

## Management of physical stress in young athletes suffering from connective tissue disorders induced by fibrillinopathies: The importance of ergophysiology

Alexia Gavriilidou<sup>1,2</sup>, Nikiforos Galanis<sup>1,2</sup>, Michail Gionis<sup>2</sup>, Ioannis Delniotis<sup>2</sup>,  
Kyriakos Ktenidis<sup>2</sup>

<sup>1</sup> 3rd Orthopedic Department, Papageorgiou General Hospital, Aristotle University of Thessaloniki,

<sup>2</sup> Department of Vascular Surgery, AHEPA University Hospital, Aristotle University of Thessaloniki

Corresponding Author: Kiriakos Ktenidis, MD, PhD, EBSQ-VASC

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**Abstract:** Ergophysiological study due to physical stress management in young persons suffering from connective tissue disorders on the basis of fibrillin's genetic mutations or metabolic defaults is extremely poor referenced to current medical literature. Fibrillin is a glycoprotein of 350kDa Molecular Weight composed by fibroblast of the extracellular matrix, and represents the main component of microfibrils which, in association with elastin form connective tissue's elastic fibers. Four different types of fibrillin with several hundreds of mutation are described nowadays. The purpose of this study is to focus on the importance at ergophysiological study before sport's activity initiation in young athletes since young athletes and their families are not aware of pathology's existence. Furthermore management of physical stress in these persons is of a high importance since fibrillinopathies affect mostly cardiovascular and myoskeletal systems and to a lesser extend respiratory ocular systems and skin. Practicing sports safely is significant in young patients with potentially disabling pathologies and can avoid psychological handicaps and social marginalization.

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### I. Introduction & Current Knowledge

The terms of fibrillinopathy stands for description of any pathology associated with genetic and /or metabolic disorder of fibrillin. This is a human glycoprotein of a 350 kDa molecular weight constructed by gene located on the chromosome 15 of human's genetic map. Construction is taking place on the extracellular matrix by fibroblasts. Polymerization of the glycoprotein gives birth to microfibrils which provide scaffold, a kind of platform, for deposition of elastin in the construction process of elastic fibers in the connective tissue(1). Four different types of fibrillin (FBN) are described (2,3,4,5). FBN1 is first isolated in 1986 by Engvall as the main component of microfibril's sheath(2). For the time being, more than 1500 different types of FBN1's mutation are known (6). FBN2 is first isolated in 1994 by Zhang, and is considered to play an important role in primary elastogenesis (3). FBN3 is isolated in 2004 mainly located in human's cerebral tissue (4). Recently, the presence of FBN4 came up to light, throughout experimental research in «zebra» fishes, an organism which is characterized by a single form gene consequence identical to humans. FBN4 is characterized by a sequential structure similar to FBN1 (5). FBN's various mutations play an important role in various human's body dysfunctions and stand on the origin of several connectivopathies. Punctiform mutations responsible for aminoacidic conversions in the inner calcium-binding part of fibrillin, is the cornerstone regarding the physiopathologic mechanism of Marfan's syndrome clinical expressions (7). In 1991, Dietz and co-workers identified the first FBN1 gene mutation in two clinical cases reported, suffering from Marfan's syndrome (8). Whilst FBN2 is responsible for elastic fibers junction during early embryogenesis, FBN1 mainly supplies the necessary material for the formation of the structural scaffold in the majority of tissue and organs of the human body. This is the reason why, various clinical expressions of fibrillinopathies are located in tissues of mesodermal origin (9). Apart from genetic mutations fibrillin's deficiency could result on the basis of metabolic defaults such as homocysteinemia (antiphospholipid syndrome) and homocystinuria. Both pathologies are the result of increased levels of high-efficiency homocystein's production, which leads to reduced number of disulfidic junctions in the inner part of FBN1, resulting to glycoproteins natural structure demolition. In fact, patients with homocystinuria often present Marfan syndrome phenotype, characterized by ocular and myoskeletal deformities (10).

## **AIM OF THE STUDY**

The purpose of this study is to enlighten and bring up to surface the important role of physical exercise's study and management in patients with connective tissue disorders due to fibrillinopathies despite the very poor bibliographic recourses in current medical literature. Additionally, we effort to trigger further future research and investigation in ergophysiology field.

## **CLINICAL EXPRESIONS OF FIBRILINOPATHIES**

Alterate production and disposal of fibrillin (FBN) is on the basis of a various number of connective tissue pathologies involving cardiovascular, myoskeletal ocular, respiratory and skin lesions. In young athletes, these kind of pathologies could result catastrophic, if not properly managed through ergophysiology study and specialists (pediatricians, sports medicine doctors and ergophysiology) collaboration, to obtain a proper and safe outcome during every day's physical exercise.

## **CARDIOVASCULAR PATHOLOGY**

The Mutation of FBN1 is clinically expressed with Marfan syndrome, characterized by cystic necrosis of the aortic media layer, resulting to vessel dissection and/or aneurysm formation, preferably located in the ascending aorta. This pathology is first described by the French pediatrician Dr. Antonio Marfan in 1986. The genetic association of this syndrome with FBN1's mutation was first described by Dietz et al. in 1991 (8).

The incidence of the pathology in the general population is 1/10000, and the percentage of FBN1's mutations rises up to 97% of the patients. (10) Gene mutation causes reduction of the total amount of FBN1 produced by fibroblast altering fibrillin's natural structural stability and finally, interfering with glycoprotein's transportation to extracellular space. Qualitative and quantitative reduction of FBN1 results to a serious decrease of microfibrils production and consequent weakness of elastic fibers with simultaneous activation of growth factors (TGF-beta) resulting to Marfan syndrome's clinical expression(11). Cardiovascular complications are hazardous and consist to the main reason of sudden death of young athletes and children practicing sports (12). Weakness of aortic connective tissue causes: a. mitral valve prolapse and insufficiency, b. ascending aortic aneurysm rupture, and c. aortic dissection with hemorrhagic and ischemic complication. Sudden death more often occurs after intense physical exercise (13). Early diagnosis associated with sport – medicine ergophysiology study and follow –up is of high importance in order to obtain optimal clinical results for these patients in relation to their desires and habits in the daily way of living. Marfan's patients are characteristically thin and tall, suitable for basketball or volley ball players. In these patients cardiovascular complications occur during intense or moderate physical stress as a result of increased cardiac afterload and high levels of systolic blood pressure. Every young athlete with this characteristic body–type should be submitted to scrupulous - and not only routine - diagnostic tests including clinical and imaging examinations by specialists (14). Mitral valve regurgitation without further abnormalities is also caused by a congenital connective tissue disorder, known a MASS syndrome, with fibrillin dysfunction association.

