

# Ugly duckling or Nosferatu? Cardiac injury in endurance sport – screening recommendations

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**Abstract.** – In the beginning sporting activity may be exhausting, but over time, physical activity turns out to have beneficial effects to the body and even extended cycling or running is an emotional and healthy enrichment in life. On the other hand, spectacular sudden deaths during marathon, football and, just recently, in the trend discipline triathlon seem to support the dark side of the sporting activity. Since years there are constantly appearing reports about a potential myocardial injury induced by intensive sporting activities. Cardiac hypertrophy is the heart's response to arterial hypertension and to physical activity, but can be associated with an unfavorable outcome – in worst case for example with sudden death. The question of the right dose of sporting activity, the question how to prevent cardiac death induced by physical activity and the question how to screen the athletes for the possible risk of sudden death or other cardiac complications during sporting activity are those that will be answered by this review article. In this review we summarize recent insights into the problem of endurance sport and possible negative cardiac remodeling as well as the question how to screen the athletes.

*Key Words:*

Triathlon, Myocardial injury, Marathon, Screening, Young athletes, Middle-aged athletes, Physical activity.

## Introduction

The probability of sudden death in connection with sporting activity is about 4.6/1,000,000/year in the average population, 6% in this cohort are young athletes<sup>1</sup>. Sudden cardiac death is a rare event in the case of a young athlete (1:25,000-1:160,000/person/year)<sup>2</sup>. Sudden cardiac death in general has an incidence of 0.36 to 1.28/1,000/year in the industrialized world<sup>3</sup>. And these are only the data of individuals having been reanimated. The number for unreported cases is much higher. So sudden death in connection with sport-

ing activity occurs only rarely. However, because it affects believed to be healthy people, the effect is more spectacular and in case such an event occurs during football, the greater is the media hype.

Physical inactivity is thought to be responsible in up to 25% of all cases for the development of breast- and colorectal cancer, up to 27% for the development of diabetes mellitus and up to 30% for the development of ischemic coronary heart disease<sup>4</sup>.

The published reports referring to the risk of sudden cardiac death<sup>1,5,6</sup> as a result of sport are causing some uncertainty, in spite of the many known positive effects on the survival rate<sup>7</sup>. Endurance athletes – hobby-athletes as well as professionals – are concerned about the spectacular sudden deaths during marathon<sup>8</sup> and triathlon<sup>9</sup>. Not only the general population but also physicians feel insecure because of reports about injury of the left<sup>10-13</sup> and right<sup>14-17</sup> ventricle. Overall all-cause mortality of professional endurance athletes is reduced<sup>18-21</sup>. In the case of a hobby-athlete the prognosis seems not to depend on the sporting activity but on the individual risk constellation of the athlete<sup>22</sup>. Due to the partly very different appearing reports it is necessary, to discuss differentiated and critically the studies referring to the negative effects of endurance-sport and its impact on cardiac injury (“cardiac fatigue”<sup>23</sup>) and sudden cardiac death.

## Pathophysiology of Endurance Performance

Different changes of the cardiac structures may occur as consequences of a chronic “bouts” of vigorous exercise<sup>24-26</sup> (Figure 1). The adaptation of the heart to greater strain is a well-known phenomenon<sup>27-29</sup> and was first mentioned by Henschen, a Finnish physician, at the end of the 19<sup>th</sup> century<sup>30</sup>. The physiological modification of the heart is a harmonious increase in size and

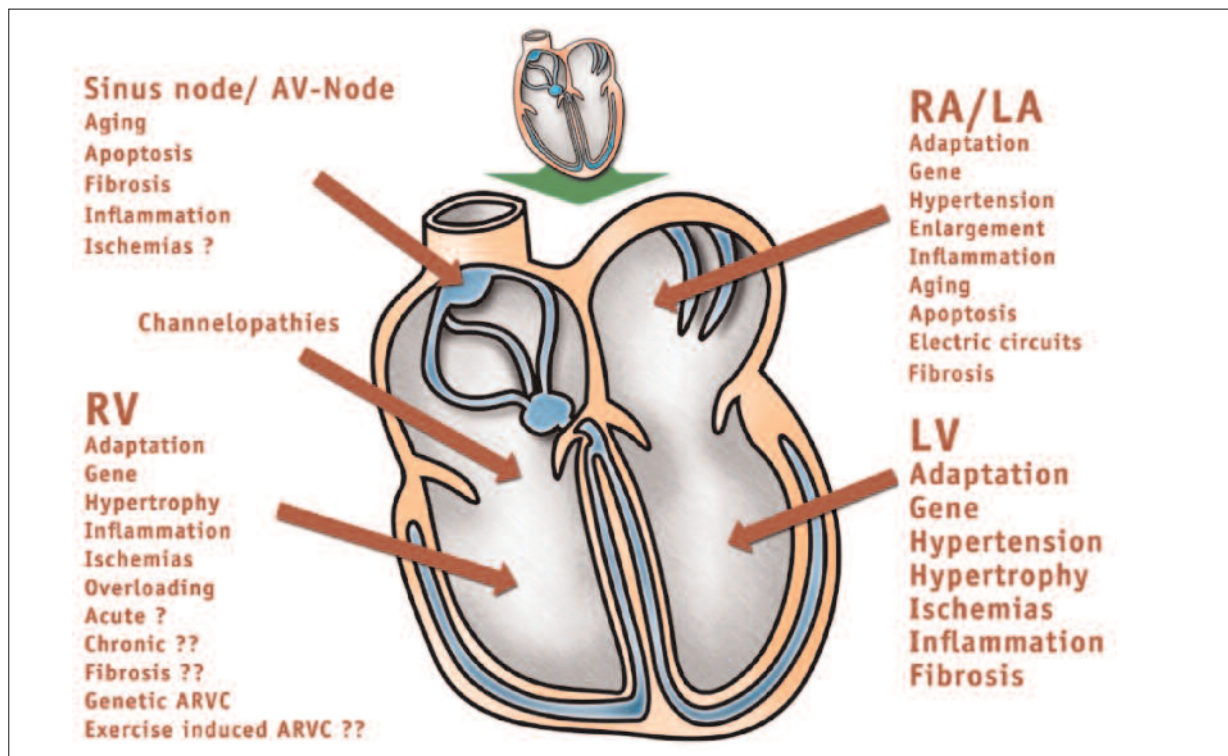


Figure 1. Possible factors that might affect cardiac function in athletes.

