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**CICLO: XXIII**

**Ventricular arrhythmias at risk of sudden cardiac death in young  
athletes.**

**Non invasive cardiac examinations during preparticipation  
screening for sport eligibility.**

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## Summary

**Background:** the pre-participation screening program of athletes has the goal of the early identification of previously unsuspected cardiovascular diseases with a prompt disqualification of the athletes from competitive physical activity. The most frequent disqualifying condition consists of rhythm and conduction abnormalities (nearly 40%).

**Aim of the study and methods:** the study of non-invasive cardiac examinations of young athletes discovered to have ventricular arrhythmias during the preparticipation screening program. A total of 145 young (<35 years) competitive athletes (M/F=106/39=2.7, mean age 17.3±5.3 years) were evaluated in the outpatient clinic of the department of Cardiology of Padua University from years 2007 to 2010. All subjects were referred to our laboratory due to ventricular arrhythmias detected during preparticipations screening, through 12 lead-ECG or during exercise stress test or ECG-Holter monitoring. The study protocol included family and personal history, 12-lead basal ECG, echocardiography-Doppler, ECG-Holter monitoring, exercise stress test, signal-averaged ECG, cardiac magnetic resonance (CMR). Moreover in selected cases invasive examination and genetic study were performed. When available, follow-up was also reported.

**Results:** In 15% of athletes ECG was pathologic. Negative T-waves beyond V2 were present in 2.1% and were associated with the presence of cardiac disease. Late potentials were present in 6.8%. Frequent echocardiographic findings were right and left ventricular enlargement, mitral valve prolapse and mild atrioventricular valve regurgitation. Congenital diseases were detected in 2.7%. Moreover a possible form of cardiomyopathy was identified in 2.1%. Premature ventricular beats (PVBs) were more frequently monomorphic (88%) and isolated (57%). Rapid ventricular tachycardia was rare (2.7%). During exercise stress test PVBs disappeared in 55.7%, were present only during recovery in 11.5%, persisted in 8.6% and in were exercise-induced in 13.7%. Most frequent PVBs morphology was LBBB with inferior axis deviation. The presence of segmental abnormalities on CMR, present in almost half of the athletes in which it was performed, is not always easy to interpretate and follow-up is needed. Overall 30% of athletes were judged to have potentially dangerous arrhythmias and in 10% of athletes antiarrhythmic therapy was initiated. A total of 44% athletes were put on detraining or disqualified.

**Conclusion:** pre-participation screening program identifies athletes with ventricular arrhythmias, of which 30% are judged to be potentially dangerous. ECG and submaximal exercise stress test are important tools that allow identification of arrhythmias in competitive sports, thus submaximal exercise stress test should always accompany ECG in the first level of evaluation of an athlete. Cardiologic screening with non-invasive techniques is fundamental for the study of young athletes with no previously known organic heart disease, suspected channelopathy or potentially dangerous idiopathic arrhythmias, as exercise may be harmful either as progression of disease or as arrhythmic death. Follow-up study demonstrated that the identification of arrhythmias in athletes, pharmacologic therapy or sport squalification, can prevent adverse outcomes. Collaboration of sports medicine and cardiology permits the identification of athletes with ventricular arrhythmias and the prevention of sudden death. Risk stratification of athletes with ventricular arrhythmias remains difficult even after a thorough investigation of the heart with all the techniques available.

## Riassunto

**Introduzione:** Il programma dello screening di prepartecipazione per gli atleti ha il ruolo dell'identificazione precoce di malattie cardiovascolari non prima sospettate e la squalificazione dell'atleta dall'attività competitive. La più frequente condizione di squalifica sono le anomalie di ritmo e conduzione (circa 40%.)

**Scopo e metodi** lo studio con esami non invasivi cardiaci, i giovani atleti che sono scoperti di avere aritmie ventricolari durante il programma dello screening di prepartecipazione. Un totale di 145 giovani atleti (>35 anni) sono studiati (età media  $17.3 \pm 5.3$  anni, M/F=106/39=2.7), valutati nell'ambulatorio "genetica clinica e molecolare delle cardiomiopatie" del Dipartimento della Cardiologia del Università di Padova dagli anni 2007-2010. Tutti i soggetti sono stati rivolti al nostro ambulatorio per aritmie ventricolari rilevate durante lo screening prepartecipazione per la presenza di BEV all'ECG, durante la prova da sforzo o all'ECG-Holter delle 24 ore. Il protocollo di studio comprendeva: storia familiare e personale, ECG a 12 derivazioni, ecocardiogramma-Doppler, ECG-Holter, prova da sforzo, ricerca dei potenziali tardivi (SAECG), risonanza magnetica (RMC). In casi selezionati esami invasivi e studio genetico è stato eseguito. Quando disponibile è stato eseguito anche il follow-up.

**Risultati** Nel 15% degli atleti l'ECG era patologico. Onde T negative dopo V2 erano presenti in 2.1% ed erano associate con cardiopatia organica. I potenziali tardivi erano presenti solo nel 6.8%. Frequenti alterazioni ecocardiografiche erano la dilatazione del ventricolo destro e sinistro, il prolasso valvolare mitralico e lieve insufficienza delle valvole atrioventricolari. Cardiopatie congenite sono identificate nel 2.7%. Inoltre forme sospette di cardiomiopatia sono identificate nel 2.1%. I battiti ectopici ventricolari (BEV) erano più frequentemente monomorfi (88%), isolati (57%). Tachicardia ventricolare veloce era rara (2.7%). Durante la prova da sforzo i BEV scomparivano nel 55.7%, erano presenti solo nel recupero nel 11.5%, persistevano nel 8.6% ed erano indotti dall'esercizio nel 13.7%. La più frequente morfologia era tipo BBsn con asse inferiore. La presenza di anomalie segmentarie nella RMC, presenti in circa la metà degli atleti sottoposti all'esame, non è sempre facile d'interpretare e serve follow-up. Il 30% degli atleti sono stati giudicati di avere potenzialmente pericolose aritmie e nel 10% terapia antiaritmica è stata instaurata. Un totale di 44% atleti sono messi in defaticamento o sono stati squalificati.

**Conclusioni:** Lo screening prepartecipazione identifica atleti con aritmie ventricolari, dei quali il 30% sono giudicate potenzialmente pericolose. L'ECG e la prova da sforzo sotto massimale sono dei test fondamentali per l'identificazione di aritmie per gli sport competitivi e la prova da sforzo sottomassimale dovrebbe sempre accompagnare l'ECG come valutazione di primo livello negli atleti. Lo screening cardiologico con esami non invasivi è fondamentale per lo studio di atleti giovani con cardiopatia organica misconosciuta, il sospetto di canalopatia o aritmie idiopatiche potenzialmente pericolose, dove l'esercizio può essere dannoso o come progressione di malattia o come morte aritmica. Lo studio di follow-up ha dimostrato che l'identificazione delle aritmie negli atleti, la terapia farmacologica o la squalificazione può prevenire la morte improvvisa. La collaborazione della medicina dello sport e della cardiologia permette l'identificazione di atleti con aritmie ventricolari e la prevenzione della morte improvvisa. La stratificazione del rischio rimane difficile anche dopo uno studio cardiaco approfondito con tutte le tecniche a disposizione.

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## 1 - CARDIOVASCULAR SYSTEM AND EXERCISE

**Exercise paradox.** Regular physical activity is known to promote a favorable cardiovascular state, offering beneficial effects on physical and mental state in every age of life, ameliorating the quality of life and contributing also to the longevity. Life expectancy can be increased by life style changes such as improvement of nutrition habits and physical activity. Physical inactivity and inappropriate diet have represented the second cause of mortality after smoke in the U.S. in the years 1990-2000. Physical inactivity is one of the most important risk factors for cardiovascular disease and a widening variety of other chronic diseases. Unfortunately no more than 20% and possibly less than 10% of adults in the U.S., Australia, Canada and U.K. obtain sufficient regular activity at an intensity that imparts discernible health and fitness benefits (1). Observational studies provide compelling evidence regarding the primary prevention of cardiovascular disease that regular physical activity and a high fitness level are associated with a reduced risk of premature death from any causes and from cardiovascular disease in particular among asymptomatic men and women. Regular physical activity is clearly effective also in the secondary prevention of cardiovascular disease and in attenuating the risk of premature death among men and women (2).

The most prevalent complication of sports activity is represented by the musculoskeletal injuries, while the most dangerous and deleterious is the sudden cardiac death. Intense physical activity does raise a small risk of cardiac death, particularly for sedentary persons with a genetic predisposition on sudden death. Nonetheless, the longer term reduction in overall death risk from regular exercise outweighs any small potential for acute cardiovascular complications (1).

The cardioprotective effects of exercise are multifactorial and are capable of reducing the impact of the major coronary risk factors: improve body composition (reducing abdominal

adiposity and improving weight control), enhance lipid lipoprotein profiles (reducing triglyceride levels and LDL levels, increasing HDL levels), reduce the blood pressure, improve glucose homeostasis and insulin sensitivity (2). However, of particular importance are the primary effects on the vessels and blood, such as to enhance or restore the endothelial function, regression or reduce progression of coronary sclerosis, improvement of coronary flow and possible collateral formation as well as improvement of vascular repair by circulated endothelial progenitor cells, decrease blood coagulation (decreasing of platelets reactivity and increasing fibrinolytic capacity). These beneficial effects can all be induced by the therapy called physical activity or endurance sports. Regular physical exercise may preserve or improve endothelial function via several mechanisms, including synthesis of molecular mediators, changes in neurohormonal release and oxidant-antioxidant balance. The augment of blood flow and laminar shear stress results in increased nitric oxide production and bioavailability. On the other hand, physical exercise can also elicit systemic molecular pathways connected with angiogenesis and chronic anti-inflammatory action (reducing protein C reactive levels) with consequent modification of the endothelial function. However, its benefit depends on the type and intensity of training performed, because strenuous exercise increases oxidative metabolism and produces a pro-oxidant environment. Thus, only regular moderate physical activity promotes an antioxidant state and preserves endothelial function (1, 2).

Exercise has important role in preventing some diseases like coronary atherosclerosis, stroke, dyslipidaemia, obesity, diabetes mellitus type II, arterial hypertension, cancer (colon and breast), bone and joint diseases (osteoporosis and osteoarthritis) and depression (2). It also has a role in rehabilitation and like a coadjuvant therapy in certain clinical-pathologic conditions. It is applied in a variety of disorders: cardiovascular, pulmonary, neuromuscular, orthopedic, metabolic and immunologic-hematologic (1). Exercise also stimulates vascular remodeling leading to formation of large conductance



arteries that are well capable to compensate for the loss of function of occluded arteries.

Routine physical activity is also associated with improved psychological well-being, buffering the effects of mental stress, reducing anxiety and depression, improving the mood and self-esteem. Numerous beneficial effects of exercise, including improved memory, cognitive function and neuroprotection, have been shown to involve an important neuroplastic component. Importantly autonomic tone is also improved owing to the antiarrhythmic effects (1).

Summarizing the physical activity has benefit effects in all sectors of life, enhancing cardiac, pulmonary and muscular function and sport must be encouraged from the early years of life mainly in young, where sedentary life prevails. However, the effects of physical exercise on the cardiovascular system are presented as a “paradox” with beneficial effects and hazards. In subjects carrying a heart disease, physical activity may be contraindicated or should be performed with moderation because it may harm. Also, strenuous exercise in some studies resulted “paradoxically” harmful in time. Interestingly, acute bouts of ultra-endurance exercise may result in the appearance of biomarkers of cardiac cell damage and to cardiac “fatigue” with alterations in systolic and diastolic function (3-9). The clinical significance of these changes is not fully understood. Could prolonged endurance exercise produce a degree of cardiac stress and/or damage that result, during the short or long term, in deleterious consequences for cardiac health? Regarding the release of the biomarkers of myocardial injury because most of the studies involve healthy individuals with no underlying cardiovascular disease it seems a benign process (10-12). The development of myocardial fibrosis and consequent risk of arrhythmias is also a topic of concern for the athlete’s heart. It is known that frequent and complex ventricular tachyarrhythmias are common in trained athletes and are usually unassociated with underlying cardiovascular abnormalities (13). Ventricular arrhythmias, when unassociated with cardiovascular abnormalities, do not convey adverse clinical outcome, appearing to

be an expression of "athlete's heart syndrome" and probably do not per se justify a disqualification from competitive sports (10). A recent study in Olympic athletes did not show deterioration of left ventricular function, significant left ventricular morphologic changes or cardiovascular event during a long term follow-up (14). On the contrary, some studies have shown the presence of left ventricular late-enhancement in cardiac magnetic resonance studies and other have shown that ventricular arrhythmias in high-level endurance athletes frequently originate from a mildly dysfunctional right ventricle (15-17). Cardiac magnetic resonance imaging studies are not concordant on the presence of late-enhancement. A recent investigation has shown that endurance athletes with arrhythmias have a high prevalence of right ventricular structural and/or arrhythmic involvement and endurance sport seems to be related to the development and/or progression of the underlying arrhythmogenic substrate (18). This could be due to the fact that endurance exercise and volume overload subject the thin-walled right ventricle to a greater increase in workload than the thick-walled left ventricle, with subsequent changes to the structure of the right ventricle. Another recent study postulated the hypothesis that an ARVC-like phenotype may be acquired through intensive exercise without an identifiable genetic predisposition. This raises the question whether endurance exercise not only acts like a trigger for these arrhythmias but also as a promoter of right ventricular changes (19, 20). Whether years of training and competition might lead to fibrotic heart prone to arrhythmias is still arguable.

The pre-participation screening program of athletes has the goal of the early identification of previously unsuspected cardiovascular diseases and the disqualifications of the athletes with the hope that these strategies will reduce sudden cardiac death. From 1979 to 2004 the Centre for Sports Medicine in Padua has evaluated with the pre-participation screening program 42.386 young athletes and 2% were found to have a cardiovascular disease (18). Earlier data showed that during follow-up the disqualified athletes did not die, which means

that identification and disqualification of athlete carrying a cardiovascular disease can really prevent sudden cardiac death (22). Importantly, the most frequent disqualifying condition consisted of rhythm and conduction abnormalities (nearly 40%) (23).

**Heart adaptations during exercise.** Exercise is a stressful condition that the cardiovascular system normally has to affront. The acute response of the organism to exercise is mediated by hemodynamic, neural and metabolic factors that lead to transitory cardiovascular adaptations. These adaptations occur at the heart level (central changes) and in the circulatory level (peripheral changes) with the final goal to provide the active muscles with a continuous stream of nutrients and oxygen to sustain a high level of energy transfer (5).

The cardiovascular response to exercise depends on the intensity of training, type of conditioning and also to external factors (24). Sports activity can be divided in two broad types respect to the type of conditioning: endurance-dynamic training (isotonic) and strength-static training (isometric) (25). The knowledge of the cardiovascular responses to exercise helps not only to understand the cardiovascular adaptations during intensive long-term exercise, but also helps to indicate the type and intensity of exercise that may be proposed in relationship with a specific heart disease. The cardiovascular risk during exercise depends not only to the specific cardiac abnormality but also to the type of sport and the specific stress that produces to the heart. The cardiovascular type of response to a sport and the psychological stress that invariably accompanies the competition are fundamental factors that have to be considered for sport recommendation. Finally, in every sport must also be considered the intensity and duration of exercise, the peak exercise, the neuro-humoral effects and the environment conditions (6).

Endurance training is the deliberate act of exercising to increase stamina and endurance. The dynamic or isotonic muscular work is characterized by length changes of muscle fiber, rhythmic contractions with wide joint movements that produce a modest power and use

principally aerobic metabolism (26). The endurance exercise in the heart predominantly produces volume load because it has to move great quantities of blood and maintain a high cardiac output for a variable time (from minute to hours) on a vascular system of low resistance (5). The acute responses to endurance exercise training include substantial increases in maximum oxygen consumption, cardiac output and stroke volume, systolic and medium blood pressure associated with decreased peripheral vascular resistance. In this group are included long-distance running, swimming, cycling, triathlon, canoeing and other sports (26).

Strength training is the use of resistance to muscular contraction to build strength, anaerobic endurance and size of skeletal muscles. It is a static or isometric work characterized by small or absent length variations of muscle fibers, small joint movements that produce much power and use principally the anaerobic metabolism (26). Strength training in the heart predominantly produces pressure load because it has to move relative small quantities of blood on a vascular system of high resistance (24). The acute responses to strength training is a modest increase of maximum oxygen consumption, of cardiac output and heart rate, an important increase in arterial blood pressure (systolic, diastolic and medium) with no appreciable change in total peripheral resistance and stroke volume. In this group are included weight-lifting, gymnastic, martial arts, sprint and other sports (5, 6).

The exercise physiology of these two types of conditioning is important. In endurance training the muscular metabolism, prevalently aerobic, can increase substantially. Maximum effort increases nearly ten times maximum oxygen consumption. Basal is 350 ml/min, in athletes can arrive 3-5 l/min (even 20 to 40 times more) and this depends on the capacity of the cardiovascular system to transport oxygen to the active muscles. Oxygen and nutrients supply are fundamental and supported by two fundamental mechanisms: 1) increase of blood flow and 2) increase in oxygen extraction from blood and thus expanded

artero-venous oxygen difference (1). These mechanisms are mediated by neurovegetative reflexes and biochemical modifications connected to metabolic processes.

The first hemodynamic response to exercise is probably represented by the lowering of the vascular systemic resistance reflecting a marked vasodilatation of the resistance vessels of active muscles. This has two hemodynamic effects: the muscular distribution of the increased cardiac output and the afterload reduction. The muscle is the only organ that can increase 20-25 times its flow. In resting conditions usually receives 18% of cardiac output while during maximal exercise can arrive to 80-85% (1). The increase in blood flow is mainly due to the vasodilatation of the muscle vessels and numerous are the contributing factors. Local autoregulation is the most important factor and is due to chemical substances (hypoxia, adenosine, lactic acid, K<sup>+</sup>) that act directly to the arterioles. The increase of blood pressure itself is also important of increasing flow having an effect of distending blood vessels. Marked vasoconstriction of the splanchnic regions due to sympathetic activation and release of vasoconstrictor substances contributes to the increased flow and redistribution of blood to the active muscles (2 l/min of extra blood).

The artero-venous oxygen difference can increase three times during effort and is due to multiple factors: release of carbon dioxide, acids, increase in temperature (leading to a more or less complete desaturation of hemoglobin) and chronic muscular adaptations (increase in microcirculation and increased aerobic ability of muscular cells). The skeletal muscles involved in the dynamic exercise training become more oxidatative and less glycolitic, with an increase in the number and size of the mitochondria and an increased number of capillaries. These changes contribute to the larger maximal artero-venous oxygen difference seen in endurance athletes. Finally, massive recruitment of dormant capillaries increases blood flow and also the surface of metabolic exchange (1, 5).

The modifications of cardiac output as a response to exercise are fundamental and depend on the heart rate and stroke volume. Cardiac output usually increases 3-4 times

(20-22 l/min) in sedentary people, while in an athlete can increase 6-8 times (up to 40 l/min). The increase of cardiac output during exercise principally depends on the increase of the heart rate. The increase of heart rate during exercise is an evident response mainly due to sympathetic stimulation and in less extension to vagal inhibition. During dynamic training the heart rate increases linearly with the intensity of exercise. In the beginning of exercise or during low intensity exercise, the increase of heart rate is due to the reduction of vagal tone, a response mediated by the central nervous system caused by the stimulation of muscular mechanoreceptors. Subsequent increase of heart rate is due to the activation of sympathetic system, that becomes important above 100 b.p.m and the circulating catecholamines released by the adrenal medulla, accelerating the spontaneous diastolic depolarization of sinus node, cause the positive chronotropic effect. Variations of heart rate are not enough to explain the increase of cardiac output and an increase of stroke volume also occurs, up to 40-50%. Venous return is mediated by the sympathetic venoconstriction, muscle pump effect and respiratory pump and it is also helped by the visceral vasoconstriction and muscular vasodilatation that decreases the resistance to venous return. During the initial period of a dynamic exercise the increase of venous return, increases the preload and thus the force of contraction (following the Frank-Starling curve). Both the increase of end-diastolic volume at rest (athletes' heart) and during exercise leads to a larger stroke volume (1). The filling capacity of the ventricles increases and the higher filling velocity can reassure adequate filling during high heart rates. During high levels of exercise, sympathetic stimulation and probably intrinsic mechanisms of cardiac adaptation increase inotropism. Maximal sympathetic stimulation can double the force of contraction (1). Vigorous contraction of ventricles leads to more complete systolic emptying contributing to increase the stroke volume during exercise (1). The biggest variations of stroke volume occur during the initial period of exercise (50% of VO<sub>2</sub> max), because the increase of heart rate decreases the diastolic period and further increase of

cardiac output is due to increase of heart rate (5).

The systolic arterial pressure increases due to the increase of stroke volume and heart rate while diastolic arterial pressure usually decreases or remains unchanged due to the decrease of the vascular peripheral resistance. Also the pulmonary arterial pressure increases during exercise (from 5 to 45 mmHg depending on the intensity), while the vascular pulmonary resistance decreases and the dormant capillaries open, but less than systemic resistance. Relative high arterial pressure may help oxygenation of blood.

The acute responses to strength training of the cardiovascular system are different from that of resistance. Isometric exercise produces a prolonged contraction of a group of muscles without producing an external work. The muscles involved usually are not many and thus why the entity of oxygen consumption is modest. There is not a proportional increase of blood flow respect the oxygen needs of the muscles involved, because there is a general vasoconstriction, mainly due to nervous reflexes. That's why there is also an increase of blood pressure (either systolic or diastolic) respect to dynamic exercise. Venous return is obstructed by an eventual maneuver of Valsalva and thus the stroke volume does not increase significantly. The mechanism that increases the cardiac output becomes the heart rate that results not proportionate respect the metabolic needs of the muscles and to less entity respect the isotonic exercises. Stroke volume and cardiac output increase result inadequate to satisfy the oxygen consumption and that's why cardiac output and oxygen consumption increase later to normalize the oxygen debt (1, 5).

The two types of training (endurance and strength) are considered as extreme examples of various intermediate possibilities. Most types of training have both components, static and dynamic, even if often one prevails to the other. In the mixed type of training the type and intensity of muscular work varies in time, often unpredictable, characterized by alteration of aerobic and anaerobic metabolism and variable hemodynamic responses.

The heart load is not exclusively pressure or volume. In this group are included tennis, box, soccer, basketball, rugby and other sports (5, 6).

**Athletes' Heart.** Acute responses to exercise are qualitative similar in athletes and not athletes but cardiovascular performance of athletes is far better thanks to cardiovascular adaptations stable in time due to systemic and intensive exercise (24). Physiological structural and electrophysiological cardiac changes enable sustained increases in cardiac output for prolonged time. These adaptations depend on genetically determined characteristics of the subject, age, type, duration and intensity of exercise and are more impressive in the endurance athletes (1). Training induces in more or less half of trained athletes some evidence of cardiac remodeling, which consists of alterations in ventricular chamber dimensions, including left and right ventricular and left atrial size, associated with normal systolic and diastolic function (26). Athletes' heart is generally considered as a benign increase in cardiac mass, with specific cardiac and circulatory morphological alterations, that represent a physiological adaptation to systematic training (25).

Hypertrophy (from Greek "υπέρ" excess + "τροφή" nourishment) is the increase in the volume of an organ or tissue due to the enlargement of its component cells. The prototype of physiological hypertrophy and one of the most common and visible forms of organ hypertrophy occurs in skeletal striate muscle in response to strength training and muscle tension, known as muscle hypertrophy. Cardiac hypertrophy is the increase of the ventricular mass with or without chamber enlargement as a response to a chronic hemodynamic overload. Hypertrophy is due to increased synthesis of contractile proteins and thus new sarcomeres and myofibrils (27).

Changes can be beneficial or healthy if they occur to aerobic or anaerobic exercise. The physiological hypertrophy is a benign adaptation without adverse cardiovascular consequences (4). The hypertrophy is due both to acquired factors (duration, type and intensity of sports) and genetic factors (1). Ventricular hypertrophy can be associated with



pathological changes due to high arterial pressure as in arterial hypertension and aortic stenosis or other disease states as hypertrophic cardiomyopathy. Pathologic hypertrophy is associated with up-regulation of fetal genes, fibrosis, cardiac dysfunction and increased mortality (3). The problem rises when exercise cardiac remodeling may eventually mimic certain pathologic condition as hypertrophic cardiomyopathy or dilated cardiomyopathy.

Two types of hypertrophy, eccentric and concentric, have been classically linked to exercise based on the cardiac adaptations to volume or pressure overload. Eccentric hypertrophy is due to volume overload, leading to the increase of the left chamber size with a proportionate increase in wall thickness and is mainly due to endurance training. Concentric hypertrophy is due to pressure overload, leading predominantly to increased left ventricular wall thickness with unchanged or reduced left ventricular chamber size and is mainly due to strength training. The chronic adaptation of the cardiovascular system to static exercise training results in little or no increase in maximal oxygen uptake (5).

Importantly in the clinical practice the classification as an “endurance-trained heart” or “strength-trained heart” is not an absolute and dichotomous concept but rather a relative concept. In every form of endurance training, blood pressure increases in addition to cardiac output just as in every form of strength training, heart rate, cardiac output and blood pressure increases (28). Intermediate forms of hypertrophy exist in combined high static and dynamic component sports. These sports as cyclism and rowing showed a significant increase in relative wall thickness and the highest increase in left ventricular internal dimensions. Rowing is first in rank according to the effect on left ventricular wall thickness, while cycling is first in rank according to ventricular dimensions (28). The most extreme increases in cavity dimensions and wall thickness have been observed in those elite athletes training in rowing, cycling, cross-country skiing, and swimming, while paradoxically, ultra-endurance sports, such as triathlon, show modest alterations in cardiac dimensions (29). Regarding parietal wall thickness, a study on hundred power training

athletes demonstrated that they presented an increased left ventricular mass and a disproportionate increase in wall thickness in relation to cavity dimensions but no athletes had a maximal absolute wall thickness exceeding the generally accepted upper limits of 12 mm (7). Another study demonstrated that only 2% of elite athletes have a wall thickness  $\geq 13$  mm and in adolescents wall thickness  $\geq 13$  mm is very uncommon (30-32). Regarding cavity dimensions some studies in elite athletes, demonstrated that only 14% have a left ventricular enlargement from 60-70 mm and adolescent athletes rarely exceed 60 mm (33). Left atrial remodeling is also relatively common and 20% may have left atrial dimension  $\geq 40$  mm (34). Finally, right ventricular remodeling may also occur in athletes (35, 36).

Resistance training also leads to vascular modifications of the coronary and peripheral system. In the coronary tree morpho-functional effects occur either at rest or during exercise. Resistance training leads to an increased diameter of the epicardial vessels, probably aiming to ameliorate myocardial perfusion in the presence of an increased ventricular mass. Testing vascular tone with nitroglycerin demonstrated a greater capacity of vasodilatation respect sedentary persons, aiming to increase blood flow during effort. In experiment animals the existence of increased myocardial capillarization was observed. If blood flow is not adequate reactive myocardial fibrosis can occur. A modification of the peripheral system of the big and medium arterial and venous vessels and muscular capillarization occurs, a mechanism that permits an increase of flow with little or no increase of the medium blood pressure (1).

Finally, neurovegetative changes also occur and physiological adaptation of the cardiac autonomic system to athletic conditioning result in sinus bradycardia, atrioventricular conduction impairment and early repolarization pattern on the ECG. The sinus bradycardia of an athlete is due mainly to modifications of the central nervous autonomic system, even though a complementary role of peripheral mechanism and genetic factors that decrease

the intrinsic rate of the sinus node, have been described (1). The reduction of heart rate is due to a prevalent withdrawal of the sympathetic activity with little or no increases of the vagal tone. Reduction of chronotropic function which occurs at rest and during submaximal effort is one of the earliest modifications that can be revealed in resistance sport. It is an adaptive mechanism that permits to the heart to work with more efficiency and economy. In well trained athletes the heart rate can decline to 45-50 b.p.m., usually with sinus rhythm. This usually needs long periods and higher levels of training. In elite athletes (mainly long distance running, cycling, cross country skiing) is not rare to observe values less than 40 b.p.m. (1).

## 2 - SUDDEN CARDIAC DEATH IN ATHLETES

Millions of people practice sports following the aphorism "mens sana in corpore sano" for the beneficial effects on the body and spirit. The athlete is generally regarded as one of the healthiest members of the society and sport is seen as a way to ameliorate health (37). Sudden death is generally defined as unexpected death as a result of natural causes in which loss of all functions occurred instantaneously or within one hour of the onset of collapse symptoms (21). Sudden death in athletes is most commonly cardiovascular in origin followed by respiratory and cerebral causes (38). In young athletes genetic and congenital cardiovascular diseases are the most prominent causes of sudden death (39, 40, 41). In the general athletic population the prevalence of a cardiac disease is low and the risk of sudden cardiac death is an infrequent event. Nonetheless, the emotional and social impact of sudden death is considerable and widespread by the mass media because occurs unexpectedly in young and apparently healthy subjects.

The incidence of athletes' sudden cardiac death according to Minnesota study is about 1 per 200.000 per year, while in Veneto region is 2.1 per 100.000 per year (42, 43). This disparity could be due to different ages, exercise intensity, pathologic substrates and different data analysis (37). In the last years in Veneto region it has been observed a decline in the incidence of sudden cardiac death after the introduction of the national pre-participation screening program with a decrease of 89% (21). This decline was due to the increased identification of the cardiomyopathies. The greatest decline occurred in death rates from arrhythmogenic cardiomyopathy (21).

In adults (>35 years) the most frequent cause of sudden death is the coronary artery disease. Sports activity is seen as a "two-edged sword" that is preventing the development and progression of the coronary lesions in subjects that exercise regularly, preventing myocardial infarction, while increases the incidence of coronary acute events in subjects

that don't exercise regularly (22). Sudden cardiac death, due to atherosclerotic coronary artery disease, account for more than 80% of cases. Acquired valve disease, mitral valve prolapse and hypertrophic cardiomyopathy have been recognized as much less frequent causes of death in this group (44).

In the young, cardiovascular diseases account for more than 80% of cases of sudden death. A wide spectrum of predominantly inherited and congenital cardiac diseases, less frequently acquired and often clinically silent, have been linked as the most common causes of juvenile sudden cardiac death in athletes (45, 46). The most important cardiovascular diseases are: 1) cardiomyopathies; most frequently arrhythmogenic and hypertrophic cardiomyopathy and in less extent dilated cardiomyopathy, 2) congenital coronary artery anomaly with wrong sinus origin, most commonly left main coronary artery origin from right sinus of Valsalva, 3) premature atherosclerotic coronary artery disease, 4) valvular heart disease (as aortic stenosis and myxomatous mitral valve disease), 5) conduction system disease (as Lenegre disease) and Wolff-Parkinson-White syndrome, 6) aortic dissection and rupture (usually associated with Marfan syndrome or bicuspid valve), 7) myocarditis, 8) congenital heart diseases, 9) channelopathies (39, 45, 46).

In the U.S. the most frequent cause of sudden cardiac death is hypertrophic cardiomyopathy (36%) following coronary artery anomalies (17%), myocarditis and arrhythmogenic cardiomyopathy (47). In Veneto region the most common cause of sudden death is arrhythmogenic cardiomyopathy (22.4%), followed by premature coronary artery disease (18.5%), coronary anomalies (12.2%), mitral valve prolapse (10.2%), conduction system disease (8.2%) and myocarditis (6%). Hypertrophic cardiomyopathy was present in only 2%. So, hypertrophic cardiomyopathy is the single most common cause of sudden death, responsible for approximately one third of cases in the U.S. while arrhythmogenic cardiomyopathy in the region of Veneto is the principal cause of sudden death in athletes, which is frequently occult (23, 48, 49). The different prevalence of diseases is not probably

due to a different genetic predisposition but probably to the pre-participation screening program in Italy that disqualifies from competition a greater number of diseases more easily identified as hypertrophic cardiomyopathy respect arrhythmogenic cardiomyopathy. This is also confirmed by the fact the prevalence of sudden cardiac death due to hypertrophic cardiomyopathy is higher in non athletes respect athletes (23). Nowadays arrhythmogenic cardiomyopathy starts to be recognized and identified (21).

Approximately 2-5% of young athletes who die suddenly are reported to show normal cardiac structure on standard autopsy examination (41, 44). A recent study in the U.K. showed that a significant number of sudden cardiac death victims (23%) exhibited a morphologically normal heart (50). Sudden death in apparently normal heart is still a problem (51). Primary electrical disorders (long QT syndrome, Brugada syndrome and CPVT) likely underlie a large proportion of these sudden cardiac deaths. One third of unexplained deaths are genetic (52). The emerging practice of postmortem molecular screening of unexplained sudden cardiac death victims promises a better defining of the prevalence of these disorders in the athletes (52, 53). The molecular bases of sudden cardiac death start to be revealed (54, 55). Accurate identification becomes important for the relatives (56). Many of these sudden cardiac deaths in young people are likely due to ion-channel disorders but also concealed diseases as Wolff-Parkinson-White syndrome, coronary vasospasm or other abnormalities of the conduction system and microvasculature. Occasionally, a tunneled segment of the left anterior descending coronary artery is the only structural abnormality evident to autopsy to explain sudden death; however it is unresolved whether this malformation can be regarded as the only cause of sudden death (52).

Sudden cardiac death may occur in a wide variety of more than 30 competitive athletic disciplines, most commonly basketball and football in the U.S. and soccer in Europe, intense sports that also have high participation levels (57).

Studies in the region of Veneto demonstrated that sudden death occurs much more frequently in males (10:1) than in females (43). The same also happens in the U.S. (81), France (58) and U.K. (50). Young women are probably less frequently affected because their lower overall participation rates and absence from sports such as football. Females also have the tendency compared to men to not deny or ignore the prodromal symptoms (44). Male sex is also an independent risk factor for sudden death in relation to exercise. This is due probably to a higher prevalence and/or phenotypic expression in men respect females of cardiovascular diseases of arrhythmic risk as arrhythmogenic cardiomyopathy, hypertrophic cardiomyopathy and premature coronary artery disease (43). Males also are usually exposed to more intensive training and achieve greater levels of intensity during athletic competitions than females. This burdens the heart with a mechanical and adrenergic stress prolonged in time, depending on the duration and intensity of exercise. In the U.S. sudden cardiac death in young competitive athletes is a source of particular concern to the black community. Deaths due to cardiovascular disease are more common in nonwhite than white athletes. Blacks account for a disproportionate number of sports-related sudden death owing to previously undiagnosed hypertrophic cardiomyopathy. Indeed, of the athletic field deaths due to hypertrophic cardiomyopathy in high school and college student-athletes in more than half occur in blacks (42).