## **MYOSKELETAL DISORDERS**

FBN1's mutations and metabolic defaults are on the basis of a large number of myoskeletal dysfunction such a kyphosis, scoliosis, pectus excavatum and other deformities of thorax, face, upper arms and limbs, resulting to excessive height and joint flexibility. Sixty percent of Marfan's patients suffer from heavy scoliosis and often come across to the necessity of surgical repair (15). Under the same spectrum of pathophysiology are induced clinical entities like Geleophysic dysplasia, Acromicric dysplasia and Marfan lipodystrophy syndrome (MFLS). FBN1's mutation also causes myoskeletal lesions with the form of a Pathology known as Beals syndrome (also known as congenital contractural arachnodactyly –CCA), a term that refers to joints contractures (shortening), that are the key features of the syndrome (16). Mutation of the genes that help build connective tissue (FBN2) cause characteristic myoskeletal deformities, like long slender fingers and toes, long-narrow body-type, scoliosis backward or lateral curved spine at birth or early childhood, chest sinks or sticks out (pectus excavatum), reduced bone mass facial deformities (unusually small joints, and for high-arched palate), and crumple appearance at the top of the ear (9). Beals syndrome arose as a clinical entity different from Marfan after the discovery of FBN2's gene, which is an adjacent to FBN1 gene causing Marfan syndrome (9, 16, 17). Characteristic differences between Beals and Marfan syndrome are: a) Beals syndrome does not affect the eyes, and b) Different body joints behavior. Other bone and joint deformities are expressions of various FBN1's mutations expressed with different clinical forms like Weill-Marchesani syndrome (17, 18). In 1994, Hadley et al. noticed remarkable disorganization of connective tissues, elastic fibers, throughout immunochemistry methods. Seems that the role of fibrillin is of great importance in joint's functionality, although that collagen fiber occupies the largest amount of joint's tissual structure (19) Elastin fibers represent 1-2% joint dry mass. Nevertheless these fibers play an important role in structural and mechanic of the joint. In fact, they are responsible for joint's ability to return in natural primary state after every deformation submitted

because of physical stress, throughout elastic recoil (20). FBN's genemutation are expressed with abnormal joint flexibility, which is also a characteristic of Marfan patients (21). Recently, Khouryl et al., for the first time in 2012 proved that FBN2's gene mutation is responsible for Achilles tendon pathology. The study recommends that this genetic default should be considered a risk factor for joint pathologies (22).

### **RESPIRATORY LESIONS**

Pathology of the Respiratory system is characterized by a significant decrease of aerobic ability, throughout increase of both, total and residual lung volume (23). Especially in FBN1 related pathologies (Marfan syndrome etc.) a respiratory collapse predisposal is often observed. Respiratory lesions are also related to myoskeletal deformities, and are not sensitive to beta-blockers administration (24). Pneumothorax and respiratory distress is present in 4-11% of the cases, as a lung-peak emphysema complication (25).

### **OCCULAR LESIONS**

Lense ectopia, spherophakia, myopia and glaucoma often occur in connective tissue disorders like Marfan and Weill-Marchesani syndrome, because of ocular joints defaults on the basis of FBN1's gene mutation (26).

### **SKIN LESIONS**

Fibrillin is seriously implicated in skin structure and pathology. Early ageing is a pathological procedure related to long-term solar exposition, as well as, to a FBN1's gene mutation. In 1991 Watson et al. published a study based on biopsy findings, referring a serious decrease of fibrillin's-rich microfibers in skin lesions of the elbow after irradiation treatment (27).

Currently, fibrillin is considered one of the most important components of antiaging cosmetics. Patients with congenital fibrillinopathies often present skin lesions like thick, rigid skin and lipodystrophy with muscle weakness, factors that can seriously affect the capacity of physical exercise. These clinical signs are typically present in Rigid Skin Syndrome, a genetic disease related to FBN1's gene mutation, and represent a dominant autosomal type of scleroderma (28).

## **II. Ergophysiologic Study And Management Of Physical Stress**

Beneficial effects of physical exercise is a well-established knowledge, first introduced by ancient Greeks ("νοῦς καὶ τὸ σῶμα ἰσχυρὰ ἔσονται" = a healthy mind in a healthy body). Kind and intense of physical exercise have several variations according to individual characteristics of each person who practices it. Ergophysiologic study and management of patients with pathologic anamnesis represents the most important step in order to obtain safest outcome in everyday sport practicing and avoid catastrophic complications in persons of any age. Weakness in connective tissue's structure resulting by fibrillin's disorders has serious side-effects in all systems and organs of the human body who submit to excessive stress during everyday physical activity (p.e. cardiovascular and myoskeletal systems). In these last ones, fibrillinopathies could provoke hazardous complications, even in cases of moderate or mild physical activity.(29) Optimal precaution with ergophysiologic study and management is necessary for children, teenagers and young adolescents who wish to practice sports on the basis of an everyday hobby, or in a competitive manner. Study and management should be done by specialists (ergophysiologist, pediatrician, and sport medicine doctors) in accordance with social establishments and sport clubs. It is worth-mentioning that often, early and even primary diagnosis of connective tissue disorders unknown to patient and his family environment up this time, is taking place after ergophysiologic study by specialists, previous to physical exercise initiation at school, or at a sport's club. The team of the specialists should include an ergophysiologist, a pediatrician, and a medicine doctor, who shall focus clinical investigation towards cardiorespiratory function (through ECG, spirometry, etc.) in order to accomplish optimal safety limits regarding aerobic metabolism, muscular strength and physical reserves of the athlete, sport's suitability with regard to athletes pathology, and optimal dosage of intensity and duration of physical stress individually adapted to each certain pathology (30). Right choice of sport is of maximum importance, but prohibition to exercise stands for a bad option. Young persons can easily present psychological handicaps, such as sense of inferiority, stress and depression in front of friends and people of the same age, which can lead to constant sorrow and social marginalization, because of inability of sport practicing.

