example, one study detected improved heart rate variability (SDNN and rMSSD) in patients with heart failure (NYHA II-III) indicating a positive effect of exercise training on autonomic dysfunction and likely prognosis (48). In patients after coronary artery bypass graft surgery (CABG) low volume high-intensity interval training had greater effects on HRV by increasing R-R interval, SDNN, rMSSD and HF, and by decreasing LF and LF/HF ratio than moderate-intensity continuous training. This indicates that training modality and intensity might have an important impact on recovery of autonomic nervous system with coronary artery disease (27). Therefore, exercise training programs in cardiac rehabilitation aim to restore sympathetic-vagal balance and try to enhance vagal activity as this seems to be based on our current knowledge one of the key mechanisms to prevent malignant arrhythmogenicity and to reduce mortality.

Nevertheless, interpretation of results still remain challenging as HRV is dynamic and sensitive to environmental conditions. Consequently, its influence by chronotype, time of the day, life style factors, genetics and diseases has to be taken into account (62, 76).

Heart Rate Recovery (HRR)

HRR functions as another important ECG-based tool in assessing autonomic dysfunction. After exercise the decline in heart rate is considered to be due to a gradual increase in vagal activity (2) and is used to monitor parasympathetic functional capability. To measure this heart rate decay after exercise different protocols exist with different time points and work loads. Here, exercise can be conducted up to maximal exhaustion or up to submaximal work load e.g. until reaching the anaerobic threshold or other differently defined endpoints. Probably most established indices of HRR are t30 and Δ60. Here, Δ60, › which is defined as the absolute difference between heart rate immediately at the end of exercise and after 60 sec recovery time, was shown to be the most reliable parameter (22). The time constant of the HR decay with the first 30 sec (t30) is usually calculated by a method shown by Imai et al. (37): Shortly, a linear regression analysis is performed on the natural logarithm of HR data plotted against the time for the first 30 s after exercise. The t30 is determined as the negative reciprocal of the slope of the regression line. We refer to the corresponding studies for further details.

HRR is significantly increased in both strength- and endurance-trained athletes compared to untrained healthy adults (37, 51). Training modalities seem to influence HRR as high-intensity interval training was shown to be more successful in improving HRR and anaerobic power in well-trained endurance athletes compared to polarized training or high volume low intensity oriented training (70). HRR after exercise can track training status and a faster HRR may be an indicator of training advances in athletes and healthy individuals as it was nicely reviewed by Daanen et al. in a meta-analysis (20). Lamberts et al. showed HRR as a monitoring tool to detect changes in endurance performance and training-induced fatigue: Athletes showing a decrease in HRR during high intensity training had a worse average power during a 40 km trial than those athletes with an increase in HRR (45). Nevertheless, other studies suggested that a faster HRR is not systematically associated with performance improvements: Therefore HRR changes have to be considered in the context of training phase and the athlete's level of fatigue and performance response and HRR measurements after submaximal exercise seem to be more precise indicating functional-overreaching than after maximal exercise (3).

Novel ECG-Based Biomarkers: Deceleration Capacity (DC) and Periodic Repolarisation Dynamics (PRD)

Deceleration capacity of heart rate is a novel parameter of HRV and its determination is visualized in figure 1. It is based on a novel mathematical signal analysis method (PRSA, phase-rectified signal averaging) which transforms complex time series, i.e. heart rate recordings, into a significantly shorter signal (5). The PRSA-signal contains periodic components of heart rate reflecting autonomic modulations, while noise and non-stationarities are eliminated. The method allows for an isolated analysis of oscillations associated with an acceleration as well as a deceleration of heart rate. Since DC represents an integral measure of oscillations associated with a deceleration of heart rate, it is believed to mainly reflect the vagal branch of the cardiac autonomic nervous system. In clinical studies in post-infarction patients, DC was shown to have a stronger predictive value for mortality when compared with conventional HRV parameters (5, 57). Since DC allows for a quite specific estimation of vagal tone, it provides a promising tool in the field of sports medicine. Up to now there are only few studies, which used DC in the context of sports medicine. McNarry et al. performed a cross-sectional study in 70 healthy adults investigating the influence of age and aerobic fitness on HRV and PRSA indices. They found that DC levels are significantly higher in participants with a higher fitness level as well as in younger participants (47). Nasario-Junior et al. adapted DC and included the measurement of the velocity of change in the PRSA curve and found that the modified index can appropriately discriminate athletes from sedentary subjects (49). However, future research is needed to profoundly investigate the role of DC in sports medicine.