The phenotypic manifestations in the majority of the cardiac diseases a risk of sudden death during exercise is age-related and is manifested prevalently during adolescence. Some examples are the cardiomyopathies, channelopathies, premature coronary artery disease, diseases of the conductive system (59). In one half of the victims, sudden death is the first manifestation (60).

The diseases responsible of sudden cardiac death during physical activity have two common aspects. The first aspect is that are clinically silent with little or no hemodynamic effects, thus permitting vigorous exertion during competitive sports. The second aspect is

the increased electrical instability of the myocardium favoring the development of lethal arrhythmias (24). Sudden cardiac death is usually the result of interactions between the cardiac disease that represents the substrate and the triggers that initiate an arrhythmic event in a vulnerable myocardium (24).

Sport acts as a trigger of sudden cardiac death in athletes affected by a cardiovascular disease that predisposes to arrhythmias (43). Young athletes having a cardiovascular disease have a higher risk of sudden cardiac death respect non athletes (43). Athletes are exposed to psychological and physiological stresses of intensive and competitive sport that lead them often to exceed their native physical limits and reach their maximum performance (48). The risk is more elevated in intense exercise respect "soft" exercise and death occurs in the majority during or immediately after athletic activities and mostly during official competitions (4 times more than training) (25, 59). Triggers for arrhythmias could be multiple as hemodynamic changes, autonomic changes, emotional stress, environment changes and ischemia (61). Recently the presence of repolarization abnormalities due to potassium channel downregulation has been postulated (62). Extreme conditions not always predictable and easily controlled can be created leading to alterations of blood volume and electrolytes (43). Intense and systemic sport can also lead to disease progression in time (61). It is important to understand that the cardiac abnormalities predispose to sudden cardiac death and not the sport (43). The cardiovascular causes at the highest risk of sports related sudden death are anomalous origin of coronary arteries from the wrong coronary sinus (RR=79), arrhythmogenic cardiomyopathy (RR=5.4), premature coronary artery disease (RR=2.6) (59). Premonitory cardiac symptoms not uncommonly occur before sudden death in subjects with congenital coronary anomaly, suggesting that a history of exertional syncope or chest pain requires exclusion of this anomaly (62). Finally sudden death is not only limited in competitive sports but it can also occur in young people during recreational activities or sedentary persons (63).



As far as the pathophysiology is concerned, cardiac arrest has two mechanisms: mechanical and arrhythmic, which is by far the most common mechanism. Rarely non arrhythmic mechanisms may cause sudden death. The mechanical sudden death has been linked to aortic rupture and genetic-congenital abnormalities as Marfan syndrome, aortic coarctation, bicuspid aortic valve or diseases not related to the heart (bronchial asthma, rupture of cerebral aneurism, exertional heat illness and sickle cell anemia). In the arrhythmic sudden death the ventricular fibrillation is the most common arrhythmia (almost 70%); followed by asystole (almost 15%), ventricular tachycardia (almost 10%), and electromechanical dissociation (that accounts for about 5% of cases) (38). Abrupt ventricular tachyarrhythmias are usually the cause of sudden death in the majority of athletes. Non penetrating blows to the chest can also produce ventricular fibrillation (commotio cordis). Finally, doping related sudden deaths (attributed to anabolic-androgenic steroids, ephedra) may be due to fatal cardiac arrhythmias, acute myocardial infarction or cardiomyopathy (64).

Targets to treat and prevent sudden death in the young consist of the following: 1) avoid triggers like effort or emotion, 2) inhibit the onset of arrhythmias with drugs or ablation, 3) switch off arrhythmias with defibrillator and 4) hinder the recurrence of the disease with genetic counseling and/or therapy. In vivo detection of cardiomyopathies is nowadays feasible by electrocardiogram and/or echocardiography, which resulted in a sharp decline of sudden death in the athletes in Italy, thanks to obligatory pre-participation screening for sport activity. Genetic screening could play a pivotal role in early detection of asymptomatic mutation carriers of cardiovascular diseases at risk of sudden death (45). Various guidelines have been published in U.S. and Europe but they do not agree in all recommendations (23, 26).

### 3 - ARRHYTHMOGENIC HEART DISORDERS AND SPORT

**Monogenic heart disorders.** Molecular biology and genetics now form the solid foundation of cardiovascular science and medicine. In 1953 the discovery of structure of the deoxyribonucleic acid by Watson and Crick laid the foundation for molecular genetics (65). With the “completion” of sequence of the human genome, that contains about 3.2 billion nucleotides and 35.000 genes, genomic discoveries in the cardiovascular science occur at a rapid pace. These discoveries led to the better understanding of cardiovascular diseases and to the development of extremely useful animal models and provided the basic principles for molecular therapies. How these discoveries will translate to the care of patients with cardiovascular disease is currently difficult to predict.

Genetic disorders are recognized to be one of the major categories of human disease. Developments in genetics and molecular biology have provided a vast amount of data and information to support the view that most human diseases have a significant genetic component (66). Genes contribute to the cause and pathogenesis of virtually any abnormality of human physiology and behavior, including disorders of the cardiovascular system. Genetic disorders are due to abnormalities in chromosomes or genes and apart from the chromosomal disorders, essentially all genetic disorders result from some form of alteration or mutation occurring in a specific gene or involving multiple loci spread across the human genome (66).

Monogenic disorders are due to mutations of a single gene (single gene diseases). They can pose a real medical and health burden from the perinatal period to adult age with a peak around mid-childhood. The phenotype of many diseases is modified by genes in different loci and environment factors, so in reality there are few diseases that the phenotype is entirely determined by one only locus. Representing any disorder as purely monogenic is an oversimplification (67). The monogenic disorders follow a Mendelian

inheritance and are classified as autosomal dominant, autosomal recessive, X-linked (recessive or dominant) and the rare Y-linked (66). Pedigree analyses of large families with many affected individuals can be used to determine whether a disease-associated gene is located on an autosome or on a sex chromosome, and whether the related disease phenotype is dominant or recessive. The single gene disorders are rare, with a prevalence ranging from 1:1000 inhabitants in the most common forms and 1:200.000 in the rarest (68).

In cardiology there are two major clusters of monogenic disorders: 1) the cardiomyopathies, 2) the arrhythmogenic disorders caused by mutations in ion channels and ion channel controlling proteins (68). Ion channelopathies could be considered as primary cardiomyopathies (69). Two features of the monogenic diseases, namely penetrance and expressivity, had been identified since the inception of molecular genetics. The penetrance is defined as the percentage of individuals with a mutant allele who develop the phenotype of the related disease and it can vary from 10 to 100%. The expressivity is the different phenotypical manifestations that can be observed among carriers of the same gene defect. In other words it refers to the variation of a phenotype in individual carrying a particular genotype. Combining the variable penetrance and expressivity, it becomes clear that carriers of a DNA mutation may manifest either no clinical phenotype or phenotypes that are not typical of the “textbook” description of the disease. As a consequence the understanding of the clinical implications of genotyping in patients affected by “simple” monogenic disorders becomes less straightforward than desired (68).

There is a good reason to be optimistic about the continuing influence of new genetic finding on our understanding of cardiomyopathies. A great deal of expectations arose that genetics will provide radical insights into disease. Even very rare Mendelian disorders can reveal new insights with far-reaching consequences, and the cardiomyopathy disease

genes remaining to be discovered are likely to be in unexpected genes, implicating new pathways (67). A simple example of how our knowledge can be changed in time is that ARVC was first thought to be familiar in 1987 and only in the 2000 was found to be due to a defective cell junction protein, there after a variety of gene defects not only making part of the desmosomal complex were identified (70-72).

Healthcare authorities should become responsive to the advancement of knowledge in the field of genetic and should help facilitate the access to genotyping for families affected by those conditions in which genetic analysis provides useful information for clinical management (73). In cardiology the knowledge of the presence or absence of a certain gene mutations, which potentially may trigger exercise related arrhythmias becomes important for making clinical decisions (26).

**Arrhythmogenic Cardiomyopathies.** Cardiac arrhythmias are responsible for an estimated 1 million cases of syncope and sudden death among Europeans and Americans each year (74). Cardiac arrhythmias can be acquired most often as a consequence of CAD or may be secondary to familial-inherited syndromes. Despite the established relation between CAD and sudden death, a complete understanding of sudden cardiac death requires recognition of the other causes that although are less common and often rare, they may be recognizable before death, have therapeutic implications and provide broad insight in to sudden death problem. Many of these entities emerge as common causes of sudden death in adolescents, young adults and athletes among whom the prevalence of coronary artery disease is much lower. Certain cardiomyopathies have an important role in these events.

In 2006 the AHA defined cardiomyopathies as “a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic”. They were divided into due major groups,

primary and secondary, based on the predominant organ involvement. The primary cardiomyopathies were further divided in genetic, mixed and acquired forms. The genetic forms included the hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, left ventricular non compaction, glycogen storage and mitochondrial cardiomyopathies, but also the conduction defects and ion channel disorders. The dilated and restrictive cardiomyopathies were included in the so called “mixed cardiomyopathies” that are predominantly non genetic (75). In 2007 the ESC defined cardiomyopathy as “a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality”. These were divided five subtypes: hypertrophic, arrhythmogenic, dilated, restrictive cardiomyopathies and unclassified cardiomyopathies. Each of them can be familial or non-familial (76). Finally, a molecular classification of the inherited cardiomyopathies was also proposed dividing them in cytoskeletalopathy, sarcomyopathy, channelopathy (77, 78). In this section most important arrhythmogenic cardiomyopathies will briefly be described.

**Hypertrophic cardiomyopathy (HCM).** HCM was described for the first time in 1958 by a British pathologist Donald Teare as a rare “tumour of the heart” based on asymmetric left ventricular hypertrophy and outflow tract obstruction (79). Visibility attached to the disease relates largely to its recognition as the most common cause of sudden death in young, including competitive athletes (80). Though, the prevalence in highly trained athletes is extremely rare and the structural and functional changes associated, naturally select out most individuals from competitive sports (81). It is a the most common genetic cardiovascular disorder, with a prevalence of 1:500 in the general population (based on echocardiographic recognition of the phenotype) that is heterogeneous with respect to disease causing mutations, presentation, prognosis, and treatment strategies (Table 1) (80). Left ventricular hypertrophy may appear for first time in adolescence, but

also in children and late-onset hypertrophy has been described (82). Clinical diagnosis is based on 2-D echocardiographic identification of otherwise unexplained increase of left ventricular wall thickness in the presence of a non dilated cavity, in the absence of loading conditions sufficient to cause the abnormality observed (80). Screening athletes with echocardiography is not cost-effective (80). ECG is often abnormal (75-95%) and thus is useful in selecting out those individuals who may have pathological left ventricular hypertrophy for subsequent echocardiography. Pre-participation screening program of athletes identifies and disqualifies from competitive sports the majority of athletes with this disease (83). If the diagnosis could not be stated using echocardiography, methods like cardiac magnetic resonance, metabolic exercise testing, histological studies if endomyocardial biopsies and genetic testing can provide further information (84). Also ambulatory ECG monitoring may reveal in 25% non-sustained ventricular tachycardia (85)

Useful elements to differentiate it from athletes heart hypertrophy are: 1) positive family history for cardiomyopathy or sudden cardiac death, 2) bizarre ECG changes, 3) asymmetric hypertrophy with wall thickness  $\geq 12$  mm in females and  $\geq 15$  mm in males with normal or reduced cavity dimensions (LVEDD  $< 45$  mm), altered geometry and often altered TDI, enlarged left atrium, 4) pick  $VO_2 < 50$  ml/kg/min in cardiopulmonary test, 5) absence or mild reversibility of hypertrophy after detraining, 6) the presence of sarcomeric protein gene mutation (positive in 35 to 65% in different international cohorts), 7) typical histology (84).

The majority of patients with sarcomeric protein gene mutations have an asymmetrical pattern of hypertrophy, with predilection for the interventricular septum and myocyte disarray. Left ventricular cavity is usually diminished and fractional shortening typically higher than normal. Concentric hypertrophy is more frequent in patients with metabolic disorders, mitochondrial and glycogen storage disease. Overall HCM confers an annual

mortality rate of about 1% and in most patients is compatible with little or no disability and normal life expectancy. Subsets with higher mortality are linked to the complications of sudden death, progressive heart failure and atrial fibrillation with embolic stroke (80)

HCM is highly arrhythmogenic and the highest risk for sudden cardiac death has been associated with: 1) family history of a premature death (particularly if occurred in a close relative or when multiple), 2) extreme left ventricular hypertrophy with maximum wall thickness  $\geq 30$  mm on echocardiography, 3) prior cardiac arrest or spontaneously occurring sustained ventricular tachycardia, 4) nonsustained ventricular tachycardia (usually asymptomatic short bursts of 3 to 6 beats at  $\geq 120$  b.p.m. (only in young  $< 30$  years)), 5) attenuated or hypotensive blood pressure response during upright exercise, indicative of hemodynamic instability; 6) unexplained syncope, particularly in young patients (84). Arrhythmic substrates reside in the cardiac hypertrophy, myocardial disarray, scarring following ischemic damage due to small arteries compression. Pathologic evidence of ischemic damage (either acute-subacute or in the form of fibrotic scar, supports that ischemia, can contribute to life-threatening arrhythmias (86).

Recently, ECG amplitudes and effort-induced arrhythmias have been described as new risk factors for sudden death (87-88). Also, recent data suggest that contrast-enhanced magnetic resonance is a potential technique to help identify patients who are at risk for sudden cardiac death and the presence of scar is a predictor of arrhythmias and poor prognosis (89).

Treatment strategies depend on appropriate patient selection, including drug treatment for exertional dyspnoea and arrhythmias (beta-blockers, verapamil, and disopiramide, amiodarone) and the septal myotomy-myectomy operation, which is the standard of care for severe refractory symptoms associated with marked outflow obstruction; alcohol septal ablation and pacing are alternatives to surgery for selected patients. High-risk patients may be treated effectively for sudden death prevention with ICD (80).

European and U.S. recommendations in athletes with definitive diagnosis of HCM, recommend the exclusion from most competitive sports, with the possible exception of low dynamic and low static sports in those individuals considered to be at low risk for sudden cardiac death. The groups differ in their recommendations regarding the genotype positive-phenotype negative athletes. U.S. guidelines do not recommend exclusion of these individuals from competition due to the lack of data and unknown natural history. The ESC consensus document excludes these individuals from competitive sports and recommends amateur and leisure sport activities.

**Table 1. Genetically determined hypertrophic cardiomyopathy.**

<b>Sarcomeric mutations causing HCM</b>	<b>Calcium-handling proteins</b>
MYH7 (beta-myosin heavy chain) (15-25%)	JPH2 (junctophilin-2) (<1%)
MYBPC3 (cardiac myosin-binding protein C) (15-25%)	PLN (phospholamban) (<1%)
TNNI3 (cardiac troponin I type 3) (<5%)	<b>Lysosomal glycogen storage diseases</b>
TNNT2 (troponin T type 2) (<5%)	PRKAG2 (gamma-2 regulatory subunit of the AMP activated PK)
TPM1 (alfa-tropomyosin 1) (<5%)	LAMP2 (lysosomal associated membrane protein 2-Danon disease)
MYL3 (ventricular essential myosin light chain) (<1%)	GAA (a-1,4 glycosidase) (Pompe's disease-type II)
MYL2 (ventricular regulatory myosin light chain) (<2%)	PHKA2 (phosphorylase B kinase a-2) (type IX)
ACTHC1 (alfa-cardiac actin)(<1%)	<b>Lysosomal glycosphingolipid storage diseases</b>
MYH6 (alfa-myosin heavy chain) (<1%)	GLA (A-galactosidase) (Fabry's disease) and other
TTN (titin) (<1%)	<b>Fatty acid metabolism disorders</b>
TNNC1 (troponin C type1) (<1%)	VLCAD (acyl CoA dehydrogenase deficiencies)
CSRP3 (cardiac LIM protein) (<1%)	SLC22A5/OCTN2 (carnitine deficiency)
LBD3 (LIM binding domain 3) (1-5%)	<b>Mitochondrial cytopathies</b>
T-CAP (telethonin) (<1%)	Mitochondrial DNA or proteins mutations
VCL (vinculin/metavinculin) (<1%)	<b>Syndromic</b> (Noonan's, Leopard, Lentiginosis, Freidrich)
ACTN2 (alfa-actinin 2) (<1%)	Other less common: ANKRD1 (ankyrin)
MYOZ2 (myozenin 2) (<1%)	

**Arrhythmogenic right ventricular cardiomyopathy (ARVC).** In 1982 arrhythmogenic right ventricular cardiomyopathy was described in 24 adult cases and later on in 1988 was identified as a previously unrecognized and an important cause of sudden cardiac death in the young and athletes and familial occurrence was demonstrated (90-92). The genetic background of the disease as a monogenic disease with incomplete penetrance is now



clears (Table 2) (93, 94). The genetic screening is now feasible for the detection of the disease-genes in the proband and family members and thus on early clinical diagnosis. Up to 40% of cases harbor rare variants in genes encoding desmosomal proteins (95). The use of genetic testing may suggest a prognostic impact, as the severity of the disease appears different according to the underlying gene or the presence of multiple mutations (96, 97). Cascade genetic screening of family members of gene-positive probands allows the identification of asymptomatic carriers who would require lifelong follow-up due to the age-related penetrance. The histological hallmark of the disease is the myocardial atrophy and fibrofatty replacement. The dystrophic process is the base for the electrical instability and reentry arrhythmias. Ultrastructure remodeling of the intercalated discs has been demonstrated (98, 99). The right ventricle is most frequently affected but there is now evidence that also left ventricle is frequently affected. Recognition of disease variants with early and/or predominant left ventricular involvement supports the use of the broader term arrhythmogenic cardiomyopathy (94).

ARVC has a prevalence of 1:1000 to 1:5000 and is a leading cause of sudden cardiac death in people <35 years (95). The clinical profile of the disease bridges the gap between the cardiomyopathies and inherited arrhythmia syndromes. The early "concealed" phase, unique among the primary myocardial diseases, is characterized by propensity toward ventricular tachyarrhythmia in the setting of well-preserved morphology, histology, and ventricular function. As the disease progresses, however, myocyte loss, inflammation, and fibroadiposis become evident. Arrhythmogenic right ventricular cardiomyopathy is also the leading cause of sudden death in athletes in the Veneto region of Italy. The incidence of sudden death from ARVC in athletes is estimated to be 0.5 cases per 100,000 persons per year (100). It leads to sudden death during exercise with an estimated 5.4 times greater risk during competitive sports than during sedentary activity (100). The propensity to effort-induced arrhythmias is not completely known, but probably myocardial stretching from

right ventricular overload may elicit ventricular arrhythmias. Fibrofatty scars, aneurysms, denervation of sympathetic cardiac trunks and gap junction remodeling could all contribute. In the last years it has been observed a decline of death rate caused by arrhythmogenic right ventricular cardiomyopathy. The annual incidence of sudden death due to ARVC decreased to 84% (from 0.9:100.000 person-years to 0.15:100.000 person-years) (21). This is mainly due to the pre-participation screening program of athletes. Importantly, more than 80% of athletes dying of arrhythmogenic right ventricular cardiomyopathy had a history of syncope, ECG changes or ventricular arrhythmias (83). A combination of diagnostic tests is needed to evaluate the presence of right ventricular structural, functional, and electrical abnormalities (101). New diagnostic criteria for the diagnosis of ARVC have lately been published (101). Accurate ECG, SAECG and echocardiographic studies may differentiate ARVC from athletes' heart adaptations (36, 102). The diagnostic utility of graded exercise testing is questionable in young patients with suspected ARVC, and the absence or suppression of VPBs during exercise should not be considered reassuring in terms of its diagnostic exclusion (103).

The main clinical targets are early detection of concealed forms and risk stratification for preventive strategies, which include physical exercise restriction, antiarrhythmic drugs, and implantable cardioverter-defibrillator therapy. Primary prevention of sudden death may then be possible by avoiding the trigger of strenuous exercise. Because of the risk of sudden death, patients with this condition should be prohibited from vigorous athletic competition. Also long term endurance athletes appear to have structurally severe forms of the disease (104). This prohibition remains in effect even after the subjects have received effective treatment such as ICD placement because athletic competition may induce incessant ventricular fibrillation that cannot be terminated, given the response patterns of current devices. Moreover, ICD devices, particularly the vulnerable leads, may be damaged by athletics. ICD has been proven to be life-saving. ICD implantation is

recommended for prevention of sudden cardiac death in patients with prior cardiac arrest, ventricular tachycardia with hemodynamic compromise, syncope, and extensive right/left ventricular involvement (105). Different antiarrhythmic drugs have been employed: amiodarone, beta-blockers, sotalol or combinations. Also catheter ablation has been accomplished in ventricular tachycardia refractory to drug treatment (106).

**Table 2. ARVC types and genes**

<b>ARVC disease (AD)</b>	<b>Gene</b>	<b>Authors</b>
ARVC1 (14q23-24)	TGF-beta3	Rampazzo 1994 e 2003, Beffagna 2005
ARVC2 (1q42.1-q43)	RYR-2	Rampazo 1995, Tiso 2001
ARVC3 (14q12-q22)	Unknown	Severini 1996
ARVC4 (2q32.1-q32.3)	Unknown	Rampazzo 1997
ARVC5 (3p32)	TMEM-43	Ahmad 1998, Merner ND 2008
ARVC6 (10p12-p14, 10p13-14)	Unknown (PTPLA polymorphism)	Li 2000
ARVC7 (10q22.3)	Unknown (with MFM)	Melberg 1999, Kuhl 2008
ARVC8 (6p24)	DSP	Rampazzo 2002
ARVC9 (12p11)	PKP-2	Gerull 2004, Award 2006 (recessive form)
ARVC10 (18q12.1-q12.2)	DSG-2	Pilichou 2006, Award 2006,
ARVC11 (18.21)	DSC-2	Syrris 2006, Heuer 2006
ARVC12 (17q21)	JUP	Asimaki 2007
ARVC13 (2q35)	DES (de novo mutation)	Van Tintellen 2009, Klauke 2010
<b>Cardiocutaneous syndromes (AR)</b>		
Naxos disease	JUP	Coorar 1998, McKoy G 2000
Carvajal syndrome (left dominant)	DSP	Norgett EE 2000
Naxos-like syndrome with pemfigous	DSP	Alcalai R 2003
Naxos-like syndrome (biventricular involvement)	DSP-I	Uzumcu A 2006
Naxos-like syndrome with mild cheratoderma	DSC-2	Simpson MA 2008

**Primary dilated cardiomyopathy.** Dilated cardiomyopathy is characterised by left ventricular chamber enlargement and systolic dysfunction (LVEF<50% or FS<25-30%) with normal left ventricular wall thickness, in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment. The estimated prevalence of dilated cardiomyopathy is 1:2.500-2.700 in the general population. Although uncommon may represent a cause of arrhythmic sudden death in young and adult individuals engaged in sport activities (107).

Idiopathic dilated cardiomyopathy is referred after exclusion of all acquired identifiable causes and includes the genetic forms. Familial dilated cardiomyopathy is referred when two or more closely related family members meet a formal diagnostic standard for

idiopathic dilated cardiomyopathy (approximately 20-50% of idiopathic dilated cardiomyopathy may have a genetic cause) (107).

Approximately 20 to 35%, although with incomplete and age-dependent penetrance are linked to diverse group of genes. Familial dilated cardiomyopathy is largely an adult-onset disease. Although genetically heterogeneous, the predominant mode of inheritance is autosomal dominant (probably 80-90%), with X-linked, autosomal recessive and mitochondrial inheritance less frequent. Several of gene mutations linked to autosomal dominant forms encode the same contractile sarcomeric proteins that are responsible for HCM (MYH7, MYBPC3, TNNI3, TTNT2, TNNC1, TPM1 and ACTC1). Genes encoding Z-disc proteins (TTN, LDB3, TCAP, ACTN2 and MYPN), cytoskeletal/sarcolemmal genes, nuclear membrane genes and variety of other genes have also been described (Table 3).

From a pathology viewpoint, the hearts with dilated cardiomyopathy present grossly with left or biventricular eccentric hypertrophy due to increase in myocardial mass and a reduction in ventricular myocardial wall thickness. At histologic examination, there is evidence of myocyte hypertrophy, attenuated myocytes with perinuclear halo due to myofibril loss, and hyperchromatic bizarrely shaped nuclei. Some inflammatory cells, mostly T-lymphocytes and macrophages, are often visible, and spots of replacement-type fibrosis are present in about one third of cases (107, 108).

From a clinical point of view usually presents with any one of the following: heart failure (with symptoms of congestion and/or reduced cardiac output), arrhythmias and/or conduction system disease, thromboembolic disease. It may also be asymptomatic. In family screening studies asymptomatic or mildly symptomatic relatives may be identified. The clinical evaluation of athletes with suspected dilated cardiomyopathy includes personal and family history, physical examination, 12-lead ECG, 2-D echocardiography and Holter monitoring. Differential diagnosis with physiologic left ventricular enlargement in trained athletes is based on the presence of normal left ventricular systolic function, no segmental

wall motion abnormalities and normal left ventricular diastolic filling and TDI pattern. Cardiopulmonary testing may be useful to assess the impairment in physical capacity (108).

Treatment by physicians skilled in management of symptomatic and asymptomatic disease with pharmacologic therapy, PM and ICD improves survival and quality of life. ICD should be implanted in patients with significant left ventricular dysfunction with sustained ventricular tachycardia or fibrillation or patients with LVEF<30-35% and NYHA II/III. Cardiac transplantation remains the definite treatment for progressive dilated cardiomyopathy and heart failure refractory to medical or device therapy (cardiac resynchronization therapy). Athletes with a clinical diagnosis of dilated cardiomyopathy should be excluded from most competitive sports, with the possible exception of those of low intensity (108)

**Table 3. Molecular genetic of familial dilated cardiomyopathy**

MYH7 (b-myosin heavy chain) (5-8%)	LMNA (lamin A/C) (7-8%)
MHC6 (myosin-6) (?)*	SCN5a (sodium channel subunit a) (2-4%)
MYBPC3 (cardiac myosin binding protein C) (?)	LDB3 (LIM domain binding 3 protein, Cypher/Zasp) (?)
TNNI3 (troponin I type 3) (?) (recessive transmission)	EYA4 (eyes absent homolog 4) (?)*
TTNT2 (troponin T) (cause pure DCM) (2-4%)	PLN (phospholamban-pure DCM) (?)
TNNC1 (troponin C type 1) (?)*	PSEN 1 and 2 (presenilin) (<1%) *
TPM1 (a-tropomyosin) (causes pure DCM) (?)	FKTN (fukutin) (?)*
ACTC1 (a-cardiac actin) (causes pure DCM) (<1%)	ABCC9 (ATP-binding cassette) (?)
TTN (titin) (causes pure DCM) (?)	TMPO (thymopoietin) (?)*
CSRP3 (cystein-glycine rich protein 3, cardiac LIM) (?)	TAZ (tafazzin) (?)
TCAP (telethonin, titin-cap) (?)	CRYAB (crystalline, alfa B)
ACTN2 (a-actinin-2) (?)	MYPN (myopalladin)
DMD (dystrophin) (?) (X-linked)	RYR2 (cardiac ryanodine receptor type 2)
SGCD (delta-sarcoglycan) (?)	HCRM2 (cholinergic receptor muscarinic 2)
VCL (metavinculin) (associated with MVP) (?)	
DES (desmin) (pure DCP, also myopathy) (<1%)	mitochondrial cytopathies

\*testing is available on a research basis only for this disorder

**Left ventricular non-compaction.** Left ventricular non-compaction is a rare cardiomyopathy characterized by multiple deep trabeculation in the left ventricular wall

with systolic and diastolic dysfunction, arrhythmias and thromboembolic events. The prevalence ranges between 0.05-0.24%. Although the lesion is postulated to result in part from an intrauterine arrest of myocardial development that stops compaction of the myocardial fiber meshwork, more recent evidence suggests that some cases may actually be acquired while other isolated cases have regressed with time (109, 110). Non-compaction can be simply a variant of normal maturation of the ventricular myocardium with only the most severe forms producing a distinct clinical-pathological entity (110). Ventricular non-compaction most probably is a secondary consequence of an underlying molecular derangement produced by a pathogenetic mutation (Table 4).

This cardiomyopathy affects the left ventricle, with concomitant right ventricular involvement in less than 50% of cases (109, 110). The disease is now seen with increasing frequency and it is clinically diagnosed by imaging techniques such as echocardiography or cardiac magnetic resonance (110). Transthoracic echocardiography remains the imaging modality of choice where diagnosis is based on the identification of multiple prominent ventricular trabeculations with intertrabecular spaces communicating with the ventricular cavity (109). Left ventricular non-compaction may be more common than previously recognized and may exist as a spectrum, which can be classified using the non-compaction/compaction ratio or left ventricular non-compaction area classification schemes (111). The diagnosis is based on the following echocardiographic criteria: the presence of at least 4 prominent trabeculations and deep intertrabecular recesses, blood flow from the ventricular cavity into the intertrabecular recesses and a typical bilaminar structure of the affected portion of the left ventricular myocardium (112). The inverse correlation between non-compaction area and ejection fraction suggests that non-compaction contributes to left ventricular dysfunction (113). Current diagnostic criteria are considered too sensitive, particularly in black individuals (109). Therefore, this condition has generated considerable controversy and demands a new definition.

Non-compaction cardiomyopathy shows variability of hereditary patterns, genetic heterogeneity, diversity in associated phenotypes, a wide spectrum of clinical presentation and pathophysiological findings. There is a broad and potentially confusing spectrum of clinical symptomatology in patients meaning that the primary diagnosis is often missed (109). Complications such as potentially malignant arrhythmias, left ventricular failure, and cardioembolic events arising as a result of non-compaction must be treated in an attempt to decrease morbidity and mortality from this disorder (109). The ultimate outcome for patients remains unclear with some boasting a prolonged asymptomatic course, to others displaying a rapid deterioration of left ventricular systolic function, leading to heart transplantation or death (109). Its mortality and morbidity are high, including heart failure, thromboembolic events and ventricular arrhythmias. Risk stratification includes heart failure therapy, oral anticoagulation, heart transplantation and implantation of an ICD (114). Athletes with a clinical diagnosis of left ventricular non compaction should be excluded from most competitive sports, with the possible exception of those of low intensity (and when there is a low risk of cardiovascular events). In conclusion while remaining a rare cardiomyopathy, it will probably be diagnosed with increasing frequency in the coming years because of heightened awareness about its natural history and clinical manifestations and because of the improved modalities available for cardiac imaging (109).

**Table 4. Genes involved in left ventricular non compaction**

TAZ/G4.5 (tafazzin)
LBD3 (LIM, cypher/zasp) (LIM domain binding protein 3) (Zaspopathy)
DTNA (Alpha-dystrobrevin) (associated with congenital)
LMNA (laminin A/C-hypertrabeculation)
MYH7 (b-myosin heavy chain)
ACTC (a-cardiac actin)
TNNT2 (Troponin T)

**Cardiac ion channelopathies.** Ion channelopathies as a group are responsible for 3% of total deaths in young athletes in U.S. In the last decade there have been considerable advances in the understanding of the pathophysiology of malignant ventricular tachyarrhythmias and sudden cardiac death. Over 80% of sudden cardiac death occurs in patients with organic heart disease, however approximately 10-15% occurs in the presence of structurally normal heart and the majority of those patients are young. In this group of patients, changes in genes encoding cardiac ion channels produce modification of the function of the channel resulting in an electrophysiological substrate of ventricular tachyarrhythmias and sudden cardiac death. Collectively these disorders are referred to as cardiac ion channelopathies. The four major syndromes in this group are: The long QT syndrome (LQTS), the Brugada syndrome (BrS), the short QT syndrome (SQTS) and the catecholaminergic polymorphic ventricular tachycardia (CPVT) (Table 5). Each of these syndromes includes multiple subtypes with different and sometimes complex genetic abnormalities of cardiac ion channels (Table 6). Many are associated with other somatic and neurological abnormalities besides the risk of ventricular tachyarrhythmias and sudden cardiac death. The current management of cardiac ion channelopathy could be summarized as follows: 1) in symptomatic patients, the ICD is the only viable option; 2) in asymptomatic patients, risk stratification is necessary followed by the pharmacotherapy, ICD or a combination of both. A genotype-specific approach to pharmacotherapy requires a thorough understanding of the molecular-cellular basis of arrhythmogenesis in cardiac ion channelopathies as well as the specific drug profile (115-116). One of the next goals to understand these syndromes is the identification of modifiers of the clinical phenotype (73).