Mild physical activity and restricted participation is recommended regarding sports associated with violent and intense physical contact like soccer, basketball, or wrestling, in patients with fibrillinopathies only in the absence of aortic root dilatation. Participation in competitive sports, with restricted activity of the patient having mild to moderate intense of physical exercise, can be allowed in case of absence of sudden death in family history, and only in concomitance with mitral valve regurgitation and aortic root dilatation absence. On the contrary, patients with aortic dilatation could participate exclusively in competitive sports of poor intensity physical stress, like snooker, bowling and golf (31). Young athletes suffering from severe mitral valve

insufficiency, aortic aneurysm and /or dissection, is prohibited to participate in competitive sports like tae-kwondo, rugby or basketball. Participation in team-competitive sports should also be avoided in case of danger installed by the "mechanic" characteristics of the physical exercise (maneuvers to change direction to goal, abrupt and violent physical contact, etc.) Adaptation of the intensity of practice is obligatory, individualizing the risk factors in each clinical case. BPM should be controlled (less than 100/min) especially in patients receiving pharmaceutical treatment with beta-blockers (30). Exercise of often and small duration is suggested as an optimal approach (3 times/week/10'). Subdiving and parachute skyfall is prohibited because of abrupt changes of atmospheric pressure which can easily to pneumothorax and respiratory distress syndrome installation. Weightlifting is also prohibited due to excessive myoskeletal stress and danger of bone fractures and serious joint damages (21,22,33). Students suffering from Marfan syndrome with concomitant cardiovascular lesions should not practice competitive sports demanding even mild physical stress, although this is an issue not always well-accepted by kids and teenagers who strongly wish to practice sports everyday (30).

### **III. Discussion**

Fibrillin's genetic or metabolic disorders result to serious connective tissue's pathologic conditions, often with catastrophic complications (9). Cardiovascular and myoskeletal systems are those who undergo to major physical stress in patient's every-day life, the vast majority of which are children, teenagers, and young adolescents. Intense physical exercise and sport practicing represent the triggering factor in inducing lethal cardiovascular complications and serious myoskeletal lesions.

Marfan Syndrome is inherited as an autosomal dominant trait with a prevalence of 0,5-1/5000.(10)This represents approximately 3% of exercise-related Sudden Cardiac Death (SCD) in young athletes and children practicing sports. Cystic medial necrosis in aorta's tunica media (Marfan's degenerative outcome) results in aortic dilatation, dissection, or rupture, which may be expedited by the increases in blood pressure associated with exercise. These young persons should be prohibited from isometric or isotonic exercise of moderate to high intensity. Individuals with an enlarged aortic root (> 40 mm)should receive a beta-blocker in order to retard vessel's dilatation. Mitral Valve Prolapse (MVP) affects 3-5% of the general population, however, less than 100 cases of SCD have been reported in which MVP was the only pathology identified in autopsy, and only 3 occurred during physical exercise. In general, young athletes suffering from MVP are allowed to continue to compete, but this is precluded when MVP is associated with moderate to severe valve regurgitation and Marfan syndrome. (Table 1)(12,31,32,34,35)

The incidence of SCD in relation to predisposing pathology (such as Marfan syndrome) in young athletes are extremely low (1/10000 - 1/200000 athletes). This, in practical terms means that only young athletes with symptoms or signs of fibrillinopathy (Marfan syndrome) and/or MVP should undergo routine maximal exercise testing when they participate in sports training programs. However, once symptoms suggestive of cardiovascular disease are present in young athletes, further investigation is mandatory by qualified specialists. (36,37)

The introduction of a pre-participation screening program in risk groups such as young athletes with Marfan phenotype with clinical and imaging exams certainly will facilitate the detection of asymptomatic young patients suffering from fibrillinopathies. Nevertheless, considering the organizational and financial aspects, as well as the high number of false-positive results, the cost-effectiveness of such an approach is under debate, especially in countries like Greece, where fiscal public deficit and economic recession lately resulted in "linear cuts" across the board on all public health disciplines. This means that the implementation of such screening program should be thoroughly debated by all interested parties (including professional sports associations, health care providers and insurance companies). (37, 38)

Marfan Syndrome has an estimated incidence of 0,5-1/5000 young athletes (more commonly in those with characteristic phenotype, or positive family history)(10). Echocardiography can be used to measure and monitor the degree of aortic root dilatation. The risk for aortic rupture is usually linked to marked enlargement of the vessel (transverse dimension greater than 50 mm). However, dissection can also occur with a normal (or close to normal)aortic root dimension. Weightlifting has been specifically associated with aortic dissection in young athletes (33). The incidence of this catastrophic lesion appears to decrease with early prophylactic surgical aortic reconstruction and beta-blocker therapy. Young Marfan patients can participate in low and moderate static/low dynamic competitive sports in the absence of aortic root dilatation combined with the additionally absence of moderate to severe mitral regurgitation, or family history of dissection, or SCD in a Marfan relative. It is recommended however, that these young patients should undergo to aortic root echocardiographic measurement every six months, for close surveillance of aortic enlargement. Nowadays, two types of recommendations (Figure 1. Tables 2) are proposed, each one propagated by American and European countries (39, 40, 41),