myocardial hypertrophy of the healthy heart, caused by physical activity. The influencing factors are the kind of physical activity on the one hand, and individual disposition and environmental effects on the other. Morganroth et al<sup>31</sup> describe – in simplified terms – that endurance performance would mainly represent a kind of volume overload; the result is an eccentric hypertrophy. However, strength endurance training is more likely to cause a concentric hypertrophy. But today there are different types of the athletic heart and the formula of Morganroth is not necessarily transferable to the sports disciplines in this simplicity<sup>28</sup>.

The influence of different clinical variables on the left ventricular size of the athlete's heart is considered up to 50% as influence of the body surface<sup>32</sup>. Additional factors are up to 15% the sport, up to 7% the gender and up to 4% the age. The influence of other factors (of individual kind) is estimated as 25%.

The so-called athlete's heart is characterized by numerous changes in ECG. 40% of the athletes show abnormalities in their ECG<sup>32,33</sup>.

The frequency of the changes in ECG depends on ethnic identity, kind and intensity of training and on the kind of sport. Mainly changes like ex-

tended QRS-complexes, diffuse modifications in T-waves, deep Q-waves or even "bizarre" ECGs are recorded<sup>32,34</sup>.

The cardiac response to the overload can be seen as a complex process; it depends on different variables like heart-rate, pre- and afterload of the ventricle, left and right ventricular enddiastolic and endsystolic volume as well as neurohumoral situation<sup>24,25,35</sup>. Changes of the preload of an athlete's heart depend on shifts in volume, for example by sweating or by increased fluid intake, the afterload may be influenced for example by heat build-up or vasodilation<sup>36-38</sup>. More changes occur on a cellular level by acidosis<sup>39</sup>, withdrawal of glycogen<sup>40</sup> or oxidation<sup>41</sup>. Oxidative physical stress has been proven in animal experiments<sup>42</sup>.

The morphologic changes after high stress, as reported by King and Gollnik<sup>43</sup>, maybe can be interpreted as shift of the balance of intramyocardial calcium ions ( $Ca^{2+}$ ). There are similar observations in the case of a chronic hypoxia<sup>44</sup>. This situation can be altered by training, at least in the case of rats, so that the effects of hypoxia and the negative impacts can be repealed<sup>45</sup>. Benito et al<sup>46</sup> were able to show by experiments with rats how intensive training induces fibrosis of the

right ventricle, including an increase of TGF- $\beta$ 1 also in the right and left atrium (potent stimulator of collagen producing myofibroblasts). Fibrosis was seen as a promotor of electrical heterogeneity and arrhythmogenesis, at least in the case of atrial fibrillation<sup>47</sup>. The underlying mechanisms, however, are far from being clarified: extent of fibrosis and atrial fibrillation, lack of atrial fibrillation in case of other major changes like amyloidosis/haemochromatosis<sup>47</sup>.

It is unclear to what extent these results concretely can be transferred to the advanced human heart. Animals were treated in part with electroshocks<sup>46</sup> and this stress factor can not be compared with a well-trained, voluntarily acting athlete. We can not completely ignore those indications for a cellular and structural remodeling in animal testing; however, the evidence of complete transferability to the human heart is still lacking.

The possibility of development of myocardial fibrosis in athletes' heart is existent. Until yet it is shown in the two cases of old died athletes more in the left ventricle (two post mortem cases<sup>48,49</sup>) and left ventricular fibrosis shown by MRI<sup>17,50,51</sup>.

For further evaluation there is a need for prospective studies. All studies, which examine endurance sport, are required to take kind, intensity, duration and environmental situation (i. e. weather, humidity, temperature, wind speed) of the action into appropriate account. Moreover, before, during and after exercise as many additional parameters as possible, should be collected (e.g. liquid and calories intake, weight, pH-values, lactate, etc.).

### **Exercise Induced Cardiac Death and Pre-Competition Screening**

Sudden cardiac death (SCD) in the case of a young athlete (Table I) is with an incidence of 1:160,000/person/years<sup>2</sup> a rare and unexpected, but always tragic event.

In the USA 50-75 deaths per year occur in young athletes, in France about 10-15<sup>1</sup>.

Marijon et al<sup>1</sup> describe the common risk of sudden cardiac death (SCD) in connection with sport with 5.4 up to 16.7/1,000,000/year – depending on the region. The mean age of the persons concerned was  $46 \pm 15$  (11-75) years, 92% died directly during sport, only 12.7% had disorders before and 86.5% had a regular training. SCD occurred in young athletes with a frequency of 9.8/1,000,000/1 year, in young non-athletes with 2.2/1,000,000/1 year. Among the general population the risk is about 9.2/1,000,000/1 year for men and 0.4/1,000,000/1 year for women. So young competitive athletes have a fivefold higher risk than non-competitive athletes and men have a twentyfold higher risk than women. Cardiac death related to sport occurred in most cases during sporting activity or within one hour later and is mainly related to a dysbalance of oxygen demand and supply<sup>52</sup>.

