

Age related cardiovascular dysfunction and effects of physical activity

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1. ABSTRACT

The aim of the present article is to review the principal pathogenetic pathways of age-related cardiovascular changes and the positive effects of physical activity on these changes as well as on related cardiovascular dysfunction. The ageing mechanisms reviewed have been grouped into reduced tolerance of oxidative stress, loss of cardiac stem cells, cardiovascular remodeling and impairment of neurovegetative control. New pathogenetic conditions and their tests are described (sirtuines, telomere length, heart rate variability). Age related cardiovascular changes predispose the individual to arterial hypertension, heart failure and arrhythmia. A broad spectrum of tests are available to identify and monitor the emerging cardiovascular dysfunction. Physical activity influences all age related cardiovascular mechanisms, improves cardiovascular function and even, at moderate intensity can reduce mortality and heart attack risk. It is likely that the translation of laboratory studies to humans will improve understanding and stimulate the use of physical activity to benefit cardiovascular patients.

2. INTRODUCTION

Age-related cardiovascular changes or dysfunctions are associated with alterations leading to reduced cardiac performance, arrhythmias and arterial blood pressure increase. Usually, these changes while they can contribute to cardiac failure do not manifest relevant clinical symptoms, if concomitant coronary heart disease (CHD), valvular disease, cardiomyopathy or severe arterial hypertension are present.

Sedentary lifestyle is responsible for a large portion of age-related changes in the cardiovascular system. Physical activity per se can produce contrasting effects e.g. severe symptoms, such as dyspnoea and arrhythmias, in the case of severe cardiovascular disease (CVD), while it can have a preventive/therapeutical effect in age-related cardiac dysfunction (1).

The aim of the present review is to examine the principal pathogenetic pathways of age-related cardiovascular changes and the positive effects of physical activity, on these changes as well as on related cardiovascular dysfunction.

3. CARDIAC AGEING

3.1. Molecular and cellular mechanisms of aged cardiomyocytes

Ageing is an independent risk factor in reduced cardiac function and of heart disease. The myocardium can undergo a number of age-related degenerative processes in which cells die and surviving cardiomyocytes become hypertrophic (2). Although recent reports suggest that cardiomyocytes can regenerate, differentiating from stem cells (2-4), it is unclear whether these cells can fully integrate in the adult myocardium and restore the lost function. The structural and functional age-related alterations and the loss of cardiomyocytes directly affect cardiac function, leading to left ventricular hypertrophy and reduction in ejection fraction, heart rate and cardiac index (5). Aged cardiomyocytes exhibit a number of molecular, morphological and functional changes when compared to young cardiomyocytes.

3.2. Oxidative stress

Aged cardiomyocytes have a reduced resistance to oxidative stress, frequently related to the decreased expression of anti-oxidative systems and heat shock proteins. Cytochrome C oxidase is barely detectable in aged cardiomyocytes and this is an important reason of reduced mitochondrial respiratory activity and ATP synthesis (6). Aged cardiomyocytes display a reduction in contractility/relaxation ability, frequently due to alterations of the cytosolic energy-requiring Ca^{++} homeostasis and to reduced cell energy charge (7).

An altered balance between an overproduction of free radicals and a decreased ability of the cell to detoxify these highly reactive molecular species results in oxidative stress, a set of changes constantly present in ageing and that cardiomyocytes share with a large number of other cells. Oxygen-derived species with unpaired electrons include superoxide anion, hydrogen peroxide, hydroxyl radicals and peroxynitrites. All are highly reactive with biological molecules, damaging proteins, lipids, sugars and, especially, nucleic acids (8). The overproduction of radicals can be caused by exogenous agents such as smoking, polluting substances, radiation, drugs and foods, and/or by endogenous condition such as chronic inflammation (activated leukocytes), inefficiency of ATP synthesis (altered respiratory chain, overexpression of uncoupling proteins, mutations in mitochondrial DNA), and other metabolic alterations (diabetes, uricemia, prolonged and strenuous exercise, etc). On the other hand, a substantial contribution to the net increase in free radical concentration may be derived from the loss of detoxifying and scavenging activity of various molecules and systems including glutathione, superoxydismutases, bilirubin, thioredoxin and vitamin E. The resistance to oxidative stress is coordinated by FOXO3, the master transcription factor controlling the expression of GADD45 (DNA repair), Mn-SOD and Cu/Zn-SOD (free radical detoxifying activity), HSP70 and HSP32 (protein protection and recovery), the inducible form of heme oxygenase (HO1, producing cytosolic bilirubin), iNOS and a large number of other genes with scavenging and cardioprotective activity (9,10).