The cost-effectiveness of such a pre-participation screening program in young athletes (including 12-lead ECG) has been recently evaluated by Wheeler et al. calculating a price of 100.000 USD per one life-year

saved (42). Currently available studies demonstrated that, although the positive effect of the pre-participation screening, this last one is characterized by important limitations such as inaccurate data collection, ambiguous subject definition, temporarily limited pre-screening period ( in which the influence of a seasonal variation of SCD incidence is not properly evaluated ), and eventually a mortality bias (false positive impact of a screening program linked to the natural variation of SCD incidence within the pre-screening period ). (38,43,44,46)

Prohibition of sport practicing in young persons could induce psychological handicaps and social marginalization because of sense of inferiority towards persons of the same age in their own community. Sport practicing for these young patients is important, but, should take place under careful selection and observation by specialists. According to Shank's classification (Figure 2) the sport participants is divided in two groups as organized and not. (46) Participants with fibrillinopathies related to connective tissue disorders should be considered for organized controlled sport activities in amateur level exclusively. It is mandatory that the certain sport and physical activity had to be adapted to the kind of lesion in relation to which the young patient is able to safely practice, although this is not always in accordance with young patient's wish. (31). In case of serious vascular lesions and potentially lethal cardiovascular dysfunction it is obvious that the patient cannot participate in team sports with life threatening physical activity (soccer, rugby, wrestling, basketball etc.). Especially for patients with aortic lesions, they are only allowed to participate in low intense sports that demand mild physical stress equivalent to Class IA sports (snooker, bowling, golf etc.) according to Mitchell's classification (Figure 3). (31,47,48). If respiratory lesions are implicated, it is strongly recommended avoidance of abrupt changes of atmospheric pressure (subdiving, parachute skyfalle etc.), due to extreme danger of pneumothorax and respiratory distress syndrome installation. Weightlifting is also to avoid in young athletes with myoskeletal expressions of fibrillinopathies because of increased danger of bone fractures and tendon ruptures (30). It is important to mention that very often, early and primary diagnosis of connective tissue disorders is established during ergophysiological study of the young athletes, by specialists, before initiation of any kind of sport activity. This is extremely beneficial for the patient, and his family, since awareness of such pathologies associated with everyday sport practicing by the patient could lead to sudden death, or permanent disabling complications (neurological, myoskeletal deficits, etc.). The incidence of sudden cardiac death (SCD) on the playing field is 0.61 in 100,000(49). Much attention should be paid to young athletes with Marfan's syndrome (the most common type of fibrillinopathy), if they not already scrupulously examined by specialists. These persons are characterized by thin, tall, and flexible phenotype. Ergophysiological study in association with clinical investigation and physical stress management should focus on avoidance of any condition which induces increased cardiac afterload and high levels of systolic blood pressure.

#### IV. Summary

Recent research data showed that routine cardiovascular screening in young athletes is not supported by the modern healthcare systems around the world as long as it is associated with high costs while the rate of sudden death or other benefits remains low. Despite that, sudden death of a young person while practicing physical activity is a hazardous situation with important social and legal side effects. On the other hand, in some subgroups of young athletes, especially those who suffer from fibrillinopathies and connective tissue disorders, ergophysiological study and physical stress management is of primary importance for these persons who wish to practice sports in a competitive, or not, way. Early diagnosis of basic disease is often primary posted during routine tests by specialists before young persons initiate to practice sports. Management of physical stress activities is also made by a team of specialists (ergophysiologicalist, pediatricians and sports physicians), and can offer for these young patients, safety in sport practicing by scheduling their everyday physical activity in accordance to their limitations, but also to their wishes and social necessities, in order not to evolve psychological handicaps through sense of inferiority, with severe consequences to themselves and their families too. Future research and investigation should be done regarding ergophysiology of fibrillinopathies, in order to minimize the danger of sudden death in young athletes, which is still present.

#### References

- [1] KieltyCM, Baldock C, Lee D, Rock MJ, Ashworth JL, Shuttleworth CA (February 2002). "Fibrillin: from microfibril assembly to biomechanical function". *Philos. Trans. R. Soc. Lond., B, Biol. Sci.* 357 (1418): 207–17.
- [2] Sakai LY, Keene DR, Engvall E (December 1986). "Fibrillin, a new 350-kD glycoprotein, is a component of extracellular microfibrils". *J. Cell Biol.* 103 (6 Pt 1): 2499–509
- [3] Zhang H, Apfelroth SD, Hu W, Davis EC, Sanguineti C, Bonadio J, Mecham RP, Ramirez F. Structure and expression of fibrillin-2, a novel microfibrillar component preferentially located in elastic matrices. *J Cell Biol* 1994; 124:855–63.
- [4] Corson GM, Charbonneau NL, Keene DR, Sakai LY (March 2004). "Differential expression of fibrillin-3 adds to microfibril variety in human and avian, but not rodent, connective tissues". *Genomics.* 83 (3): 461–72.
- [5] Gansner JM, Madsen EC, Mecham RP, Gitlin JD (October 2008). "Essential role for fibrillin-2 in zebrafish notochord and vascular morphogenesis". *Dev. Dyn.* 237 (10): 2844–61.
- [6] Jensen SA, Iqbal S, Lowe ED, Redfield C, Handford PA (May 2009). "Structure and interdomain interactions of a hybrid domain: a disulphide-rich module of the fibrillin/LTBP superfamily of matrix proteins". *Structure.* 17 (5): 759–68.
- [7] Robinson PN, Godfrey M. The molecular genetics of Marfan syndrome and related microfibrilopathies. *J Med Genet* 2000; 37:9-2.