Most deaths concerning athletes occur during or soon after sports activity. Literature differentiates between "young" and "old" athletes (< 35 and > 35 years). So far, depending on age and country there are significant differences in pre-competition screening<sup>2,5</sup>. Potential causes of SCD are shown in Table I. More attention should be

**Table I.** Causes of sudden death in young athletes 12-35 years in %.

Cause of sudden death	Maron et al, 2007	Corrado et al, 2003	Solberg et al, 2010	Marijon et al, 2011
Aortic rupture	2	1.8	4.3	2
Aortic stenosis/cong. HD	5		4.3	6
ARVC	4	22		4
Channelopathies (QT, WPW)	3	1.8	8.7	12
Coronary artery anomalies	17	11	3.3	
Coronary disease	3	18	48	6
Dilatative CM	2	1.8		4
Hypertrophic CM	36	1.8	4.3	10
MVP	4	7.3		2
Myocarditis	6	9	22	4
Possible HCM	8			4
RIVA muscle bridge	3	3.6		2
Unclear		1.8		36
	n = 1435	n = 55	n = 22	n = 50

cong HD = congenital heart disease; ARVC = arrhythmogenic right ventricular cardiomyopathy; QT = QT-syndrome (including Romano-Ward syndrome and Jervell-Lange-Nielsen syndrome); WPW = Wolff-Parkinson-White syndrome; CM = cardiomyopathy; HCM = hypertrophic cardiomyopathy; MVP = mitral valve prolapse.

paid to the variety of causes than to the absolute figures, which may vary widely over the years among the authors.

In their most recent publication Maron et al<sup>5</sup> regard hypertrophic cardiomyopathy in 36% as cause of sudden cardiac death. In their update from 2006 Corrado et al<sup>53</sup> classify a silent coronary heart disease in young non-athletes as determining cause of sudden death. Physical exercise in the case of young athletes < 35 years is not per se associated with risk, but depends on a possible individual and silent disposition. This may be for example hypertrophy, coronary heart disease or arrhythmogenic disposition and can be triggered by physical exercise. Altogether what is important is not the knowledge of percentage rates mentioned in the literature, but the variety of findings and possibilities, which can not be diagnosed by simple 12-channel-ECG. ECG is an orientating examination, without correlation to hypertrophy<sup>54,55</sup> and information about the dimensions of heart cavities.

40% of the athletes show abnormal changes in their ECGs<sup>32</sup>. The frequency of ECG-changes depends on ethnic origin, as well as on type and intensity of training and kind of sport. Here, mainly changes such as prolonged QRS-complexes, diverse changes in T-waves (negativities), deep Q-waves or even “bizarre” ECGs are recorded<sup>34</sup>. Changes in ECGs should be analyzed according to “Seattle criteria”<sup>56</sup> or to the European recom-

mendations<sup>55,57,58</sup>. Ethnic differences in repolarization changes should be considered<sup>55,59</sup>. QT-segments > 470 ms<sup>55,57</sup> always require an individual approach and at least anamnestic-familiar or even genetic examinations. There is always a need of carefully monitoring of ECG-changes and course. ECG-changes are described as a “traffic light scheme” in Figure 2 in terms of their significance. Sinusbradycardia < 35/min can be a sign of overtraining.

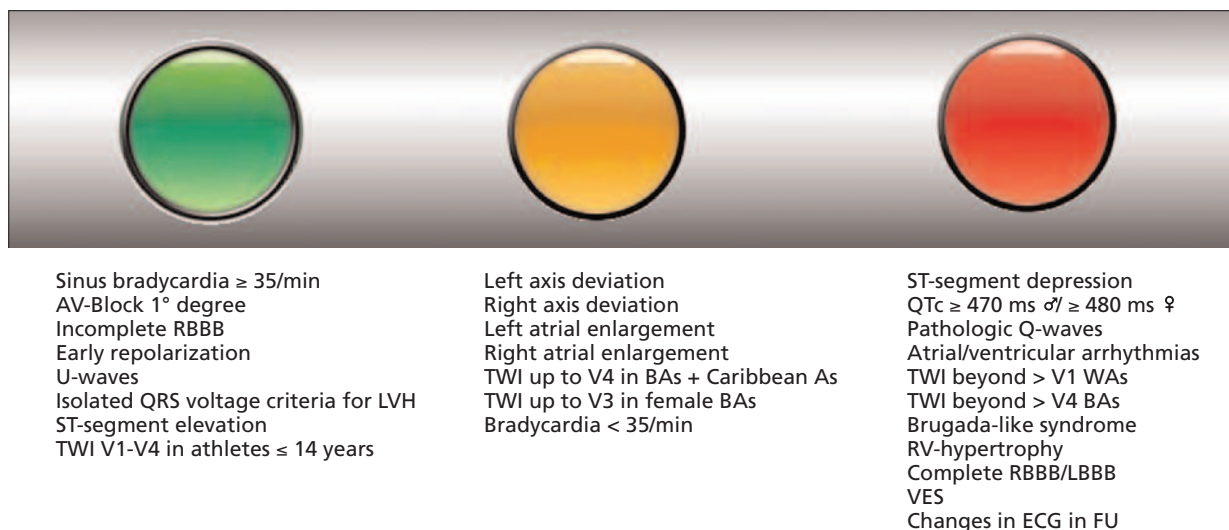
Changes in the heart-valves of an athlete (acceleration of the extent of stenosis in the elderly), aortic dilatation<sup>60</sup>, enlargement of the atriums<sup>61</sup>, represent only a few of the changes that are easily detectable by echocardiography. Functional changes can be excellently investigated by Doppler, tissue Doppler Imaging (TDI) or strain-technique.

The situation among active more than 35 years old is quite different. The primary cause for sudden death is almost always coronary heart disease<sup>62</sup>. General recommendations to identify persons at risk are available<sup>63,64</sup>.

However, coronary heart disease is relatively common in young athletes < 35 years<sup>65</sup>, so also the younger athletes should undergo exercise tests.

In the case of abnormal ECG-findings a stress echocardiography should be carried out<sup>66,67</sup>.