Figure 1 describes the protective role of SODs in cardiovascular diseases. FOXO3 can be activated by the redox state of the cytosol. In humans sirtuins are associated with longevity and appear to be involved in the protection of myocardiocytes from oxidative stress. Sirtuins are members of a large family of deacetylases that, together with acetylases, form one of the most important and dynamic mechanism of modulation of histones and proteins. It is likely that their beneficial effects depend on the maintenance of the efficiency of energy metabolism and on the activation of FOXO to insure protection from oxidative stress (9,11). Table 1 summarizes the characteristics of sirtuins and underlines those involved in cardiac protection.

3.3. Mitochondrial DNA (mtDNA) mutations

Mitochondria, producing large amount of oxygen reactive metabolites and containing insufficient detoxifying activity (mt Mn-SOD), accumulate mutations in their mtDNA, transmitting these mutations to their lineage, which disappear only when the cells die. Therefore, in post-mitotic tissues mutated mtDNA accumulated with a resultant abnormal synthesis of mitochondrial proteins resulting in altered electron transport, uncoupling of oxidative phosphorylation, a sharp decrease in ATP synthesis and overproduction of oxygen metabolites. Since cardiomyocytes contain a large number of mitochondria, this represents one of the most important factor in ageing of cardiomyocytes (12).

3.4. Impairment of DNA repair

Another important target of free radicals are the proteins of the DNA repair systems. Their inactivation reduces the ability of the cell to correct errors during DNA synthesis, and to correct mutations produced by mutagens, including free radicals. An accumulation of mutations occurs in the proliferating cells leading to either cell transformation (cancer) or to cell death, in post-mitotic cells, such as myocardiocytes or neurons, mutated proteins interfere with the normal life of the cell leading to degradation of function, accumulation of lipofuscins and finally to cell death (6).

3.5. Accumulation of lipofuscins

Lipofuscin particles are yellow-brown, autofluorescent pigment granules composed of oxidized proteins, abnormal proteins and lipid residues which cannot undergo definitive lysosomal digestion. Lipofuscins represent an indirect sign of cell senescence (wear and tear pigment) and contain other indigestible materials, including iron, copper and zinc. Since iron and copper catalyze the paralysosomal generation of oxygen species (Fenton reaction), peroxidation of lysosomal membranes occurs leading to the intra/extracellular release of lysosomal enzymes (13). Moreover, lipofuscin accumulation, engulfing the phagolysosomal system, may result in depressed autophagy and malfunctioning of organellar and supramolecular turnover (14).

3.6. Shortening of telomeres

Telomeres are abnormal in aged cells and are repetitive DNA sequences associated with proteins located