- [8] Dietz HC1, Cutting GR, Pyeritz RE, Maslen CL, Sakai LY, Corson GM, Puffenberger EG, Hamosh A, Nanthakumar EJ, Curristin SM, et al Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature*. 1991 Jul 25;352(6333):337-9.
- [9] Robinson PN, Godfrey M. The molecular genetics of Marfan syndrome and related microfibrilopathies. *J Med Genet* 2000; 37:9-2.
- [10] Judge DP, Dietz HC. Marfan's syndrome. *Lancet*. 2005 Dec 3; 366(9501): 1965–1976.
- [11] BenkeK, ÁggB, SzilveszterB, TarrF, NagyZB, PólosM, DaróczyL, MerkelyB, SzabolcsZ. The role of transforming growth factor-beta in Marfan syndrome. *Cardiol J*. 2013;20(3):227-34. doi: 10.5603/CJ.2013.0066. Review.
- [12] Mendelson, M. (2011). Participation in sports for the athlete with the Marfan syndrome. In *Sports Cardiology Essentials: Evaluation, Management and Case Studies* (pp. 299-311). Springer New York. DOI: 10.1007/978-0-387-92775-6\_16
- [13] Anderson JL et al. ACC/AHA Guideline Revision - Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction. *Journal of the American College of Cardiology*. Volume 50, Issue 7, 14, Pages e1-e157, (2007)
- [14] Vlahovich N, et al. Ethics of genetic testing and research in sport: a position statement from the Australian Institute of Sport. *Br J Sports Med* 2017;51:5–11. doi:10.1136/bjsports-2016-096661
- [15] Gjolaj, J. P. et al. Spinal deformity correction in Marfan syndrome versus adolescent idiopathic scoliosis: learning from the differences. *Spine (Phila Pa 1976)* 37, 1558–1565 (2012).
- [16] Beals RK, Hecht F. Congenital contractural arachnodactyly: a heritable disorder of connective tissue. *J Bone Joint Surg* 1971; 53A:987-593.
- [17] Faivre L, Gorlin RJ, Wirtz MK, Godfrey M, Dagoneau N, et al. In frame fibrillin-1 gene deletion in autosomal dominant Weill-Marchesani syndrome. *J Med Genet*. 2003;40:34–36.
- [18] Faivre L, Collod-Beroud G, Adès L, Arbustini E, Child A, et al. The new Ghent criteria for Marfan syndrome: what do they change? *Clin Genet*. 2012;81:433–442.
- [19] Hadley-Miller N1, Mims B, MilewiczDM. The potential role of the elastic fiber system in adolescent idiopathic scoliosis. *J Bone Joint Surg Am*. 1994 Aug;76(8):1193-206.
- [20] Butler DL, Grood ES, Noyes FR, Zernicke RF. Biomechanics of ligaments and tendons. *Exerc Sport Sci Rev*. 1978; 6():125-81.
- [21] GiustiB, and Pepe G,\* Fibrillins in Tendon. *Front Aging Neurosci*. 2016; 8: 237. Published online 2016 Oct 20. doi: 10.3389/fnagi.2016.00237
- [22] El Khoury1 L, Posthumus M, Collins M, Handley CJ, Cook J and Raleigh SM. THE ELASTIN and FIBRILLIN2 GENES and THE RISK of ACHILLES TENDON PATHOLOGY. *Sports Medicine Journal* 2012: 8-21
- [23] Giske L1, Stanghelle JK, Rand-Hendrikssen S, Strøm V, Wilhelmsen JE, RøeC. Pulmonary function, working capacity and strength in young adults with Marfan syndrome. *J Rehabil Med*. 2003 Sep;35(5):221-8.
- [24] Cistulli PA1, Sullivan CE. Sleep apnea in Marfan's syndrome. Increased upper airway collapsibility during sleep. *Chest*. 1995 Sep;108(3):631-5.
- [25] Hall R T, RhodesP G. Pneumothorax and Pneumomediastinum in Infants With Idiopathic Respiratory Distress Syndrome Receiving Continuous Positive Airway Pressure. *Pediatrics*. April 1975, VOLUME 55 / ISSUE 4 Tsilou E, MacDonald IM. Weill-Marchesani. *GeneReviews*® [Internet]. Initial Posting: November 1, 2007; Last Update: February 14, 2013.
- [26] Tsilou E, MacDonald IM. Weill-Marchesani. *GeneReviews*® [Internet]. Initial Posting: November 1, 2007; Last Update: February 14, 2013.
- [27] Watson RE, Griffiths CE, Craven NM, Shuttleworth CA, Kieley CM. Fibrillin-rich microfibrils are reduced in photoaged skin. Distribution at the dermal-epidermal junction. *J Invest Dermatol*. 1999 May;112(5):782-7 Zeyer KA, Reinhard DP. Fibrillin-containing microfibrils are key signal relay stations for cell function. *Cell Commun Signal*. 2015 Dec; 9(4): 309–325.
- [28] Loeys B. L. et al. Mutations in Fibrillin-1 Cause Congenital Scleroderma: Stiff Skin Syndrome. *Science Translational Medicine* 17 Mar 2010; Vol. 2, Issue 23, pp. 23ra20
- [29] Lavie CJ, Milani RV, Marks P, de GruiterH. Exercise and the Heart: Risks, Benefits, and Recommendations for Providing Exercise Prescriptions. *Ochsner J*. 2001 Oct; 3(4): 207–213.
- [30] Germanakis I, INTRODUCTION IN PEDIATRIC CARDIOLOGY. Greek Academic library association, Athens 2015, ISBN 978-960-603-055-0, URL <http://hdl.handle.net/11419/304>,
- [31] Maron B.J., Zipes D.P. Eligibility recommendations for competitive athletes with cardiovascular abnormalities. *J Am CollCardiol*. 45 (2005), pp. 1312-1375
- [32] Maron BJ, Haas TS, Ahluwalia A, Murphy CJ, Garberich R Demographics and Epidemiology of Sudden Deaths in Young Competitive Athletes: From the United States National Registry *Am J Med*. 2016 Nov; 129(11):1170-1177.
- [33] Ahmadi H, Shirani S, Yazdanifard P. Aortic dissection type I in a weightlifter with hypertension: a case report. *Cases J* 2008;1:99.
- [34] Pelliccia A. et al. Recommendations for competitive sports participation in athletes with cardiovascular disease A consensus document from the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *European Heart Journal* (2005) 26, 1422–1445 doi:10.1093/eurheartj/ehi325
- [35] Chandra N1, Bastiaenen R, Papadakis M, Sharma S. Sudden cardiac death in young athletes: practical challenges and diagnostic dilemmas. *J Am CollCardiol*. 2013 Mar 12;61(10):1027-40. doi: 10.1016/j.jacc.2012.08.1032.
- [36] Noakes TD. *Sportscience* 2(4), [sportsci.org/jour/9804/tdn.html](http://sportsci.org/jour/9804/tdn.html), 1998
- [37] Koester MC. A Review of Sudden Cardiac Death in Young Athletes and Strategies for Preparticipation Cardiovascular Screening. *J Athl Train*. 2001 Apr-Jun; 36(2): 197–204.
- [38] Kubuš P, Janoušek J. Sudden cardiac death in children and young adults—epidemiology and prevention. *Cor et Vasa* Volume 54, Issue 4, July–August 2012, Pages e223-e226
- [39] IOC Medical Commission. IOC preparticipation cardiovascular screening. December 10, 2004. Available at: [http://multimedia.olympic.org/pdf/en\\_report\\_886.pdf](http://multimedia.olympic.org/pdf/en_report_886.pdf). Access date: November 28, 2010
- [40] Halabchi, F, Seif-Barghi T, MazaheriR. Sudden Cardiac Death in Young Athletes; a Literature Review and Special Considerations in Asia. *Asian J Sports Med*. 2011 Mar; 2(1): 1–15.
- [41] Maron BJ, Thompson PD, Ackerman MJ, et al. Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update: A scientific statement from the American heart association council on nutrition, physical activity, and metabolism: endorsed by the American College of Cardiology Foundation. *Circulation*. 2007;115:1643–55
- [42] Wheeler MT, Heidenreich PA, Froelicher VF, Hlatky MA, Ashley EA. Cost-effectiveness of preparticipation screening for prevention of sudden cardiac death in young athletes. *Ann Intern Med*. 2010 Mar 2;152(5):276-86. doi: 10.7326/0003-4819-152-5-201003020-00005.