Athletes > 35 years of age, undergoing an extreme endurance competition, for example triathlon or marathon, should be examined by stress echocardiography from a prognostic point



**Figure 1.** 12-Leads ECG-Traffic Lights (regarding<sup>55-59</sup>). Green Light: no recommendation for further examination; Yellow Light: borderline changes, potentially further recommendation for evaluation; Red Light: further evaluation strong recommended. *Abbreviations:* RBBB = right bundle branch block; LVH = left ventricular hypertrophy; TWI = T-wave inversion; BAs = Black Athletes; As = Athletes; WAs = White Athletes; LBBB = left bundle branch block; RV = right ventricular; FU = follow up; VES = ventricular extrasystole.

of view<sup>66</sup>. Competitive ambitious athletes < 35 years should undergo a specific cardiologic examination and regular annual check-up examinations, if problems occur and before starting a training. When myocarditis, fibrosis or right-ventricular dysplasia is suspected, cardio-MRT examination is recommended<sup>51,68</sup>.

The cost-benefit ratio of a combined exercise-ECG and echocardiography or spiroergometry and echocardiography in terms of the costs of an ambitious physical exercise is acceptable. The costs for screening-examinations should be regarded as negligible given the high expenditures for preparation and participation in marathon and triathlon competitions<sup>69</sup>.

In daily routine ambitious amateur and competitive athletes represent only 50% of the patients of a cardiologic practice focused on sports medicine (internal data). Drop in performance, hypertension<sup>61</sup>, atrial fibrillation<sup>70</sup> and possible coronary disease<sup>62</sup> rather dominate the clinical spectrum in the case of ambitious amateur athletes. In the other 50% of amateur sports medical work in the field of popular sports consists in performance assessment and determining indications for measures of exercise if coronary heart disease, obesity, arterial hypertension or metabolic syndrome is present or to maintain physical abilities in the elderly. Optimization of performance or competition preparation here plays a minor role.

### ***Previous Official Screening Recommendations***

Due to the increase in sport related deaths among the elderly and during intensive competitions (master tourneys), the question arises whether previous official recommendations are still up-to-date<sup>71</sup>. The recommendations of the associations, as presented in the publications of Maron et al<sup>5</sup> and Corrado et al<sup>2</sup>, are partly characterized by historical and economic factors. The previous official concepts include a physical examination and the medical history of the young athlete and in the Italian characterized version additionally a resting-ECG. These concepts may have been sufficient in the past for young athletes, but are no longer sufficient considering today's standards. Compared with the investment of time and money of the athletes the previously recommended measures represent the strict minimum. New and ever more elaborated examination procedures are discussed in literature<sup>63,64</sup>.

In fact, the FIFA has taken a lead<sup>72</sup> in the respect of recommendations and postulates a well-founded echocardiography, based on the publications of Dvorak et al<sup>73</sup> and Thunenkotter et al<sup>74,75</sup>. FIFPro fights for national and international standards in pre-competition screening of football players (young and old)<sup>76</sup>. An exercise-test not only provides information concerning an ischemia or physical condition, but also arterial hypertension during exercise, course of heart rate and arrhythmias, which might occur during exercise. Echocardiography carried out in an athlete provides together with the description of cardiac structures (extent of hypertrophy<sup>61,77</sup>, aorta, atrium<sup>78</sup>, dimensions of ventricle<sup>61</sup>, structure of myocardium, wall thickness<sup>79</sup>) also functional information<sup>80</sup>. Doppler measurements give information about the blood flow rate, diastolic function<sup>81</sup>, segmental velocity (Tissue Doppler Imaging) and strain-technique offers segmental and global myocardial values/curves of deformation within the cardiac cycle<sup>80,82,83</sup>.

### ***Current Situation of Screening and Preventive Medical Care in Daily Routine***

Previous official recommendations are subject of constant change<sup>60,63,73,74,84</sup> and should follow the recommendations for patients with coronary heart disease<sup>85</sup> and new knowledge/experience<sup>73-75</sup>. Not only sudden cardiac death represents a kind of complication, but also structural changes of the heart (aorta, atrium, ventricle) and possible arrhythmias. Occurrence of atrial fibrillation can alter an active and quasi healthy leisure-athlete to a physically not very active athlete. A drop of performance can have a lot of causes.

In most cases the health situation of an ambitious athlete is very complex and may claim a wide interdisciplinary range from immunology, cardiology, orthopaedics up to orthodontics.

The following recommendations for the screening are based on active care of competitive and amateur athletes since 20 years and own sports experience.

In principle, the following four reasons for examination can be distinguished:

1. Screening-examination (baseline examination)
2. General preventive check-up (periodical follow-up examinations)
3. Check-up in the case of discomfort (loss in performance, dyspnoea, thoracic pain, infection)
4. Performance diagnostics for training recommendation

Because of the potential coronary heart disease<sup>62,65</sup>, arterial hypertension during exercise<sup>61</sup>, premature beats/heart rate changes during exercise and the additional information provided by echocardiographic examination<sup>79,86</sup> in the area of popular sport as well as in competitive sport similar measures can be recommended that in principle apply to athletes with coronary heart disease<sup>85</sup>. This means that echocardiography and an exercise test can be regarded as basic examination for physical fitness and in pre-competition screening of an athlete < 35 and > 35 years.

### ***Screening-Examination (Baseline Examination)***

The baseline examination includes, in addition to the physical basic examination and medical history, the following tests: echocardiography, exercise-ECG and pulmonary function testing as well as a basic blood test (differential blood count, CRP, creatinine, GPT, GOT, Gamma-GT, LDH, LDL-/HDL-cholesterol, triglycerides, blood glucose, iron, ferritin, TSG, electrophoresis). In addition (athletes > 35 years) a duplex sonography of carotids<sup>87</sup> (determination of intima-media-thickness, plaques) is carried out in order to calculate the state of atherosclerosis. In case of abnormal findings in resting- or exercise-ECG a stress-echocardiography is performed. Within echocardiography all modern examination techniques are applied, including strain-echocardiography.