**Table 5. Cardiac ion channelopathies**

<b>Four major syndromes at risk of SCD</b>	Brugada syndrome (BrS 1-6) and J wave syndrome
	Congenital long QT syndrome (R.W. LQT 1-12 and J.L.N. 1-2)
	Short QT syndrome (SQTS1-5)
	Catecholaminergic polymorphic ventricular tachycardia (CPVT1-2) and ARVC2
<b>Less frequent channelopathies</b>	Familial atrial fibrillation
	Familial sick sinus syndrome (SSS) and Familial sinus bradycardia
	Progressive cardiac conduction disease (PCCD)
	Atrial standstill
	Idiopathic ventricular fibrillation
	Dilated cardiomyopathy
<b>Overlapping forms (mixed phenotypes of SCN5A mutation)</b>	BrS (PCCD, PCCD+LQT3, PCCD+SSS (+/-LQT3), LQT3, LQT3+SSS, SSS)
	QT3 (BrS, PCCD, BrS+PCCD, BrS+SSS, BrS+PCC+DSSS)
	PCCD (SSS, AS-AF-DCM, BrS (+/- LQT3), BrS+SSS (+/-LQT3), LQT3)

**Table 6. Channels, subunits and channel regulating proteins involved in cardiac channelopathies.**

<b>Potassium channel (different types)</b>
Delayed rectifier (voltage-gated) K channel-subunits KvLQT1, mink, HERG, MiRP, 1B, 3B, 4B
Inwardly rectifying K channel Kir2.1 (Ik1 current) and inwardly rectifying ATP-sensitive K channel Kir6.1
K transport channels with ultrarapid activation located in the atrial myocytes (Ikiur current)
<b>Sodium channel</b> -subunit 5A, 4B, 1B
<b>Calcium channels</b> -subunit A1C, B2b, A2D1
<b>Hyperpolarization channel</b> -subunit HCN4
<b>Intracellular potassium regulating proteins</b> (A-kinase-anchoring protein)
<b>Intracellular sodium regulating proteins</b> (caveolin-3, $\alpha$ 1-syntrophin, glycerol 3-phosphate dehydrogenase 1-like)
<b>Intracellular calcium channels or regulating proteins</b> (ryanodine receptor-2, calsequestrin)
<b>Other anchoring proteins</b> (ankyrin-B)

**Brugada syndrome and other J-wave syndromes.** In 1953 Osher and Wolff, described and ECG pattern of a young male which consisted of ST-segment elevation in the right precordial leads, simulating acute myocardial injury (117). In 1989 Martini, Nava and Thiene published a detailed article with the description of 6 cases of ventricular fibrillation without apparent heart disease (118). In 1992 Brugada brothers (Pedro and Joseph) proposed it for the first time as a distinct clinical entity and thus coined the term of Brugada syndrome. They reported 8 patients with a history of aborted sudden cardiac death caused by ventricular fibrillation and a characteristic ECG pattern, consisting of RBBB and ST-segment elevation in the right precordial leads V1-3 (119). Later on became evident that

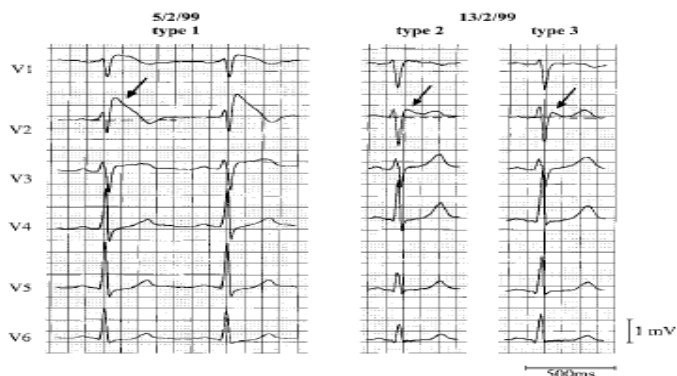
the right intraventricular conduction delay is present only in one third of patients and the ST-segment elevation which is the ECG signature of the disease, can be dynamic in nature or concealed, making difficult the diagnosis (120).

Brugada syndrome is closely related to the sudden unexpected death syndrome described in male Thai patients, responsible for an annual mortality rate of 1:2.500 among young Thai males (121). Vatta et al demonstrated that sudden unexpected nocturnal death syndrome and Brugada syndrome are phenotypically, genetically, and functionally the same disorder (122). The prevalence of the disease is estimated to be 1-5:10.000 inhabitants worldwide, while it is 5:10.000 in Southeast Asia (especially Thailand and Philippines) (123). In these countries is considered to be a major cause of sudden death in young adults and that is the reason of generating increasing interest (124). In Japan the Brugada syndrome ECG type-1 has been observed in 12:10.000 inhabitants (123). The incidence is ranging between 5- 66:10.000 (125).

In 2002 the Brugada Consensus Report delineated the diagnostic criteria for the syndrome. It suggested three patterns of ST-segment elevation: 1) Type-1 is characterized by a coved-type configuration, displaying a J-wave amplitude or ST-segment elevation  $\geq 2$  mm at its peak, followed by a negative T-wave, with little or no isoelectric separation; 2) Type-2 shows a saddleback configuration, which has a high take-off ST-segment elevation (2 mm), followed by a gradually descending ST-segment elevation and a positive or biphasic T wave, 3) Type-3 is a right precordial ST-segment elevation  $< 1$  mm of a saddle back, coved, or both types (125). In 2005, the second Consensus Report emphasized that type-1 ST-segment elevation is required to diagnose Brugada syndrome, because the type-1 ECG is reported to relate to a higher incidence of ventricular fibrillation and sudden cardiac death. Importantly, type-1 ST-segment elevation recorded only in the higher V1–2 leads (3rd and 2nd intercostal spaces) is reported to increase the sensitivity of the ECG of

detecting the Brugada phenotype and show a similar prognostic value for subsequent cardiac events as that recorded in the standard V1–2 leads (123).

**Figure:** Dynamic ECG changes in course of couple of days in the same patient



Brugada syndrome is definitively diagnosed when the so-called Type-1 ST-segment elevation is observed in at least one right precordial lead, in the presence or absence of sodium channel blocker, in conjunction with one or more of the following: documented ventricular fibrillation, self terminating polymorphic ventricular tachycardia, family history of sudden cardiac death (<45 years), coved-type ECG's in family members, inducibility of ventricular tachycardia with electrophysiological study, syncope, nocturnal agonal respiration or a mutation compatible with the syndrome (123, 126). The appearance of the ECG features without these clinical symptoms is referred to as an idiopathic Brugada ECG pattern (not Brugada syndrome) (125). The ECG abnormalities that constitute the hallmark of the disease must be in the absence of identifiable structural cardiac abnormalities, other conditions or agents known to lead to ST-segment elevation in the right precordial leads (125). The characteristic electrocardiographic picture can develop spontaneously or as a result of drugs, fever or electrolyte imbalance (125). Drugs that block the Na channels could reveal latent forms (IC: ajmaline, flecainide, procainamide). Also central nervous system could modify the ECG (isoprotenerol, aceticolin, male). The ECG pattern of ST-segment elevation in the right precordial leads should not be seen as a marker of a specific syndrome, but rather as a common electrical expression of abnormalities in the right ventricle that may have genetic, infective or inflammatory origins. Thus the Italian

scientists in 1988 correctly associated this ECG pattern with anatomic defects and ARVC/D (118).

Brugada syndrome is a familial disease and inheritance occurs as an autosomic dominant trait with incomplete penetrance (25). In up to 60% of patients the disease can be sporadic (126). It is characterized by the characteristic ECG abnormalities and high incidence of sudden death in patients with structurally normal hearts (123). The latter concept is not always true because morphologic alterations on MRI have been lately described and recent studies have revealed in the histologic examination of the biopsy samples fatty tissue infiltration, interstitial fibrosis, lymphocyte infiltration and/or myocyte disorganization in some patients (127-130). It has a male predominance (80-90%), probably due to differences in the I(to) current (which is more prominent in men). Men also present with a greater risk clinical profile than women and have a worse prognosis.

Brugada syndrome is characterised by the occurrence of episodes of polymorphic ventricular tachycardia. Fever is one of the most important precipitating factors. Sudden death occurs usually during sleep and can be the first manifestation of the disease (125), accounting in 4-12% of sudden cardiac deaths (123, 126). It is now recognized as the most common cause of genetically determined malignant ventricular arrhythmias and sudden cardiac death in young patients with structurally normal hearts, estimated to be responsible for at least 20% to 50% of these deaths (126). The first arrhythmic events occur during the third-fourth decade of life but could also occur in children even during the first months of life (youngest person diagnosed is 2 days of age) (123).

In 1998, Chen et al identified the first mutation linked to Brugada syndrome in SCN5A gene (that translates the  $\alpha$ -subunit of the sodium channel, type V). SCN5A mutations are reported responsible to account for 18–30% of clinically diagnosed Brugada syndrome patients at present. Later, mutations in GPD1-L, CACNA1c, CACN2b, SCN1B, KCNE3

and CACNA2D1 gene were discovered (table 7). The decrease in the inward sodium or calcium current (late INa, I<sub>Ca-L</sub>) or increases in the outward potassium currents (I<sub>to</sub>) produce a Brugada phenotype in all genotypes, as indicated by previous experimental studies. Approximately two-thirds of Brugada patients have not yet been genotyped, suggesting the presence of genetic heterogeneity (126).

**Table 7. Defect of ion channel or membrane adaptor responsible for Brugada syndrome.**

BrS	Locus	Gene	Ion channel	function	notes	Authors
BrS1	3p21	SCN5A	Nav1.5-INa (α-subunit)	loss of function	account for 18–30%	Chen
BrS2	3p24	GPD1L	glycerol-3-phosphate dehydrogenase 1-like protein-INa	decreases trafficking of Na channel to cell membrane	described in a large Brugada family	London
BrS3	12p13.3	CACNA1c	Cav 1.2-ICa-L (α1-subunit)	loss of function	identified in 8.5% of probands (in 3 associated with QTc <360 ms)	Antzelevitch
BrS4	10p12	CACNAB2b	Cav 2b-ICa-L (β2b-subunit)	loss of function		
BrS5	19q13.1	SCN1B	INa (β1-subunit) function-modifying sodium channel β1-subunit	Decrease of INa when α-subunit was co-expressed with mutant β1-subunit	associated with cardiac conduction disease	Watanabe
BrS6	11q13-q14	KCNE3	K channel β-subunit that interacts with Kv4.3 (transient outward current: I <sub>to</sub> ) channel	Gain of function Co-expression of the mutant KCNE3 with KCND3 increases the I <sub>to</sub> intensity	identified in a proband with Brugada syndrome	Delpon
BrS7	3p21.3	CACNA2D1	Cav α 2δ-Ica-L (α 2δ-subunit)	Loss of function	Identified in 3 probands	Burashnikov

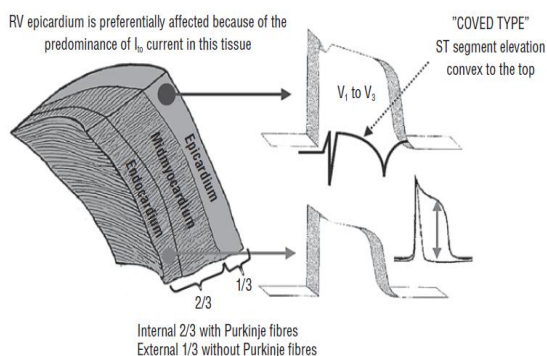
The hallmark electrocardiographic feature of the disorder has been attributed to: 1) premature repolarization of the right ventricle epicardial action potential secondary to the loss of the action potential dome, 2) conduction delay in the right ventricular epicardial free wall in the region of right ventricular outflow tract, or a combination of two (131). Local depolarization abnormalities have been described as the dominant pathophysiologic mechanism for type-1 ECG in a study of ECG, vectorcardiograms and body surface potential maps during ajmaline provocation, suggesting that the typical signs of repolarization derangements seen on the ECG are secondary to these depolarization abnormalities (132).

Other ECG abnormalities have also been described. In isolated cases ST-segment elevation has been described in the inferior leads or left precordial leads and in rare cases in all leads (124). Although RBBB is now believed not to be necessary for definitive diagnosis, Brugada patients have a higher incidence of complete or incomplete RBBB than

normal populations. Other conduction abnormalities are represented by widening of the P-wave and prolongation of the PQ interval, which likely reflects HV conduction delay and other specific (i.e. left anterior hemiblock) or non-specific (QRS widening) conduction disorders. A slight prolongation of the QT interval is sometimes observed associated with the ST-segment elevation. The QT interval is prolonged more in the right versus left precordial leads. Also fragmented QRS appears to be a marker for the substrate of ventricular fibrillation and predicts patients at high risk of syncope (133).

Arrhythmogenesis in Brugada syndrome (and also SQTS) is thought to be due to amplification of heterogeneities in action potential characteristics among the different transmural cell types. In Brugada syndrome a decrease of inward currents ( $I_{Na}$  or  $I_{Ca}$ ) or augmentation of outward currents (including  $I_{Kr}$ ,  $I_{Ks}$ ,  $I_{Cl}$ ,  $I_{to}$ ) can cause preferential abbreviation of the right ventricular epicardial action potential secondary to all-or-none repolarization of the action potential at the end of phase 1. This leads to loss of action potential dome and the development of spatial dispersion of repolarization and thus the substrate and trigger for ventricular tachycardia, which is usually polymorphic and less frequently monomorphic (124).

**Figure.** Differences on action potential between the different layers of myocardium.



The hypothesis for the development of malignant arrhythmias postulates that when there is a loss of function of the sodium channel with relatively unopposed transient outward current ( $I_{to}$ ), results to the shortening of the epicardial action potential duration at the right

ventricular outflow tract, that leads to electrical heterogeneity within the right ventricular epicardium and “phase 2 reentry”, which then precipitates ventricular fibrillation secondary to closed coupled PVBs. In detail the region of why Brugada syndrome is a right ventricular disease is thought to be the more prominent Ito-mediated phase 1 in the action potential in this region. This is explained by the observation that the loss of the action potential dome more readily occurs in the right versus left canine ventricular epicardium. The accentuation of the right ventricular epicardial action potential notch underlies the ST-segment elevation. The eventual loss of the dome of the right ventricular epicardial action potential but not endocardium further exaggerates ST-segment elevation and results in the development of a marked transmural dispersion of repolarization and refractoriness, responsible for the development of a vulnerable window. The vulnerable window created within the epicardium as, as well as transmurally, serves as the substrate. The cells with shorter refractory periods have the potential to be re-excited by cells on the surrounding tissue that have normal action potential durations a phenomenon referred as phase-2 re-entry. Conduction of the action potential dome from sites at which is maintained to sites at which it is lost causes local re-excitation leading to a very closely coupled PVB (reentrant PVB in phase 2) that serves as a trigger to precipitate and induce a circus movement in the form of ventricular tachycardia or fibrillation (124). However, several studies have revealed a high incidence of late potentials and high rate of ventricular fibrillation induced by programmed ventricular stimulation. Slow conduction at the right ventricular outflow tract may contribute to the induction of ventricular fibrillation by programmed ventricular stimulation and various pathomorphologic changes may contribute to slow conduction at the right ventricular outflow tract (130). Also significant myocyte apoptosis in both ventricles in a histological study in patients with SCN5A mutations, suggests that abnormal function of the sodium channels may lead to a marked degree of cellular damage, contributing to arrhythmic events. These electrocardiographic and histologic data indicate

that progressive depolarization abnormalities (conduction slowing) with ageing may contribute to the pathogenesis.

The genotype–phenotype correlation has been less investigated than that in congenital LQTS, because more than two-thirds of patients clinically affected with Brugada syndrome are not genotyped. The most common phenotype of gene carriers of a Brugada syndrome-type SCN5A mutation is a progressive cardiac conduction defect similar the Lenegre disease phenotype. Various types of conduction defects were found, with a clear predominance of RBBB and parietal block. That's why the carriers of a SCN5A mutation need a clinical and ECG follow-up because of the risk associated with severe conduction defects with ageing. 60-70 % of the subjects have also the post-potentials.

Controversy exists on risk stratification and therapeutic management, particularly in asymptomatic individuals with such an ECG pattern type-1. Drug induced type-1 ECG in asymptomatic patients does not have an additional value in risk stratification of cardiac events, but is useful in symptomatic (134). Second consensus report states that drug induced or spontaneous type-1 ECG with family history of sudden death should undergo EPS, but this approach involves performing a large number of APS and a large number of ICD placements. While Brugada et al showed that the only predictor of arrhythmic events is inducibility during programmed ventricular stimulation, other studies failed to find an association (135). For example Echardt et al reported a very low incidence of severe arrhythmic events, particularly in asymptomatic individuals. In the presence of very few arrhythmic events on follow-up, programmed ventricular stimulation showed very little accuracy in predicting outcome (136). Importantly the use of aggressive protocols could lead to false positive programmed ventricular stimulation (135). Interestingly in the FINGER study, event rates in asymptomatic patients are low and inducibility of ventricular tachyarrhythmia and family history of sudden cardiac death are not predictors of cardiac events (137). The only independent predictors of arrhythmic events are the presence of



symptoms and the spontaneous type 1 ECG. Giustetto et al stated that programmed ventricular stimulation should be performed in asymptomatic subjects with spontaneous type 1 ECG and in subjects without spontaneous 1 ECG but with syncope (138). Delise et al stated that highest risk subjects are those with spontaneous type ECG type 1 and 2 or more risk factors (syncope, family history, positive EPS) (139). Although the most effective therapy is the implantation of an ICD, the rate of serious complication is high (26-35%) and the main long term complication was inappropriate shocks (135). Alternative approaches, even if not entirely risk free, such as pharmacological therapy with quinidine should be considered in asymptomatic patients.

The contribution of Brugada syndrome to athletes' sudden cardiac death is not well defined. Although no association between sudden cardiac death or malignant ventricular arrhythmias due to Brugada syndrome and exercise has been established, the general consensus in Europe and U.S. recommends exclusion of young athletes from competition. These are based on the theoretical consideration that increased vagal tone, resulting from athletic conditioning could potentially increase the risk of malignant ventricular arrhythmias and sudden cardiac death at rest or even post exercise. The potential impact of hyperthermia caused by exercise, which very often unmasks the electrocardiographic manifestations of Brugada syndrome further, supports the recommendation of both panels of experts (140). In athletes with Brugada syndrome, repolarization anomalies may be markedly attenuated during vigorous exercise and considerably increased immediately after exercise. The observed J-wave amplitude dynamics suggests enhancement of pre-existing autonomic dysfunction through heavy exertion.

Lately, Brugada syndrome, the so called "Haissaguere syndrome" and the early repolarization syndrome have been named as J-wave syndromes. The early repolarization syndrome is a common electrocardiographic pattern, with prevalence of 1-2% in the

normal population. Its prevalence is higher in the general athletic population reaching 10% and 100% in selected groups of endurance trained subjects. Early repolarization syndrome is characterized by the presence of a deflection (J-wave), immediately following the QRS complex or on the downsloping portion (slurring or a “late delta-wave”), usually followed by an elevation of the ST-segment with upward concavity of the surface ECG, in most cases in mid to lateral precordial leads. The first description of the J-wave appeared in the 1920s in animal experiments involving hypercalcemia and after 30 years the first extensive description by Osborn in a study involving experimental hypothermia in dogs (141). The prominent J-wave induced by hypothermia is the result of a marked accentuation of the spike-and-dome morphology of the action potential of M and epicardial cells. Until recent years it was considered as a benign condition and a variant of normal repolarization, mostly seen in young healthy men and athletes (141,142).

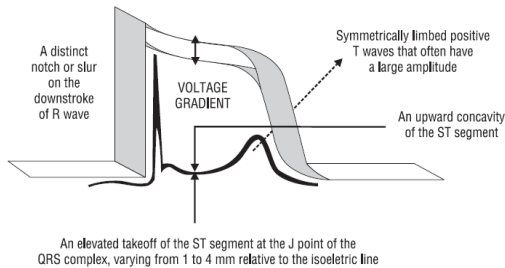
In 2008, it was demonstrated that 31% of the so-called idiopathic ventricular fibrillation victims had an early repolarization pattern in the infero-lateral leads (143). J wave and/or QRS slurring without ST elevation was found more frequently among athletes with cardiac arrest/sudden death than in control athletes. Nevertheless, the presence of this ECG pattern appears not to confer a higher risk for recurrent malignant ventricular arrhythmias. Several lines of evidence have suggested that arrhythmias associated with an early repolarization pattern in the inferior or mid to lateral precordial leads, Brugada syndrome, or arrhythmias associated with hypothermia and the acute phase of ST-segment elevation myocardial infarction are mechanistically linked to abnormalities in the manifestation of the transient outward current  $I_{to}$ -mediated J-wave. Although Brugada syndrome and early repolarization syndrome differ with respect to the magnitude and lead location of abnormal J-wave manifestation, they can be considered to represent a continuous spectrum of phenotypic expression that were proposed be termed as J-wave syndromes. Early repolarization syndrome was divided into three subtypes: type 1, which displays an early

repolarization pattern predominantly in the lateral precordial leads (it is prevalent among healthy male athletes and is rarely seen in ventricular fibrillation survivors); type 2, which displays an early repolarization pattern predominantly in the inferior or infero-lateral leads (it is associated with a higher level of risk); and type 3, which displays an early repolarization pattern globally in the inferior, lateral, and right precordial leads (it is associated with the highest level of risk for development of malignant arrhythmias and is often associated with ventricular fibrillation storms) (144). The risk of sudden death depends on the location of early repolarization, magnitude of the J-wave and degree of ST-elevation (144, 145).

The presence of a prominent action potential notch in epicardium but not endocardium gives rise to a transmural voltage gradient during ventricular activation that manifests a J-wave (or Osborn wave). A transmural gradient in the distribution of  $I_{to}$  is responsible for the transmural gradient in the magnitude of phase 1 and action potential notch, which in turn gives rise to a voltage gradient across the ventricular wall responsible for the inscription of the J-wave or J-point elevation in the ECG. When partially buried in the R wave, the J-wave appears as J-point elevation or ST-segment elevation. Humans more commonly display a J-point elevation rather than a distinct J-wave. The arrhythmogenicity of this syndrome is thought to be related to the heterogeneity of the action potentials across the ventricular wall at the end of the phase 1. Any perturbation on the balance of the currents may amplify the disparity in voltage gradient and precipitate local re-entries and polymorphic ventricular arrhythmias, providing both the trigger and substrate of VF (143). The so-called “Haissaguerre syndrome” associated with the early repolarization pattern and malignant arrhythmias have 3 aspects in common with Brugada syndrome: 1) the ECG abnormality occurs at the early phase of repolarization, 2) the electrical heterogeneity is during phase 1 responsible for the arrhythmogenicity 3) efficacy of

isoprotenerol and quinidine to the arrhythmias. Calcium and potassium channels have already been identified responsible for the j-wave syndromes (146, 147)

**Figure:** early ripolarization mechanism



**Inherited long QT syndromes (LQTS).** In 1957 two Norwegian physicians Dr Jervell A. and Lange-Nielsen F. published an article of cases with “congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death”, a disorder now known as Jervell and Lange-Nielsen syndrome were a double homozygous dominant mutation of *KCNQ1* gene provokes an extremely severe cardiac condition (148). Later on, Dr Romano in 1963 and Dr Ward in 1964 reported cases with rare cardiac arrhythmias of the paediatric age, now referred as Romano-Ward syndrome, with autosomal-dominant pattern of inheritance (149).

The LQTS is a hereditary disorder in which most affected family members have delayed ventricular repolarization manifest as QT prolongation on the ECG (149). The long QT interval could be acquired due to multiple causes: drugs (IA, III, procainamide, disopiramide, sotalol, amiodarone, fenotiazine, ATC, Li, cisapride), electrolyte alterations (hypoK, hypoMg), bradiarrhythmias, hypothermia, central nervous system damages, anorexia or mitral valve prolapse, but it could also be hereditary or in sporadic forms (Table 9, 10). Inherited LQTS is characterized by the prolonged QT interval in the ECG, syncope and sudden death due to ventricular tachyarrhythmia, typically torsade de pointes. It is relatively infrequent and has an estimated prevalence 1:2500 in the general population (150). The upper limit of QT interval is usually considered 460 msec for subjects between 1-15 years, 450 ms for the men and 470 ms for women (149). So, a QTc

interval of 460-480ms or longer is suspected. The existing clinical criteria have good specificity in identifying mutation carriers (table 8). However, their sensitivity is too low for clinical use. Analysis of QTc duration alone is more useful to screen for LQTS carriership (QTc $\geq$ 430 ms) as its sensitivity is far superior, although its specificity remains acceptable. In genotyped families, genetic testing is the preferred diagnostic test (152).

The significance of an isolated long QT interval in athletes remains unknown and studies of the long-term outcome of this phenotype in elite athletes are needed. It is clear that normal ventricular repolarization standards involving QT, heart rate, and QTc need to be developed in highly trained athletes, with clinical follow-up for outcome. The report by Basavarajaiah et al. is a step in the right direction (153). They reported that the prevalence of prolonged QTc in elite athletes is 0.4% and a QTc of  $>500$  ms is highly suggestive of LQTS, while a QTc of  $<500$  ms in the absence of symptoms or familial disease is unlikely to represent LQTS in elite athletes. Genetic testing for LQTS is still in its infancy, and a negative genetic test does rule out LQTS. QTc is only a surrogate marker for ventricular repolarization, and borderline QTc interval prolongation in trained athletes does not warrant disqualification from competitive sports in the absence of findings indicative of LQTS or structural heart disease. For athletes with QTc $\geq$ 500 ms, it is reasonable and prudent to recommend that they do not participate in competitive sports (153).

The ECG aspects are variable. The QTc interval duration may be in normal range, borderline or prolonged; usually is more than 460-480 msec. QT dispersion is frequently associated indicating a ventricular repolarization heterogeneity which could provide a substrate for functional re-entry and reduce the threshold for ventricular fibrillation. On the ECG there is frequently a relative bradycardia, but it is also seen in well-trained athletes, and is therefore of limited value. Severe bradycardia has been reported in children with LQT1, while adults can have normal resting heart rates but attenuated exercise rate responses. Sinus bradycardia has also been seen in patients with LQT3 and LQT4. T-

wave alterations (2:1 changes in repolarization morphology) and T-wave variability (non 2:1 T-wave alternans) maybe present. T-wave alternans can occur in 2.5% in standard ECG and is a beat to beat alternation in the T-wave morphology, amplitude, QT interval and polarity without concomitant QRS changes. Specific ECG alterations have been described to specific genotypes (Figure). T humps can be seen created by EADs caused by the reopening of the Ca channels due to the prolongation of the QT. Prominent U waves and T-U complexes are frequently seen. Characteristic complex U waves have been described in LQT7. Importantly, 10 to 15% of the subjects does not have this characteristics (1/3 have normal QT), the so called silent carriers (149).

The classical arrhythmia is a polymorphic ventricular tachycardia in the form of the torsade de pointes. Although it usually terminates within seconds, it can occur repeatedly, cause faintness or syncope, and degenerate to ventricular fibrillation, resulting in sudden cardiac death. Torsade de pointes is often preceded by a bigeminal rhythm “short-long” or after a bradycardia or a long pause. The arrhythmia is due to EADs (in phase 2 and 3) from an increase of the intracellular calcium and increase in the transmural dispersion of the repolarization due to increase of action potential in the M cells (149).

LQTS has low penetrance and variable. Syncope is usually the first symptom while in 10% sudden cardiac death may be the first symptom, SIDS has also been documented. . Arrhythmias are frequently due to specific triggers due to adrenergic activation: emotional or physical stress (fear, anger, exercise and diving), wake-up (or sleep), noises (loud noises) (154). 30-46% of the LQT1, 2 and 3 syndromes has a cardiac event until the age of 40 years and the mortality if not treated is 13% (151). Sometimes there are syndromic with ipoacusia (JLN) or malformations. Andersen syndrome causes in 50% of death before the age of 13 years.

The risk stratification is based on: 1) symptoms (syncope, arrhythmias, aborted sudden cardiac death), 2) genotype (high risk of sudden death mutations in LQT2 and 3, compound mutations or JLN syndrome), 3) gender (LQTS boys experience a significantly higher rate of fatal or near-fatal cardiac events than girls during childhood, males also increased risk during preadolescence, females have higher event rates in adolescence and beyond), 4) QT interval prolongation (>500 msec) and QT alternans, 5) history of cardiac events (torsade de pointes or ventricular fibrillation documented). Family history of sudden cardiac death in adulthood is not considered a risk factor (155-157)

Diagnosis is based on: 1) genetic testing for molecular study, 2) family history and screening (family members with definite LQTS or unexplained sudden cardiac death in immediate family member <30 years), 3) clinical history (syncope with or without stress, congenital deafness) and physical examination, 4) basal 12-lead ECG and repetitive ECGs (measurement of QTc, notched T-waves and T-wave alternans). ECGs performed with various stimuli (auditive, cold, psychological, exercise, hyperventilation). Valsalva manoeuvre prolongs QT and could provoke T-wave alternans and ventricular tachycardia, 5) Holter-monitoring (QT measurements, QT and T-wave amplitude morphology adaptations to changing heart rate, torsade de pointes), 6) exercise stress test (exercise-induced repolarization changes or T-wave alternans-indicative of electrical instability), 7) catecholamine testing (may improve diagnostic sensitivity, especially in borderline cases). Echocardiogram is usually normal (late contraction of the posterior wall has been documented). Electrophysiologic study is usually not helpful and does not provoke the arrhythmias (23, 149).

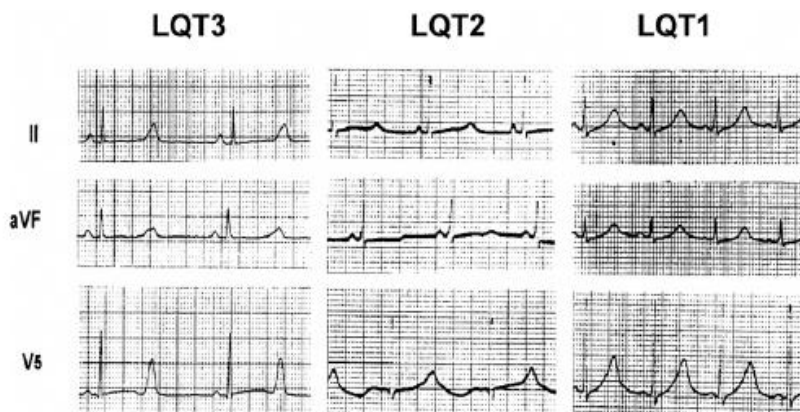
For primary prevention beta-blockers are most commonly used but a significant risk of sudden death remains. Beta-blockers decrease the adrenergic trigger but may provoke bradycardia and pauses that increase QTc and predispose to torsade de pointes and

that's why PM is often used. PM is considered only when it is documented that the bradycardia is favouring arrhythmias. Also the disqualification of competitive sports, avoiding sudden bursts, lifestyle modifications and follow-up is important. For secondary prevention implantation of ICD is considered in high-risk patients, symptomatic with beta-blockers (syncope, ventricular tachycardia or aborted sudden death). ICD is used with PM algorithms for post-extrasystolic pauses and in combination with beta-blockers, because ICD shocks could activate the sympathetic system and trigger further arrhythmias. Finally, left cardiac sympathetic denervation can be indicated when there is a failure to therapy or frequent ICD shocks mostly used in LQT1 sensitive at the catecholamines (when the therapy is not tolerated or if we have arrhythmias and syncope with the ongoing therapy).

The ESC consensus document recommends exclusion of the athlete with definitive diagnosis of LQTS from any type of competitive sports, while those asymptomatic genotype-positive, phenotype-negative athletes are discouraged from participation in competitive sports. The Bethesda conference #36 document also recommends exclusion of most competitive sports of those individuals with definitive diagnosis of LQTS, except from low dynamic and low static sports. Unlike the ESC, these guidelines allow participation in competition of genotype-positive, phenotype-negative athletes, with special consideration of individuals with LQT1 mutation. Due to the strong association between swimming deaths and LQT1 mutation, these genotype-positive, phenotype-negative athletes should refrain from competitive swimming.



**Figure:** T-wave morphologies.



**Table 8.** Diagnostic criteria for long QT syndrome

<b>ECG findings (a)</b>		(5) Low heart rate for age (d)	(0.5 point)
(1) QTc (b)		<b>Clinical history</b>	
QTc $\geq$ 480 ms	(3 points)	(1) Syncope with stress	(2 points)
460 – 479 ms	(2 points)	Without stress	(1 point)
450 – 459 ms (in males)	(1 point)	(2) Congenital deafness	(0.5 point)
(2) Torsade de pointes (c)	(2 points)	<b>Family history (e)</b>	
(3) T-wave alternans	(1 point)	(1) Family members with definite LQTS (f)	(1 point)
(4) Notched T wave (in 3 leads)	(1 point)	(2) Unexplained SCD below age 30 among immediate family members	(0.5 point)

(a) In the absence of medications or disorders known to affect these ECG features. (b) Calculated by Bazett's formula. (c) Mutually exclusive. (d) Resting heart rate below the second percentile for age. (e) The same family member cannot be counted in 1 and 2. (f) Definite LQTS is defined by a score  $\geq$ 4.

Scoring:  $\leq$ 1 point, low probability of LQTS; 1.5–3.5 points, intermediate probability of LQTS;  $\geq$ 4 points, high probability of LQTS.