- [43] Corrado D et al Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Consensus Statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Eur Heart J. 2005 Mar;26(5):516-24. Epub 2005 Feb 2.
- [44] Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? J Am Coll Cardiol. 2003 Dec 3;42(11):1959-63.
- [45] Deligiannis A et al. Recommendations for the Cardiovascular Screening of Athlete. Hellenic J Cardiol 2010; 51: 530-537
- [46] Shank MD, Sports Marketing: A Strategic Perspective, 4th Edition, Northern Kentucky University, ©2009 | Pearson
- [47] Mitchell JH, Haskell W, Snell P, Van Camp SP. 36th Bethesda Conference. Task force 8: classification of sports. J Am Coll Cardiol. 2005;45(8):1364-1367.
- [48] Rice SG and the Council on Sports Medicine and Fitness. Medical Conditions Affecting Sports Participation. Pediatrics April 2008, VOLUME 121 / ISSUE 4
- [49] Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. Circulation. 2009 Mar 3; 119(8):1085-92

**TABLES & FIGURES**

**Table 1:** Recommendations for participation in competitive sports in athletes with potential causes of sudden cardiac death (31, 34, 35)

	36th Bethesda Conference	European Society of Cardiology
<b>STRUCTURAL CARDIAC ABNORMALITIES</b>		
HCM	Exclude athletes with a probable or definitive clinical diagnosis from all competitive sports	
	Genotype-positive/phenotype-negative athletes may still compete	Exclude genotype-positive/phenotype-negative individuals from competitive sports
ARVC	Exclude athletes with a probable or definitive diagnosis from competitive sports.	
CCAA	Exclude from competitive sports. Participation in all sports 3 months after successful surgery would be permitted for an athlete with ischemia, ventricular arrhythmia or tachyarrhythmia, or LV dysfunction during maximal exercise testing.	Not applicable
<b>ELECTRICAL CARDIAC ABNORMALITIES</b>		
WPW	Athletes without structural heart disease, without a history of palpitations, or without tachycardia can participate in all competitive sports. In athletes with symptoms, electrophysiological study and ablation are recommended. Return to competitive sports is allowed after corrective ablation, provided that the ECG has normalized.	
LQTS	Exclude any athlete with a previous cardiac arrest or syncopal episode from competitive sports.	
	Asymptomatic patients restricted to competitive low-intensity sports. Genotype-positive/phenotype-negative athletes may still compete.	
BrS	Exclude from all competitive sports except those of low intensity.	Exclude from all competitive sports.
CPVT	Exclude all patients with a clinical diagnosis from competitive sports.	
	Genotype-positive/phenotype-negative patients may still compete in low-intensity sports	Genotype-positive/phenotype-negative patients are also excluded.
<b>ACQUIRED CARDIAC ABNORMALITIES</b>		
Commotio cordis	Eligibility for returning to competitive sport in survivors is a matter of individual clinical judgment. Survivors must undergo a thorough cardiovascular workup including 12-lead electrocardiography, ambulatory Holter monitoring, and echocardiography	Not applicable.
Myocarditis:	Exclude from all competitive sports. Convalescent period of 6 months. Athletes may return to competition when test results normalize.	