Using echocardiography nowadays not only the extent of hypertrophy, the size of aorta, ventricles and atriums and the functioning of cardiac valves as well as the visual contractions can be analyzed and recorded but also complex measurements of function in the area of both ventricles and atriums can be carried out by means of tissue Doppler Imaging (TDI), strain technology<sup>80,82</sup> as well as conventional CW-/PW-Doppler for systolic and diastolic blood velocities<sup>81</sup>. Thus, changes – particularly over the course<sup>83</sup> – can be registered. These – for a non-cardiologist – highly complex echocardiographic examinations have now become routine for an experienced cardiologist.

As standard, we offer a spiroergometry to athletes, in order to document the physiological performance profile (amongst others threshold of fat burning, aerobic capacity, anaerobic threshold) and to estimate the maximum oxygen uptake (VO<sub>2</sub>max in ml/min/kg)<sup>79,88</sup>. Optional the body composition might be documented by means of a more complex impedance scales<sup>89</sup>.

In hobby-athletes/patients with metabolic syndrome or diabetes<sup>90</sup> a spiroergometry is carried out, to check the current performance level and to plan an aerobic training schedule. The focus lies here on fat burning and careful planning of activities in the aerobic zone<sup>91</sup>.

Screening with radiodiagnostics<sup>63</sup> (cardio-CT, EBT) has so far not been accepted in the routine because of financial reasons, lack of acceptance (exposure to radiation) and available less expensive alternatives for arteriosclerosis and coronary disease screening (carotis duplex sonography and exercise stress echocardiography). It will be necessary to await further developments in this respect.

In Germany sports medical performance tests in the physician's practice are meanwhile subsidized by statutory health insurance funds up to 80%<sup>92</sup>.

If a myocarditis or fibrosis (clinical symptoms) or an extremely rare arrhythmogenic cardiomyopathy is suspected, a cardio-MRT as screening examination is used.

### ***General Preventive Check-up***

The usually annual carried out check-up includes always an echocardiography<sup>79</sup> and a performance<sup>74,79,88</sup> test. We attach particular importance to the documentation of hypertension<sup>61</sup> during exercise and documentation of heart rate changes or premature heart beats. Echocardiography is conducted mainly to compare the size of ventricles/atriums and to detect possible changes in heart valves and aorta or to assess the myocardial hypertrophy. A dilatation of the aorta with consecutive aortic insufficiency<sup>60</sup> is not a rare event in the case of an endurance athlete (2%)<sup>79</sup>. Ambitious and competitive athletes are often examined “off-season” by spiroergometry, to check their training schedule. That is also the case for competitive athletes in their pre-competition season.

### ***Check-up in the Case of Discomfort or Drop of Performance***

Here, the examination is focused on the clinical situation. Overtraining should be considered. All new changes in resting-ECG, syncopes, or a drop of performance need to be clarified consequently. In addition to the basic examination, including echocardiography and resting-ECG, all further examinations are carried out to the clinical demand (stress echocardiography, Holter-ECG, Angio-CT<sup>93</sup>, Cardio-MRI (myocarditis/fibrosis) up to coronary angiography and electrophysiological examination).

A detailed blood analysis as described above and additionally antibodies and hormones (e.g. on account of inflammation or hormonal changes), including the determination of virus-antibodies (*Epstein-Barr*, *Cytomegalovirus*, *Herpes*, *Parvo*, *Echo*, *Coxsackie*, etc.) and bacterial antibodies (*Chlamydia pneumoniae*<sup>94</sup> and *Borrelia*), should be considered in case of a drop of performance. Negative findings of virus-antibodies do not exclude a myocarditis. Further step in the diagnostic is cardiac-MRI and in some cases myocardial biopsy (reduced cardiac function). With this approach, so far we haven't had any case of death or undetected myocarditis. In cases of possible coronary disease, stress testing<sup>66</sup>/EBT/CT-angiography<sup>93</sup> or coronary angiography should be considered.

### **Performance Diagnostics**

Diagnostics by means of spiroergometry<sup>79,95</sup> is extremely helpful planning the training<sup>79,96</sup> and to specify the performance level of active athletes<sup>79</sup> and planning activities of affected patients<sup>90,91</sup>. The cost-benefit ratio of a combined exercise-ECG and echocardiography or spiroergometry and echocardiography in terms of the costs of an ambitious physical exercise is acceptable without any problems at least in Germany. Particularly by participation of the public German health insurance system in the costs, the medical care of the athletes here is ensured<sup>92</sup>. But also in other countries the costs for screening-examinations should be regarded as negligible, given the high expenditures for preparation and participation in marathon and triathlon competitions<sup>69</sup> or intensive costs in professional football and other team players.

### **Right Ventricular Injury by Sport**

The description of acute deaths relating to arrhythmogenic right ventricular cardiomyopathy (ARVC) is based on the publication of Thiene et al<sup>97</sup>. In 12 of 56 acute cardiac deaths ARVC was diagnosed (athletes < 35 years). This has never been confirmed to this extent by another working group. 2007 Maron et al<sup>5</sup> described a quote of 4% and Marijon et al<sup>1</sup> of 1.4%. Heidbüchel<sup>15</sup> postulates the term of a "load induced, right-ventricular arrhythmogenic cardiomyopathy", that could lead from repetitive microtraumas to chronic and structural changes of the right ventricle and to "pro-arrhythmogenesis". In his view, ventricular tachycardia originating from the right ventricle is responsible for the acute deaths. His hypothesis

is based on a retrospective analysis of the electrophysiological examinations in 2003<sup>14</sup>. A cohort of only 46 athletes from three centers was analyzed retrospectively – without further details on period and overall cohort. In 28/46 cases a MRT-examination was carried out, in 12 cases with abnormal findings of the right ventricle (hypokinesia, dilatation or fat tissue). The entire theory is based on these cases. Unfortunately, statements concerning the prevalence or incidence of a remodeling of the right ventricle among athletes are not possible, because of the lack of information for the necessary statistical values. Also the number of cases is low.