**Table 9.** Long QT syndrome type 1-3

Romano-Ward	Gene-chromosome	Channel affected	Freq	Triggers	Notes
LQT1	KCNQ1 (Kv7.1, KvLQT1) (11p15.5)	loss of function a-subunit Iks Iks decrease	45%	Exercise 68% (swimming, diving) emotion 14% rest-sleep 9% other 9%	-Risk of arrhythmias (++) -30% risk of events, 13% of mortality -ECG: broad based T-waves, -failure to shorten QTc during exercise -Therapy: b-blockers is very effective (+++), denervation, nicorandil, avoid strenuous exercise
LQT2	KCNH2 (Kv1.1, HERG) (7q35-36)	loss of function a-subunit Ikr Ikr decrease	45%	rest-sleep 49% emotion 29% (sudden arousal, auditori stimuli-telephone-alarm ring), other 22%	-Risk of arrhythmias (+++), -46% of events (+++), 13% of mortality, -ECG: low amplitude notched T-waves -during exercise normal QTc -Therapy: b-blockers failure is common (+), ICD, K supplement, spironolactone, telephone (gene-specific)
LQT3	SCN5A (Nav1.5) (3p21-23)	Gain of function a-subunit I <sub>Na</sub> it increases I <sub>Na</sub>	7%	Sleep-rest 64% exercise 4% emotion 12% other 20%	- 42% risk of events, but more lethal (20%), -ECG: late appearing narrow-peaked T-waves, long isoelectric ST (sinus bradycardia may be present) -during exercise supranormal shortening -Therapy: beta-blockers not very effective (still fatal events), mexiletine in patients with ICD, benefit PM

**Table 10. Rare long QT syndromes**

	Gene (protein) chromosome	Loss or gain of function Channel affected	Frequ ency	Triggers	Notes
<b>Romano Ward</b>					
LQT4 (ankyrin-B syndrome)	ANK2 (ankyrin B)  (4q25-27)	Loss of function Adaptor (I <sub>Na</sub> -k pump, I <sub>Na</sub> -ca exchanger, I <sub>Na</sub> ) possible late sodium increase leading to increased intracellular Ca	<1%- 1.8% (several families)	exercise	ECG:Bradycardia,longQT,polyphasic T waves, AF Exercise aggravates QT prolongation Syncope and sudden death occur in response to exercise or emotional stress Therapy: No specific treatment
LQT5	KCNE1 (minK)  (21q22.1-q22.2)	Loss of function b-subunit I <sub>ks</sub> I <sub>ks</sub> decrease	<1 %	exercise emotion	Mild form Similar clinical phenotype and treatment with LQT1
LQT6	KCNE2 (MiRP1)  (21q22.1-q22.2)	Loss of function b-subunit I <sub>kr</sub> (MiRP1) I <sub>kr</sub> (I <sub>Kv</sub> ) decrease	<1%	rest exercise	Mild form Similar clinical phenotype and treatment with LQT2
LQT7 (ATS1) Andersen- Tawil*	KCNJ2 (Kir2.1)  (17q23.1-24.2)	Loss of function a-subunit I <sub>k1</sub> rectifier decrease-ultimate fase of ripolarization	<1%	rest exercise	Multisystemic disorder ECG: characteristic T-U wave patterns Frequent ventricular ectopy (70% of VT is bidirectional) Therapy:B-blocker and in some Ca- blockers, ICD for high risk patients
LQT8 Timothy syndrome**	CACNA1C (Cav1.2)  (12p13.3)  (de novo mutation)	Gain of function a-subunit I <sub>ca</sub> Increase I <sub>ca</sub> -L, increase plateau	<1%	exercise, emotion	Severe variant Mortality more than 50% before 3 years of age Therapy: Ca channel blocker, ICD
LQT9	CAV-3 (caveolin-3)  (3p25)	Loss of function Adaptor (I <sub>Na</sub> ) I <sub>Na</sub> increase	<1%	rest-sleep	Also found in SIDS Therapy : no specific treatment
LQT10	SCN4B (Nav1.5b4)  (11q23.3)	Loss of function b-subunit I <sub>Na</sub> I <sub>Na</sub> increase	<0.1%	exercise, post-partum	Therapy: no specific treatment
LQT11	AKAP9 (Yotiao A-kinase anchoring protein)  (7q21-q22)	Loss of function Adaptor (I <sub>ks</sub> ) I <sub>ks</sub> decrease	<0.1%	exercise	
LQT12	SNTA1 (a1- syntrophin)  (20q11.2)	Loss of function Scaffolding protein I <sub>Na</sub> increase (via S-nytrosilation)	<0.1% (3%of SIDS)	rest	
<b>S. Jervell Lange- Nielsen***</b>					
S. JLN 1	KCNQ1  (11p15.5)	loss of function I <sub>Ks</sub> decrease (++)		exercise emotion	Malignant Therapy: b-blockers (+++)
S. JLN 2	KCNE1  (21q22.1-q22.2)	loss of function I <sub>Ks</sub> decrease (++)		exercise emotion	Malignant Therapy: b-blockers (++)

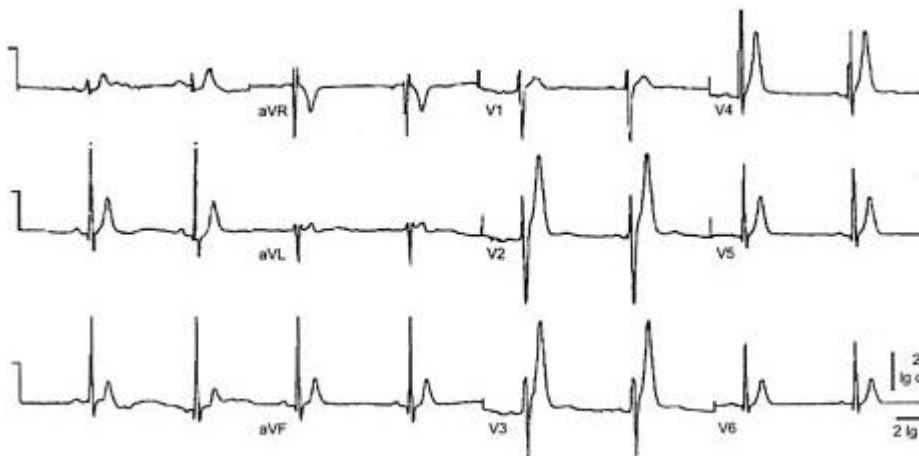
\*S. Andersen: multisystem disease with dysmorphic features, muscular paralysis (hypopotassemia), 70% have a very prolonged QTc.

\*\*S. Timothy: multisystem disease with immunodeficiency, autism, prolonged QTc interval, SCD of children.

\*\*\*S JLN id due to omozygous mutations of the genes causing also LQT1 and LQT5 with deafness.

**Short QT syndrome (SQTS).** The SQTS is a rare familial clinical-electrocardiographic entity characterised by ion channel mutations and a malignant phenotype (158). The true incidence may be largely underestimated, as symptomatic patients are identified while asymptomatic remain under-diagnosed (159). Algra et al first recognised that the short QT intervals had an increased risk of sudden death when analysing retrospective Holter monitor strips (160). Gussak et al in 2000 were the first to propose it as a unique clinical entity in a case series of three patients from one family with similar ECG findings in the setting of atrial and ventricular arrhythmias (160). In 2003 Gaita et al studied several members of two families who exhibited short QTc interval (<300 ms) who presented family history of sudden cardiac death and clinically syncope and palpitations (161). The electrophysiologic study confirmed short atrial and ventricular refractory periods consistent with increased vulnerability to atrial and ventricular fibrillation (161). In 2004 Brugada R. et al discovered that SQTS and sudden death was linked to KCNH2 gene mutation and was also found to be associated with mutations in the KCNQ1 (162, 163). Other genes were later discovered (KCNJ2, CACNA1C, CACNAB2b) (Table 11) (159). SQT4 and SQT5 is probably premature to consider them as SQTS but as a new clinical entity characterized by overlapping phenotype with Brugada syndrome and a QT interval <360 msec (159).

**Figure:** ECG pattern of genotype HERG (QTc=293 msec)



Nowadays is known that it is a genetically heterogeneous disease characterized by at least 5 gene mutations of ion channels, with autosomic dominant inheritance. There is often a remarkable family background of sudden cardiac death. The family history of sudden cardiac death occurs with a variable age of distribution ranging from 3 months to 70 years. It is characterized by an ECG interval of typically  $<320$  ms that in certain forms is accompanied by tall peaked, narrow-based, symmetrical T-waves (SQT1). The mean age of diagnosis is 30 years (164, 165). Asymptomatic remain 38% (166). Sudden cardiac death is the most frequent first symptom and first clinical presentation (164). Triggers of sudden death in SQT1 syndrome have been adrenergic dependent (exercise, loud noise), although at rest have also been reported (164). SIDS may in some cases attributed to this syndrome. Clinical spectrum can range from palpitations, nausea, syncope, aborted sudden cardiac death, ventricular arrhythmias (premature ventricular beats, idiopathic ventricular fibrillation) and atrial arrhythmias (paroxysmal or permanent atrial fibrillation or flutter). Lone atrial fibrillation in young patients is vital to exclude short QT.

The lower normal limit of the QT interval remains to be defined (165). Some studies have shown that 99% of the normal population have a QTc interval greater than 360 ms (men) or greater than 370 ms (women) (166). Other authors propose that the suspect of the disease should arise when the QTc interval is less than 340 ms and are present other arrhythmogenic factors (syncope, family sudden death). The classical sign is the very short QTc interval and when is  $<320$  msec it is called ultra-short. Other ECG signs have been described but are not present in all syndromes. Alterations of the T-waves have been described in SQT1, SQT2 and SQT3 syndrome making possible a genotype-phenotype relationship. Occasionally the PR segment may be depressed consistent with abnormal atrial repolarization. The ST-segment is often very short or completely absent, while ST-segment elevation has been described in SQT4 and SQT5. An appearance of a U-wave has been reported in a few cases. High prevalence of early repolarization has been

recently described (167). A relevant future is the lack of adaption of the QT interval at the heart rate (159). Finally, it is important that the presence of an abnormally short QT interval (<340 ms) may not by itself predict risk of life-threatening arrhythmias but rather should be taken in context of each individual patient. The presence of a short QT in the ECG is not sufficient to make a diagnosis of SQTS (159, 168). For example in asymptomatic subjects, especially males, with low heart rates, that have short QTc (<320 msec) without family history of sudden cardiac death or serious arrhythmias and a Jpoint-Tpeak intervals not shortened (>150 msec) diagnosis should not be made (168). One should also consider other factors suggestive of arrhythmias such as syncope or family history of sudden death (165).

It is important to exclude other potential aetiologies of acquired SQTS. Short QT could be provoked from an increase of heart rate and thus it can be difficult to make diagnosis of SQTS when the heart rate is above 100 b.p.m. The aetiologies are: hyperkalemia, hypercalcemia, metabolic acidosis, hyperthermia, autonomic alterations, digoxin therapy or overdose. The QT is influenced by the testosterone and that is the reason why it is more frequent in young adults.

Electrophysiological study showed extremely short ERPs at both atrial and ventricular level that might explain atrial and ventricular vulnerability to arrhythmias. A heterogeneous shortening of the action potential duration among the different cell types spanning the ventricular wall, creating a transmural dispersion of repolarization has been proposed as an additional mechanism for re-entry arrhythmias. Programmed stimulation has a high yield of inducing ventricular arrhythmia, with easily inducible atrial fibrillation and polymorphic ventricular tachycardia with programmed electrical stimulation (164).

Risk stratification is difficult. The predictive value of electrophysiological studies is poorly known and risk stratification based on the QTc interval is probably unreliable. The

implantation of ICD is the first choice therapy, except in very young children. Usually ICD is proposed if there is an unexplained syncope, a personal history of sudden death or family history of sudden death and induction of ventricular fibrillation in otherwise asymptomatic subjects. Inappropriate shocks may occur, causing concern for the implantation in younger adults. Only hydroquinidine (which blocks HERG channels) has shown some efficacy, prolonging the QT and reducing the inducibility of ventricular arrhythmias in the context of the SQT1 syndrome and maybe proposed in children and patients that refuse the implant. In patients without HERG mutations the therapy should be evaluated individually. Also disopyramide may prolong QT interval. Both drugs need additional confirmatory data. Propafenone is used for prophylaxis of atrial fibrillation and to decrease the discharges of the ICD and arrhythmias (168-170).

**Table 11.** Short QT syndrome

Type of syndrome	Gene (protein)	Current-pathophysiology	Authors
Short QT 1	KCNH2 (HERG)	Ikr-subunit a (gain of function)	Brugada R 2004, Hong K 2005
Short QT 2	KCNQ1(KvLQT1)	Iks-subunit a (gain of function)	Bellocq C 2004, Hong K 2005
Short QT 3	KCNJ2 (Kir2.1)	Ik1 (gain of function)	Priori SG 2005
Short QT 4	CACNA1C	Ica (loss of function)	Antzelevitch C 2007
Short QT 5	CACNB2b	Ica (loss of function)	Antzelevitch C 2007

\*short QT4 and 5 syndromes for some authors are considered apart as a new syndrome with mixed phenotype.

**Catecholaminergic polymorphic ventricular tachycardia and ARVC2.** Ryanodine receptor type 2 (RyR2) is the largest calcium release channel protein located in the sarcoplasmic reticulum membrane of the cardiac myocytes (171-174). RyR2 has a pivotal role in intracellular calcium homeostasis, in regulating excitation-contraction coupling in cardiac myocytes, and in sinoatrial node cell function (171, 174-176). It is involved in the calcium-induced calcium release mechanism and store-overload-induced calcium release mechanism (175-178).

RyR2 gene mutations alter channel activity upon adrenergic activation, increasing the likelihood of spontaneous calcium release. The abnormal calcium leak during diastole is

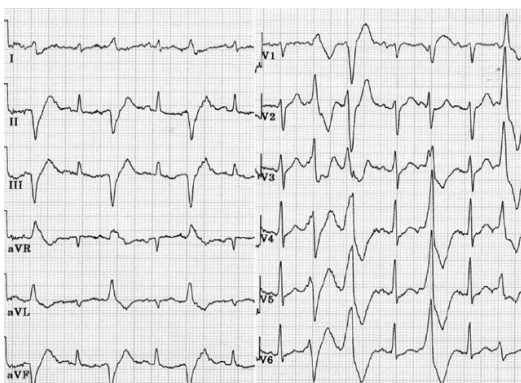
the basis for the triggered arrhythmias and their polymorphic pattern (179-181). In recent years, several studies have tried to clarify the molecular mechanisms behind the dysfunctional RyR2 channel (174, 178, 182). Effort-induced polymorphic ventricular arrhythmias can also be linked to CASQ2 gene mutations a recessive form called CPVT2 or they could map to chromosome 7p14-p22 (183, 184).

**Table 12.** CPVT forms

form	gene	protein	inheritance
CPVT1	1q42.1-q43	Ryanodine receptor 2	Autosomal dominant
CPVT2	1p13.3-p11	Calsequestrin 2	Autosomal recessive
CPVT3	7p14-p22	?	Autosomal recessive

Effort-induced polymorphic ventricular arrhythmias linked to RyR2 mutations have been described mainly in a peculiar form of arrhythmogenic right ventricular cardiomyopathy (named ARVD2) and in catecholaminergic polymorphic ventricular tachycardia (named CPVT1) (171-173). Several RyR2 mutations and polymorphisms have been described in both diseases (185-187). Whether ARVD2 and CPVT1 are allelic diseases or overlapping forms of the same disease is still debated. A recent study suggests that the two entities may correspond to different degrees of expression of the same disease (188).

**Figure:** Polymorphic PVBs on exercise stress test also in couplets



ARVD2 and CPVT1 are both transmitted via an autosomal dominant inheritance with a variable penetrance (186, 189). The 12-lead resting ECG is usually normal (186, 189, 190). Exercise stress test usually triggers the onset of a broad spectrum of ventricular

arrhythmias with a heart rate threshold generally between 110 and 130 b.p.m (186, 190, 191). A highly-reproducible polymorphic or bidirectional ventricular tachycardia has been described that occurs at different heart rate thresholds in different individuals, and that fades on stopping exercising, although there may be no bidirectional tachycardia (186, 189, 192, 193). The occurrence of a bidirectional tachycardia and progressively worsening of ventricular arrhythmias on exercising have been described as diagnostic markers of CPVT1 (190).

RyR2 channelopathy is an important cause of sudden cardiac death in children and young adults with or without structural abnormalities (176, 178, 191, 194, 195). The clinical presentation of RyR2 mutation carriers is due to an external stimulus (exercise or emotion) that triggers- through the catecholaminergic activation of beta-receptors – an abnormal calcium release from the sarcoplasmic reticulum (176). The characteristic electrophysiological phenotype of RyR2 channelopathy is a highly-reproducible polymorphic pattern of effort-induced ventricular arrhythmias occurring often at individual HR threshold, exacerbated by exercise, and fading on resting (176, 189, 190). Basal ECG is usually normal, though sinus bradycardia has been described in some cases (186, 189, 190). Late potentials may be present in a minority of cases (186). The imaging techniques in the majority of the cases reveal normal findings (172, 191). Exercise stress test is indicated for assessing subjects with known or suspected effort-induced ventricular arrhythmias and ascertaining the efficacy of medical therapy in such patients. Anti-arrhythmic strategies usually consist in high-dose beta-blockers with no ISA; nadolol and propranolol are generally used (190). Beta-blocker therapy is associated with lower event rates, but usually fails to suppress completely ventricular arrhythmias. Further studies on concomitant therapies, e.g. verapamil, flecainide, ICD and left ventricular sympathetic denervation, are needed to improve the outcome of these patients (196-200).



**Less frequent channelopathies.** Less frequent channelopathies are idiopathic sick sinus syndrome and familial sinus bradycardia, Lenegrè disease, familial atrial fibrillation and atrial standstill.

Sick sinus syndrome (SSS) is characterized by sinus bradycardia and sinus arrest in the absence of any structural disease. SCN5a mutations were identified with sinus node disease resulting in loss of function (SSS1, autosomal recessive). The phenotype in these subjects included bradycardia that progressed to atrial inexcitability. In four independent studies mutations in hHCN4 gene (Hyperpolarization-activated Cyclic Nucleotide-gated potassium channel 4), encoding the main  $\alpha$ -subunit of the pacemaker current  $I_f$  (funny channel, f-channel), were identified (4 isoforms of HCN channels have been identified). These HCN4 mutations result in loss of function. Pacemaker channels of the sinoatrial node generate spontaneous activity and mediate cyclic AMP-dependent autonomic modulation of the heart rate. The basic characteristics are activation upon hyperpolarization in the range of voltages comprising the diastolic depolarization phase of the pacemaker action potential, and a mixed  $Na^+$  e  $K^+$  inward current. Mutations in this gene have also been linked to SSS2, also known as atrial fibrillation with brady-arrhythmia or familial sinus bradycardia. One mutation of HCN4 has been linked to sinus node dysfunction characterised by marked sinus bradycardia, episodes of syncope, intermittent atrial fibrillation and chronotropic incompetence even under maximal workload. Another mutation has been linked to severe bradycardia, recurrent syncope, QT prolongation and polymorphic ventricular tachycardia. Sinus bradycardia in members of two large families was found to be also associated with mutations in this gene (201, 202)

Lenegrè disease, also known as progressive cardiac conduction defect (PCCD) or Lenegrè-Lev disease is one of the most common cardiac conduction disturbances. It is characterised by primary progressive development of cardiac conduction defect, slowing of electrical conduction through atria, atrioventricular node and in the His-Purkinje system. It

manifests in the ECG as progressive prolongation of the conduction parameters (P-wave, PR and QRS intervals), right or left bundle branch block, without ST-segment elevation or QT prolongation, leading to complete atrioventricular block, long pauses, and bradycardia that may trigger syncope and sudden death. PCCD is considered a primary degenerative disease or an exaggerated aging process with sclerosis affecting only the conduction tissue. In heritable PCCD, conduction may be attributed to loss of function mutations in SCN5A (202). Whether the age-related degenerative process, in which fibrosis affects only the cardiac conduction system is a primary degenerative process in PCCD, or a physiologic process that is accelerated by I<sub>Na</sub> reduction remain to be investigated. It represents the major cause of pacemaker implantation in the world (0.15 implantations per 1.000 inhabitants per year in developed countries). Mutations of SCN1B, PRKAG2, NKX2-5 and LMNA could be linked alone or in combination with cardiomyopathies (203).

Atrial fibrillation is the most common sustained cardiac arrhythmia and is characterized by chaotic electrical activity of the atria. It increases in prevalence with advancing age to about 6% in people older than 65 years. This arrhythmia accounts for about one-third of all strokes, and 30% of all patients with atrial fibrillation have a family history of the disease. In 1997, Brugada et al identified the first locus for familial atrial fibrillation on chromosome 10q22-24. Since that time, further loci have been mapped and relevant genes identified (KCNQ1, KCNE2, KCNE3, KCNJ2, KCNH2, KCNA5, NPPA, NUP155, SCN5A). Some of these genes encode potassium-channel subunits and the mechanism of action on inducing atrial fibrillation is via shortening of the action potential duration and atrial effective refractory period. Common atrial fibrillation often occurs in association with acquired diseases such as hypertension, valvular heart disease, and heart failure. By genetic association study, some genetic variants or inherited DNA polymorphisms related to the mechanism of atrial fibrillation have been found to be associated with common atrial fibrillation, including genes encoding for subunits of potassium or sodium channels,

sarcolipin gene, renin-angiotensin system gene, connexin-40 gene, endothelial nitric oxide synthase gene, and interleukin-10 gene. These observations suggest that genes related to ionic channels, calcium handling protein, fibrosis, conduction and inflammation play important roles in the pathogenesis of common atrial fibrillation. Within the next decade, most of the genes responsible for atrial fibrillation and the single-nucleotide polymorphisms that confer predisposition will probably be identified, and therapies will be developed on the basis of individuals' genomic profiles (204).

Atrial standstill can be caused by a mutation in the SCN5A gene in combination with a rare connexin-40 genotype. The last years many overlapping phenotypes have been described. The most frequent overlapping phenotype of the SCN5A channelopathies is the concomitant presentation of Brugada syndrome and PCCD (205).

**Congenital diseases at risk of athletes' sudden death.** The congenital heart diseases are an important cause of sudden cardiac death in young. One of the most frequent congenital diseases that cause malignant arrhythmias a risk of sudden death are the coronary artery anomalies. Important examples are the origin from the wrong aortic sinus, deep intramyocardial course and ostial valve-like stenosis (39, 46, 63). Other congenital abnormalities causing sudden death are the Wolff-Parkinson-White syndrome, the conduction system anomalies, congenital valvular disease (i.e. aortic valve stenosis) and the post-operative congenital heart diseases (i.e. Tetralogy of Fallot) (39). Congenital causes of arrhythmic sudden death that can also be genetically determined are the familial Wolff-Parkinson-White syndrome due to gene defects as PRKAG2, Marfan syndrome due to a defect of fibrillin1 or TGFBR1 (arrhythmic death has also been described), familial mitral valve prolapse (due to one of the three locus identified or a defect in filamin A) and supravalvular aortic stenosis (due to a defect in elastin). In Marfan syndrome sudden death is usually due to aortic rupture.

Regarding Wolff-Parkinson-White syndrome, although diagnostic assessment and

treatment have been described in detail in patients with symptomatic Wolff-Parkinson-White syndrome, the management of asymptomatic subjects remains controversial. Usually they are assumed to have a benign prognosis, although they do very occasionally present with ventricular fibrillation as the first manifestation of the syndrome. Discovering a WPW pattern in a previously asymptomatic athlete on a routine ECG identifies the necessity for more accurate screening tests. However, non-invasive methods (Holter monitoring, exercise treadmill testing) seem to be relatively incomplete for risk stratification, especially for athletes. Current guidelines do not always recommend a routine electrophysiological study in patients with an asymptomatic WPW ECG pattern, especially in children younger than 12 years or subjects with intermittent WPW at rest or during effort. Individuals who engage in high-risk occupations or those patients who have a pre-excitation pattern which precludes them from following their chosen career or activities may be exceptions.

**Acquired diseases at risk of arrhythmias during exercise.** The most frequent acquired diseases are atherosclerotic coronary disease, myocarditis, valvular heart disease and acquired lesions of the specialized conduction system leading to heart block. Commotio cordis is another cause of sudden death in apparently normal heart (39, 46, 51).

Regarding the coronary artery disease, in some post-mortem studies it has been documented as the leading cause of sudden death in the young (25%). It consists mostly of a single obstructive plaque with a fibrocellular intimal proliferation. Vasospasm superimposed to the plaque seems to play a major role as a precipitating mechanism leading to transient coronary occlusion. Coronary thrombosis is much less frequent than sudden death in adults and it is due more to endothelial erosion than plaque rupture (45).

Myocarditis is an inflammatory heart muscle disease associated with cardiac dysfunction and it is diagnosed by established histological, immunological and immunohistochemical criteria. It is a cause of sudden death in nearly 10% of young people. Currently it is listed

among specific cardiomyopathies and, as such, called inflammatory cardiomyopathy. It is characterized by the histological evidence of inflammatory infiltrates associated with myocyte degeneration and necrosis of nonischemic origin. The gold standard for the diagnosis is the endomyocardial biopsy by showing the inflammatory infiltrate and necrosis, but is limited by low sensitivity and specificity. To increase the diagnostic accuracy the use of immunohistochemistry is mandatory to identify and characterize the inflammatory infiltrate. The diagnostic yield of endomyocardial biopsy can be further enhanced by routine molecular analysis with DNA-RNA extraction and polymerase chain reaction and reverse transcriptase amplification of the viral genome. Myocarditis may be classified based on histologic or etiologic criteria (infective or non infective). Infective causes most commonly include viral (coxsackievirus, adenovirus, parvovirus), bacterial, fungal or parasitic agents, while among non-infective causes are the hypersensitivity type and toxic causes. Acute myocarditis, especially viral forms, can be resolved without sequel; however progression in the chronic form of dilated cardiomyopathy is not rare. The clinical presentation is highly variable from palpitations or chest pain to syncope, congestive heart failure, cardiogenic shock and sudden death. A review of major autopsy series of sudden death in the young demonstrated that may account for up to 42% of fatal events (108). A recent study in the Veneto region of Italy demonstrated that myocarditis account for 13% of fatal events (108). The clinical evaluation of patients includes personal and family history, physical examination, 12-lead ECG, echocardiography, 24-hour ECG monitoring while additional exams may be required. Myocarditis should be suspected in athletes with unexplained cardiac arrhythmias and dysfunction, especially if preceded by a flu-like syndrome. An early diagnosis is desirable in order to avoid the risk of fatal consequences, since physical activity can enhance the inflammatory process. Athletes with myocarditis should respect the adequate period of rest until the disease is completely resolved and should be withdrawn from all competitive and amateur-leisure time sport

activities for at least 6 months and resume training when ventricular function and cardiac dimensions return to normal and the clinically relevant arrhythmias disappear. Clinical reassessment is indicated before the athlete reenters to sport activities. In the presence of life-threatening arrhythmias or rapidly progressive cardiac dysfunction an antiviral or an immunosuppressive treatment should be considered depending on whether a viral agent is present or absent, respectively, in the myocardium (108).

Regarding valvular heart disease, physical check-ups among athletes are of significant relevance. Patients with mild-to-moderate mitral valve regurgitation can participate in all types of sport associated with low and moderate isometric stress and moderate dynamic stress. Patients under anticoagulation should not participate in any type of contact sport. Asymptomatic athletes with mild aortic valve stenosis can take part in all types of sport, as long as left ventricular function and size are normal, a normal response to exercise at the level performed during athletic activities is present and there are no arrhythmias. Asymptomatic athletes with moderate aortic valve stenosis should only take part in sports with low dynamic and static stress. Aortic valve regurgitation is often present due to connective tissue disease of a bicuspid valve. Athletes with mild aortic valve regurgitation, with normal end diastolic left ventricular size and systolic function can participate in all types of sport (206). A mitral valve prolapse is often associated with structural diseases of the myocardium and endocardium. In patients with mitral valve prolapse Holter-ECG monitoring should also be performed to detect significant arrhythmias. The prevalence of mitral valve prolapse has been reported to be between 0.6 and 21%. The prevalence of mitral valve prolapse in young athletes mostly in southern California was found to be less than 1%, and was similar in both genders. Apparently isolated MVP has been documented in 10% of sudden death in the young (207). Even clinical benign cases in young adults may lead to sudden cardiac death (208). Altered papillary muscle tips may lead to arrhythmias (209).

**Idiopathic arrhythmias.** Ventricular arrhythmias are common in trained athletes and are usually not associated with underlying cardiovascular abnormalities. Athletes trend towards more frequent ventricular arrhythmias. Arrhythmias can be a marker of heart disease and generate appropriate concern when discovered in athletes. In a study of athletes with PVBs identified in the ECG and/or palpitations 7% harbored a cardiovascular disease (13). The clinical assessment of ventricular tachyarrhythmias in trained athletes is of particular significance because of the recognition that a young and otherwise healthy athlete may have unsuspected and potentially lethal cardiovascular disease, which can result in sudden arrhythmic death. Therefore, the risk associated with competitive sports and training in athletes with ventricular tachyarrhythmias is still not completely resolved. Recent studies have shown that such arrhythmias, in the absence of heart disease, do not convey adverse clinical significance and probably do not per se justify disqualification from competitive sports (210).

The ventricular arrhythmias can originate in the context of a structural heart disease or occur in the absence of a structural heart disease, a channelopathy or metabolic/electrolyte abnormalities and are called idiopathic. Idiopathic ventricular arrhythmias are a generic term which refers to ventricular arrhythmias in patients without overt structural heart disease. It is likely however that there are cellular or channel abnormalities that are not visible. These arrhythmias, particularly in forms of tachycardia, are uncommon but certainly not rare. They offer an exciting therapeutic challenge because the majority of patients are young. The idiopathic ventricular tachycardia accounts for 10% of ventricular tachycardia cases evaluated by electrophysiology centres in the U.S. and 20% of those in Japan (211). The prognosis is generally benign, and is several pharmacologic and non pharmacologic options. Although the prognosis is general excellent in the majority of patients, it could be associated with considerable mortality and symptoms. They are rarely life threatening but may be associated with hemodynamic

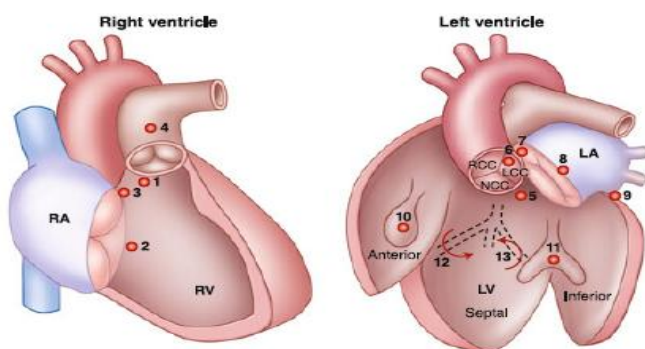
compromise and syncope when rapid and sustained. There are reports of more malignant variants but whether these represent a distinct disorder of repetitive monomorphic tachycardia is unclear. Finally, tachycardia induced cardiomyopathy has been described and reversible left ventricular dysfunction can occur (211).

The classification could be based on the 1) ventricle of origin, 2) specific morphologic feature, 3) catecholamine dependence, 4) response to drugs (adenosine, verapamil, and propranolol) and 5) response to electrophysiologic study (table 13).

**Table 13:** Classification of idiopathic arrhythmias

<b>Monomorphic PVBs/VT</b>	
Outflow tract arrhythmias/VT	RVOT, LVOT, aortic cusp, Pulmonary Artery (PAVT) or epicardial LV
Fascicular PVBs/VT	LAF, LPF, septal VT
Adrenergic monomorphic PVBs/VT	Left or right ventricle
Annular PVBs/VT	mitral, tricuspid
<b>Polymorphic PVBs/VT</b>	LQTS, BS, SQTS, short coupled torsades, catecholaminergic polymorphic, idiopathic VF/TV

**Figure:** Sites of origin of most frequent idiopathic arrhythmias



**Fig. 1** Origins of idiopathic arrhythmias in the right and left ventricle. 1 = classical RVOT, 2 = tricuspid annulus, 3 = His-bundle, 4 = pulmonary artery, 5 = classical LVOT, 6 = aortic root (eg, LCC), 7 = aortomitral continuity, 8 = mitral annulus, 9 = epicardium, 10 = anterior papillary muscle, 11 = posterior papillary muscle, 12 = anterior fascicle, 13 = posterior fascicle. LA left atrium; LCC left coronary cusp; LV left ventricle; LVOT left ventricular outflow tract; NCC noncoronary cusp; RA right atrium; RCC right coronary cusp; RV right ventricle; RVOT right ventricular outflow tract



**Malignant idiopathic tachyarrhythmias.** In the majority of cardiac arrest patients, a structural or functional abnormality can be identified, coronary artery disease being the most common, but 5 to 10% of hearts are apparently normal (60). The ischemic heart disease is the most common cause of sustained ventricular arrhythmias. Acute ischemia is a cause of polymorphic ventricular tachycardia and/or ventricular fibrillation. Sustained monomorphic ventricular tachycardia in a structural heart disease is most commonly a result of reentry involving a myocardial scar. The most common cause of a scar is an old infarct. The histological examination in nearly 80% of SCD victims that have a macroscopically normal heart can disclose a concealed pathologic substrate (focal myocarditis, “segmental” arrhythmogenic cardiomyopathy and conduction system disease). These diseases should not be included in the term of idiopathic because a diagnosis of a structure abnormality does not make them any more idiopathic.

Malignant tachyarrhythmias are considered the ventricular fibrillation, polymorphic ventricular tachycardia and rapid ventricular tachycardia. They could also be classified according to the morphology in monomorphic when each QRS complex resembles the next or polymorphic when it varies in appearance from beat to beat. Ventricular fibrillation is one of the leading causes of death in North America. It causes more than 300,000 sudden deaths each year in the U.S. alone. The occurrence of ventricular fibrillation in patients without clinical evidence of heart disease is unusual. In approximately 5-12% of these cases, there are no demonstrable cardiac or non cardiac causes to account for the episode, which is therefore classified as idiopathic ventricular fibrillation (213). The subgroup of patients with sudden death in apparently normal heart appears in the literature with the designation of idiopathic ventricular fibrillation. However, it is likely that the idiopathic ventricular fibrillation is not an independent disease but rather a conglomeration of conditions with normal gross and microscopic findings in which risk undoubtedly derives from molecular abnormalities, most likely linked to ion channel mutations (214,215).

Torsade de pointes is a form of polymorphic ventricular tachycardia characterized by changing amplitude of the complexes with a characteristic twist around the isoelectric baseline that is often associated with prolonged QT. A rare variant of torsade de pointes is the short-coupled variant a rarely described cause of ventricular tachycardia.

The number of sudden cardiac death victims with structurally normal hearts is small and is being narrowed thanks to the post-mortem DNA analysis and diagnosis of the channelopathic syndromes (51, 54). A number of genetic conditions cause polymorphic ventricular arrhythmias and sudden death in the absence of a visible structural heart disease. Most of these disorders are ion channelopathies. In Brugada syndrome, syncope and sudden death result from a polymorphic ventricular tachycardia. Torsade de pointes occur in the setting of long QT syndrome. The short-coupled variant of torsades de pointes, rarely is initiated by a premature beat with a remarkably short coupling interval. Also, all the ventricular premature beats display this short interval. The CPVT causes exercise-induced polymorphic ventricular tachycardia.

In 1987 Belhassen et al reported the first series of idiopathic ventricular fibrillation (216). In 1994 Leenhardt and colleagues described for the first time 14 patients and proposed it as a new electrocardiographic entity (217). Until then only a limited number of cases similar to the short-coupled variant of torsade de pointes were published. The ECG pattern was a typical torsade de pointes but with an unusually short coupling interval (always less than 300 milliseconds, mean 245 ms) of the first beat or of the isolated PVB. The proper rate of the tachycardia was slightly faster (mean 240 bpm) than classical torsade de pointes (200-220 bpm). Torsade de pointes degenerated in ventricular fibrillation in 10 of 14 cases. There was no evidence of structural heart disease or acute illness. The electrophysiological study found no abnormalities in the basic electrophysiological parameters, including ventricular refractoriness. In most cases no ventricular arrhythmias were obtained using complete stimulation protocol. During exercise stress test only 2 of 9

cases presented single PVBs. Holter monitoring evidenced in 8 of 12 patients frequent PVBs with short coupling interval (average 849 PVBs). Vagal activity was apparently more depressed than sympathetic activity. There was a history of familial sudden death in 30% of the cases. Treatment with ICD was strongly suggested.