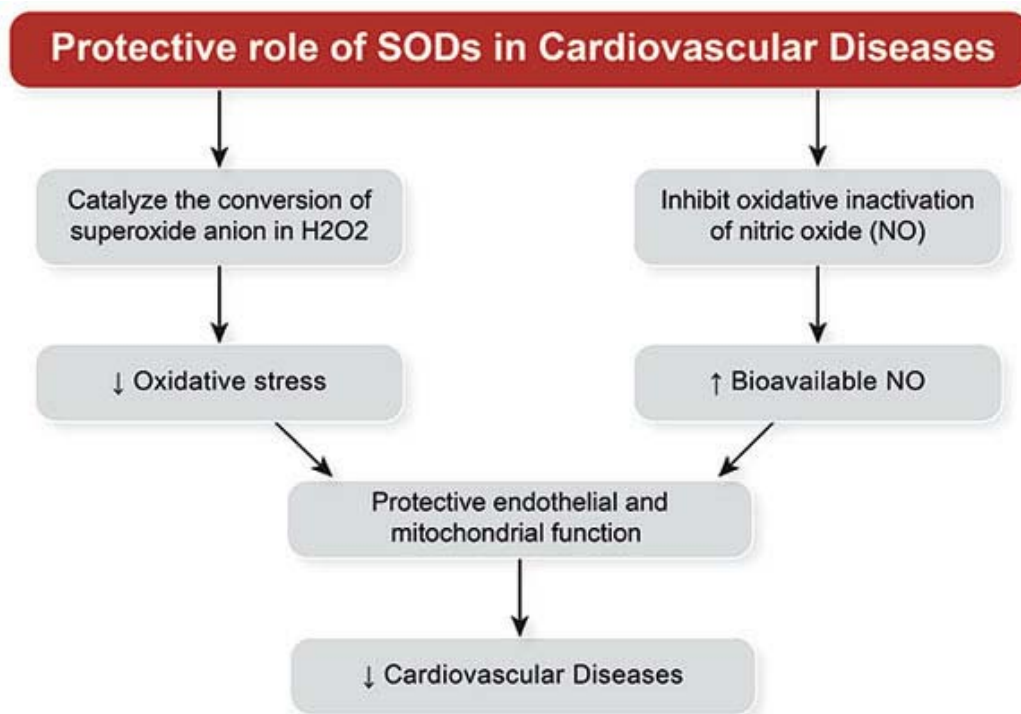


Figure 1. Describes the protective role of SODs in cardiovascular diseases.

at the ends of each chromosome. Chromosomal caps formed by telomeres inhibit end-to-end fusion of chromosomes, preventing their degradation and/or the recognition of chromosome ends as DNA breaks by damage signaling systems (15). Telomeres are considered indicators of biological age since they progressively shorten during each cell cycle (Hayflick limit) (16). DNA polymerases are unable to completely replicate telomeric DNA and, when telomeres reach a critical shortening, also genomic DNA cannot be replicated, losing gene information and leading to apoptosis and tissue senescence (15,16). Telomeres shortening may be considered the physiological numerator of cell cycles and thus determine the life limit of a specific cell lineage. Telomerase, an enzyme able to prevent telomere shortening in embryonic and adult stem cells is active. Telomerases add TTAGGG repeats to chromosomal ends thus maintaining or increasing telomeres length (17). In humans telomerase activity has been demonstrated in cancer cells, being responsible for increased proliferative potential and immortalization (18). Telomerase activity is increased by HIF-1 α in hypoxic conditions and helps repair tissue damaged by hypoxia (19). Coronary artery disease (CAD) has been associated with telomere alterations (20-22). Telomere length in white blood cells (WBC) from CAD patients is significantly reduced when compared with that from healthy patients (20). It has also been shown in CAD patients that endothelial cells derived from atherosclerotic plaques have shorter telomeres when compared with endothelial cells isolated from vessels not involved in atherosclerotic processes (21,22). Similarly, telomeres are shorter in WBCs of patients affected by type I (23) and type II (24,25) diabetes, hypercholesterolemia and low

HDL levels (26-28), than in healthy controls. The relationship between hypertension, insulin resistance and oxidative stress with telomere length in a cohort of patients from the Framingham Heart Study indicates that hypertensive subjects exhibited shorter telomere (TRF, terminal restriction fragment) length when compared with normotensive patients (29). Benetos *et al.* also reported that shorter telomere length in WBC is associated with a higher probability to develop carotid artery atherosclerosis in the presence of chronic hypertension (30). A relationship has been demonstrated between telomere length and mortality in patients aged 60 or older (30). Other factors, such as socioeconomic status (31) and psychological stress (32,33), have been associated with telomeres length and telomerase activity. Taken together, these findings suggest a relation between telomeres length and the classical risk factors for CHD. Therefore, it has been proposed that telomere length could be considered a predictor of CHD events and an useful parameter to identify patients who could benefit from statin treatment (34).

Aged cardiomyocytes show a reduction in telomere length, strongly suggesting a role in heart failure. Evaluating telomere length in endomyocardial biopsies and in circulating leukocytes and comparing healthy controls to patients with heart failure has demonstrated that telomeres are shorter in patients affected by dilated cardiomyopathies and heart failure (4,35-39). *In vitro* studies in cultured rat cardiomyocytes and in human myocardium from patients with heart failure show that apoptosis is associated with the defective expression of the telomere repeat-binding factor TRF2. In addition, down-regulation of TRF2 leads to telomere attrition and Chk2 activation; in contrast, up-

Table 1. Summary of characteristics of Sirtuins or Class III Deacetylases (Modified from Haigis, 2010) Sirtuins involved in cardiac protections (1,3,4 and 7) are underlined