In 2012, La Gerche et al<sup>17</sup> reported a structural remodeling of the right ventricle among 40 endurance athletes from different disciplines, that are in part not comparable with respect to disciplines, intensity and mode of exercise. 2008, based on a study similar in design with 20 male and 7 female triathletes, they also reported about a left- and right-ventricular dysfunction among participants of the Australian ironman competition performed in 2004 (3.8 km swim, 180 km bike, 42.195 km run).

As regards to trials in the USA and France a participation of the right ventricle (RV) as cause for sudden cardiac death could be rarely demonstrated.

A RV remodeling should also have been described by the echocardiographic examinations of Maron et al<sup>98</sup> (screening of 4111 young athletes). The statements by La Gerche<sup>17</sup> based on 40 athletes are rather problematic, because Basavarajaiah et al<sup>99</sup> describe no abnormal findings of the right ventricle in their examination of 3500 athletes, as this applies to the cohort of Maron et al<sup>98</sup> with 4111 athletes. In the small cohorts of Heidbüchel and La Gerche et al<sup>15</sup> those changes occur frequently. The data give some cause for skepticism. A correct quantitative assessment of the right ventricle volume is difficult or impossible caused by the possibility of different ultrasound angles and very individual anatomic geometry<sup>100</sup>. The interobserver-variability to determine the volume of the right ventricle can be as much as up to 16% using MRI<sup>101</sup>. The interobserver-variability as well as the day-to-day variability in the study of La Gerche remains unknown. An interobserver-variability between 10 and 15% could be expected. A "post-race" increase in volume of the right ventricle of 9 ml (5% of 170 ± 30 ml) is very small and is well below the interobserver-variability. It is question-

able to call this difference clinically relevant. However, this change can not be uncritically reason for an “injury-theory” of the right ventricle to be valid for all of the endurance-athletes. The acute changes of the right ventricular volumes are possible, but they do not mean a chronic injury.

The shifts in plasma and volume under endurance-exercise have a significant influence on cardiac function<sup>25,38</sup>. These changes (weight/fluid intake) have not been adequately described and documented in the study of La Gerche. It is also unclear why the right-ventricular mass, which only amounts to 25% of the left-ventricular mass, should be responsible for the increase of biomarkers and not the left ventricle or rather the massive degradation of the muscle. A further problem concerning this study is the lack of documentation about attending athletes, time periods and races. A balancing act concerning the participants from 2006 up to 2012 across all disciplines and distances is problematic in any case considering such an important phenomenon. Also long term training marathon runners did not suffer any long term injury of the right ventricle (incl. strain-technology)<sup>102</sup>. Accordingly, before any further extension of the “exercise-induced right ventricular fatigue/fibrosis” hypothesis further prospective studies on this issue are recommended. The hypothesis has interesting aspects, but the dose of the exercise bouts and the individual (phenotype<sup>103</sup>/environment<sup>38</sup>) dependency has to be regarded. An exercise induced chronic right ventricular injury in athletes has not been documented so far.

In new studies an accurate monitoring of liquid intake before, during and after the competition, incl. weight measurements should be carried out as well as precisely documented courses of calories intake, because also loss of glycogen of the myocardium may cause fatal consequences<sup>40</sup>.

#### ***Left Ventricular Dysfunction, Increase in Bio-Markers in Combination with MRI***

Numerous investigations regarding the increase in bio-markers (mainly Troponin cTnI and NTproBnP) in marathon<sup>13,104</sup> as well as in triathlon<sup>12,105</sup> competitions have been conducted. A significant increase in bio-markers after the race was found in all those studies. At first, uniformly, this was considered as proof of a possible injury of the heart muscle<sup>106</sup>, but more recently it

has been seen rather as physiologic response to exercise<sup>107</sup>. Intensively facing the subject of a cardiac dysfunction after physical exertion (often called “cardiac fatigue”<sup>23</sup>) was mainly pushed forward by the observations in marathon and triathlon (ironman-distance 3.8 km swim, 180 km bike and 42.125 km run). Also deaths during marathon-competitions<sup>108</sup> boosted the idea of cardiac injury by endurance-competitions.

In addition, numerous studies using imaging techniques in marathon as well as in triathlon have been conducted. The studies of Neilan et al<sup>13</sup> and Möhlenkamp et al<sup>109</sup> have been the source of very controversial discussions<sup>110,111</sup>.

Tulloh et al reported<sup>112</sup> a decrease of the ejection fraction from 64.2 to 58.6% with a simultaneous rise in cardiac output from 6.66 to 7.23 l/min. There was no documentation of shifts in volume or weight before or after the race, respectively. Accordingly, these findings can hardly be interpreted. The changes in the cardiovascular system after an ironman-competition are so significant that an analysis about a systolic left ventricular injury is not possible based on the presented data. Neilan et al<sup>13</sup> found no significant changes of the systolic function or dimensions of the left ventricle after marathon at all, but an alteration of the diastolic function of the right and left ventricle. These changes combined with the increase in biomarkers were judged to be a sign of myocardial injury with consecutive increase in pulmonary pressure and right ventricular enlargement. The enddiastolic right ventricular area was  $17 \pm 4$  cm<sup>2</sup> before and  $20 \pm 3$  cm<sup>2</sup> after race. Weight and liquid intake have not been documented, lactate values have not been measured. Considering the minimal echocardiographic changes and massive changes of the cardiovascular system due to competition at the same time, the evaluation of the results of the study as myocardial injury is highly questionable. The overall constellation, incl. the increase of bio-markers, is not convincing and doesn't underline left ventricular injury necessarily.

The biochemical and functional abnormalities have also been reported by La Gerche et al<sup>105</sup>. Here was a decrease in left ventricular ejection fraction after the ironman competition from 60.4 to 57.5% (*p*-values not given). There was only a significant increase in bio-markers in 2 athletes out of 27, in these cases, however, significant, with remarkable impact on the statistic values.