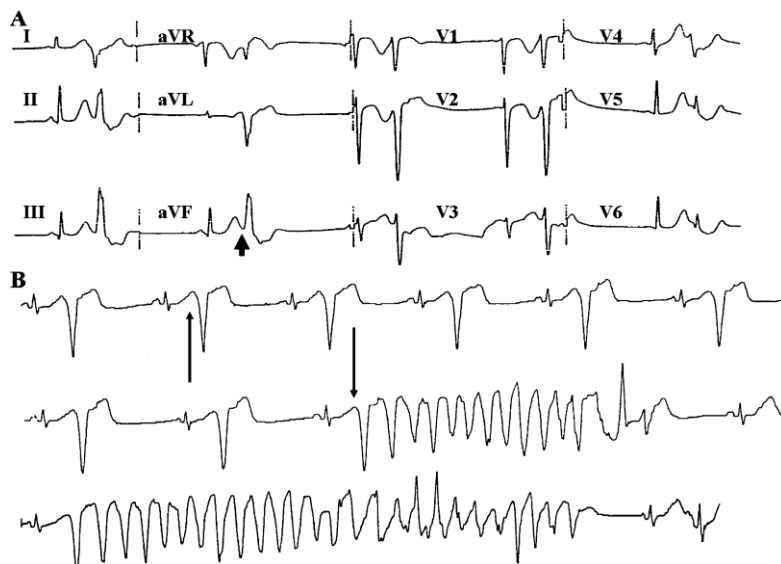
In 1997 an article of 9 patients with idiopathic ventricular fibrillation described the mode of onset of malignant arrhythmias (218). In all instances, spontaneous ventricular fibrillation followed a rapid polymorphic ventricular tachycardia, which was initiated by PVCs with very short coupling intervals. The PVC initiating ventricular fibrillation had a coupling interval of  $302 \pm 52$  msec. These PVCs occurred within 40 msec of the peak of the preceding T wave. Pause-dependent arrhythmias were never observed. In almost all published reports single PVC, with a very short coupling interval, initiated a rapid polymorphic ventricular tachycardia that immediately deteriorated in ventricular fibrillation. Overlapping between short-coupled variant of torsade and idiopathic ventricular fibrillation exists: 1) both conditions affect young adults of both genders (age  $36 \pm 16$  yy), 2) the morphology and the very short coupling interval of PVBs initiating the non sustained polymorphic ventricular tachycardia are striking similar, 3) high incidence of sudden cardiac death. However a positive family history is relatively common in the short-coupled variant and absent in the idiopathic ventricular fibrillation (219).

In 2002-2003 studies by Haissaguerre et al reported that idiopathic ventricular fibrillation initiated by dominant triggers from the distal Purkinje system or right ventricular outflow tract (RVOT) were successfully ablated by radiofrequency catheter ablation (220-222). Later in 2005, Viskin et al described three patients with a “short-coupled” variant of RVOT tachycardia in analogy to the “short-coupled variant of torsade de pointes” (223-224). The term would not fit because the coupling interval triggering polymorphic ventricular tachycardia was longer or better intermediate ( $340 \pm 30$  msec) (longer than the coupling interval in idiopathic ventricular fibrillation but shorter than that of truly benign

monomorphic RVOT-VT). The same year Noda et al described a malignant entity of idiopathic ventricular fibrillation and polymorphic ventricular tachycardia initiated by PVC from the RVOT describing it as variant form of “benign” RVOT ventricular tachycardia (225). The coupling intervals were not as short as those described in patients with short coupled TdP or idiopathic ventricular fibrillation ( $409\pm 62$  msec) and only PVBs preceding the polymorphic ventricular tachycardia had a short cycle length ( $245\pm 28$  msec). Interestingly Noda et al suggested a significant difference of the cycle length of ventricular tachycardia between malignant and benign forms of RVOT VT ( $245\pm 28$  vs.  $328\pm 65$  msec) (225). Recently early repolarization patterns have been described in 31% of cases of sudden death victims of idiopathic ventricular fibrillation (143). In some cases mutations in the subunit Kir6.1 (KCNJ8) of the KATP channel have been identified (147).

Finally, sudden infant death syndrome (SIDS) is defined as the sudden death of an infant that is unexpected on the basis of the child's history and unexplained by a thorough post-mortem examination. It is the most common mode of death occurring in post-neonatal period in infants less than 1 year of age. It accounts for about 25% of all deaths between 1 month and 1 year of age. The incidence is less than 0.5/1000 live births. Various causes have been described: occult heart disease, asphyxia caused by bed position or suffocation by respiratory failure, poisoning, abuse, other natural disease processes. Overall, it is estimated that 5-10% of SIDS are associated with a defective cardiac ion channel. Long QT syndrome and Brugada syndrome have been described as a cause of sudden death in infants. Interestingly, simultaneous sudden death infant syndrome has been described in Long QT syndrome when both infants meet the definition of SIDS individually (described 44 cases in the literature) (226).

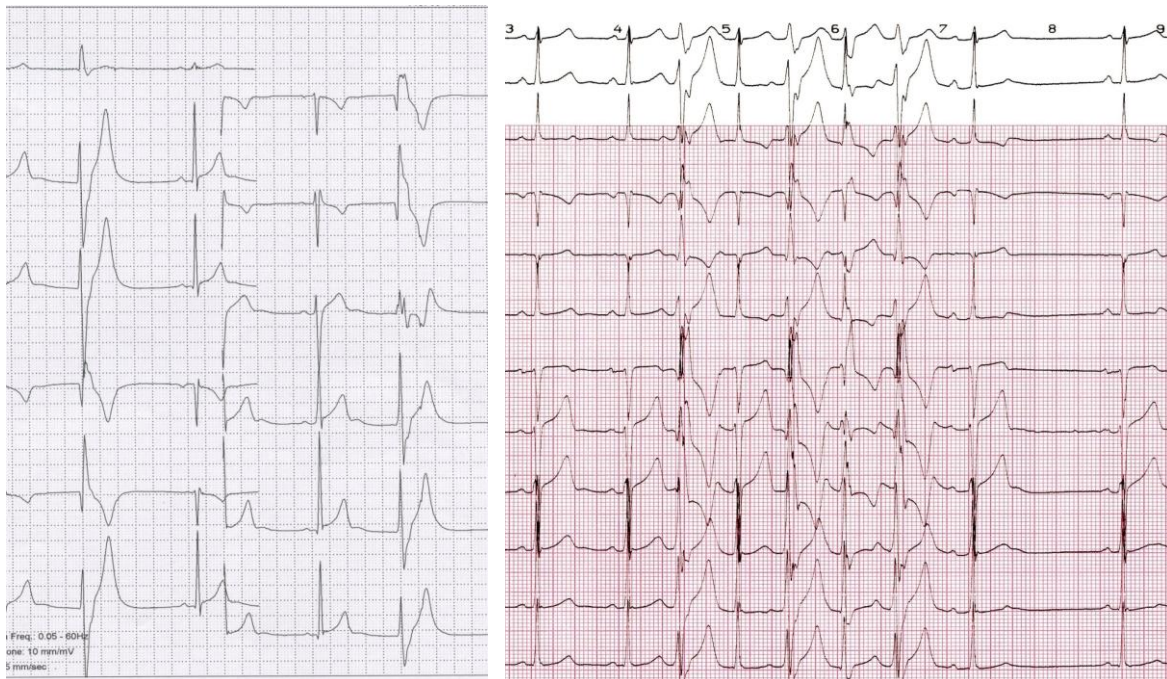
**Figure.** Syncopal nonsustained polymorphic ventricular tachycardia in a woman who received a diagnosis of “benign RVOT extrasystoles” 15 years earlier. A: The RVOT-extrasystoles originate shortly after the end of the T-wave (arrowhead) B: Ventricular bigeminy and nonsustained polymorphic ventricular tachycardia recorded during a cluster of syncopal episodes. The extrasystoles now originate close to the peak of the T-wave (arrows). ; (Noda et al)



**Benign idiopathic tachyarrhythmias.** The paradigm for understanding the genesis of ventricular tachyarrhythmias rests on the notion that structural heart disease provides an electroanatomic substrate for re-entrant arrhythmias. Although this is sufficient for explaining most forms of clinical ventricular tachyarrhythmias, approximately 10% occur in the absence of structural heart disease.

The syndrome of idiopathic ventricular tachyarrhythmias refers specifically to monomorphic arrhythmias because polymorphic arrhythmias differ mechanistically and prognostically (227). The diagnosis of idiopathic arrhythmias or with no apparent heart disease is made after a thorough cardiac evaluation that excludes a structural heart disease, genetic conditions as long QT-syndrome or metabolic/electrolyte abnormalities (228). Pioneering studies within the last few years have shown that some of these arrhythmias are caused by inherited channelopathies (for example: long QT syndrome, Brugada syndrome, and catecholaminergic ventricular tachycardia). Distinguishing these patients is usually not difficult as they former usually present with syncope, cardiac arrest and have PVBs with short coupling interval (229).

**Figure.** PVBs with RBBB morphology with superior axis deviation in the absence of organic heart disease. Usually PVBs are single, in the second case a slow triplet was observed in the ECG. In this case ECG was done for at least 100 beats.



The two most common cardiac regions for idiopathic ventricular tachycardias are the right ventricular outflow tract and the left posterior fascicle. Both of these ventricular tachycardias can be triggered by exercise and both these ventricular tachycardias are readily curable with ablation. The initial evaluation consists of the resting ECG and ventricular function and further evaluation also by SAECD. Cardiac MRI may reveal mild structural abnormalities, the significance of which is still debated. An evaluation of coronary perfusion should be considered in appropriate patients to exclude CAD as an etiology of tachycardia. Further studies as right ventricle perfusion imaging and right ventricle biopsy are rarely performed but may be used in differentiating idiopathic tachyarrhythmias and arrhythmias in the setting of organic heart disease.

The prognosis in the patients with frequent PVCs originating from the outflow tract without any structural heart disease appeared benign after at least a 4-year follow-up. However, because the patients with highly frequent PVCs may exhibit a considerable decrease in

the left ventricular ejection fraction, the possibility of left ventricular dysfunction should be given attention during the long term follow-up (230). When left ventricular ejection fraction exhibits a considerable decrease, catheter ablation may be indicated (230). The prognosis of patients with PVBs originating from the right ventricle (LBBB with vertical or left axis deviation and RBBB with positive QRS from V1-V6) also appeared benign. In 50% of patients' ectopy disappeared. Focal fatty replacement in the right ventricle was present in most cases (231). Interestingly no patient develop ARVC.

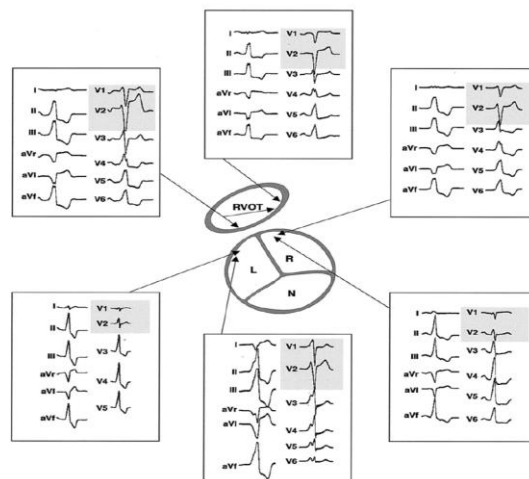
### **Idiopathic ventricular outflow tract tachycardias.**

The most common form of idiopathic ventricular tachycardia originates from the ventricular outflow tract. Approximately 80-90% of ventricular tachyarrhythmias arise from the right ventricular outflow tract. However other origins like the left ventricular outflow tract, septum, pulmonary artery, aortic sinus of Valsalva, the area near the His bundle and epicardial surface of the ventricles have been described (229).

Despite disparate sites of origin of left and right ventricular outflow tachycardias the electrophysiological properties (induction with programmed ventricular stimulation and facilitation by catecholamine infusion) and pharmacological properties (response to adenosine and verapamil) are similar. These data suggest a common arrhythmogenic mechanism, consistent with cyclic AMP-mediated triggered activity. Thus, they may be considered as a single entity and classified together as "outflow tract arrhythmias" (232).

Symptoms occur usually between 20-50 years. Clinical presentation is variable (229). Two clinical manifestations of this tachycardia are the most frequent: exercise-induced VT and repetitive monomorphic VT (which occurs at rest) (229). The ECG is usually normal, though complete or incomplete RBBB may show nearly 10% of patients (229). Most of the patients show a benign course suggesting that this arrhythmia does not represent occult cardiomyopathy and is generally not accompanied by hemodynamic deterioration (229).

**Figure.** Outflow tract PVBs morphologies



**Right ventricular outflow tract arrhythmias (RVOT).** In 1969, Rosenbaum defined ventricular ectopy with LBBB morphology and the main QRS forces directed inferiorly a “typical for normal subjects” (233). Later on was demonstrated that this type of arrhythmia most often had an origin of the right outflow tract of the infundibulum and to lesser extend of the interventricular septum in the region of the RVOT (234). Three forms of right outflow arrhythmias have been described based on the distinct clinical grades of ventricular ectopy and tachycardia: 1) premature ventricular beats, 2) repetitive monomorphic nonsustained ventricular tachycardia (RMVT), usually suppressed with exercise, 3) paroxysmal sustained monomorphic ventricular tachycardia, which is exercise-induced (or during recovery). These arrhythmias may represent a continuum of a singular mechanism with differential levels of arrhythmia expression. The basic underlying electrophysiological mechanism appears to be the triggered activity caused by c-AMP mediated calcium-dependent delayed after depolarizations (235). The outflow tract arrhythmias in apparently normal heart are considered mostly idiopathic and thus benign, but recent studies have described rare cases of malignant arrhythmias also (223). Accelerated idioventricular rhythm originating of infundibulum and monomorphic repetitive rhythms have also been described in concealed forms of arrhythmogenic right ventricular dysplasia (8, 9). Recently Corrado et al evidenced in 26% of patients with right ventricular outflow



tract idiopathic tachycardia, right ventricular electroanatomical scar areas in the 3-dimensional electroanatomical voltage mapping that correlated with fibrofatty myocardial replacement at endomyocardial biopsy. This exam could help to distinguish the two entities (ARVC and idiopathic RVOT) and thus on the differential diagnosis (236). Regional ARVC must be excluded by: 1) History (usually negative in RVOT VT), 2) ECG (usually normal), 3) SAECG (usually absent), 4) serum brain natriuretic peptide, 5) echocardiography and MRI, 6) electrophysiological study (sensible to adenosine, only 3% inducible tachycardia), 7) CARTO (scars in ARVC), 8) RV biopsy.

The PVBs occur more often during day than night and are transiently suppressed by sinus tachycardia. The ECG is usually normal. The PVBs may diminish or disappear with exercise during stress testing (237), while RVOT tachycardia may initiate during exercise stress test (on a critical heart rate that differs in each patient) or recovery. An echocardiogram is normal in most of these patients, although anatomic changes, such as focal thinning, fatty replacement of the RVOT and abnormal wall motion have been demonstrated with MRI (in up to 70%) (237). Coronary angiography is normal. RVOT ventricular tachycardia is usually diagnosed in females and in adults (20-50 years), although cases at extremes of ages have been reported. It occurs more frequently in women. Most patients (80%) present with palpitations or presyncope, but rarely present with frank syncope. Exercise or emotional stress usually precipitates the tachycardia. Sudden death is rare (only single cases) (237)

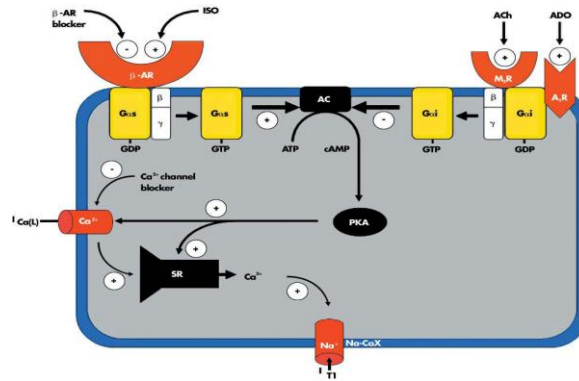
Although most of these arrhythmias have their origin in the septal aspect of the RVOT (anterior septum under the pulmonic valve), some originate from the free wall of the RVOT (20-25%) and the posterior septal aspect of the superior RVOT, while other sites are recognized much less commonly (238,239). Finally, while most RVOT or PVBs are known to arise from endocardial sites, it was recently reported that this arrhythmia may originate within the pulmonary artery (240). Often originate from the septal side of pulmonary artery

(241). Ventricular tachycardia originating also from near the His-bundle region has also been described (211).

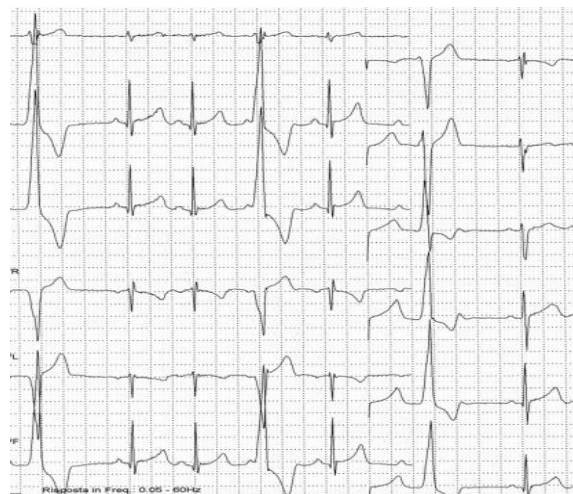
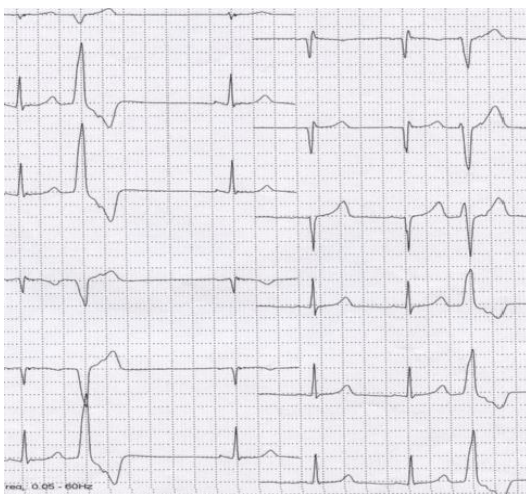
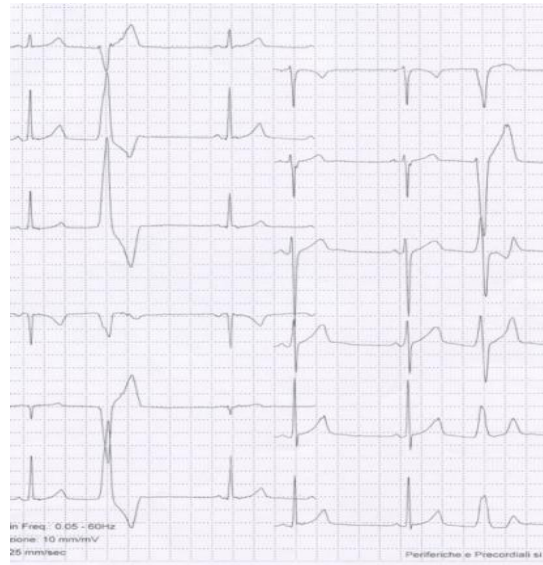
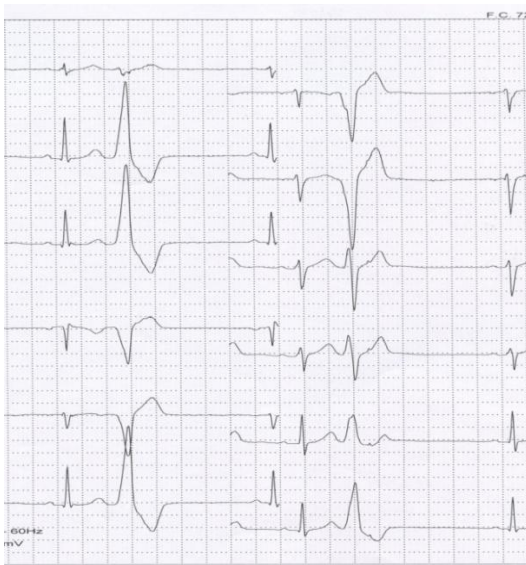
Treatment for acute termination of ventricular tachycardia is administration of adenosine or vagal manoeuvre, while long-term treatment options include medical therapy (b-blockers, sotalol, Ca-blockers, flecainide) if symptomatic (with 25 to 50% rate of efficacy) or radiofrequency ablation (211). Since many of these patients are young and otherwise healthy, radiofrequency ablation is considered to be a particularly attractive alternative to drug therapy. Radiofrequency ablation now has cure rates of 90% and relapse in 5%. Radiofrequency ablation should be considered in the patients with high risk characteristics: 1) history of syncope, 2) very fast ventricular tachyarrhythmias (because ventricular rates >230 beats/min are associated with polymorphic ventricular tachyarrhythmias), 3) extremely frequent PVBs (>20.000 extrasystoles/day) because such degree of ectopy causes cardiac desynchronization and may eventually lead to cardiac dilatation, 4) ventricular ectopy with short coupling interval (because the shorter the coupling interval, the higher the probability for polymorphic arrhythmias), noting that the absence of short coupling intervals is no guarantee against polymorphic RVOT-VT. Occasionally RVOT tachycardia can be associated with tachycardia-induced cardiomyopathy that improves after successful treatment (242, 211).

Interestingly, somatic mutations involving the G-protein signalling cascade could give rise to ventricular tachycardia by disrupting adenosine signalling. Of interest, mutations of the G protein subunit  $\alpha_2$  have been described on myocardial biopsy in only the RVOT and not in myocardium remoter from the site of VT (249).

**Figure:** Receptor schema for activation and inactivation of cAMP mediated triggered activity caused by delayed afterdepolarisations. (b adrenergic receptor stimulation (b-AR) results in the stimulatory G-protein (Gs) releasing its bound GDP and binding GTP. The active Gas-GTP complex then dissociates from Gbc and stimulates adenylyl cyclase (AC), leading to an increase in cAMP and activation of protein kinase A (PKA). This results in an increase of the slow inward calcium current (ICa(L)) as well as an increase in calcium release from the sarcoplasmic reticulum (SR), with consequent activation of a transient inward current (ITI) through the Na+-Ca2+ exchanger (Na-CaX). Adenosine (ADO), by binding to the adenosine A1 receptor (A1R), acts via an inhibitory G-protein Gi. In response to adenosine binding, Gi releases its bound GDP and binds GTP. The active Gai-GTP complex then dissociates from Gbc and inhibits adenylyl cyclase. This leads to a decrease in Ica (L) and SR calcium release with consequent attenuation of (ITI). ACh, acetylcholine; ISO, isoproterenol; M2R, muscarinic cholinergic receptor (249)).

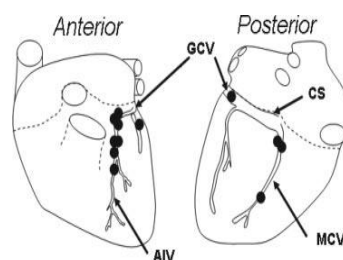


**Figure:** Single PVBs of LBBB with inferior axis (-75 to -105) that origin from the RVOT. The early R/S transition on the last ECG may indicate LVOT arrhythmias.

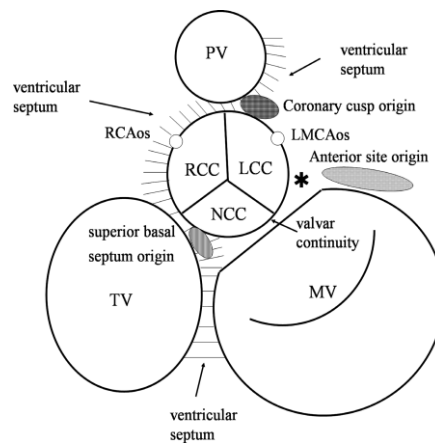


**Left ventricular outflow tract ventricular tachycardia:** The mechanism of left ventricular outflow tract ventricular tachycardia is most likely adenosine-sensitive triggered activity. This ventricular tachycardia can be classified into three subtypes according to the location where catheter ablation is successful: 1) endocardial origin, 2) coronary cusp origin, and 3) epicardial origin. Recognition of the characteristics of the various forms of this group of arrhythmias should facilitate appropriate diagnosis and therapy. Despite similar QRS morphology, idiopathic repetitive monomorphic ventricular tachyarrhythmias of left ventricular outflow tract are known to have the variants of different adjacent origins, including the aorto-mitral continuity, anterior site around the mitral annulus, aortic sinus cusps and epicardium (244). Idiopathic ventricular arrhythmias arising from the aortic root are more common in the left coronary cusp, than in the right and rarely arise from the non coronary cusp. The electrocardiogram is useful for differentiating the site of origin and from right ventricular outflow tract tachycardia (245, 246). Most idiopathic left ventricular tachycardias originate from the left ventricular endocardium, and the responses of these tachycardias to pharmacological agents, programmed electrical stimulation, mapping, and catheter ablation have been defined. An inability to successfully ablate some idiopathic left ventricular tachycardias from the endocardium led to the recognition of epicardial sites of origin, particularly adjacent to the aortic sinus of Valsalva (247). However, occasional examples of epicardial idiopathic left ventricular tachycardias have been reported that arise remote from the aortic root and are not amenable to ablation via the aortic sinus of Valsalva. Although clinically underrecognized, idiopathic ventricular tachycardias may originate from the perivascular sites on the left ventricular epicardium. The mechanism is consistent with triggered activity. It is amenable to ablation by transvenous or transpericardial approaches, although technical challenges remain. Tachycardia arising from the epicardial site of origin are fortunate rare, since their ablation is a much more complex process (211, 247).

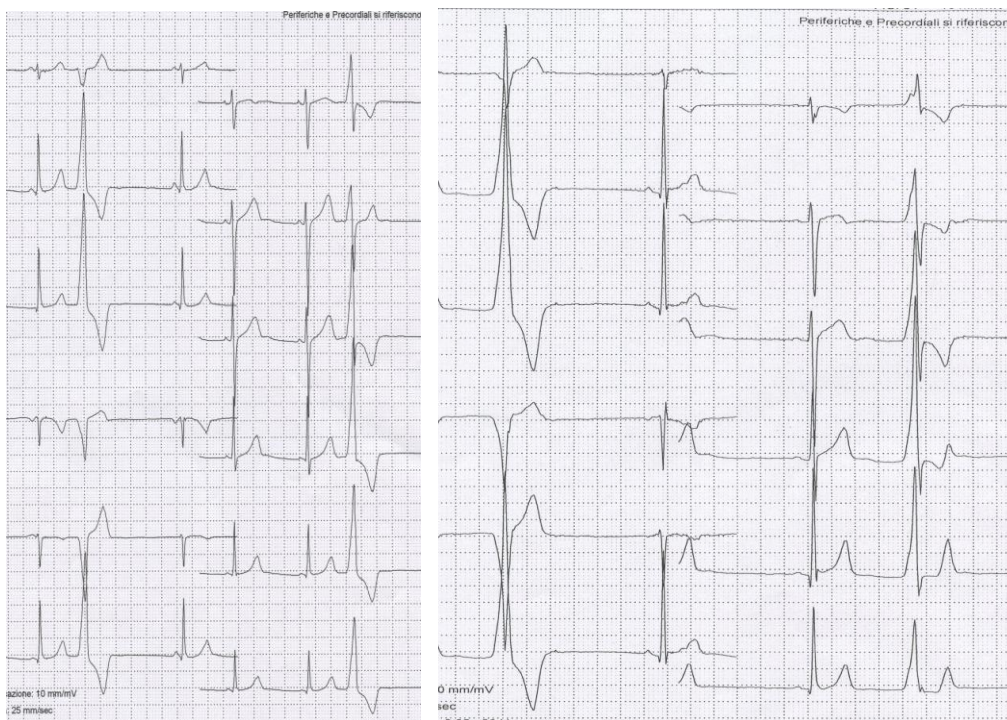
**Figure.** Anterior and posterior surfaces of the left ventricle demonstrating distribution of the sites of origin of epicardial ventricular tachycardia. CS indicates coronary sinus



**Figure.** The sites of origin of the LVOT-VTs are illustrated (This figure is viewed from the base of the ventricles. The asterisk represents the origin of AMC-VTs. LCC = left coronary cusp; RCC = right coronary cusp; NCC = non coronary cusp; AV = aortic valve; MV = mitral valve; TV = tricuspid valve; PV = pulmonary valve; LMCAos = the ostium of the left main coronary artery; RCAos = the ostium of the right coronary artery).



**Figure** PVBs with tall R wave from V1 to V6 and inferior axis deviation (mild RAD), originating from the LVOT.



**Idiopathic left ventricular tachycardia (fascicular ventricular tachycardia).** Idiopathic left ventricular tachycardia has been classified into three subgroups according to mechanism: reentry (verapamil-sensitive), triggered (adenosine-sensitive), and automaticity (propranolol-sensitive) types. Ventricular tachycardia can be categorized also into left fascicular ventricular tachycardia and left outflow tract ventricular tachycardia.



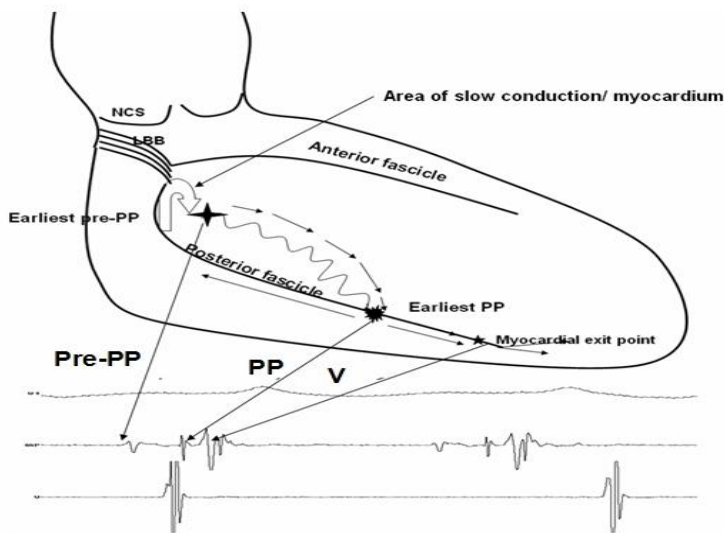
Although the mechanism of fascicular ventricular tachycardia is verapamil-sensitive reentry, the mechanism of left outflow tract ventricular tachycardia is not homogeneous (248-250).

Idiopathic fascicular ventricular tachycardia is an important cardiac arrhythmia with specific electrocardiographic features and therapeutic options. It is characterized by relatively narrow QRS complex and right bundle branch block pattern. The QRS axis depends on which fascicle is involved in the re-entry. Fascicular ventricular tachycardia can be classified into three subtypes: (1) left posterior fascicular ventricular tachycardia with a right bundle branch block (RBBB) and superior axis configuration (common form-90-95%), suggesting an exit site from the inferoposterior ventricular septum; (2) left anterior fascicular ventricular tachycardia with RBBB and right-axis deviation configuration (uncommon form); and (3) upper septal fascicular ventricular tachycardia with a narrow QRS and normal axis configuration (rare form). Posterior and anterior fascicular ventricular tachycardia can be successfully ablated at the mid-septum or at the ventricular tachycardia exit site. Upper septal fascicular ventricular tachycardia also can be ablated. Fascicular ventricular tachycardia is usually seen in individuals without structural heart disease. It is seen in the second to fourth decade of life predominantly in men (60-80%). Response to verapamil is an important feature of fascicular tachycardia (variable with propranolol). Rare instances of termination with intravenous adenosine have also been noted. The proposed diagnostic triade is: 1) induction with atrial pacing 2) RBBB with LAD 3) no evidence of structural heart disease (248-250).

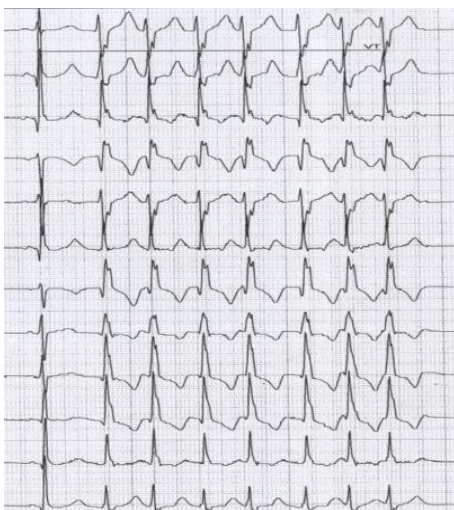
The commonest form of fascicular tachycardia is the posterior fascicular type accounting for nearly 90% of the cases. At present this tachycardia is well characterized, most of the episodes presenting at rest; however it can be triggered by emotional stress or exercise (presenting as exercise-related ventricular tachycardia). It is typically seen in the age group of 15-40 years and predominantly in males (60%-80%). Fascicular ventricular

tachycardia is usually paroxysmal, but it can occasionally be incessant in nature resulting in tachycardiomyopathy. Catheter ablation is the preferred choice of therapy in patients with fascicular ventricular tachycardia and severe symptoms or intolerant or resistant to therapy. The success rate for ablation is more than 80% (85-90%) and complications are infrequent. Patients with moderate symptoms can be treated with oral verapamil (248-250).

**Figure.** Diagrammatic representation of the tachycardia circuit in fascicular ventricular tachycardia (The antegrade limb of the circuit proceeds through the verapamil sensitive zone (curved line) from basal to apical left ventricular septum giving rise to the Pre PP as seen in the accompanying electrogram. The lower turn around site of the reentrant circuit occurs in the lower third of the septum with the capture of the fast conduction Purkinje fibers along the posterior fascicle. From here, antegrade activation occurs down the septum to break through septal myocardium below, and retrograde activation occurs over the posterior fascicle from apical to basal septum forming the retrograde limb of the tachycardia. The reentrant circuit is completed by a zone of slow conduction at the upper turn around point of the circuit located close to the main trunk of the left bundle branch) (250).



**Figure.** A single episode, during the day, of idiopathic fascicular ventricular tachycardia (RBBB with RAD).



**Adrenergic monomorphic ventricular tachycardia.** This form is also referred to as propranolol-sensitive automatic ventricular tachycardia. It is usually seen in young patients (<50 years of age). The clinical and electrophysiological characteristics of this form of ventricular tachycardia have not been well defined. Adrenergic monomorphic ventricular tachycardia can present with either RBBB and/or LBBB morphology on the ECG. Some of these patients present with pleomorphic ventricular tachycardia. This form of ventricular tachycardia is initiated by exercise and catecholamines; it cannot be initiated or terminated with programmed stimulation. It is responsive to beta-blockers (211).