Periodic repolarization dynamics is another promising autonomic marker based on the assessment of dynamic beat-to-beat changes of cardiac repolarization (60). It can be assessed non-invasively by the use of a high-resolution ECG in orthogonal (i.e. Frank lead) configuration. The spatiotemporal information of each T wave is integrated into a single vector T, defining the main direction of the T wave in space. The instantaneous degree of repolarization instability can be calculated by the angle dT between two successive repolarization vectors. When plotted over time, the dT-signal shows typical low-frequency (ca. 0.1 Hz) oscillations at rest (Figure 2).

Physiological and experimental studies revealed that PRD correlates with efferent sympathetic activity, known to be clustered in low-frequency bursts. Physiological provocations that lead to an enhancement of sympathetic activity (i.e. exercise) result in increased PRD levels. On the other hand, PRD can be suppressed by pharmacological beta-blockade (60). In post-infarction and heart failure patients, increased PRD has been shown to be closely linked to poor prognosis, malignant arrhythmias and appropriate ICD shocks (59). Recently, PRD was also shown to predict the ICD-treatment effect on mortality which was greatest in patients with high PRD values (6).

However, PRD might also have important implications in sports medicine. In a recent study of our group, we tracked the spatiotemporal modulations of cardiac repolarization in healthy individuals undergoing a standardized exercise test (31): In all individuals we could observe a three-phasic pattern: Repolarization instability gradually increased with start of exercise and in parallel to the increase of heart rate. In the second phase, repolarization instability abruptly dropped discordantly to heart rate. This time point significantly correlated with the anaerobic threshold estimated by two established methods. During the third phase of exercise, both repolarization instability and heart rate increased again. Since several mechanisms have influence on cardiac repolarization, i.e. changes in the central command, local cardiometabolic changes, altered activity of beta-receptor activity, altered feedback from mechano- and metaboreceptors etc., the characteristic change of repolarization instability during exercise is challenging to interpret and future studies are needed.

Autonomic Biomarkers under Special Conditions: High Altitude and Diving

High altitude (HA) medicine is closely connected to sports medicine due to increasing numbers of athletes participating in mountain sports such as skiing, Nordic skiing or mountaineering as well as due to HA training in endurance athletes. HA exposure leads to numerous physiological changes of the body especially in the cardiorespiratory system. Altitude training increases the volume of red blood cells and consequently the maximal oxygen consumption due to physiological acclimatization responses of the body. Furthermore altitude exposure reduces lactate threshold significantly (77). Acute hypobaric hypoxemia activates sympathetic nervous system, increases heart rate and pulmonary and systemic blood pressures. Sympathetic nerves show increased activity, receptors in cardiovascular and central nervous systems are altered in density and peripheral catecholamines are found to be elevated (30). This shift towards a sympathetic nerval predominance under HA conditions is supported by a high low frequency (LF)/high frequency (HF) ratio as observed in Caucasians as well as Sherpas at appr. 5000 m above sea level (53) and has been demonstrated in other trials accordingly (79). Power spectral HRV indices at all frequency bands depress according to the increase of altitude (80).

HA-induced reduction of heart rate variability is sex dependent with significant changes between men and women (14). Acute sudden hypobaric exposure at 8302 m altitude showed in military pilots decreased linear HRV indices and increased nonlinear HRV similar to findings during heavy exercise or in patients with ischemic heart disease (75). Long-term exposure to HA seems to sustainably alter autonomic nervous system: In a study highlanders (raised >3000m above sea level) showed significantly faster heart rate recovery as well as recovery of HRV parameters (such as RMSSD, NN50, pNN50 and HF power) after a submaximal exercise test compared to lowlanders (9).

Since DC reflects the vagal branch of the cardiac autonomic nervous system at the sinus node level and PRD reflects the sympathetic branch at the level of the ventricular myocardium, both parameters are promising tools to distinguish the sympatho-vagal interplay during exposure to high altitude. Recently we were able to show, that DC decreases significantly after acute moderate altitude exposure (2650m) (33). Of note, there were no significant changes of conventional HRV parameters in this study, which might indicate a superior sensitivity of DC detecting autonomic changes already at lower altitudes.