Overall, the increase in bio-markers in athletes with intensive muscle work should not necessarily be interpreted as heart specific<sup>113</sup>, because it also depends on the athlete's weight<sup>114</sup>. So there is still the option of loss in specificity of the assays, when such a high muscular destruction has occurred (possible increase in CK up to 10,000 U/l)<sup>115</sup>. The assays have not been developed for this massive muscular destruction.

Magnetic resonance imaging (MRI) can visualize myocardial scars, but any clear evidence for de novo scarring directly after competitions is still pending<sup>116</sup>.

**Competitive/Ambitious Endurance Sport – Positive/Negative Effects?**

Generally, endurance athletes live longer in comparison to the general population (Table II). In some cases (genetic aetiology<sup>103</sup>/chan-

nelopathies<sup>117</sup>) and individual situations (infections/inflammations) the live expectancy can be shorter<sup>48,49,94</sup>. The study by Marijon et al<sup>20</sup> reports positive effects of professional endurance sport. Professional cyclists presented a 41% lower all-cause mortality than the general population (see Table II). Also the current meta-analysis by Teramoto and Bungum<sup>118</sup> reports a lower mortality (especially cardiovascular) and a longer life span of elite athletes. Of course, the results have to be interpreted with caution. Lifestyle and genetic predisposition may be more advantageous than the variables in the general population. The investigation of 2612 male elite athletes of Sarna et al<sup>119</sup> also showed an increase in life-expectancy of endurance athletes compared with the control group (75.6 vs. 69.0 years).

The long-term analysis of the standardized mortality ratio of athletes between 1924 and

**Table II.** Longevity/mortality in athletes.

Author/kind of athletes	n	Years	AGEy (longevity/SMR/OR (mortality))
Sarna et al, 1993	2613 m	1920-1965	75.7y endurance sport 73.9y team sport 71.5y contact sport 69.0y references
Gajewski et al, 2008	1689 m	1946-2000	SMR 0.50 athletes 0.78 actors 0.64 monks
Karvonen et al, 1974	396 m	1893-1967	73.0y all 70.2y (1950-67) controls 68.7y (1946-50) controls 68.9y (1931-35) controls
Saase et al, 1990	259 m	1956-1988	SMR 0.59 non-elite racer 0.72 "elite" participants 0.80 "non-elite" participants 0.90 racer
Zwiers et al, 2012	9889 m	1896-2011	OR 1.01 cardiovasc moderate mortality 0.98 cardiovasc high intensity 0.94 moderate static 0.99 high static 0.94 moderate dynamic 0.97 high dynamic
Marijon et al, 2013	786 m	1947-2012	1.65 controls 0.56 (1947-1970) cyclists 0.54 (1971-1990) cyclists 0.62 (1991-2010) cyclists
Farahmand et al, 2003	49219 m	1989-1998	SMR 0.72 (100-120% winner time) 0.53 (121-160% winner time) 0.47 (161-200% winner time) 0.49 (201-240% winner time) 0.48 (> 240% winner time) 0.32 succesfull all 6 races
Schnohr et al, 2013	1878	1976-2003	6.2y > controls men 6y controls women

SMR = standardized mortality ratio, OR = odds ratio.

2000 from Poland showed a clearly higher life expectancy of male athletes (Olympic athletes)<sup>18</sup>.

Athletes with intensive cardiovascular training in their disciplines have shown a slight decrease in mortality<sup>120</sup>.

Similar results were obtained by two other studies investigating prospective not professional athletes, but ambitious and semi-professional athletes. The Swedish study of Farahmand et al<sup>121</sup> examined 73,622 participants of the traditional Vasa cross-country skiing across 90 and 30 km. The reduction of total deaths was 52% compared with the general population. In the second study 2,259 male Dutch skaters<sup>122</sup> having participated in the race across eleven towns in 1956 got a follow-up after 32 years. They were divided into the group of competitors (259) and into the group of hobby-athletes (2000). The reduction of mortality was only seen in the group of ambitious athletes. Here total mortality was reduced by 24%. However, among the over 50-years-old athletes there was no significant difference compared with the general population regarding the survival rate.

On average joggers live 6.2 years longer than non-joggers (women 5.6 years)<sup>21</sup>.

Ambitious sporting activity up to 6,300 kJ/week and more showed a reduction of mortality with increasing physical activity in the “Harvard Alumni Health” study<sup>123</sup>.

The follow-up analyses of top athletes practicing their sport up to 17 years showed no cardiac damage<sup>124</sup>. Pelliccia et al examined 114 Olympic athletes (48% canoeists, 17% cyclists, 15% middle- and long-distance runners, 13% cross-country skiers, 5% middle-distance swimmers and 2% triathletes). None of them showed signs of left cardiac damage, even though all athletes trained at the highest level.

How intensive the training should be, to achieve a positive effect on life expectancy, is unclear<sup>125</sup>. Maybe it's corresponding to the approximated calorie consumption of 490 kcal/day derived from evolution<sup>126</sup>; but even physical activity up to 1000 kcal/week reduces the mortality rate up to 30%<sup>7</sup>. There is also a positive relation between intensity of training and general survival rate<sup>127</sup>. Those over 45 years should train daily (30-60 min) in a moderate way (41 METs hour/day)<sup>128</sup>. Higher physical efforts would have no sure advantage regarding the survival rate, perhaps even negative effects<sup>128</sup>.

There is no doubt, that there is a higher incidence of atrial fibrillation and bradyarrhythmias in aged athletes<sup>70,129</sup>. The relevance of possible fi-

bro sis of the left atrium remains open<sup>47</sup>. In the case of 52,755 cross-country skiers of the Vasarace<sup>129</sup> atrial fibrillation and bradyarrhythmia occur more frequently (14.3/10,000/patients/years and 1.9-2.8/10,000/patients/years). However frequent occurrence of supraventricular/ventricular tachycardia and cardiac arrest compared with the general population was not seen.