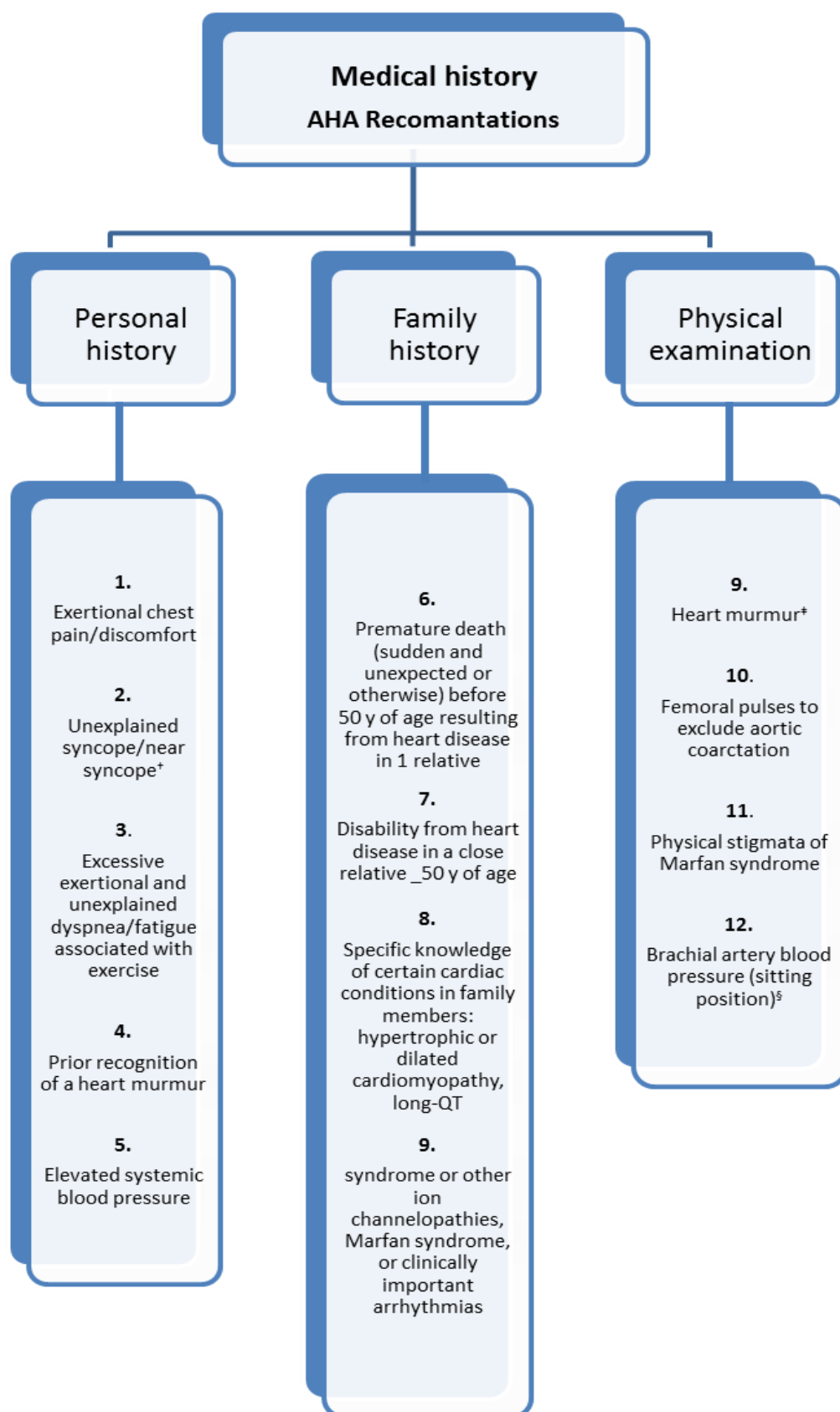
**Abbreviations:** ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; CCAA = congenital coronary artery anomalies; CPVT = catecholaminergic polymorphic ventricular tachycardia; ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome; LV = left ventricular; WPW = Wolff-Parkinson-White syndrome



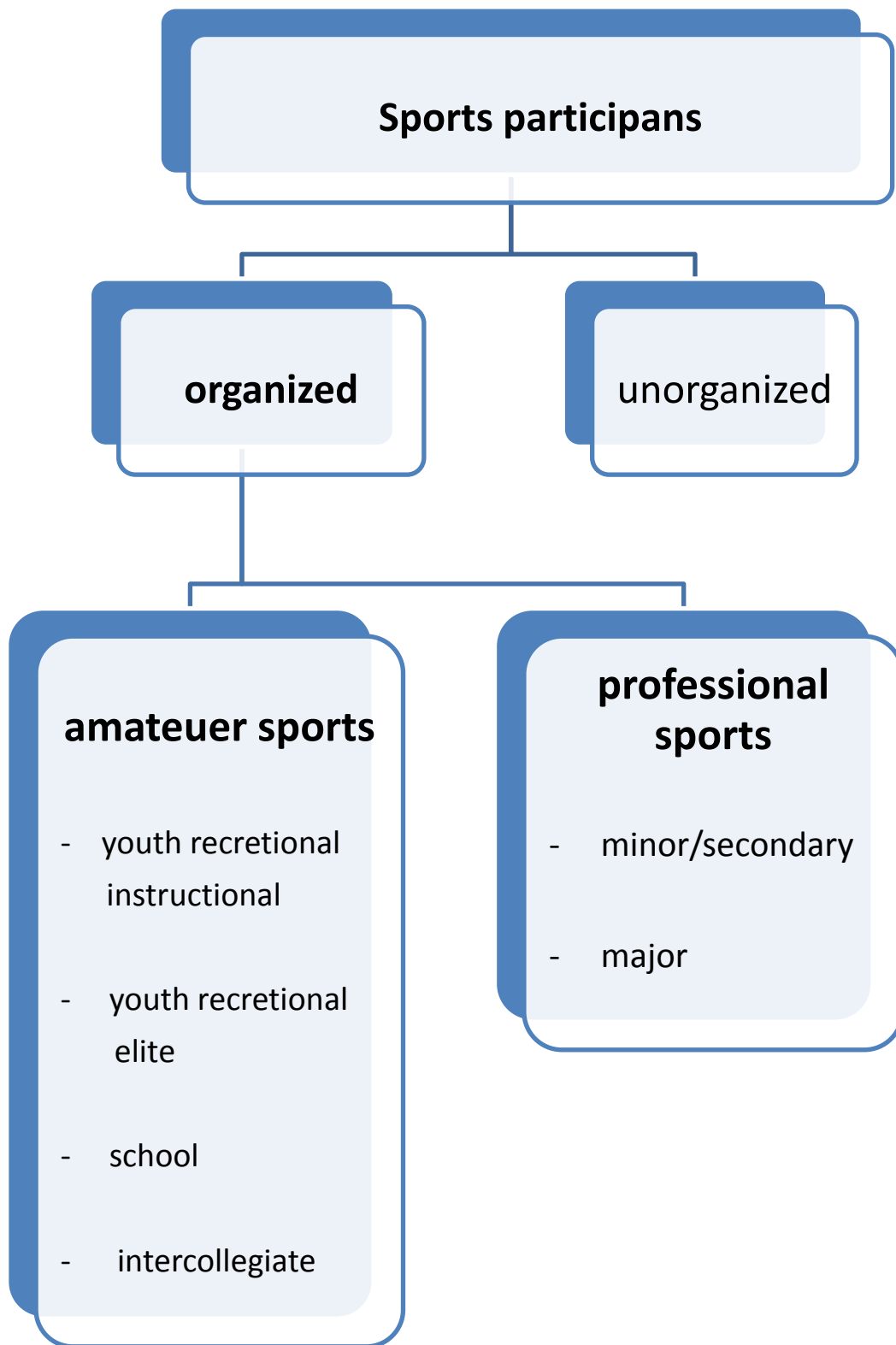
**Table 2:**Recommended assessment for all participants at the beginning of competitive activities until 35 years of age (39,40)