Sirtuin	Chromosome	SubcellularLocation	Targets/Interaction	Function/Pathology	Transgenic mice: KO or SIRT overexpressing (+/+)
<u>SIRT1</u>	10q21.3	Nucleus/ cytosol	histones H1/H4, FOXO, NFkB, PGC1 α , Ku70, p53, AROS, WRN, PPAR γ , LXR, E2F, E22F1, NCOR, MyoD, ecc.	Oxidative stress resistance Metabolism, ageing, mitochondriogenesis, inflammatory response, genomic stability, etc.	KO: developmental defects or lethal SIRT1^{+/+}: anti-aging, anti stress, cardioprotective, neuroprotective
SIRT2	19q13.2	Cytosol	Tubulin, cytoskeleton, H4, FOXO, 14-3-3 protein	Cell cycle, apoptosis	KO: normal development SIRT2^{+/+}: neuroprotective
<u>SIRT3</u>	11p15.5	Mitochondria Nucleus (Cytoplasm)	AceCS2, GDH, Cytochrome complex I, Ku70, FOXO3a, PGC1a, histones H3/H4	Thermogenesis, Energy metabolism, ATP production Scavenging ROS, antiapoptotic (Ku70/Bax interaction)	KO: normal development, hyperacetylated mt-proteins SIRT3^{+/+}: protects from agonist induced hypertrophy
<u>SIRT4</u>	12q24.31	Mitochondria	GDH, IDE, ANT2, ANT3	Energy metabolism, insulin secretion and diabetes	KO: normal development SIRT4^{+/+}:
SIRT5	6p23	Mitochondria	CPS1	Urea cycle, neuropathology	KO: normal development SIRT5^{+/+}:
SIRT6	19p13.3	Nucleus	Histone H3, NFkB	BER or base excision repair, metabolism, genomic stability, glucose homeostasis	KO: premature ageing SIRT6^{+/+}:
<u>SIRT7</u>	17q25.3	Nucleolus and condensed chromatin	RNA polymerase I, p53	Recombinant DNA transcription, maintenance of tissues, myocardium repair	KO: smaller size, short lifespan, heart defects, hypertrophy and inflammatory cardiomyopathy SIRT7^{+/+}:

AceCS2 : Acetyl-CoA-Synthetase, ANT : Adenine Nucleotide Translocator, AROS : Active Regulator of SIRT1, CPS1 : Carbamoyl phosphate synthetase 1, E2F, E2F1 : transcription factors, FOXO : Forkhead box, subgroup O, GDH : glutamate dehydrogenase, IDE : Insulin degrading enzyme, Ku70 : deubiquitinating protein for Bax and a number of other substrates, IDE : Insulin degrading enzyme, LXR : Liver X receptor, AceCS2 : Acetyl-CoA-synthase 2, MyoD : Muscle Transcription Factor (development and maintenance), NCOR : Nuclear Receptor Corepressor, NFkB : Nuclear Factor k in B (lymphocyte), PGC1 α : Peroxisome proliferator activated receptor gamma coactivator 1 alpha, PPAR γ : peroxisome proliferator activated receptor gamma, p53 : protein 53, an oncosuppressor protein, SIRT : Silencing Information Regulator Two or Sir-2, WRN : Werner syndrome gene or Werner progeria, an enzyme of DNA repair mechanism, 14-3-3 protein : adaptor protein for phosphorylated serine in a number of pathways, including Akt

regulation of TRF2 appears to confer protection from oxidative stress (40). *In vitro* experiments demonstrated that statin therapy enhances TRF2 levels in endothelial progenitors, suggesting the basis for new therapeutic strategies in the treatment of cardiovascular disease (41).

Therefore, oxidative stress plays a central role in ageing since free radicals induce somatic mutations in nuclear and mitochondrial DNA, alter protein structure facilitating their proteosomal degradation, and damage cellular membranes by lipoperoxidation. All these changes progressively degrade cardiomyocytes thereby losing function and, ultimately, leading to cell death by either necrosis or apoptosis.