**Figure 12.** RVOT PVBs, also in couplets (LBBB and inferior axis deviation).



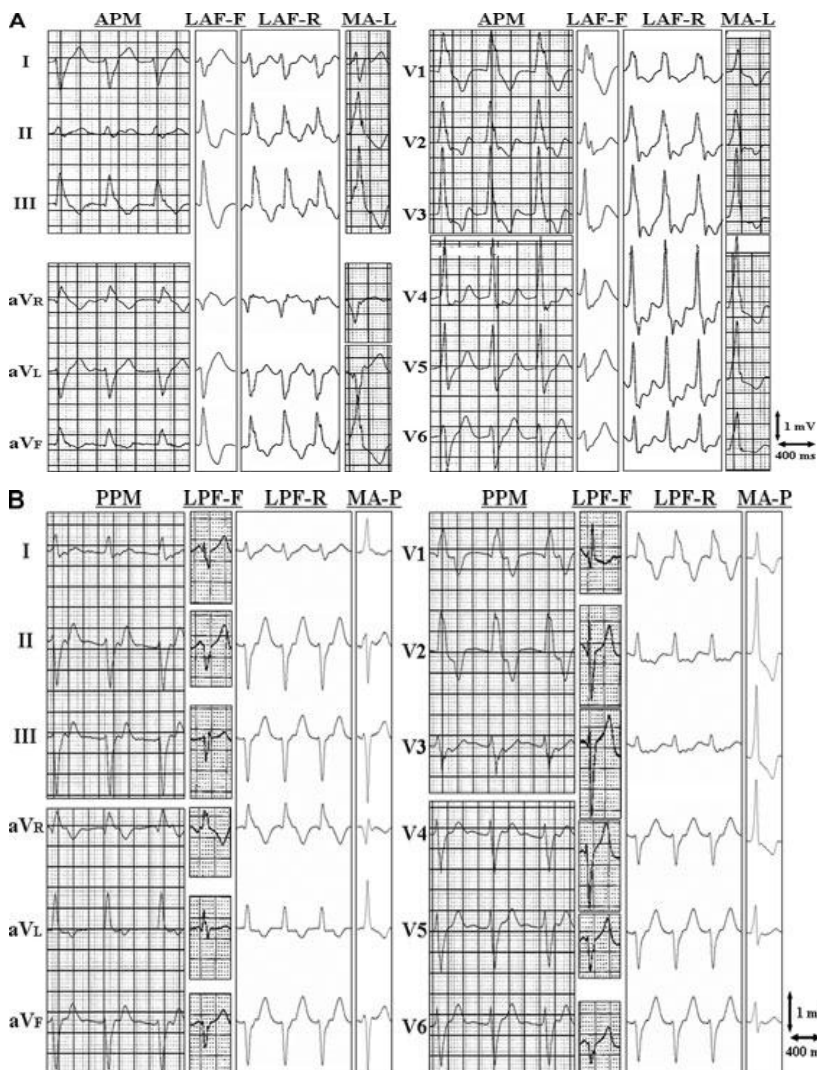
**Annular ventricular tachycardia.** Mitral annular PVBs/ventricular tachycardia is a rare but identifiable subgroup of idiopathic ventricular arrhythmias with distinctive ECG characteristics. Anterolateral and posteroseptal sites are preferential (251). Radiofrequency catheter ablation has been demonstrated effective for eliminating arrhythmias. Advance knowledge of the mitral annular origin of arrhythmias may be useful in planning and facilitating the radiofrequency ablation procedure. Finally tricuspid annular tachycardia has been noted in 7% of the patients presenting with ventricular tachycardia (211).

**Papillary muscle tachycardia.** Newly recognized entities of idiopathic ventricular tachycardias are those originating in the papillary muscles and in the atrioventricular



annular regions. Radiofrequency catheter ablation of idiopathic left ventricular papillary muscles ventricular arrhythmias is challenging probably because the arrhythmias origin is located relatively deep beneath the endocardium of the ventricular papillary muscles. Arrhythmias often exhibit multiple QRS morphologies, which may be caused by a single origin with preferential conduction resulting from the complex structure of the ventricular papillary muscles (252).

**Figure.** Showing the various morphologies from anterior papillary muscle, left anterior fascicle and mitral valve annulus laterally (A) and posterior papillary muscle, left posterior fascicle and mitral annulus posteriorly (B).



#### **4 - CARDIAC EXAMINATION FOR THE STUDY OF ATHLETES' HEART**

Heart disease, arrhythmias and the risk of sudden death are important problem that often have to face the family doctor, sport medicine physician or cardiologist. Primary prevention of sudden cardiac death must be orientated particularly in the high risk groups (athletes, young with symptoms or with family history of sudden cardiac death, relatives of sudden cardiac death victims). The pre-participation screening of athletes has become an important tool. Systemic pre-participation of competitive athletes constitutes an Italian medical programme established by legislation in 1982. Italy is the only country in the world where law mandates every subject engaged to competitive sports activity must undergo a clinical evaluation to obtain eligibility before entering in competitive sports. Pre-participation screening in young athletes can prevent sudden death, progression of disease or other complications and it does not exist in many countries or it exists in an incomplete mode and sudden cardiac death remains a problem. It also enables the so-called cascade screening of relatives once an inherited heart disease has been identified in an athlete, saving additional lives. Imperative becomes the information and education of the persons (athletes, trainers) in the risks that sport may have and the knowledge of the symptoms so that pathologic conditions can be identified before a fatal event.

The divulgation of sports activities in the general population led in scientists to a more intensive study of athletes' heart, the cardiovascular pathologies at risk during exercise and recommendations for exercise and sport cardiology has become a dynamic and in evolution theme. It is very important for the cardiologist to have an expertise in the rare arrhythmic syndromes and a common pathway of evaluation. Simple and non invasive investigations to be considered are medical history, physical examination, 12-lead ECG, signal averaged ECG, exercise stress testing, 2D-echocardiogram, ambulatory ECG Holter monitoring. Other more "complex" exams are the cardiovascular magnetic

resonance, pharmacological challenge tests, electrophysiological studies and endomyocardial biopsy (253). Also, the molecular genetic analysis and the genetic screening now day has become an important tool because certain mutations could be more malignant with different prognosis and treatment and specific triggers may be avoided (exercise for CPVT, specific triggers for the long QT syndrome). Sports activity in silent mutation carriers is still a problem. Non-invasive risk stratification techniques, for identifying patients at high risk of sudden cardiac death are still triggering (254).

Morphologic adaptations of athlete's heart can closely resemble certain cardiovascular diseases and lead to a different diagnosis mostly with hypertrophic cardiomyopathy, dilated cardiomyopathy and arrhythmogenic cardiomyopathy. Clinical distinctions between physiologic athletes' heart and pathologic conditions have critical implications for trained athletes, because cardiovascular abnormalities may trigger disqualification from competitive sports to reduce the risk of sudden death or disease progression. An over-diagnosis may lead to unnecessary restrictions, depriving athletes of the psychological, social, or possibly (in some elite athletes) economic benefits of sports (26).

Clinical dilemmas not infrequently arise when cardiac dimensions fall outside clinically accepted partition values. For example, 2% of highly trained adult male athletes show relatively mild increases in left ventricular wall thickness (13-15 mm) and 15% have left ventricular cavity enlargement  $\geq 60$  mm. Both fall into a borderline and inconclusive "gray zone" for which extreme expressions of benign athlete's heart and mild morphologic forms of cardiomyopathy overlap. Indeed, the two most common clinical scenarios encountered that unavoidably generate ambiguous diagnoses in trained athletes are: 1) differentiating hypertrophic cardiomyopathy from athlete's heart in athletes with an left ventricular wall thickness of 13-15 mm, non-dilated and normally contractile left ventricle, and absence of mitral systolic anterior motion, and 2) differentiating early presentation of dilated

cardiomyopathy from athletes' heart with left ventricular end-diastolic cavity dimension  $\geq 60$  mm with low-normal left ventricular function (i.e. ejection fraction of 50-55%). Such uncertainly are not uncommon and may be resolved in many athletes by a number of independent noninvasive clinical parameters, including the response of cardiac mass to short periods of deconditioning, or assessment of diastolic filling. Clarification of such diagnostic ambiguities may also be achieved with CMR imaging, genotyping, and serial acquisition of clinical and morphologic evidence over time. Finally, LBBB arrhythmias with a mildly dilated right ventricular cavity may have to exclude regional ARVC.

**Family and personal history.** The role of family history is a fundamental tool, because the majority of conditions at risk of sudden death during exercise are genetically determined with autosomal dominant pattern of inheritance (23). Moreover in the sudden arrhythmic death syndrome, familial evaluation identifies inheritable disease in the majority of families (56). Compilation of a detailed family history, covering a minimum of three generations is mandatory (253). Family history is considered positive when close relatives had experienced a premature heart attack or sudden death (<55 years in males and < 65 years in females), or in the presence of a family history of cardiomyopathy, channelopathy, Marfan syndrome, severe arrhythmias, coronary artery disease or disabling cardiovascular diseases. Simply inquiring about sudden deaths is seldom instructive. Construction of a pedigree stimulates patients to recall events and encourages open discussion. The personal history is considered positive in the case of exertional chest pain or discomfort, syncope or near-syncope, irregular heart beat or palpitations, and in the presence of shortness of breath, or fatigue out of proportion to the degree of exertion (23). Prior recognition of a heart murmur and elevated systemic blood pressure must also be asked.

**Physical examination.** Positive findings include physical stigmata of Marfan syndrome (musculoskeletal and ocular features), long QT syndrome features, Naxos syndrome palmoplantar chearatosis or wooly hear, diminished and delayed femoral artery pulses,

mid- or end-systolic clicks, a second heart sound single or widely split and fixed with respiration, marked hearts murmurs (any diastolic and systolic grade >2/6), irregular heart rhythm, and blood pressure >140/90 mmHg (on >1 reading) (23).

**Rest 12-lead Electrocardiogram.** ECG changes in athletes are common and usually reflect structural and electrical remodeling of the heart as an adaptation to regular physical training (athletes' heart). The ECG performed in the competitive athlete may manifest abnormal electrocardiographic findings; these findings may indicate either normal variant syndromes as well as true cardiac pathology. In rare cases, abnormalities of an athletes' ECG may be an expression of an underlying heart disease putting the athlete at risk of sudden cardiac death during sport. It is imperative that ECG abnormalities resulting from intensive physical training and those potentially associated with an increased cardiovascular risk are properly defined. The ECG abnormalities have been divided in common and training related and uncommon and training-unrelated (Table 14). Numerous studies have studied the ECG alteration (257-262)

In cross-sectional analysis, a spectrum of abnormal ECG patterns is present in 40% of trained athletes, occurring 2-fold more commonly in men than women, and particularly in those participating in endurance sports. The frequency with which these ECG patterns occur is highly dependent on the type, intensity and level of training. Abnormal resting ECG findings are more frequent in African-American athletes as compared with Caucasian athletes. Distinctly abnormal and bizarre ECGs intuitively suggestive of cardiac disease are encountered in an important minority of elite athletes (5-15%). The vast majority of such ECGs represent only extreme manifestations of physiological athletes' heart (263). In some cases of bizarre ECG patterns SCN5a and KCN gene mutations were identified (264).

Importantly, markedly abnormal ECGs in young and apparently healthy athletes may represent the initial expression of underlying cardiomyopathies that may not be evident

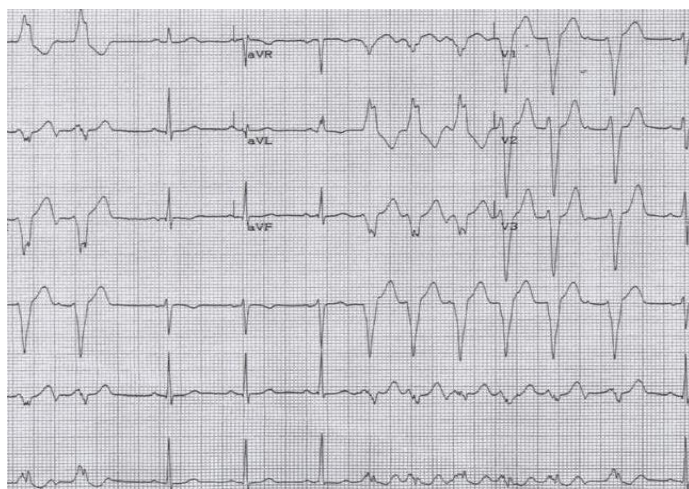
until many years later and that may ultimately be associated with adverse outcomes. Athletes with such ECG patterns merit continue clinical surveillance. When evaluating patients for inherited cardiovascular disease the single most important finding in a resting ECG is abnormal repolarization, which is almost always a sign of cardiovascular disease. The juvenile pattern of T-wave inversion in V1-V3 should not persist beyond childhood. A consensus document in 2005 was published aiming to reinforce the principle of the need for pre-participation medical clearance of all young athletes involved in organized sports programmes, on the basis of: 1) the proven efficacy of systematic screening by 12-lead ECG (in addition to history and physical examination) to identify hypertrophic cardiomyopathy and to prevent athletic field fatalities, 2) the potential screening ability in detecting other lethal cardiovascular diseases presenting with ECG abnormalities (other cardiomyopathies, channelopathies) (23, 265). The consensus document recommends the implementation of a common European screening protocol essentially based on 12-lead ECG. The analysis of data coming from the long-running Italian experience indicates that ECG screening has provided adequate sensitivity and specificity for detection of potentially lethal cardiomyopathy or arrhythmias and has led to substantial reduction of mortality of young competitive athletes by approximately 90%. On the basis of current scientific evidence the implementation of a mass-screening program aimed to prevent athletic-field sudden cardiac death should be at least carefully considered by public health administrators worldwide. Other countries than Italy also suggest ECG inclusion in the preparticipation screening program (266). In the U.S. a large population pre-participation screening that mandates ECG, such that proposed by the European Society of Cardiology and International Olympic Committee, is probably impractical and would require considerable resources that do not currently exist. Such a program might be expected to provoke strong opposition on the issue of cost-effectiveness. The substantial size of athletic population, the relatively low prevalence of cardiovascular disease, the relative low

specificity of the ECG and the absence of a physician-examiner are main problems (267). Interestingly, one retrospective analysis on 134 athletes who died suddenly showed that history and physical examination alone would have identified only 3% of athletes and less than 1% would receive an accurate diagnosis.

**Table 14.** Abnormalities of the athletes electrocardiogram and their frequency.

Common and training-related ECG changes	Corrado (review)	Swiatowiec (73 athletes)	Pellicia (32.652 athletes)	Sofi (30.065 athletes)	Thunenkotter (522 athletes)	Crouse (77 athletes)
Sinus bradycardia	common	75.3%	1%	2.9%		9.1%
First degree AV block	35%	8.2%	7%	0.1%	0.2%	11.7%
Incomplete RBBB	35-50%	71.2%		1.1%	0.4%	? (2.5% IVCD)
Early repolarisation	50-80%	23.3%		0.07%	?	33.8%
Isolated QRS voltage criteria for left ventricular hypertrophy	24% to 80%	19.2%	0.8%	?	0.4% (signs of LVH)	64.5% (LVH)
<b>Uncommon and training-unrelated ECG change</b>						
T-wave inversion	2.3-4.4% postpubertal 1.4%	1.4%	2.3%	0.5%	1.5%	6.5%
ST-segment depression	rare	?	?			
Pathological Q waves	?	?	?	?	?	?
Left atrial enlargement	?	1.4%	?	?	?	48.1%
Left axis deviation/left anterior hemiblock	? / 0.5-1%	2.7% / 2.7%	? / 0.5%	?/0.02%	?	? (2.5%IVCD)
Right axis deviation/left posterior hemiblock	0.6% / ?	12.3% / 9.6%	?	?	?	20.8% / ?
Right ventricular hypertrophy	0.6%,12%in junior	2.7-5.5%	?	?	?	?
Ventricular pre-excitation	0.1-0.3%	0%	0.1%	0.09%	?	1.3%
Complete LBBB or RBBB	0.4%, <1%	0% / 2.7%	0.1% / 1%	? / 1.1%	2.5% / ?	
Long or short QT interval	?	0%	0.003% / ?	?	?	
Brugada-like early repolarization	?	?	0% (?)	?	?	

**Figure.** Ventricular tachycardia on the 12-lead ECG (LBBB with LAD). The athlete had many episodes during the day of non-sustained tachycardia in the absence of an organic heart disease.



**Exercise stress test.** Maximal exercise stress test is an integral component of the cardiac evaluation, primary to unmask arrhythmias in ARVC, HCM, CPVT and long QT syndrome. Frequent PVBs during exercise stress test are a sensitive indicator of underlying cardiac disease and should not be presumed normal in young person. The diagnostic utility of graded exercise testing is questionable in young patients with suspected ARVC, and the absence or suppression of PVBs during exercise should not be considered reassuring in terms of its diagnostic exclusion. Exercise stress test is of limited value in the diagnosis of HCM but has an important role in risk stratification. Unfortunately both baseline and exercise ECGs show relatively poor sensitivity in detecting silent coronary artery disease, whether obstructive or anomalous origin or course. In CPVT exercise stress test is the only method that can identify the arrhythmias. Long QT syndrome may be associated with failure of the QT interval to shorten normally with increasing heart rates in some patients, and persistent shortening during recovery in others. However QT adaptability during exercise is exceptionally difficult to interpret without extensive experience in the area. Finally adrenergic effort-induced arrhythmias may be idiopathic in origin

Among young, asymptomatic adults, a larger absolute number of coronary events will occur among those with an unremarkable exercise stress test than those with abnormal ST-segment changes. This discrepancy is explained by the observation that many acute coronary events result from sudden occlusion of a previously unobstructed segment of the artery, while ST-depression on exercise detects ischemia from pre-existing stenosis. This phenomenon of thrombosis in angiographically normal coronary arteries may be related to vulnerability of a small, non stenotic atherosclerotic plaque and appears more common among smokers.



**Figure.** PVBs of RBBB morphology with LAD in absence of heart disease. Rare effort induced PVBs may appear during exercise stress test, induced by the adrenergic drive.



**Ambulatory ECG monitoring.** It is a method of recording an ECG for long period, generally 24 - 48 hours (the Holter name is in honor of Norman J. Holter an engineer who invented this procedure in 1961). Modern Holter monitors are cassette recorders or digital recorders that usually record 2-3 ECG leads, with some models recording up to 12-leads. In addition to providing a 24 hour ECG recording, almost all systems can also provide information regarding hourly heart rates and counts, hourly rhythm disturbances, hourly and day/night ST-segment deviation trends, and hourly rates of both supraventricular and ventricular ectopic activity. Most systems also provide information regarding heart rate variability. With newer models accurate assessment of ST-segment deviation and QT measurement is allowed. Various parameters have to be evaluated:

1) Heart rate. In subjects who do not participate in a regular exercise program heart rate may range from 35-190 b.p.m, with an overall average rate of about 80 b.p.m. Maximum heart rate usually occurs during late morning and minimum heart rate at 3-5 AM. The heart rate in normal subjects increases not only with physical exercise but also with mental stress. It is well known that the heart rate of trained athletes is slower than that of the general population and during the sleeping hours may be as slow as 24 b.p.m (in endurance athletes). Sinus arrhythmia is also frequent (15-20%) and so are sinus pauses

that last longer than 2 seconds (up to one third of patients), whether at night or during the day.

2) Bradyarrhythmias and conduction disturbances. The various bradyarrhythmias are more common in trained athletes. Marked sinus bradycardia is common on healthy subjects, particularly during sleep hours. Moderate and asymptomatic sinus bradycardia (40-50 b.p.m.) is the most common disorder in sport practitioners. It is due to neurovegetative changes related to training (parasympathetic predominance) and its prevalence is especially remarkable in high-level aerobic resistance sports occurring up to 50-100%. Severe bradycardia (<35-40 b.p.m.) is rare, although it can be present in older sport practitioners (>40 years) and preferably at nighttime. An extreme example is the winner of Tour de France in 1993 with a heart rate at rest of 22 b.p.m. Sinus bradycardia is considered benign if the patient remains asymptomatic and a normal increase in heart rate is observed during exercise. The bradycardia is often associated with transient atrioventricular junctional escape rhythm (observed in 4-22% of healthy subjects). When the baseline heart rate is low, it is possible to find competing nodal rhythm (0.5-2.5%) or an ectopic atrial rhythm (13.5%-69%). Again these findings are not worrying if normal sinus rhythm appears during exercise. Brief periods of sinus pauses or sinoatrial block are seen in 28-34%. First- and second-degree AV blocks with Wenchebach phenomenon may be seen (1-12% and 3-6% of normal subjects, respectively). They are seen mostly in young individuals and during sleep. The prevalence of first degree AV block increases to 27.5-40%, while type I second degree AV block can be present in 10-22% of athletes. Both are secondary to parasympathetic hypertony, and are especially common among high aerobic resistance athletes. Both are benign conditions and must disappear during exercise or hyperventilation. More severe AV conduction disturbances are rare. Episodes of Mobitz type II second degree block and less frequently third-degree AV block may be present in some high level athletes at night, but if present during the daytime, structural

heart disease or other conditions should be ruled out, especially if this disorder does not disappear during exercise.

3) Tachyarrhythmias. Isolated asymptomatic PSVBs may be observed in up to 64% of healthy young subjects. Usually fewer than 2% have >100 PSVBs/24 hour. Short episodes of atrial tachycardia, usually lasting not more than a few seconds, are occasionally seen in otherwise healthy subjects. A prevalence of 2-5% was reported in young adults. It is the most common ectopic tachycardia seen on ambulatory ECG. The supraventricular tachycardia such as AV nodal reentrant tachycardia, AV reciprocating tachycardia and atrial tachycardia are not common in athletes.

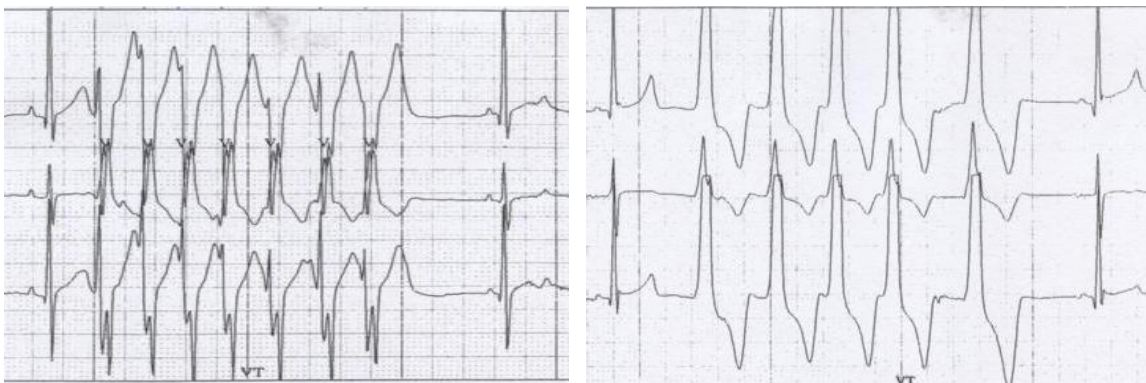
Atrial fibrillation is the most frequent cause of prolonged palpitations in young competitive athletes, even including those performing elite sport activity. There are limited data that atrial fibrillation may be more common in athletes. Competitive sport has a significant impact on the autonomic nervous system. In fact, long-term regular intense physical training determines an increase in vagal tone leading to resting bradycardia (affecting atrial refractory period). In fact atrial fibrillation typically initiates during sleep. During physical activity, particularly in the setting of competition, a marked release of catecholamines occurs as a result of both the intense physical effort and emotional stress. Both of these adaptive phenomena may precipitate atrial fibrillation. Increases in left atrial dimensions seen in athletes and subsequent increase in atrial wall strain/stretch may also play a role. Structural atrial changes such as dilatation and fibrosis are probably present. Furthermore, in several athletes with atrial fibrillation an association with sick sinus syndrome has been found, even though the pathophysiological basis of this finding is not clear. Endurance sport practice increases between 2-10 times the probability of suffering atrial fibrillation, after adjusting for other risk factors.

The prevalence of PVBs in otherwise healthy adults ranges most commonly from 40-55%. As a rule, the total number of PVBs in healthy young adults is small (<100/24 hours).

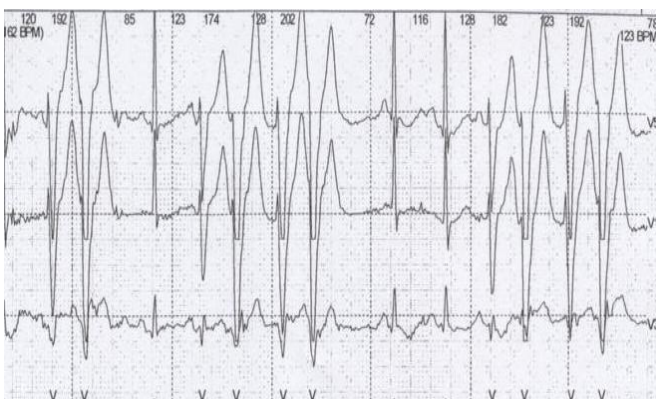
Complex PVBs are present in 7-22% of subjects. PVBs may appear or increase in healthy individuals with physical or non physical stress. Nonsustained ventricular tachycardia is uncommon. It is usually asymptomatic with a mean rate of 150 b.p.m. In athletes however 24 hour ambulatory ECG has shown a higher prevalence of PVBs (70%) and frequent and/or complex forms (25-63%).

Lown and Graboys proposed a grading system evaluating the presence or absence of PVBs, the number of PVBs (occasional<30 /1h, frequent>30/1h), the presence or absence of more than one site of origin (multiform), repetitivity (couplets, or salvos of 3 or more), the coupling interval and eventual R-on-T phenomenon. Other characteristics that must be studied are the distribution during the day and the response to effort or increased heart rate.

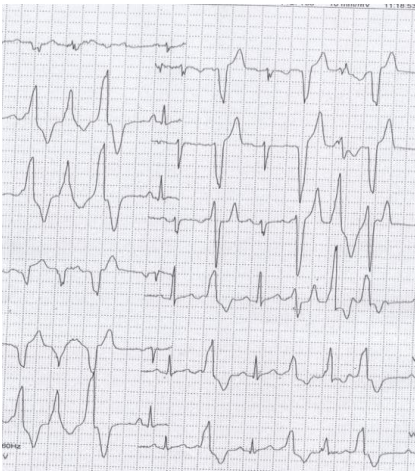
**Figure.** Fast and slow ventricular monomorphic tachycardia in 2 different athletes in 3-lead ECG Holter monitoring. In this cases description of PVBs morphology is difficult.



**Figure.** Repetitive runs of ventricular tachycardia (a not frequent event).



**Figure.** A short run of polymorphic ventricular tachycardia (alternating LBBB and RBBB with inferior axis) in an athlete with single LBBB PVBs during exercise test.



4) QTc interval measurements, ST-T segment changes or appearance of J-waves. As during the graded exercise test, horizontal or downsloping ST-segment depression may be a falsely positive finding.

5) Efficacy of drug therapy. Readings are obtained before and after institution of therapy. Suppression of episodes of ventricular tachycardia or a significant reduction in PVBs is considered to indicate efficacy of the drug. The frequency of PVBs varies widely from hour to hour and from day to day. The spontaneous variation is even greater when the ambulatory ECG is repeated at weekly or longer intervals. Such fluctuations in frequency have led to difficulty in deciding whether an observed reduction in ectopic activity is due to a drug effect or to spontaneous variations. It has been proposed that if a 24-hours Holter monitoring ECG is obtained before and another 1-2 weeks after therapy begins a reduction by more than 85% of the total number of PVBs is necessary before the changes can be attributed to a drug effect.

Finally, symptoms (as palpitations, dizziness, syncope, chest pain) in relationship with rhythm or ST changes must be studied; arrhythmic mechanism may be evaluated and other studies for specific conditions may be done.

Interestingly, several investigators have reported patients who had cardiac arrest or sudden death during Holter monitoring. The terminal event at the time of cardiac arrest

was ventricular tachyarrhythmia in most cases (about 80%) (ventricular tachycardia or flutter, torsade de pointes and ventricular fibrillation). Ventricular fibrillation was always preceded by ventricular tachycardia or ventricular flutter. In patients with cardiac arrest due to bradyarrhythmia, the mechanism is mostly sinus arrest with some cases of complete AV block. In patients who sustained ventricular fibrillation, there is usually increased frequency of PVBs during the hour before the event. The PVBs initiating ventricular tachycardia that degenerates into ventricular fibrillation do not display the R-on-T phenomenon in most instances.

**2D-Echocardiography, M-mode and Doppler study.** Echocardiography in athletes differs in some characteristic aspects respect to the echocardiography in a normal subject. These differences have been observed only or almost exclusively in highly trained athletes in resistance or mixed sports. The knowledge of these modifications is necessary to avoid to attribute a pathologic significance and correctly achieve a different diagnosis with the organic pathologies that present with similar characteristics (24). Such diagnostic testing requires interpretation by physicians trained in echocardiography, but cannot guarantee full recognition of all relevant lesions, and some important diseases may escape detection despite expert screening methodology (24).

Training induces some evidence of cardiac remodeling; it is not possible to clearly separate the endurance sports effects from that of strength, but generally dilatation prevails to endurance sports, while increase of wall thickness prevails to strength sports (24). In a study the left ventricular end-diastolic dimensions ranged from 40-66 mm (mean 52 mm) and exceeded the normal value for a nonathletic population ( $\leq 54$  mm) in 38% including 4% in whom dimension was  $\geq 60$  mm. In another study, according to an arbitrary clinical cut-point value of 60 mm, the left ventricular size was substantially enlarged in 14% with a global left ventricular systolic function within normal limits and without regional wall motion abnormalities. Only 1.6 % of those athletes had an increased wall thickness ( $\geq 13$

mm) (30-31). In another study 1.7% of elite athletes had wall thickness  $\geq 13$  mm (from the 16 athletes 15 were rowers or canoeists and 1 was a cyclist). The thickest left ventricular wall among them was 16 mm. Thus a ventricular wall thickness of  $\geq 13$  mm is very uncommon in highly trained athletes, while athletes with a wall thickness of  $\geq 16$  mm and a non dilated left ventricular cavity are likely to have a pathologic hypertrophy, such as hypertrophic cardiomyopathy. Black athletes develop a greater magnitude of left ventricular hypertrophy compared with white athletes; therefore, extrapolation of conclusions derived from white athletes has the potential of generating false-positive diagnoses of HCM in black athletes (270).

Also the right ventricle presents morphological adaptations due to endurance exercise and not strength athletes. Modifications are represented mainly by an increase in the mean transversal ventricular diameter. The ventricle becomes globular with an increase of the dimensions of the influx and apical region that contributes to evidence better the trabeculation and moderator band (24, 35, 36).

Left atrial remodeling is an additional physiological adaptation frequently present in highly trained athletes; most commonly in those with combined static and dynamic sports (cycling, rowing), and is largely explained by associated left ventricular cavity enlargement and volume overload. Increased transverse left atrial dimensions ( $\geq 40$  mm) are present in 20% of athletes and more substantially enlarged dimensions ( $\geq 45$  mm) are evident in 2%. These later dimensions overlap with those observed in patients with cardiac disease. Nonetheless, left atrial enlargement in athletes appears to be benign and largely confined to training in endurance sports, and is only rarely associated with atrial fibrillation (<1% of cases) (34).

2-D echocardiography is the principal diagnostic modality for clinical identification of HCM by demonstrating otherwise unexplained and usually asymmetric left ventricular wall thickening. In this regard, a maximal left ventricular end-diastolic wall thickness of 15 mm



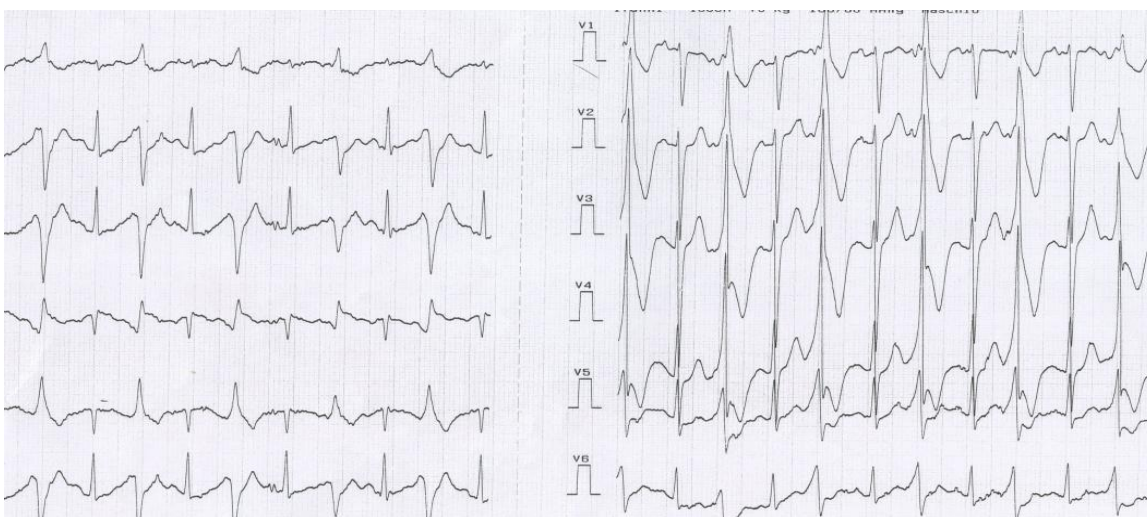
or more (or on occasion, 13 or 14 mm) is the absolute dimension generally accepted for the clinical diagnosis of HCM in an adult athlete. However, any left ventricular wall thickness (including normal) is teorically compatible with the presence of a mutant HCM gene. Annual echocardiography is recommended during all adolescence and beyond in family members.

Echocardiography is would also be expected to detect and define other specific and relevant congenital structural abnormalities associated with sudden death or disease progression in young athletes such as valve heart disease (mitral valve prolapse and aortic valve stenosis), aortic root dilatation and mitral valve prolapse in Marfan syndrome, and left ventricular dysfunction and/or enlargement (myocarditis and dilated cardiomyopathy) (26).

Finally, frequent PVCs can induce subtle cardiac dysfunction detected by speckle tracking imaging analysis in patients without apparent cardiomyopathy. Radiofrequency ablation can successfully eliminate PVCs and improve cardiac function (271).

Other echocardiographic techniques may be also indicated (esophageal or stress echocardiography)

**Figure.** Effort induced PVBs. The echocardiogram showed a mitral valve prolapse. In this case PVBs may be secondary to the prolapse of the valve because they have a RBBB morphology and LAD.





**Signal averaged ECG.** The main purpose of the SAECG is detection of signals of microvolt amplitude. This requires reduction of noise, the principal source of which is skeletal muscle.