The general discussion of arrhythmias and sport remains controversial, because the causes and effects are still not clear at present (underlying disease, predisposition, training situation, circumstances). Sport itself is not arrhythmogenic. It needs perhaps a “triggerpoint”: an inflammation<sup>94</sup>, coronary disease<sup>65</sup>, exercise induced hypertension<sup>61</sup> or genetic disposition<sup>117,130</sup>.

The recent general reviews on the potential side effects of ambitious endurance sport have different views. Scharhag et al<sup>131</sup> came up with a thesis that ambitious endurance sport will not lead to a myocardial damage or negative effects. O'Keefe et al<sup>132</sup> agree with the statement that ambitious endurance athletes have lower mortality ratios, although they also suggest the hypothesis that excessive endurance training may lead to negative cardiovascular remodeling. To verify this hypothesis, a confirmatory longitudinal work is necessary. The latest publication of the Nixdorf-Recall study revealed that for older athletes > 50 years, it is not the increase in troponin-markers during a marathon, but the individual risk of cardiovascular disease that is of prognostic significance<sup>22</sup>. These studies indicate that endurance sport per se does not present a risk, but that “individual burden of disease” determines the risk for mortality.

## Conclusions

Based on the studies discussed in this review we can say that ambitious physical exercise can result in cardiovascular side effects in athletes < 35 and > 35 years. In particular, a life-threatening complication may be caused by ischemia, when coronary heart disease is not yet known. Also an unknown structural disease may be triggered negatively by massive physical load. Here, individual predisposition and genetics have to be considered<sup>103,117,133</sup>.

The studies carried out on the phenomenon “negative right ventricular remodeling” are based on a very small number of cases<sup>14,17</sup>, compared to those studies not detecting any alterations of the

right ventricle<sup>98,99</sup> (the last studies were not focused to the right ventricle). Both studies<sup>14,17</sup> show introductory methodical deficiencies. An impact of negative right ventricular remodeling exists, but the frequency seems to be more rarely than suggested by La Gerche et al<sup>17</sup>. The general incidence, the dose of exercise bouts and individual sensitivity has to be defined and evaluated by further prospective studies. There is a lack of information on prevalence and incidence and the post mortem studies on SCD do not provide the expected and assumed frequency. Here as well the theoretical model of a cardiac remodeling can not be transferred to all athletes. Although it is possible, it's depending on genetics<sup>117,133</sup> or environmental influences (reg. bacterial/viral/oxidative inflammation). An individual predisposition to premature fibrosis/remodeling may exist<sup>49,50</sup>. Cardiac injury/sudden cardiac death may be triggered with strain, although dose response relationship, extent, clinical relevance and frequency remain unclear.

Considering the dominant probability of coronary heart disease in ambitious athletes < 35 years<sup>65</sup> and > 35 years<sup>62</sup>, risk stratification with exercise-tests/imaging techniques is advisable in addition to basic examination (medical history/physical examination/12-channel-ECG). Spiroergometry/lactate diagnostics are recommended to ensure predominantly aerobic training. Marijon et al<sup>1</sup> reported a fivefold higher cardiac mortality in young ambitious competitive athletes (relative risk 9.8, 95%, CI 3.7 up to 16) than in non-competitive athletes (2.2, 95%, CI 1.4 up to 3.0). This fact supports the need for a more detailed examination of the athletes < 35 years and to identify persons at risk.

For all athletes < 35 years minimal screening by 12-channel-ECG and basic examination prior to the start of training or if discomfort occurs are not sufficiently, based on today's criteria and should be complemented by echocardiography and exercise-test (ECG or stress-echocardiography). Depending on medical history, Holter-ECG or MRI scan may become necessary. MRI can provide additional information concerning a possible myocarditis or fibrosis of the myocardium<sup>51,68</sup>. The value of strain-echocardiography seems to be also very promising<sup>80,82,83</sup>, but still has to be verified<sup>64,134</sup>.

In all athletes with suspicious inflammation/myocarditis or in cases of power/performance lost, blood tests must be performed (especially for *Chlamydia pneumoniae*<sup>94</sup> or other bacterial or viral infections).

Increased risk remains for arrhythmias (particularly atrial fibrillation) at an advanced age, but these are well treatable<sup>135</sup>. Arrhythmias are declining by de-conditioning up to 90%<sup>136</sup>. In rare cases a pacemaker implantation in nodal disease is required<sup>137</sup>. It is certain that elite-athletes (particularly men) have a longer life because of rare occurrence of cardiovascular diseases<sup>18,20,118,121</sup>. Early deaths in individual cases due by myocardial fibrosis are possible<sup>48,49</sup>. Regarding the results of the longevity or mortality studies in athletes it is not possible to say "the fastest lives longer" (Table II). The standardized mortality ratios (SMR) are lower for the successful participants of all races and with finisher time > 240% of winner time<sup>121</sup> and "non-elite" racer<sup>138</sup>. Moderate sport activity for the long time in the elderly could be the possible "best" solution<sup>126,128</sup>.

Further prospective studies on possible cardiac "negative remodeling" by sport ("exercise induced cardiac-fatigue") with larger cohorts and under clearly defined conditions should be conducted. In addition, the optimal training volume of physical activity concerning the general survival rate should be investigated prospectively.

Regarding all the competitive sporting activities with an enormous importance for hobby-athletes, media and industry, physical activity in general population is of fundamental importance<sup>4,7,139</sup>. Here, the idea of evolution and a recommended calorie consumption of 490/kcal/day are very valuable<sup>126</sup>.

Sport is of great social and medial importance. Accordingly, prevention of sudden sport-related deaths or a "negative remodeling" by sport has not only an individual component, but also a significant social impact on physical activity in general population. In this regard, further expenses, studies and well-founded pre-competition screening in the industrialized world are socially justified and financially reasonable.

#### Conflict of Interest

The authors declare that there are no conflicts of interest.

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