3.7. Cardiac activation and conduction system

In elderly a sinus nodal disease may be present due to various ageing process occurring at the cellular level composing the sinoatrial node (P cells or pacemaker cells, transitional cells, Purkinje cells). These ageing process include apoptosis (only 10% of P cells are left in 70 year

olds), substitution with adipose or connective tissue, and deposition of amyloid, collagen and other fibrils (42). These structural changes occur at the level of the atrioventricular node and bundle of His and to a greater extent within the bundle branches (42). With ageing, the action potential and thus the duration of contraction are prolonged due to the prolonged release of cytosolic Ca²⁺. The prolongation of the action potential is due to deceleration of the deactivation rhythm of L-type Ca²⁺ channels and the decreased outflow of K⁺ (43). Ca²⁺ reuptake from the sarcoplasmic reticulum (SERCA Ca²⁺ pump) is decreased, while the activity of the Na⁺/Ca²⁺ exchanger is increased. Ageing can affect the efficiency of Ca²⁺ spark signaling in cardiomyocytes, altering the pulsatile nature of Ca²⁺ and degrading cardiac function (43). These changes in the Ca²⁺ cycle influence myocardial relaxation and are responsible for the deceleration of the premature diastolic filling rhythm, which characterizes ageing.

3.8. Ageing and cardiac stem cells

Adult cardiac stem cells (CSCs) are a multipotent lineage, able to differentiate into cardiomyocytes, endothelial and smooth muscle cells. When injected into the rat infarcted myocardium, CSCs repair necrotic tissue,

apparently restoring cardiac function (44). The origin of CSCs is unclear, although it appears that they have an extra-cardiac origin and migrate to the myocardium in post-natal life (45). The number of CSCs in the myocardium is low under normal conditions, but increases in response to damaging stress such as myocardial infarction (45,46) and aortic stenosis (47). Many cellular and biological aspects of CSCs remain unclarified, including their origin, the mechanism of their differentiation, their effective functional integration into an adult tissue and their precise role in the maintenance and repair of adult myocardium.

Both the quantity and the age-related quality of CSCs appear important for their biological activity. In older humans CSCs are to be functionally impaired, thus contributing to heart failure (48).

4. EFFECTS OF PHYSICAL ACTIVITY ON THE BIOLOGICAL MECHANISMS OF CARDIAC AGEING

4.1. Oxidative stress and telomeres

Molecular mechanisms through which physical activity exerts its beneficial effect over almost all age-related alterations in humans may be elucidated by exploring sirtuin activity in target-tissues (Table 1). Sirtuin activity increases with physical activity and has an evident beneficial effect on post-mitotic tissues/cells, such as cardiomyocytes, skeletal myocytes, neurons, and sensory cells thereby either preventing or slowing typical age-related diseases of these tissues (9).

Regular exercise increases the expression and the activity of SIRT1 and thus decreases the level of oxidative damage through activation of FOXO and thereby, increasing the number of antioxidant molecules. Sirtuins are activated by physical activity (49).

The action of SIRT1 on cardiac and skeletal striated muscle has been well characterized. In KO mice heart malformations, decreased resistance to paraquat-induced apoptosis and premature death are present. The cardiac-restricted overexpression of SIRT1 influences muscle mass, deacetylating MyoD (hypertrophy), stem cell recruitment after injury (dystrophy or infarct) and facilitates myocardial tissue and function recovery.

Myocardial tissue, similarly to other tissues, accumulates oxidative damage with ageing. Regular exercise, increasing the expression and the activity of SIRT1, decreases oxidative damage through the activation of FOXO, thereby increasing a number of antioxidant molecules. Myocardiocytes are also protected from abnormal inflammation and from age-related cardiomyopathy.

In humans SIRT3 has been associated with longevity and appears to be involved in the protection of myocardiocytes from oxidative stress. It is likely that most of the of the beneficial effects depend on the maintenance of the efficiency of energy metabolism and on the

activation of FOXO for the protection from oxidative stress (9,11).

SIRT4 catalyzes ADP-rybosylation of many mitochondrial proteins, including glutamate dehydrogenase (involved in energy metabolism), insulin degrading enzyme (a protease that controls the level of insulin) and adenine nucleotide translocators (ATP synthesis) (9).

SIRT7 increases stress resistance of cardiomyocytes and prevents apoptotic and inflammatory cardiomyopathy in mice. In SIRT7 KO mice decreased resistance of the myocardium to genotoxic and oxydative stress and increased susceptibility to apoptosis has been reported (9). Table 1 summarizes the characteristics of Sirtuins i.e. Class III Deacetylases.