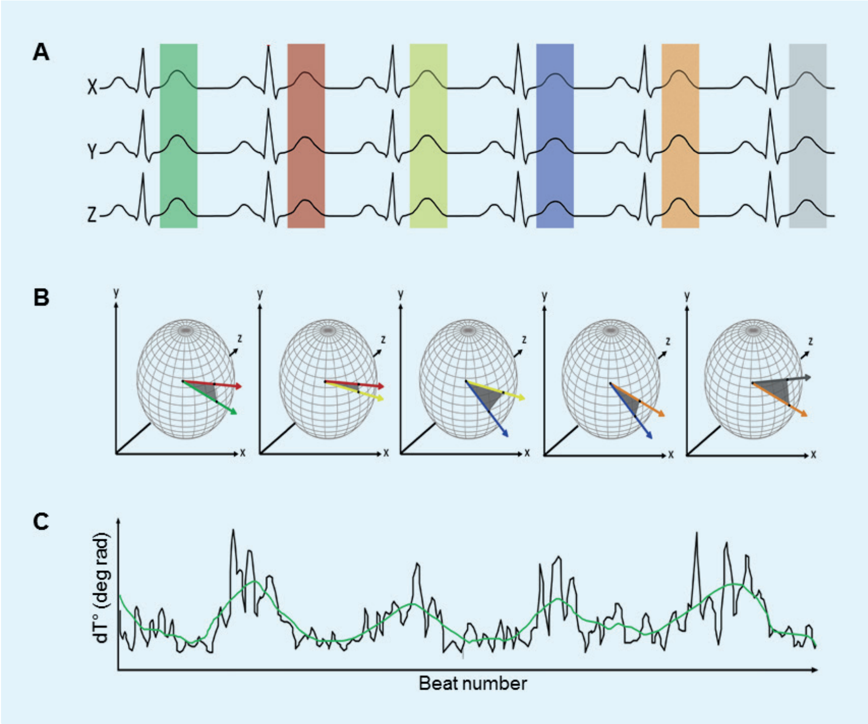

Figure 2

Assessment of PRD: A=Recording of surface ECG in Frank leads configuration (X, Y, Z). B=Visualization of the vector of each T-wave in virtual spheres. Two successive vectors are illustrated in each sphere. C=The angle dT° of two successive T-wave vectors of each heart beat is illustrated in the y-axis. It reveals a periodic pattern in the low frequency range (green line). PRD is quantified by wavelet analysis. PRD=periodic repolarization dynamics. Adapted from (58).

The connection between altitude training and changes in autonomic biomarkers was clarified by Schmitt et al. who measured HRV parameters in elite swimmers during HA training at 1200 and 1850 m and found increased performance in correlation with increases in supine parasympathetic activity (high frequency activity) (64). Schmitt et al. further developed with HRV spectral analysis four different patterns of fatigue in elite Nordic skiers (66) and found increase prevalence of fatigue with training time spent at altitude showing a higher risk of overreaching due to altitude training (65). This emphasizes the possibility of HRV analysis for monitoring training effects of hypoxia, guiding training loads, avoiding overreaching and optimizing performance.

Acute mountain sickness is a common and frightened complication among mountaineers. Some studies found changes in HRV parameters at lower altitudes predicting the occurrence of acute mountain sickness (AMS) in higher altitudes (35, 42). Nevertheless, other studies failed to show a correlation between AMS and changes in HRV (14).

Just like low pressure conditions in high altitude, high pressure conditions while self-contained underwater breathing apparatus (SCUBA) diving lead to physiological changes including alterations of the autonomic nervous system (50): While diving, ANS is activated. The parasympathetic branch through the diving reflex (a reflex leading to bradycardia due to increased vagal activity when a face is immersed into water), the sympathetic branch due to psychological stress. External factors further effect ANS activity: Changes in hydrostatic pressures shift blood volumes, increased oxygen partial pressures increase cardiac parasympathetic influences.

Schipke and Pelzer found vertical immersion to be stimulating both sympathetic and parasympathetic system while SCUBA diving predominantely increased parasympathetic activity (63). This dominance in parasympathetic activity while diving has been confirmed in recreational divers as well with increases in sympathetic activity during recovery after diving (17). Noh et al. evaluated HRV indices for different depth (33-200 ft.) and gas mixes: For all depths and gas mixtures they detected dominance in the parasympathetic activity. Especially at 33 and 66 ft. they found significant decreases in heart rates (HR) with increases in parasympathetic activities (e.g. RMSSD), while additional increases in sympathetic activity emerged at 150-200 ft (50).