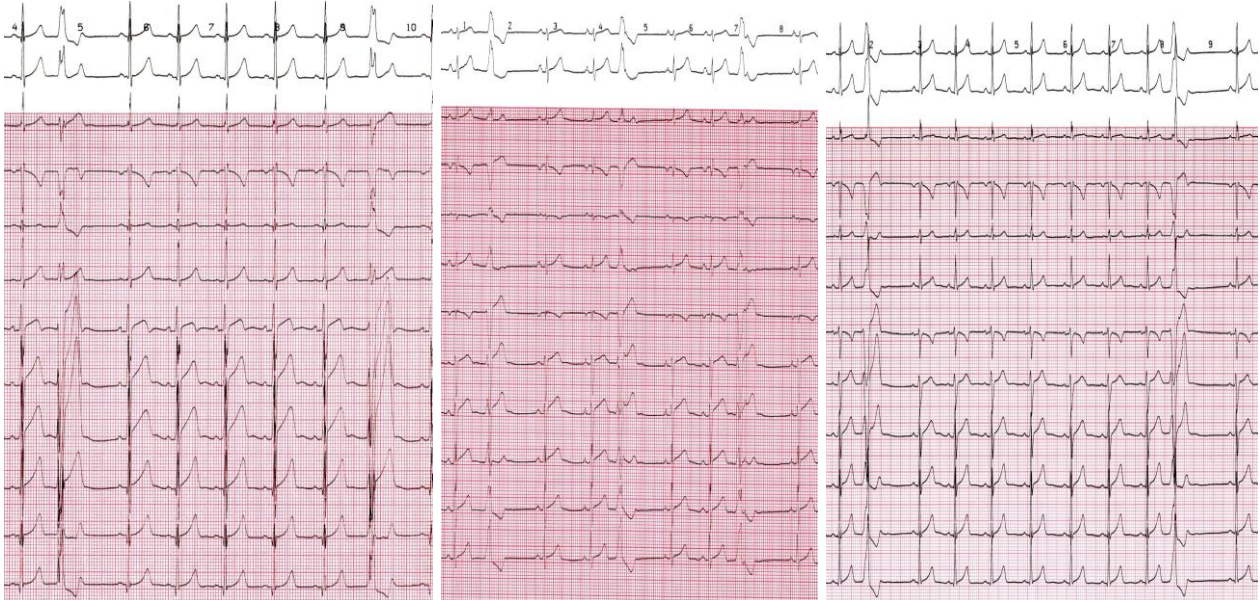
Continuous anaerobic exercise may induce abnormal SAECGs through the development of delayed myocardial conduction or electrical inhomogeneity in cardiac tissue. The presence of an abnormal SAECG is unrelated to the development of arrhythmias in young athletes. In only one study, ventricular late potentials were present in a selected population of top-level athletes with frequent and complex ventricular arrhythmias and without overt heart disease and it is correlated to a non-sustained ventricular response during an electrophysiological study. The presence of late potentials is not influenced by left ventricular mass, even if extreme.

The application of SAECG is often carried out in the study of the right ventricle in the suspect of ARVC. SAECG variably showed the presence of late potentials in patients with ARVC, highlighting the altered ventricular conduction. They can therefore be useful in detecting the underlying morphologic myocardial damage and monitoring disease progression and related degree of electrical instability.

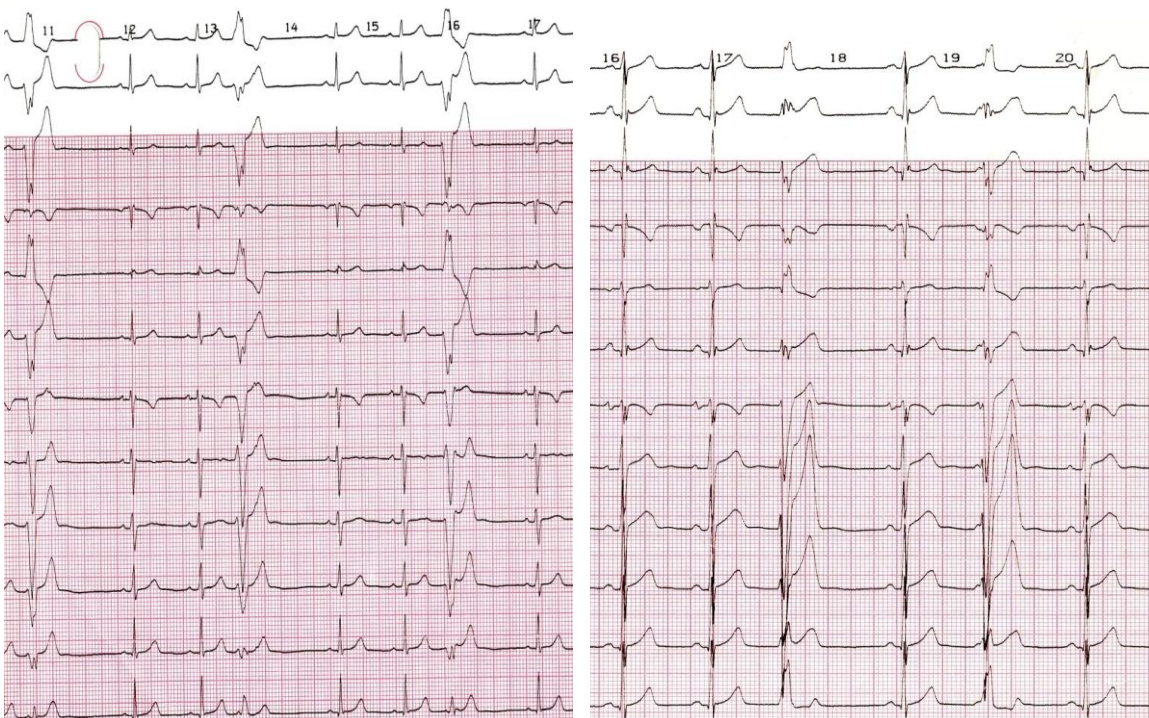
Late potentials were also shown to be useful in identifying high risk patients in Brugada syndrome and thus in risk stratification. Importantly the RMS40 parameter may predict the history of life threatening events and the recurrence of ventricular fibrillation (272, 273).

**Figure.** In cases of PVBs of LBBB morphology with different axis deviation, SAECG is done to exclude the presence of late potentials not evident on the basal ECG.

PVBs of LBBB morphology with intermediate axis ( $15^{\circ}$  to  $60^{\circ}$ ) that origin from the posterolateral wall of the right ventricle.



**Figure.** PVBs with LBBB and LAD ( $-45^{\circ}$ ,  $-30^{\circ}$ ) origin from the right apex



## **Cardiac magnetic resonance (CMR) and multidetector computed tomography (CT).**

Advanced cardiac imaging, using cardiac magnetic resonance imaging and multidetector computed tomography is increasingly used in the work-up of athletes with suspected abnormalities on screening. Both imaging modalities produce highly accurate and reproducible structural and functional cardiac information. CMR has the advantage of imaging without radiation exposure or the use of iodine-containing contrast agents, but is sometimes not possible due to claustrophobia or other contraindications. Although cardiac CMR can rule out coronary artery anomalies (often indicated when are suspected but could not be excluded on transthoracic echocardiography), multidetector CT is superior to cardiac CMR for visualizing the full extent of the coronary arteries and atherosclerotic coronary artery disease. For patients less than 35 years of age, cardiac CMR is the first option after initial echocardiography for further assessment of cardiomyopathies, myocarditis and coronary anomalies, which are major causes of sudden cardiac death in young athletes. CMR in particular offers both accurate delineation of the morphological abnormalities associated with these and other conditions and the possibility for risk stratification for development of ventricular arrhythmias with demonstration of macroscopic scar by delayed enhancement imaging with intravenous gadolinium (273). For athletes over 35 years of age the most common cause of sudden cardiac death is coronary artery disease, whereby cardiovascular screening requires further diagnostic modalities and may include multidetector CT(274 ,275).

In 2010 an Expert consensus document on cardiovascular magnetic resonance was published where the most important applications are described. Coronary artery disease, ischemic heart disease and infarction, non-ischemic cardiomyopathies, congenital heart disease, valvular heart disease, cardiac masses and pericardial heart diseases, artery disease are some of the most frequent applications (276).

Interestingly areas showing late gadolinium enhancement correspond to zones of myocyte

necrosis or myocardial fibrosis as shown by comparison with histopathology. Typical patterns of hyperenhancement exist in ischemic heart disease but also in dilated cardiomyopathy, hypertrophic cardiomyopathy and other inflammatory or infiltrative myocardial disease. Late gadolinium enhancement is helpful to distinguish advanced ischemic heart disease from nonischemic dilated cardiomyopathy. Late gadolinium enhancement may also become useful to predict malignant arrhythmias in patients with ischemic heart disease or nonischemic cardiomyopathy. This may lead in the near future to an increased role of late gadolinium enhancement LGE as a prognostic tool (277).

Cardiac magnetic resonance imaging is also used in subjects with idiopathic arrhythmias. In patients with idiopathic right ventricular outflow tract PVBs revealed that there was a higher rate of morphological and functional abnormalities of the right ventricular outflow tract than in the normal subjects. Large studies and long follow-up are needed to confirm whether these findings could help identify a localized form of arrhythmogenic cardiomyopathy, and its clinical significance (278).

Also in patients with Brugada syndrome, the findings of subtle structural changes, such as right ventricular outflow tract dilation may support the view and point to a localized arrhythmogenic substrate (127).

In athletes cardiac magnetic resonance is largely used. Cardiac magnetic resonance imaging measurements enable studying the mechanisms of left and right ventricle adaptation in athletes, which reflect the ventricular response to combined endurance and strength based training (279). Cardiac MRI reference values show increased ventricular volumes, diameters, wall mass, and wall thickness for endurance athletes compared with nonathletes. High training (hours/week) and male sex result in an increased overlap with standard thresholds for cardiomyopathy (280). MRI is often used in differentiating athletes' heart from a suspected cardiomyopathy.



**Figure.** Athlete with the presence of an akinetic area of RV apex (confirmed with cardiac magnetic resonance 2 times) presented a single episode of polymorphic ventricular tachycardia in the ECG-Holter monitoring.



### **Invasive investigations and endomyocardial biopsy.**

Cardiac catheterization with EMB is often necessary for the diagnosis of suspected myocarditis and primary cardiomyopathies (dilated cardiomyopathy or ARVC). EMB may be necessary in complex idiopathic ventricular arrhythmias in the absence of a certain pathologic entity with the non-invasive techniques or in the suspect of an initial form of ARVC. Coronary arteriography is done usually for the diagnosis or exclusion of coronary artery disease, anomalous origin of a coronary artery and myocardial bridge.

Electrophysiologic studies, pharmacologic tests and ablations. The majority of electrophysiologic studies and ablation done in athletes is due to the finding of: 1) supraventricular arrhythmias (prevalently WPW syndrome, atrioventricular re-entry on AV node), 2) ventricular non sustained or sustained tachycardia (generally from the right outflow tract of the right ventricle), 3) syncope not explained by other exams. Electrophysiologic studies are necessary to find the ablation point of origin in some PVBs. Finally, the CARTO study may be necessary for the diagnosis of ARVC or differential diagnosis between RVOT tachycardia and ARVC (236). Electrophysiologic studies are also done in some channelopathies for risk stratification (Brugada syndrome, short QT syndrome).

Other examinations may be useful (nuclear cardiology-SPECT, tilt test) in the study of

athletes' heart but are not going to be explained.

**Genetic screening.** With the identification of mutations in the cardiomyopathies optimism had grown for affordable, rapid, sensitive, and specific genetic testing. For modest costs and less than 10 ml blood, patients on their physicians can now test directly for the sarcomeric gene mutations in HCM (67). With the simplification of the genetic techniques, molecular genetics should be introduced in medical practice as the measurement of the blood pressure or the values of cholesterol and hemoglobin.

The gene identification first of all led to the understanding of the pathogenesis of the disease. We do know that hypertrophic cardiomyopathy is a sarcomeric disease (force generation), that arrhythmogenic right ventricular cardiomyopathy is predominantly a cell-junction disease and that dilated cardiomyopathy is a prevalently cytoskeleton disease (force transmission) (78). The identification and study of the genetic substrate of these diseases are relevant because they help to understand the function of different proteins in humans. So, genetic testing is nowadays applied not only as for diagnostic purposes, but also as a research tool for the study of the pathophysiology of the inherited diseases (68). In addition to the interest underlying this disease, genetics contributed also to the reclassification of the cardiomyopathies based on genetic or nongenetic etiologies (69).

Molecular genetics have also ameliorated the medical assistance for various reasons. The availability of molecular testing for mutation screening of disease genes offers the possibility to identify genetically affected individuals. The clinical/commercial genotyping for diagnosis is important for identifying patients with reduced penetrance of the phenotype since effective strategies and therapies to prevent sudden death do exist. Genetic screening is valuable in evaluating of the families of index patients known to have a disease. If the proband mutation is identified, the rest family can be definitively and rapidly screened at much lower cost, the so called "cascade screening" (67). The identification of the gene mutation could also confirm the diagnosis in uncertain cases, as the different

diagnosis between right ventricular outflow tachycardia and ARVC, and thus it becomes an important diagnostic tool.

The identification of “healthy” or “silent” gene-carriers, pre-asymptomatic could have at least two practical implications: 1) they are more susceptible than age-matched population to develop cardiac arrhythmias and 2) they have 50% probability of transmitting the disease to their off-spring. The inherited risk of developing the clinical phenotype and thus the disease can lead to important medical decisions. This individuals could be potential patients and this leads to education of the subject, prevention strategies (reducing exercise, avoiding certain drugs, keeping more attention in fever states) and close follow-up. The consideration of preventive therapy should only be considered in selected cases/disease and the risk of over-treatment should be in mind. In the CPVT, b-blockers are often used even in silent carriers because of the highly malignant phenotype. Healthy gene carriers could be discriminated as having the disease-gene (from work, sports etc.), but the positive effects are far more important.

The absence of a gene mutation is also important for the non-carriers that will constitute approximately 50% of those tested. Healthy individuals are afforded in a lifetime reassurance and they can be excluded from the follow-up study, have a normal life, with no risk to transmit the disease. Thus they allow clinical resources to be targeted to proven gene-carriers (93)

The role of mutations analysis in the assessment of prognosis is still unclear. The first obstacle is that all cardiomyopathy mutations are individually rare and many families will turn out to have a “private mutation” not previously described (67). Risk stratification based on the mutations (benign or malign) is in certain diseases feasible in other ongoing. Only in some cases, we can personalize the medical assistance based on the genotype and some gene mutations can influence therapeutic options (pharmacological or other). The LQT1 syndrome is an example where the “genotype-specific therapy” is possible. There is a high

risk of exercise induced malignant arrhythmias and b-blockers are known to work well, strict exercise restriction, in particular swimming or diving, is required, especially for males (281). Genotype-phenotype assessments of large cohorts could lead to the better understanding of the natural history disease. Further investigations of the genotype-phenotype correlations are required. Clinical genotyping for therapeutic advantage has limited application at present but will become more important if and when genotype-mutation type specific therapies are shown to be effective. The recommendations will progressively change as new research findings and new genotyping technologies appear. Finally, systematic investigation of the modifier genes and environmental influences will be pivotal to the understanding of the clinical diversity in the genetically determined arrhythmogenic diseases, refining prognostication, and developing targeted therapies. So the identification of the causative gene mutations is helpful not only for research purposes, but can ameliorate the prognosis of the disease and the quality of life of the patient. Genetic counseling could also be done in the persons that want to have children, discussing the probability of having a children carrier and their feature.



## **5. AIM of the study**

The main goal was the study of the heart and the assessment of heart diseases, either organic or functional, with non-invasive cardiac examinations, in young athletes discovered to have ventricular arrhythmias during the preparticipation screening program.

## 6. MATERIAL and METHODS

A total of 145 young competitive athletes (<35 years) (mean age  $17.3\pm 5.3$  years, M/F=106/39=2.7), were studied evaluated in the laboratory “Genetica clinica e molecolare delle cardiomiopatie” of the department of Cardiology of Padua University from the years 2007 to 2010. All subjects were referred to our laboratory due to ventricular arrhythmias detected during preparticipations screening, PVBs on the 12 lead-ECG or during exercise stress test and ECG-Holter monitoring. When available, follow-up was also reported.

**Study protocol.** The study protocol included:

- Family and personal history
- 12-lead basal ECG
- Echocardiography-Doppler
- ECG-Holter monitoring
- Exercise stress test
- Signal averaged ECG
- Cardiac magnetic resonance
- Other Exams if needed (electrophysiological study and genetic test)

**12-lead ECG.** ECG was evaluated using digital calibres on a standard speed paper (25 mm/sec). Moreover a long-length ECG, thus to evaluate PVBs morphology and coupling interval at rest was performed. The following ECG parameters were considered: 1) type of rhythm (heart rate, sinus bradycardia, ectopic rhythms), 2) electrical axis of the QRS complex in the frontal plane (normal between  $-30^\circ$  and  $+100^\circ$ ) and electrical axis deviation, 3) P wave abnormalities: a) right atrial abnormality determined by a tall, peaking P wave in lead II and/or an increased positive portion of the P wave in lead V1 and right axis

deviation, b) left atrial abnormality determined by a prolonged duration or a prominent notching in II lead and/or an increased depth of the terminal negative portion of the P wave in lead V1 and left axis deviation, 4) duration of the PQ interval (normal 120 to 200 ms) and first degree AV block, 5) incomplete right bundle branch block (duration <120 ms, presence of a secondary R wave in V1 or a S wave, notched with a prolonged duration in V1 or a S1-S2-S3 aspect with a secondary R wave in aVR lead), 6) presence of a complete RBBB (QRS duration  $\geq$ 120 ms with notched R waves in V1/V2 and wide deep S waves in V5/V6), 7) left ventricular conduction delays defined as: left anterior fascicular block (rS pattern in the inferior leads and qR pattern in aVL with a front plane mean QRS axis between  $-45^\circ$  and  $-90^\circ$  and QRS duration <120 ms); left posterior fascicular block (Rs pattern in I, aVL and qR pattern in the inferior leads with a frontal plane mean QRS axis  $>120^\circ$  and QRS duration <120 ms); complete left bundle branch block (deep S waves in V1/V2 with small or absent initial r waves and a broad notched R wave in V5/V6 and usually in I/aVL with absent Q waves and QRS duration  $\geq$ 120 ms), 8) nonspecific inter-ventricular conduction delay (IVCD) with QRS duration  $\geq$ 120 ms without meeting the RBBB or left bundle branch block criteria, 9) ST-segment elevation (defined as the maximal displacement of ST-segment  $\geq$ 0.1 mV from the isoelectric line), early repolarisation or Brugada type ECGs, 9) Sokolow Lyon criteria for right and left ventricular hypertrophy 10) presence of pathological Q waves (Q wave duration  $\geq$ 40 ms and amplitude  $\geq$ 2/3 of the QRS complex), 11) corrected QT interval (calculated with the Bazett formula), 12) early repolarization pattern, 13) T-wave inversions in the precordial and inferior leads, considering pathological T wave inversion beyond V1. Other aspects as R-wave progression through V1-V3, R/S wave ratio in V1 and V2, qrs duration, voltage amplitude in the precordial leads.

ECG abnormalities were divided in common-physiological and uncommon-pathological (256).

**Table.** Classification of abnormalities of the athletes ECG (Corrado et al BJSM 2009)

Common and training-related ECG changes	Uncommon and training-unrelated ECG changes
<ul style="list-style-type: none"><li>▶ Sinus bradycardia</li><li>▶ First degree AV block</li><li>▶ Incomplete RBBB</li><li>▶ Early repolarisation</li><li>▶ Isolated QRS voltage criteria for left ventricular hypertrophy</li></ul>	<ul style="list-style-type: none"><li>▶ T-wave inversion</li><li>▶ ST-segment depression</li><li>▶ Pathological Q waves</li><li>▶ Left atrial enlargement</li><li>▶ Left axis deviation/left anterior hemiblock</li><li>▶ Right axis deviation/left posterior hemiblock</li><li>▶ Right ventricular hypertrophy</li><li>▶ Ventricular pre-excitation</li><li>▶ Complete LBBB or RBBB</li><li>▶ Long or short QT interval</li><li>▶ Brugada-like early repolarisation</li></ul>

Normal ECG was considered when characterized by sinus rhythm with an electrical axis not abnormally deviated, normal P waves and PQ interval, normal QRS voltages and duration, absence of pathological Q and epsilon waves, with the presence of a normal or inverted T wave only in V1 lead, absence of a significant ST-segment elevation.

The early repolarization pattern was defined as J point and ST-segment elevation of 1 mV or presence of J waves.

**SAECG study.** SAECG was performed using a MAC15 system (Marquette Inc., Milwaukee, IL, USA). The graphic representation of late potentials and the numeric parameters were visually look out. The patients with complete RBBB were excluded from the study. The skin was cleaned with ethanol. The electrodes of the X lead were insert in the al the level of the middle axillar line in the level of the V5 lead at the left (+) and right (-). The electrodes of the Y lead were put in the superior part of the sternum (-) and inferior part (+). The electrodes of the Z lead were inserted in the 5th intercostal space, at the left border of the sternum (+) and in the same position in the posterior part of the chest. The signals were analyzed in the time domain. Time domain amplifies the QRS vector, obtained by the mean square root of the signals obtained by the standard orthogonal leads X, Y, Z, which are digitally filtered. The filtered QRS is the Vector magnitude of the lead X, Y, Z. The time domain analyses is obtained in every patient by 3 different filters, 25-250,

40-250, 80-250 Hertz. For the 80 Hz filter, RMS is automatically calculated in the last 20 msec of the filtered QRS. The medium number of beats analyzed varies from, 250 to 400 in order to obtain a noise level  $<0.7 \mu\text{V}$ .

The following parameters for each filter were evaluated: filtered QRS duration (fQRSD), high frequency low amplitude signals duration in the terminal portion of the filtered QRS with a voltage amplitude  $<40 \mu\text{V}$  (or  $<20 \mu\text{V}$  only for the 80-250 Hz filter) (HFLA), root mean square of the voltage in the last 40 ms of the filtered QRS (RMS). The normal values were established in a population of 146 healthy subjects: for the 25-250 Hz filter: fQRSD $<120$  ms, HFLA $<40$  ms, RMS $>25 \mu\text{V}$ , for the 40-250 Hz filter: fQRSD $<118$  ms, HFLA $<40$  ms, RMS $>20 \mu\text{V}$  and for the 80-250 Hz filter: fQRS $<106$  ms, HFLA $<34$  ms, RMS $>12 \mu\text{V}$ . The SAECG was considered positive when at least two parameters were abnormal in one filter.

**Echocardiographic study.** The echocardiogram was done with a 2.5 MHz transducer (Hewlett Packard model 5500) and included M-Mode, two-dimensional and Doppler examinations. Parasternal, apical and subcostal views were performed and the presence of wall motion abnormalities was carefully analysed. Left ventricle end-diastolic volume was calculated using an ellipsoid biplane area-length model derived from the left ventricle images in the apical four-chamber view. The left ventricle ejection fraction was calculated using the formula: end-diastolic volume minus end-systolic volume divided by end-diastolic volume. Left telediastolic diameter was calculated in the parasternal long axis view using M-Mode.

Right ventricle end-diastolic and end-systolic volumes were calculated using an area-length method derived from orthogonal planes (apical four chamber and short axis subcostal views) and the right ventricular ejection fraction was calculated using the formula right end diastolic volume minus right end systolic volume divided by end diastolic volume. Right ventricular fractional area change, right ventricular end-diastolic area and right

ventricular end-systolic area were calculated from the apical four chamber view using the formula. Patients were classified into three groups (mild, moderate and severe dilatation) according to right ventricular dimensions evaluated using right ventricular end-diastolic volume and right ventricular end-diastolic area values. We considered as a cut-off value for the mild forms a right ventricular end-diastolic volume  $<70 \text{ ml/m}^2$  and right ventricular end-diastolic area  $<25 \text{ cm}^2$ , for the moderate forms a right ventricular end-diastolic volume ranging from  $70\text{-}90 \text{ ml/m}^2$  and a right ventricular end-diastolic area ranging from  $25\text{-}30 \text{ cm}^2$  and for the severe forms a right ventricular end-diastolic volume  $>90 \text{ ml/m}^2$  and a right ventricular end-diastolic area  $>30 \text{ cm}^2$ . The dimensions of the right ventricle were obtained by the protocol of Foale et al, calculating the dimensions of the RVOT and RVIT. Right ventricular outflow tract was measured RVOT1 in the parasternal long axis view in diastole (defined as the distance between anterior wall of the RV and right septum) and RVOT4 in the parasternal short axis view (defined as the maximum distance between the anterior wall of aortic valve and the free wall of RV in diastole) .

From the inflow tract RVIT3 was measured beneath the tricuspid valve in the four chamber view. In the four chamber view was also considered the LAX (long axis, defined as the distance from the apex to the middle of the tricuspid valve) and SAX (short axis on the third middle of the right ventricle). The structural abnormalities (disarray of the trabeculation, hyperechogenicity of the moderator band) were carefully evaluated. Also alterations as bulging and sacculations were searched in all views.

**Exercise stress test.**The maximum heart rate was calculated for age from the universal formula  $(220\text{-age} \times 85\%)$ . Modification of the ST-segment was carefully evaluated. Supraventricular and ventricular arrhythmias and presence of ventricular arrhythmias were carefully evaluated. Ventricular arrhythmias were divided in to 4 groups: 1) present at the first stages and disappearing during exercise (eventually appearing in the recovery phase), 2) PVBs persisting during all exercise stress, 3) exercised-induced PVBs, 4) PVBs

appearing only in the recovery period. Other patterns were rare.

**ECG-Holter monitoring.** The test was performed with 12-lead monitoring mainly and rarely in 3-lead ECG registration lasted 24 hours. The number PSVBs and PVBs were recorded. The number, morphologies, coupling interval of PVBs were calculated. Coupling interval was based on the media of 3 beats usually present in normal heart rates (from 60 to 80 bpm).

**Cardiac magnetic resonance study.** MR was executed in the bases of the clinical state and the suspect of disease or reassurance that is in athletes' heart. MRI was done in different centers. The images registrated in CDs were also studied by the group. Cardiac Magnetic Resonance (CMR) was performed on a 1.0-T clinical scanner (Harmony, Siemens, Germany) using a phased-array cardiac receiver coil. Electrocardiogram-gated breath-hold cine imaging was used to determine LV function, with a segmented steady-state free-precession pulse sequence (TrueFISP) in multiple short-axis views every 10 mm, encompassing the LV from base to apex; vertical and horizontal long-axis views were also acquired. The presence of fat infiltration with T1 sequence, before and after fat suppression using a double-inversion recovery fast-spin echo sequence (TR= 1, R-R interval, time to echo TE= 5 ms, slice thickness =5 mm, interslice gap=5 mm, and field of view FOV=24 to 28 cm) was also evaluated. After the intravenous administration of gadolinium chelate (0.2 mmol/kg), inversion recovery prepared breath-hold cine gradient-echo images were obtained (21). The sequence parameters were: TR = 600 ms, TE = 3.8 ms, flip angle = 25°, slice thickness 8 mm, gap 2 mm. The inversion time was set to null the viable myocardium signal and typically ranged from 250 to 300 ms (22). Cine, morphologic, and gadolinium late-enhancement (LE) images acquired during the same imaging session were matched by slice position. The location in the RV was described for the following regions: inflow, inferior wall, antero-lateral wall, outflow, right septum and apex. The traditional 17-segment model was used for LV (23). CMR was not performed in

asymptomatic subjects under 10 yrs old for ethical reasons. In the other cases, CMR was performed subject to parents' written consent.



## 7- Results

**Basal 12 lead–Eletrocardiogram.** 12-lead ECG was performed in all athletes. ECG measurements were performed (Table 1). In 123 athletes (85%) the ECG was normal, of which 90 (62%) showed the so-called common abnormalities, which are considered to be training related (Table 2). In 22 athletes (15%) the ECG presented pathologic features; in detail, 21 athletes (14.4%) showed the so-called uncommon abnormalities and 1 had an aspecific intraventricular conduction delay (Table 3). Values of rhythm, electrical axis, PR and QRS interval, QTc interval were normal, as well as QRS medium voltage based on the Sokolow-Lyon criteria (SV1+RV5-V6) (Table 1).

**Table 3.** ECG quantitative measurements

Parameter	measurement
QRS axis(°)	73 ± 2
Heart rate (b.p.m.)	69 ± 11
PQ interval (msec)	147 ± 22
QRSD (msec)	93 ± 14
QRS voltage V1+V5/V6 (mV)	27 ± 8
QTc interval (msec)	414 ± 19

**Table 2.** Common ECG abnormalities

<b>Common ECG abnormalities</b>	90 (62%)
Early ripolarizzazation	50 (34%)
Incomplete RBBB	37 (25.5%)
Sinus bradycardia	28 (19.3%)
Isolated QRS voltage criteria	17 (11.7%)
AVB Ist degreee	4 (2.7%)

Legend: AVB: atrioventricular block, RBBB: right bundle branch block

**Table 3. Uncommon ECG abnormalities**

ECG abnormalities	18 (12.4%)	findings
T wave inversion V1-V3	2 (1.4%)	- borderline ARVC - secondary to WPW
V1-V4	1 (0.7%)	- partial anomalous venous return
V3-V6	1 (0.7%)	- MVP
2 inferior leads	2 (1.4%)	- idiopathic
ST-segment depression lateral leads	1 (0.7%)	-MVP
inferior leads	1 (0.7%)	-idiopathic
Pathologic Q waves	-	-
Abnormal P waves	4 (2.8%)	2 MVP, probable PFO, idiopathic
LAD –left anterior emblock	0 (0%)	-
RAD-left posterior emblock	0 (0%)	(16 athletes mild RAD+105°)
Probable RV hypertrophy	2 (1.4%)	No disease
Ventricular preexcitation (intermittent)	1 (0.7%)	
RBBB	3 (2.1%)	probable ARVC, 2 idiopathic
Long QT interval	3 (2.1%)	(QTc was between 440-450 msec and considered borderline)
Brugada type ecg type 1	0 (0%)	(4 athletes presented type 2 or 3 ECG in one lead and was considered normal variant)
Short QT	0 (0%)	-

\*16 athletes had mild axis deviation (+105°) which was not considered as pathologic with no echocardiographic specific findings.\* 3 athletes had 2 uncommon findings together (WPW+negative T waves, atrial enlargement+ negative T waves inferior lead, ST depression+ negative T waves inferior leads) Importantly 33 athletes had PVBs on the ECG.

Legend: LAD: left axis deviation, RAD: right axis deviation, RBBB: right bundle branch block, ARVC arrhythmogenic right ventricular dysplasia, MVP: mitral valve prolapsed

All athletes had sinus rhythm. Sinus bradycardia was present in 28 athletes (19.3%) and was frequently (46%) associated with the early repolarization pattern. The QRS electrical axis was normal in most athletes (between -15° to +90°), while 15 (10%) had mild right axis deviation (+105°) with no specific abnormalities on echocardiographic study. Atrioventricular conduction was normal, apart of 4 athletes with 1st degree AV block. A right ventricular conduction delay was present in 36 athletes and was also confirmed by the vectorcardiogram. Isolated QRS voltage criteria of Sokolow-Lyon were present in 12.4% (Table 1). The most common finding was the J-ST segment elevation, the so-called early repolarization pattern that was detected in 50 athletes (34.5%) (Table 2). In 19 athletes J point and ST-segment elevation was present, in 27 athletes isolated ST-

segment elevation, while in 4, isolated J waves were visible. P-waves apart of 4 athletes were normal. Among the 4 athletes with P wave abnormalities, 2 had a mild MVP and 1 PFO. Duration of QRS was normal (<110 msec), a part of 14 athletes which was >110 msec. In 9 athletes the QRS prolongation was present simultaneously with an incomplete or complete right bundle branch block on the ECG. Complete right bundle branch block was rare (3 athletes) (Table 3). Isolated intraventricular aspecific conduction delay was rare (1 case), as well as ST-segment depression (2 athletes, 1.4%). Negative T-wave in V1 was present in 99 athletes (68.2%), while negative T-waves in V2-V3 or in other leads were rare (Table 2, 4). One athlete with negative T-waves in V1-V3 had a diagnosis of borderline ARVC and in another athlete negative T-waves were secondary to a WPW pattern. One athlete had negative T-waves in V1-V4 and was diagnosed to have a partial anomalous pulmonary venous return. One athlete with negative T-waves in the lateral leads had mitral valve prolapse. Brugada-type ECG patterns and long QT interval corrected by the Bazget formula were rare and not considered as pathologic (Table 3). Four athletes had in only one lead a saddle back ST-segment elevation (type 2 or 3) which was considered a normal variant of ECG. Three athletes had a borderline QTc interval (440-450 msec) without T-wave changes with normal adaptations to heart rate. Short QTc interval <320-360 msec was never observed.

**Table 4. Negative T-waves**

Normal T waves N (%)	137 (94.5%)
Positive T waves in precordial leads	38 (26%)
Negative in V1	99 (68%)
Negative T waves V1-V2*	3 (2%)
Negative T waves V1-V3	2 (1.4%)
Negative T waves V1-V4	1 (0.7%)
Negative T waves lateral leads**	1 (0.7%)
Negative T waves inferior leads (>1 lead)	2 (1.4%)
Negative T waves in aVL	26 (18%)

\*inverted T waves in lead V1-V2 in one athlete was present mild regurgitation of the pulmonary valve

\*\* One athlete had inverted T waves in the inferior and lateral leads

In 33 athletes (22.7%) PVBs were present in the basal ECG. All patients with PVBs in the basal ECG had PVBs on ECG-Holter and all than 5 also in the exercise stress test. Ten athletes had also the uncommon ECG abnormalities. The sum of athletes with pathologic ECG including those with PVBs was 35 athletes (24%), which means that the other 110 athletes had the diagnosis of PVBs thanks to the exercise stress test. None of the athletes came as a family screening. Only three athletes were found to have PVBs with ECG-Holter monitoring alone, due to cardiologic screening for a heart murmur and subsequent finding of MVP.

**SAECG.** SAECG was performed in 129 athletes (89%). Late potentials were performed to exclude basically a right ventricular conduction delay not evident in the basal ECG. Ten athletes (6.8%) showed late-potentials (Table 5). None of the athletes had late potentials at all 3 filters, while 4 had at 2 filters and 6 at 80-Hz filter. Almost all of these athletes had right ventricular dimensions at the upper normal limits or mild increased (Table 5). The only parameter that was borderline was the medium filtered QRS duration on the 25-filter which was 120 msec (Table 6).