Sirtuins mediate the effects of resveratrol. Resveratrol is a small molecule that mimics the effects of physical activity conferring protection against CVD (49). Resveratrol pretreatment protects myocardium and limits cell death during acute ischemia/reperfusion damage. This effect is due to the sirtuin-mediated activation of PPAR α , a transcription factor that controls the expression and the activity of both the inducible and endothelial isoforms of NOS, increasing NO production (49). Inhibiting NOS results in the abolishing of the beneficial effects of resveratrol on ischemic damage (49). Finally, resveratrol upregulates sarcoplasmic calcium ATPase, thereby improving cardiac function in diabetic cardiomyopathy (11).

Resveratrol provokes vasorelaxation *in vitro* and lowers blood pressure in obese Zucker rats and in various experimental models of hypertension. It is able to restore acetylcholine-dependent relaxation of aortas from both obese and aged animals: this effect seems to be mediated by NO signaling (49,50). Resveratrol, in vessel tissues, upregulates the expression NADPHoxidase, the major producer of oxygen radicals, in vessel tissues thus protecting from oxidative stress and maintaining active NO signaling.

Resveratrol suppresses NADPH oxidase in vasculature activating SIRT1 and thus inhibiting NF κ B. Overexpression of SIRT1, activating PGC-1 α in endothelial cells, further suppress NADPH oxidase expression.

Resveratrol inhibits platelet aggregation both *in vitro* and *in vivo*, in normal mice and hypercholesterolemic rabbits. Platelet aggregation is impaired by the inhibition of Mitogen-activated protein kinase (MAPK) signaling of phosphoinositol metabolism and by the high levels of cGMP due to NO signaling, however it is still unclear the precise mechanism by which an increased activity of SIRT1 is able to interfere with all these pathways. Resveratrol, similarly to low-dose aspirin, could be responsible for an irreversible inhibition of cyclooxygenase I activity resulting in a decreased production of thromboxane A2 and other arachidonic acid metabolites by activated platelets, thus weakening and/or blocking complete platelet aggregation and efficient vasoconstriction (49,50).

Leukocyte telomere length is positively associated with increasing levels of physical activity (51). Physical activity prevents cellular senescence regulating telomere-stabilizing proteins in mice and in humans. Physical activity also protects from apoptosis in stressed endothelial cells (52), leukocytes of marathon runners (10), cardiomyocytes and skeletal myocytes of rats running to exhaustion (53). While moderate physical activity has been shown to be beneficial for the maintenance of telomere length, intense physical activity can be detrimental (54). Interestingly, similar results have been obtained studying the effect of physical exercise on the immune system (the Exercise Immunology). Moderate exercise increased the immune response and reduced the risk of infection as compared to both low and intense exercise (55). In conclusion, the relationship between exercise and telomere length requires further studies. Radak *et al.* analyzed telomerase activity in skeletal muscle of rats under regular strenuous exercise and found that enzyme was independent of exercise training level (56).

4.2. Effect of physical exercise on cardiac and skeletal muscle

Skeletal muscle, myocardium and some nervous tissue should not be considered as classical stable post-mitotic tissue (57). In skeletal muscle, satellite cells, located between the basal lamina and the muscle fibers, can proliferate and differentiate to form adult myocytes (58). Their proliferation is necessary for routine maintenance, hypertrophic adaptation, and repair of adult muscle. Despite satellite cells being able to differentiate from hematogenous stem cells, it appears that they constitute a completely independent niche. In fact, when bone marrow-derived circulating cells with myogenic potential are inactivated by localized irradiation, muscle regeneration and function is unaffected (59). Ageing is associated with a significant decline in the total mass, strength, and endurance of skeletal muscles (60). Physical exercise can induce a proliferation of satellite cells (61-64). Although the proliferative potential of satellite cells is conditioned by their telomere length, contrasting results suggest that telomere length in satellite cells does not reflect the number of cell divisions. This could be due to an unknown alternative mechanism that controls telomere length *in vivo* (57).

Many protective effects of physical exercise have been described in cardiac muscle. Both short and long-term running increases cardiac telomerase activity and expression of TERT and TRF2 protein and reduces the expression of proapoptotic proteins Chk2 (cell cycle checkpoint kinase 2), p53, and p16. Interestingly, after 6 months, TRF2 and TERT expression remained elevated, while the expression of Chk2, p53, and p16 was decreased. Physical activity increases cardiac-specific expression of IGF-1 (paracrine insulin-like growth factor 1); this is an important survival factor, which, through the activation of Akt, induces the activation of many transcription factors, including NFkB, and the up-regulation of a set of genes including sarcomeric proteins, NOS, and mitochondrial genes, thereby contributing to the maintenance and to the hypertrophy of skeletal muscle. Interestingly, an