Medical history	Recommended ESC & IOC Assessment
<b>Personal History:</b>	<p>Have you ever fainted or passed out when exercising? Do you ever have chest tightness? Does running ever cause chest tightness? Have you ever had chest tightness, cough, or wheezing that made it difficult for you to perform sports? Have you ever been treated/hospitalized for asthma? Have you ever had a seizure? Have you ever been told that you have epilepsy? Have you ever been told to give up sports because of health problems? Have you ever been told that you have high blood pressure? Have you ever been told that you have high cholesterol? Do you have trouble breathing or do you cough during or after activity? Have you ever been dizzy during or after exercise? Have you ever had chest pain during or after exercise? Do you have or have you ever had racing of your heart or skipped heartbeats? Do you get tired more quickly than your friends during exercise? Have you ever been told that you have a heart murmur? Have you ever been told that you have a heart arrhythmia? Do you have any other history of heart problems? Have you had a severe viral infection (e.g., myocarditis or mononucleosis) within the last month? Have you ever been told that you had rheumatic fever? Do you have any allergies? Are you taking any medications at the present time? Have you routinely taken any medication in the past 2 years?</p>
<b>Family history:</b>	<p>Has anyone in your family with less than 50 years of age: Died suddenly and unexpectedly? Been treated for recurrent fainting? Had unexplained seizure problems? Had unexplained drowning while swimming? Had unexplained car accident? Had heart transplantation? Had pacemaker or defibrillator implanted? Been treated for irregular heart beat? Had heart surgery? Has anyone in your family experienced sudden infant death (cot death)? Has anyone in your family been told they have Marfan syndrome?</p>
<b>Physical examination:</b>	<p><i>General</i> : Radial and femoral pulses, Marfan stigmata  <i>Cardiac auscultation</i>: Rate/rhythm, Murmur: systolic/diastolic, Systolic click, Blood pressure  <i>Diagnostic tests</i>: 12-lead resting ECG (after the onset of puberty)From the ESC and the IOC Meeting on Sudden Cardiovascular Death in Sport, Lausanne, Switzerland, December 9 to 10, 2004; Lausanne recommendations adopted.                      ESC: European Society of Cardiology/ IOC: International Olympic Committee / ECG: Electrocardiography</p>





**Figure 1:** The 12-Element AHA Recommendations for Pre-participation Cardiovascular Screening of Competitive Athlete (41)



**Figure 2:**Shank’s classification of sports participants (46)

		INCREASING DYNAMIC COMPONENT →		
		A. Low ( $< 40\%$ Max O <sub>2</sub> )	B. Moderate (40-70% Max O <sub>2</sub> )	C. High ( $> 70\%$ Max O <sub>2</sub> )
↑ INCREASING STATIC COMPONENT	III. High ( $> 50\%$ MVC)	<b>IIIA (Moderate)</b> Bobsledding/luge <sup>a,b</sup> Field events (throwing) Gymnastics <sup>a,b</sup> Martial arts <sup>a</sup> Sailing Sport climbing Water skiing <sup>a,b</sup> Weight lifting <sup>a,b</sup> Windsurfing <sup>a,b</sup>	<b>IIIB (High Moderate)</b> Body building <sup>a,b</sup> Downhill skiing <sup>a,b</sup> Skateboarding <sup>a,b</sup> Snowboarding <sup>a,b</sup> Wrestling <sup>a</sup>	<b>IIIC (High)</b> Boxing <sup>a,c</sup> Canoeing/kayaking Cycling <sup>a,b</sup> Decathlon Rowing Speed-skating <sup>a,b</sup> Triathlon <sup>a,b</sup>
	II. Moderate (20-50% MVC)	<b>IIA (Low Moderate)</b> Archery Auto racing <sup>a,b</sup> Diving <sup>a,b</sup> Equestrian <sup>a,b</sup> Motorcycling <sup>a,b</sup>	<b>IIB (Moderate)</b> American football <sup>a</sup> Field events (jumping) Figure skating <sup>a</sup> Rodeoing <sup>a,b</sup> Rugby <sup>a</sup> Running (sprint) Surfing <sup>a,b</sup> Synchronized swimming <sup>b</sup>	<b>IIIC (High Moderate)</b> Basketball <sup>a</sup> Ice hockey <sup>a</sup> Cross-country skiing (skating technique) Lacrosse <sup>a</sup> Running (middle distance) Swimming Team handball
	I. Low ( $< 20\%$ MVC)	<b>IA (Low)</b> Billiards Bowling Cricket <sup>d</sup> Curling Golf Riflery	<b>IB (Low Moderate)</b> Baseball/softball <sup>a</sup> Fencing Table tennis Volleyball	<b>IC (Moderate)</b> Badminton Cross-country skiing (classic technique) Field hockey <sup>a</sup> Orienteering Race walking Racquetball/squash Running (long distance) Soccer <sup>e</sup> Tennis

**Figure 3:** Mitchell's classification of sports based on peak static and dynamic components achieved during competition (47) modified with permission by Stephen G. Rice and the Council on Sports Medicine and Fitness (48)

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