**Table 5.** SAECG findings in 130 athletes

Positive SAECG	10 athletes (6.8%)	Ecg-eco-arrhythmia findings
3 filters	0 athletes (0%)	
2 filters	4 athletes (2.7%)	VT, effort-induced PVBs, RIVA, no significant arrhythmias
1 filter	6 athletes (4.1%)	3 MVP (one with >5000 PVBs), 2 incomplete RBBB, 1 no significant arrhythmias

**Table 6.** SAECG

	25	40	80
F-QRSD	120.1±11.4	110.9±14.8	97.1±13.02
HFLA	17.8±10.4	28.8±26.9	25.1±11.3
RMS	105.6±58.3	50.5±22.3	34.7±23.6

Legend: F-QRSD: filter duration of QRS complex, HFLA: high frequency low amplitude signs, RMS: root mean square

**Echocardiographic alterations.** In 38 athletes (26%) echocardiographic alterations typical of athletes' heart were present. Left ventricular end diastolic diameter was increased in 15 athletes (10%). The upper limit of telediastolic diameter was 61 mm (in 1 athlete) and the upper limit of telediastolic volume was 82 ml/m<sup>2</sup> (in 2 athletes). Ejection fraction was below the lower limit in 1 athlete (EF=54%) and borderline in 3 athletes (EF=55%). No athlete had parietal wall thickness >11 mm. One athlete had altered E/A value (E/A=1). Ea/Aa was performed in 68 athletes and it was always normal. One athlete had regional kinetic abnormality on the left ventricle (which was not confirmed by the CMR). Left atrial enlargement was present in 10 athletes (8.5%). One or more false tendons were common (27%) (Table 7).

**Table 7.** Echocardiographic findings of the left ventricle.

	value	Altered n (%)	Normal value
Left atrium (mm)	32±4	10 (6.8%)	(n.v <38 mm)
Telediastolic diameter (mm)	50±5	15 (10.3%)	(n.v<56 mm)
Telediastolic volume (ml/m <sup>2</sup> )	65±8	33 (22.3%)	(n.v<71 ml/m <sup>2</sup> )
Ejection fraction (%)	61±4	1 (0.7%)	(n.v>55%)
Interventricular Septum (mm)	8±1.2	5 (3.4%)	(n.v <10mm, <9 mm)
Posterior Wall (mm)	7.8±1.2		
M/V	0.97±0.09	1 (0.7%)	(n.v=0.8-1.2)
False tendons (one or more)	32 (22%)		
Aortic Root (mm)	28.6±4.3	3 (2.1%)	(n.v<38 mm)
Ascending Aorta (mm)	26.7±3		(n.v<34 mm)

Legend: M/V=mass/Volume

Right ventricular enlargement, based on the end diastolic diameter was present in 15% of athletes. RVIT3 was the diameter of right ventricle that mostly increased. RVOT1 and RVOT4 were also increased in 16 and 29 athletes, respectively. Two athletes presented RVOT4/diameter of aortic valve>1.2. RV ejection fraction was decreased in 1 athlete. Ea/Aa was performed in 60 athletes and was normal in all of them. Rich trabeculation, globular shaped apex and hyperechogen moderator band were common findings. Finally, 6 athletes had biventricular enlargement (Table 8).

**Table 8.** Echocardiographic findings of the right ventricle.

Parameter	medium value	Altered- N of pts (%)	
End diastolic area (cm <sup>2</sup> )	21±4	22 (15%)	(n.v.<25 cm <sup>2</sup> )
End diastolic volume (cm/m <sup>2</sup> )	66±10	18 (12.4%)	(n.v.<70 cm/m <sup>2</sup> )
Fraction Shortening (%)	45±5	0 (0%)	(n.v.>30%)
Ejection Fraction (%)	61±4	1 (0%)	(n.v.>55%)
SAX (mm)	25±4.5	0 (0%)	(n.v.<38 mm)
RVIT3 (mm)	39±5	72 (50%)	(n.v.<31 mm)
LAX (mm)	82±9	18 (12.4%)	(n.v.<90 mm)
RVOT1 (PLAX) (mm)	27±4.2	16 (11%)	(n.v.<31 mm)
RVOT4 (PSAX) (mm)	29±4	29 (20%)	(n.v <33 mm)
Right atrium (mm)	45±6, (41±5)	18 (13.1%)	(n.v <45 mm)
Apex globular	-	23 (16%)	
Moderator band	-	23 (16%)	
Trabeculation	-	42 (29%) (one with dissary)	

\*Only 2 athletes had infundibulum diameter in PSAX/Aortic diameter>1.2

Legend: SAX: short axis, RVIT: right ventricular inflow tract, LAX: long axis, RVOT: right ventricular outflow tract.

Trivial atrio-ventricular valve regurgitation was frequent finding. Trivial tricuspid regurgitation was present in most athletes (103 athletes). One athlete had increase of PVD with a subsequent diagnosis of partial anomalous pulmonary venous return of the pulmonary veins to the right atrium (Table 9).

**Table 9.** Doppler findings

Left ventricle	measurement	Right ventricle	measurement
Ea wave	19.4±4.8	Ea	14.9±3.3
Aa wave	7.9±2.3	Aa	8.2±2.9
Sa wave	11.5±2.9	Sa	13±2.6
Mitral regurgitation +/-	92 (63%)	Tricuspid regurgitation +/-	109 (75%)
Aortic regurgitation +/-	16 (11%)	Pulmonary regurgitation +/-	60 (41%)
E/A wave	81.9±12.9/44.2±11.8	PVD	23.1±4.4
Aortic gradient	1 (0.7%)		

The most frequent echocardiographic alteration was the mitral valve prolapse (MVP), associated in 2 athletes with mild regurgitation. In 11 athletes (38%), MVP was associated with PVBs of RBBB morphology at rest or during effort. Congenital diseases (bicuspid aortic valve, ventricular septal defect, partial anomalous pulmonary venous return and persistent left superior vena cava) were found in 4 athletes and the suspicion of cardiomyopathy (ARVC) was raised in 3. Atrial septal aneurism was found in 3 athletes, and in 1 was also associated with patent foramen ovale. In one athlete mild aortic stenosis was associated with bicuspid aortic valve. One athlete showed a hypertrophic papillary muscle of left ventricle, without other signs of hypertrophy or of hypertrophic cardiomyopathy (Table 10).

**Table 10.** Most frequent echocardiographic alterations.

<b>Most frequent alterations</b>	<b>N (%)</b>
Mitral valve prolapse	29 (20%)
Right ventricular dilatation*	22 (15%)
Left ventricular dilatation**	16 (11%)
Mild pulmonary regurgitation	12 (8.4%)
Mild tricuspid regurgitation	8 (5.5%)
Mild mitral regurgitation	7 (4.8%)
Congenital disease	4 (2.7%)
Atrial septal aneurysm	3 (2.1%)
Suspected cardiomyopathy	3 (2.1%)
Mild aortic regurgitation	2 (1.4%)
Apical hypokinesia	2 (1.4%)
Mild aortic stenosis	1 (0.7%)
Pericardial effusion	1 (0.7%)
PFO	1 (0.7%)
Papillary muscle hypertrophy	1 (0.7%)

\*mild in 15 athletes, moderate in 7 athletes, \*\* mild in 12 athletes, moderate in 4 athletes

\*\*\* biventricular enlargement in 8 athletes

**ECG-Holter.** All athletes performed the ECG-Holter monitoring. Premature supraventricular beats were present in 83 athletes (63%), with a medium of 61 PSVBs/day. Twelve athletes (7.8%) had >100 PSVB/day and 11 had 3 or more consecutive beats (table 11).

**Table 11.** Premature supraventricular beats (media 61 PSVBs in 24 hours)

<b>PSVB</b>	<b>83 (57%)</b>
single	83 (57%)
ripetitive	16 (11%)
couplets	14 (9.6%)
triplets	5 (3.4 %)
More than 4	6 (4.1%)
Effort induced (exercise test)	2 (1.4%)

PVBs were recorded in 142 athletes. 3 athletes had no PVBs, while 23 presented an insignificant number (<20 PVBs/24 hours). The number of PVBs is reported in Table 12.

**Table 12.** Number of premature ventricular beats calculated in the ECG-Holter.

<b>Number of PVBs/24 hours</b>	<b>N (%)</b>
0-720	49 (33.7%)
720-5.000	46 (31.7%)
5.000-10.000	29 (20%)
10.000-20.000	17 (12%)
>20.000	4 (2.7%)

PVBs were monomorphic in 88% of the athletes, with a wide coupling interval when single (98% of athletes). The coupling interval of the isolated PVBs was 506±104 msec. Most frequent morphologies were: 1) LBBB with inferior axis deviation, 2) RBBB with left axis deviation, 3) LBBB with left axis deviation (Table 13, 14)

**Table 13.** Single repetitive PVBs, polymorphism and coupling interval.

<b>Single or repetitive PVBs</b>	<b>N (%)</b>	<b>polymorphism</b>	<b>Medium coupling interval</b>
single	83 (57%)	14 (12%)	506±104 msec*
couplets	45 (31%)	12 (%)	457±181 msec**
ventricular tachycardia	31 (21%)	4 (%)	460±209 msec

\*only 2 athletes (1.4%) with short R-R=360msec. \*\* 11 (7.5%) athletes with short R-R interval. 62 (43%) athletes had repetitive forms



**Table 14.** Morphologies of PVBs on ECG-Holter.

<b>morphology</b>	<b>119 (%)</b>
Monomorphic	105 (88%)
Polymorphic (2 or more morphologies)	14 (12%)
LBBB inferior axis (mild RAD, +90°, +75°)	59 (49.5%)
RBBB left axis deviation	21 (17.6%)
LBBB left axis deviation	18 (15.1%)
RBBB right axis deviation	14 (12%)
LBBB normal axis (0° to 75°)	14 (12%)
RBBB inferior axis (tall R wave V1-V6)	8 (5.5%)

\*3 athletes had no PVBs, and 23 athletes had a non significant number (<20 PVBs/24 hours), thus 26 athletes (18%) were not considered in the count of the morphologies.

\*\*In 7 athletes with more morphologies it was not possible to describe the second morphology

Legend: LBBB: left bundle branch block, RBBB: right bundle branch block, RAD: right axis deviation

A total of 44 athletes had ventricular couplets and in 11 of them, the coupling interval was less than 400 msec (medium  $457 \pm 181$  msec). In 32 athletes the couplets were monomorphic, in 8 were polymorphic and in 4 were present both monomorphic and polymorphic couplets (Table 13).

Ventricular tachycardia was present in 21% of the cases and in 71% of them was a single event, always non-sustained (from 3 to 10 beats in 87%). Ventricular tachycardia was usually asymptomatic with a mean ventricular rate of 130 bpm ( $R-R=461 \pm 208$  msec). The ventricular rate varied from slow idioventricular rhythm to faster tachycardia. Four athletes (13%) had a ventricular rate >220 bpm and 4 showed a tachycardia with more than 10 consecutive beats. In addition, 4 athletes presented polymorphic ventricular tachycardia (Table 15-17).

**Table 15.** Repetitive beats detected in 31 athletes.

<b>Number of repetitive beats</b>	<b>N (%)</b>	<b>Medium Ventricular rate</b>
3 beats	17 (55%)	138 bpm
4 to 10 beats	10 (32%)	170 bpm
More than 10 beats*	4 (13%)	140 bpm

\*Only one athlete with > 10 beats had a high ventricular rate (>220 bpm). In the other 3 athletes ventricular rate was <120 bpm.

**Table 16.** Ventricular rate of ventricular repetitive beats

Ventricular Rate (bpm)	N (%)
<100	7 (22.5%)
100-150	11 (35%)
150-220	9 (29%)
>220	4 (13%)

\*Only 4 athletes (2.7%) had VR>220: 3 beats (220 bpm), 6 beats (250 bpm), 7 beats (270 bpm), 11 beats (225 bpm)

**Table 17.** Repetitive beats ordinated by number of run.

run	N (%)
1 run	22 (71%)
2 run	2 (6.5%)
3 run	3 (9.6%)
4 run	1 (3.2%)
more	3 (9.6%)

**Exercise stress test** was performed in 138 cases (95%) (Table 18). All reached at least 85% of the maximum heart rate predicted for their age. Four basic patterns of PVBs response to effort, were described: 1) PVBs that disappear during effort and reappear on the recovery phase, 2) PVBs that appear only in the recovery phase, 3) PVBs that persist during the exercise, 4) PVBs that are exercise-induced. The first two patterns were usually associated with frequent PVBs on the ECG Holter. The second pattern was not always related with PVBs at rest during ECG-Holter. Exercised-induced PVBs during the exercise stress test were usually not associated with PVBs at rest during ECG-Holter monitoring. PVBs appeared usually during exercise or were rare at rest. In only 4 athletes exercised induced PVBs were associated with PVBs also at rest. All athletes that had PVBs persisting during the exercise stress test had PVBs during the day. Most frequent effort induced PVBs were LBBB with inferior axis deviation (Table 19). One subject with polymorphic PVBs during exercise was screened for RYR2 mutations and one with a prolonged QTc interval during recovery phase genetic screening for LQTS was performed.

**Table 18.** Exercise stress test (Exercise stress test was available in 138 athletes (95%))

Findings	138 (%)
Presence of PVBs	124 (90%)
PVBs that disappear with exercise	77 (55.7%) *
PVBs during only recovery phase	16 (11.5%)
PVBs persisting during all exercise stress test	12 (8.6%)
PVBs effort-induced	19 (13.7%) **
SVPB during effort	2 (1.4%)
SVPB in the recovery phase	3 (2.1%)
QTc prolongation	1 (0.7%)

\*in 61 athletes (79%) reappear during the first 3 to 5 minutes of recovery phase, \*\*1 pts only intermediate stages. 3 athletes had numerous PVBs, 3 athletes had repetitive and 1 athlete had polymorphic  
 Legend: PVBs: premature ventricular beats, SVBS: supraventricular premature beats

**Table 19.** Effort induced PVBs in 19 athletes

LBBB 90	7 (37%)	11 (58%)
LBBB LAD	3 (16%)	
LBBB intermediate axis	1 (5%)	
RBBB RAD	1 (5%)	7 (39%)
RBBB LAD	6 (31%)	
Polymorphic	1 (5%)	1 (5%)

**Legend:** LBBB: left bundle branch block, RBBB: right bundle branch block, RAD: right axis deviation, LAD left axis deviation

**Cardiac magnetic resonance.** Thirty athletes in whose the presence of myocardial disease was suspected underwent cardiac magnetic resonance (CMR). In 2 athletes the diagnosis of a congenital heart disease was confirmed (left superior vena cava and partial anomalous pulmonary venous return). In one subject the presence of a hypertrophic papillary muscle was confirmed in the absence of other signs of hypertrophic cardiomyopathy. In a total of 14 athletes CMR was normal, while 14 athletes had one or more abnormalities mainly localized on the right ventricle (RV dilatation in 3, RV wall motion abnormalities in 11, presence of LE in 3 and fatty infiltration in 4). In 5 athletes both wall motion abnormalities and adiposis or fibrosis were present (Table 20).

**Table 20.** Pathologic CMR findings in 13 athletes

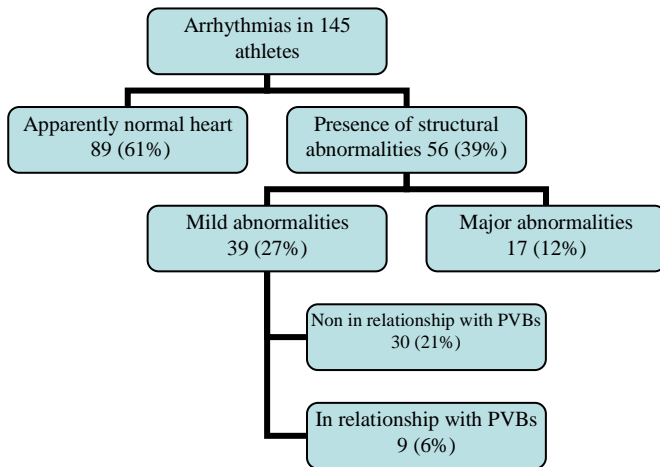
Cavity	Motion abnormalities	Fibrosis-adiposis
Moderate dilatation	-	-
-	Mild hypokinesia	-
-	Apical hypokinesia	-
-	Apical hypokinesia	-
Mild dilatation	Apical hypokinesia	-
-	bulging	-
-	Akinetic area RV+LVEF 48%	-
-	-	Septal LE
-	2 bulging	Regional adiposis
-	Diskinesia of infundibulum	Regional adiposis
Mild dilatation	Akinesia of anterior wall+apical hypokinesia	Regional adiposis *
-	bulging	LE LV (inferior-lateral wall)*
-	Diffuse hypokinesia RV	LE LV (lateral wall)*

\*ARVC: 1 borderline e 2 possible, \*\*14 athletes had normal findings, 3 athletes had: 1 LSVC, 1 TAPVR, 1 papillary muscle hypertrophy

**Follow-up:** a follow-up was done in 91 athletes and the mean follow-up lasted 28 months (max 192 months, min 1 month). An improvement was considered the presence a decrease of at least 70% of the PVBs' number in respect to the first ECG-Holter, in the absence of important repetitive rhythms. A total of 34 athletes (37%) improved, 31 (34%) had no clinical significant changes and 28 (31%) showed an increase of PVBs. During follow-up no athlete presented major cardiac events (syncope or sudden death). Fourteen athletes (10%) were treated with antiarrhythmic drugs, while 50 athletes (34% of athletes) were put in detraining or were disqualified.

Finally two figures were created reassuming the structural and functional abnormalities detected in the athletic population (figures 1, 2). Structural abnormalities may be more or less important and may be related or not related to the arrhythmias. Idiopathic arrhythmias were the most frequent finding, but some of them may be potentially dangerous. A total 30% of athletes may have potentially dangerous arrhythmias in the presence or absence of an organic substrate.

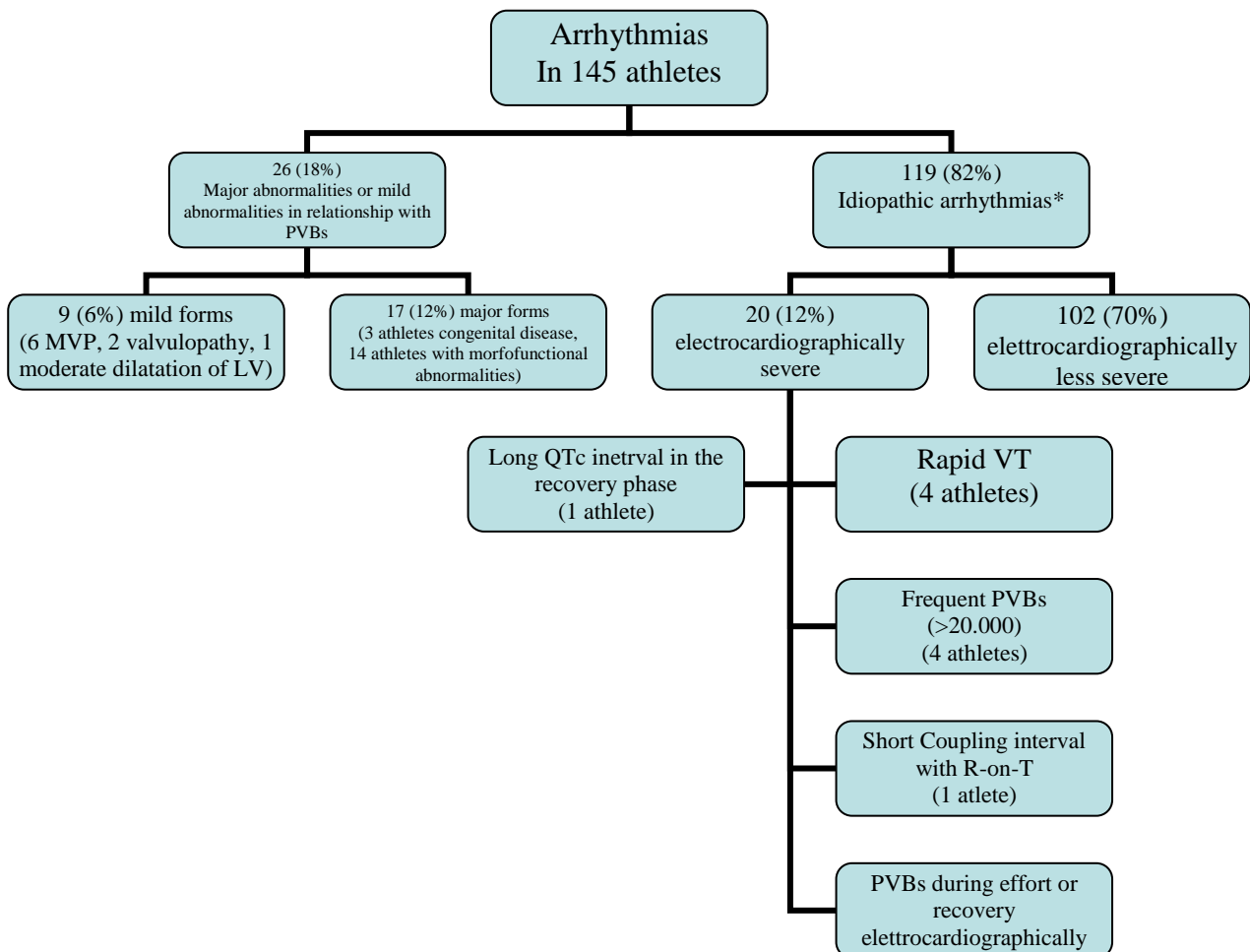
**FIGURE 1:** Results of the second and third level screening in 145 athletes with ventricular arrhythmias



Mild abnormalities: MVP, mild valvular regurgitation

Major abnormalities: congenital disease, morphofunctional alterations (with or without a relationship with PVBs)

**FIGURE 2:** More detail analysis of most potentially dangerous PVBs. In 48 athletes (30%) PVBs were potentially dangerous, in the presence or absence (idiopathic) of heart disease.



\* Idiopathic arrhythmias were considered arrhythmias in the absence of a structural heart disease or in the presence of a structural mild abnormality that do not correlate with the arrhythmias origin.

## 8. Discussion

Evaluation of cardiac arrhythmias in young competitive athletes constitutes an important medical and legal issue. A competitive athlete is one who participates in an organized team or individual sport that requires regular competition against others and requires vigorous training. Athletes are more often young and they start sports in the pre-adolescent period (screening program usually starts between 8 and 12 yrs of age). The adolescence is often the period in which cardiac pathologies, which can lead to sudden death, become clinically evident (22). Athletes' heart is "stressed" more often than sedentary people (at least 3 exercise trainings per week) and it has been demonstrated that athletes have an increased risk of sudden cardiac death when harboring a disease in respect to the sedentary population (43).

Pre-participation screening can identify most cardiac abnormalities and thus prevent sudden death and/or disease progression (21). Potentially lethal pathologies that must be excluded by the cardiologist can be divided into 3 groups: 1) structural pathologies which may be genetic-congenital or acquired, 2) chanellopathies, 3) malignant arrhythmias in the presence of an apparently normal heart.

In our study arrhythmias in athletes were proved to be more frequently idiopathic (82%) or rarely to arise from an organic cause (congenital heart disease, valve disease or cardiomyopathy). On the contrary a total of 46 athletes (30% of cases) were found to have functional or structural abnormalities that should avoid competitive sports for the risk of sudden cardiac death or progression of disease. Of these, 14 (10%) needed pharmacological therapy. In addition, 18 athletes (12.4%) were put in detraining. Thus, after cardiac evaluation competitive sport was not allowed in 44% of subjects.

Ventricular arrhythmias are common in the general population ( $\approx 50\%$ ), but generally sporadic in number (268). Even if arrhythmias in athletes with no heart disease are

generally considered benign, malignant entities originating from the right ventricular outflow tract have been described recently (223, 225). Frequent PVBs may rarely result in tachycardiomyopathy and the possibility that apparently benign PVBs become malignant and lead to a rapid sustained ventricular tachycardia or even to ventricular fibrillation, cannot be excluded (230, 145). Moreover, the presence of an occult disease as a channelopathy or an initial form of cardiomyopathy is one of the worst nightmares of the cardiologist, and in particular in those dealing with athletic screening (236, 263).

The research of a morphologic substrate that can be linked to the arrhythmias' origin is the primary goal of the cardiologist. Nonetheless, arrhythmias without an apparent heart disease may be equally dangerous and must be excluded (223, 225). Evaluation of arrhythmias has to be pluriparametric, analyzing carefully and methodically all data coming from the instrumental studies as well as patient's personal and familial history. In this study we screened 145 athletes to assess the characteristics of the arrhythmias and to exclude the presence of an organic substrate.

ECG is usually the first exam to be performed. In our series a total of 85% of subjects had a non-pathologic ECG and 62% of athletes had the so-called common ECG abnormalities, related to training (Table 2). Thus, arrhythmias on athletes are frequently associated with non-pathologic signs on the ECG. The most common ECG findings were the early repolarization pattern followed by the mild right ventricular conduction delay and the sinus bradycardia. The significance of the early repolarization pattern in presence of arrhythmias in the athletic population is not clear. Interestingly, 78% of athletes with right ventricular conduction delay had mildly dilated right ventricle, which supports the hypothesis that the right ventricular dilatation produces a delay in the time of conduction of the electrical impulse to the right ventricle. Finally sinus bradycardia was not as frequent as reported in other series, probably because our subjects were not elite athletes, thus nervous system adaptations were not so evident.

Uncommon abnormalities on the ECG with particular regard to ECG signs of a channelopathic syndrome or cardiomyopathy need to be carefully researched in athletes (Table 3). Uncommon abnormalities are infrequent, and in our series were found in 12.5% of the athletes. Significant ECG alterations as right ventricular conduction delay, preexcitation and altered repolarization (ST segment depression, negative T waves in the precordial leads) were found in 6.3%. In our study 3 athletes had a relative long QTc interval and 4 athletes presented a Brugada-like pattern. In none of these athletes ECG alterations were considered pathologic and no further investigation, as genetic screening, was performed. Genetic screening, instead, was carried out in 2 athletes with ECG alterations during exercise stress test. One athlete with effort induced polymorphic PVBs was screened for mutation of the RYR2 gene and one athlete with abnormal prolongation of the QTc interval in the recovery phase was screened for long QT syndrome mutations (in both cases genetic analysis is ongoing). None of the athletes had a short QT interval on the basal ECG .

Negative T-waves beyond V2 are usually considered a marker of disease and our study confirmed this result. In our series only 3 athletes (2%) had negative T-waves from V1-V3/V4; of these one was found to have a congenital heart disease and in one a borderline diagnosis of ARVC was made, while in the third one the negative T-waves were secondary to a WPW pattern. This data is similar to previous reports that found negative T-wave in 0.5-6.5% (257-261). No significant echocardiographic alterations were found in an athlete with negative T-waves in the inferior leads, while in one athlete negative T-waves in the lateral leads were associated with MVP (Table 3). In one case ST-depression was also associated with MVP.

Importantly, detection of PVBs on basal ECG has been considered a pathologic finding as among the total 33 athletes with PVBs on the basal ECG, all presented frequent PVBs also on the ECG-Holter. It is noteworthy that one third of these subjects showed also



uncommon ECG abnormalities. In addition, the sum of athletes with PVBs on the ECG and those with the ECG uncommon alterations was 35, thus meaning that the remaining 110 athletes (76%) wouldn't have done the cardiologic screening program based only on the resting 12-lead ECG features. Thus, exercise stress test resulted to be fundamental for PVBs detection, as the majority of athletes were recognized not due to the uncommon abnormalities on the ECG but because of the detection of arrhythmias at exercise stress test.

SAECG is often performed in athletes with arrhythmias (prevalently with LBBB morphology) to exclude the presence of late potentials, a right ventricular delay not evidenced with the normal ECG, usually to rule out an initial form of ARVC. In our study most athletes did not show late potentials (table 5). Moreover, subjects with late potentials did not have significant arrhythmias or echocardiographic alterations. Surprisingly among the 3 athletes with a possible form of ARVC, only 1 had late potentials at all filters but in presence of complete RBBB. Absence of late-potentials remains an important clinical finding that can reassure the physician of the absence of a subtle conduction abnormality that may lead to reentrant arrhythmias and help the risk stratification in certain diseases. Finally, the only parameter that was borderline was the medium filtered QRS duration on the 25-filter (value: 120 msec), which is probably due to the right ventricular conduction delay, normally in relation to the exercise-induced ventricular dilatation (table 6).

Regarding to the echocardiographic features, the most frequent findings detected during our screening were right and left ventricular dilatation which were rarely associated with a cardiomyopathy (in 4 cases suspected) (Table 7, 8,10). Right ventricular enlargement was more frequent than the left, probably due to the thinner wall of the right ventricle. Trivial atrio-ventricular regurgitation was also a common finding (table 9). Particularly, trivial tricuspid regurgitation was present in most athletes and could be related to an increased right ventricular inflow tract. Mitral valve prolapse was the most frequent left ventricular

abnormality, rarely associated with mild regurgitation (2 out of 29 with MVP, 7%), and sometimes associated with arrhythmias of RBBB morphology (in 11 athletes out of 29 athletes with MVP, 38%). The most frequent alterations of the right ventricle consisted in mild tricuspid (5.5%) and pulmonary regurgitation (8.4%). It is noteworthy that only one subject showed LV ejection fraction <55% and 6 athletes (4.1%) regional kinetic abnormalities of the right ventricle. From these athletes, 3 had the suspect of ARVC (without a definite diagnosis of ARVC based on the new criteria), 1 an anomalous venous pulmonary return and 2 apical hypokinesia alone.

Analysis of ventricular arrhythmias demonstrated that PVBs were mostly isolated (60%), monomorphic (88%) and often frequent (average 4700 PVBs/24 hours), with a wide coupling interval (medium 506 msec) (Table 12, 13). Only 2 athletes (1.4%) presented short coupling interval. The most frequent morphologies were: 1) LBBB with inferior axis deviation originating mostly from the right outflow tract, 2) RBBB with left axis deviation, originating from the left posterior fascicle of the conduction system, 3) LBBB with left axis deviation originating from the apex- inferior wall of the right ventricle (table 14). Ventricular tachycardia was most often a single event (71%), in short run, most often of 3 beats (55%), and often in slow ventricular rhythms. Only 4 athletes (2.7%) presented fast ventricular rates >220bpm. (Table 15-17). Thus, most tachycardia do not seem electrocardiographically severe.

Four patterns of response of PVBs during effort may be described: 1) PVBs that disappear during effort and reappear on the recovery phase (55.7%). Usually these athletes have frequent PVBs during the day; 2) PVBs that appear only in the recovery phase (11.5%). These athletes may have sporadic or frequent PVBs during the day or not have any at all, 3) PVBs that persist during the exercise stress test (usually in small number) (8.6%). These athletes usually have frequent PVBs during the day. 4) exercise-induced PVBs (13.7%). Usually, these athletes have PVBs only when exercising. Other responses to

exercise were rare (one athlete had PVBs only in the intermediate stages). Arrhythmias at rest usually disappear with effort, while arrhythmias during effort are usually not present at rest. Because most of the athletes had PVBs at rest, the PVBs usually disappeared during exercise and only in 12 cases persisted, while they were never increased (except one athlete). Finally, the most frequent effort-induced PVBs' morphologies were LBBB with inferior axis deviation, RBBB with LAD and LBBB with LAD, similarly to those usually observed at rest (Table 19).

Regarding CMR results, the significance of localized abnormalities in terms of diagnosis and prognosis is not currently known and more follow-up studies are needed to clarify the nature of these abnormalities. A recent study demonstrated that in subjects with frequent PVBs of LBBB morphology RV abnormalities detected with CMR were associated with a worse outcome (282). Nonetheless more studies to confirm these results are needed. In our cohort the presence of arrhythmias were associated with localized abnormalities (functional or morphologic) at CMR in nearly half of the cases that performed the CMR, while the results of other instrumental tools (ECG, SAECG and 2D-echo) were normal at the majority of the subjects. Thus, in these borderline cases diagnosis remains difficult and minor forms of disease could be underdiagnosed. Abnormalities secondary to frequent arrhythmias or due to the extreme training are also possible hypothesis. In our opinion, in these cases clinical management has to be very careful with a close follow-up, considering on one hand that minor alterations at CMR may be present also in normal subjects and on the other hand that these findings could be the first clinical sign of a heart disease. Another important aspect to consider is that in our series the site of origin of arrhythmias did not correlate with the localization of the abnormalities at CMR, making this finding difficult to interpretate. It is noteworthy that in presence of morphofunctional abnormalities sport participation can be dangerous and competitive exertion could lead to reentrant arrhythmias, thus competitive sport has to be allowed only after the exclusion of

a pathologic substrate, even with a follow-up program. Finally, during follow-up no adverse events were recorded, thus proving that that a careful management could have a role in major cardiac events prevention.

## **9. Conclusions**

Pre-participation screening program identifies athletes with ventricular arrhythmias, of which 30% are potentially dangerous. ECG and submaximal exercise stress test are fundamental examinations for the identification of arrhythmias in competitive sports and submaximal exercise stress test should always accompany ECG in the first level of evaluation of an athlete. Cardiologic screening with non-invasive techniques is fundamental for the study of young athletes with no previously known organic heart disease, suspected channelopathy or potentially dangerous idiopathic arrhythmias, that exercise may be harmful either as progression of disease or as arrhythmic death. Follow-up study demonstrated that the identification of arrhythmias in athletes, pharmacologic therapy or sport disqualification, can prevent adverse outcomes. Collaboration of sports medicine and cardiology permits the identification of athletes with ventricular arrhythmias and the prevention of sudden death. Nonetheless, risk stratification of athletes with ventricular arrhythmias remains difficult and challenging even after a thorough investigation of the heart with all the techniques available.

## **10. Limitations**

1) The close collaboration between cardiologist and sports medicine physician during the preparticipation screening evaluation decreases the need to evaluate all arrhythmic athletes in specialized arrhythmologic centers, resulting in a selection of more severe cases that come to our center. Thus prevalence of alterations that we found may overestimate the true prevalence of organic heart disease in athletes with arrhythmias, due to a bias in the selection of subjects.

2) As our outpatient clinic is a referral centers for the study of arrhythmias and in particular for evaluation of subjects with a possible form of ARVC, athletes in whom other cardiomyopathy were suspected, in particular HCM, could be underrepresented in our series.

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