Autonomic Biomarker as Promising Markers to Assess Sports Eligibility

The assessment of sports eligibility focus primarily on prevention of sports-related sudden cardiac deaths (SCD). Autonomic dysfunction is directly linked to the occurrence of malignant cardiac arrhythmias (36) and SCD (4). Therefore, these autonomic biomarkers have been initially evaluated and tested in this context in high risk patients for cardiovascular events: Vagal HRV values were found to be significantly decreased in patients after a recent myocardial infarction and with chronic coronary disease compared to a matched healthy cohort (11). Depressed SDNN below 70ms was found to be independently and significantly associated with increased mortality after AMI in a large cohort (44). An increase of 10 ms in SDNN led to a 20% decrease in risk of mortality in patients with chronic heart failure (12). Spectral HRV analysis found novel indices as predictors of SCD and non-sudden cardiac death after AMI (43). ›

Acute viral myocarditis is linked to impaired HRV and autonomic nervous function and myocarditis patients with decreased indices show significantly increased arrhythmias (26). Vagally mediated HRR after exercise is accelerated in athletes, but blunted in patients with CHF compared to normal (37). Decreased HRR not only predicts cardiovascular complication, but is also associated with systemic complications such as multiorgan dysfunction after surgery (1). Increased PRD under resting conditions is a strong predictor of mortality in post-myocardial infarction patients (59) as well as in patients undergoing prophylactic ICD implantation as it has been demonstrated recently in a large trial (6). Noteworthy, increased PRD was not only a significant predictor of mortality as well as SCD but also predicted Non-SCD (59). An increased PRD was shown to be the strongest single risk predictor of 5-year total mortality after acute myocardial infarction and was not related to underlying respiratory activity or heart rate variability (60). DC assessed from short-term recordings was found to be a strong and independent predictor of mortality and cardiovascular mortality after acute myocardial infarction (57). In patients admitted to emergency departments decreased DC was found to be a strong and independent predictor of short-term mortality (23). A combined assessment of the sympathetic and vagal cardiac autonomic nervous system via assessment of both, PRD and DC improves prediction of mortality after acute myocardial infarction (32).

Consequently, there is strong evidence for a correlation between altered autonomic biomarkers and the occurrence of malignant arrhythmias and SCD in high risk cohorts such as patients with AMI or heart failure. Therefore, controlling exercise training with autonomic biomarkers in cardiac diseased patients could be potentially helpful to adapt training intensities in order to gain improved autonomic function and to establish a safety net to avoid adverse events such as malignant arrhythmias.

In 1999 a large study found delayed HRR during the first minute of exercise to be a powerful predictor of overall mortality in a cohort of adults without known heart disease or heart failure (19). In general, resting heart rates of more than 75/min, an increase during graded exercise testing of less than 89 beats/min in total and a recovery in heart rate after exercise of less than 12-25 beats/min were shown to be strong predictors of SCD by Jouven et al. and Cole et al. in large cohorts (19, 38). These two major studies showed a connection between alterations in autonomic function and an increased mortality in apparently healthy cohorts for the first time. Consequently, autonomic biomarkers could be another piece of the puzzle when assessing sports eligibility and help to prevent sports-related SCDs. It might provide a useful tool to identify recreational or competitive athletes under risk for SCD or malignant arrhythmias and to disqualify them from different sports and/or intensities. But clearly, further large trials are needed here to determine the relationship between altered autonomic biomarkers and SCD and its influences by certain types of sports (e.g. endurance sports or resistance training) or certain training load in apparently healthy athletes.

Conclusion and Future Perspective

Autonomic biomarkers have been increasingly integrated in sports medicine over the previous years. Since recording technologies are improving rapidly with a broad availability of small mobile devices including breast belts and smartwatches (10, 78) assessment of these markers will be easier during rest and sports in healthy as well as diseased cohorts. Data analyses have the potential to become more and more integrated in controlling training intensities and optimize performance in recreational as well as professional athletes. Though research groups have integrated autonomic biomarkers in training analyses with competitive athletes it is still not routinely used due to contradictory findings, a lack of methodological consistencies and often large typical errors when assessing autonomic biomarkers.

Furthermore, although there is already some knowledge regarding autonomic dysfunction and risk stratification in patients with underlying heart disease and their eligibility for different sports, there is unfortunately little evidence about altered autonomic biomarkers in low-risk and healthy cohorts. Further research will be needed to determine clinical relevance and prognosis as well as the effect of exercise training in these cohorts, possibly a multi-biomarker approach could be beneficial here.

Conflict of Interest
The authors have no conflict of interest.

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