overexpression and activation of SIRT1 and SIRT3, induced by physical exercise (10), have been demonstrated both in humans and in animal models (10) associated with a number of beneficial effects on basic skeletal muscle and myocardial maintenance (11). Doxorubicin treated mice develop an apoptotic cardiomyopathy which is either mitigated or reversed by physical exercise through the up-regulation of telomere-stabilizing proteins and the reduction of doxorubicin-induced p53 expression, in this way preventing apoptosis (65), probably through the overexpression and activation of various sirtuins. Taken together, these observations suggest that the protective effects of physical activity on cardiomyocytes is achieved through typical anti-ageing mechanisms such as the prevention of apoptosis and the increased ability in repairing and substituting damaged molecules (66).

4.3. Effects of physical exercise on cardiac hypertrophy

The relationship between physical exercise and cardiac hypertrophy is well documented (67). Hypertrophy is manifest by an increase in cardiac mass which occurs in response to both pathological and physiological stimuli. It is characterized by increases in both major and minor axis of myocardiocytes and by an increase of myofibrillar and mitochondrial mass. Myocardiocyte hypertrophy represents the adaptation of the cell to an increased wall stress and to an increased demand on contractile work. Physiological hypertrophy typically occurs in trained athletes with preserved sarcomeres/mitochondria ratio and well preserved architecture of contractile proteins into well-oriented sarcomeres. Pathological hypertrophy (also called concentric hypertrophy) occurs in patients with hypertension, with valvular defects and with loss-of-function mutations of sarcomere-related proteins. Typically, there is a continuously increasing demand on contractile work, which leads to a pathological hypertrophic adaptation. This consists in the abnormal expression of sarcomeric proteins, including embryonic and foetal isoforms, abnormal assembly of the sarcomeric proteins, deviating from the vector of the contraction and leading to an abnormal architecture of the cell. Therefore, concentric hypertrophy of myocardiocytes is characterized by a sharp increase of both long and short axis of myocardiocytes, by an increased ratio sarcomeres/mitochondria, by sarcomeric disarray with a decrease in contractile efficiency, by the expression of immature contractile protein isoforms and by many electrical abnormalities, such as decreased outward currents.

Increased total volume of cardiomyocytes produces an increase in sarcolemmal area which, in turn, may determine disorders in membrane ion currents and in excitation-contraction coupling. One of the most important changes observed in all grades of hypertrophy is a prolonged action potential duration. This may result either from a decreased outward current and/or an increased inward current. The first represents the major electrical alteration of membrane currents that occurs in hypertrophy. The altered outward K⁺ current induces a delayed repolarization which, in turn, determines a prolonged action potential duration, frequently triggering arrhythmias (68-

70). However, more studies are necessary in order to define the precise mechanisms underlying arrhythmias in hypertrophy, either spontaneous or exercise-induced.

4.4. Physical activity and EPCs

Studies to assess the effect of exercise on endothelial progenitors cells (EPCs) levels provide contrasting results. Adams *et al.* (71) demonstrated an age-dependent increase in circulating EPCs in patients affected by symptomatic CAD, responding to exercise-induced myocardial ischemia. This increase appeared related to/ and preceded by an increase in plasma VEGF, likely associated to the activation of the transcription factor HIF1 α by the hypoxic stimulus. In contrast, Thijssen *et al.* (72) examined the effect of long-term physical exercise on the number of hematopoietic stem cells (HSC) and EPCs. Young athletes (18-28 year old) were compared with older men over an 8-week period endurance training. Older subjects showed significantly lower baseline and exercise-induced levels of HSCs and EPCs than the younger athletes; however in both groups, acute exercise significantly increased HSCs, but not EPCs. Interestingly, the increase in numbers of HSCs was reduced in older men, suggesting that ageing may reduce the acute exercise-induced recruitment and/or production HSCs. Sarto *et al.* (73) demonstrated that patients with chronic heart failure in response to aerobic exercise exhibited a parallel increase of EPCs and of VEGF plasma levels. Laufs *et al.* (74) showed that intensive and moderate physical exercise in 25 healthy volunteers for 30 min, increased circulating EPCs. Luk *et al.* (75) showed that more intense habitual physical activity was associated with higher brachial artery flow-mediated dilation and EPCs count. In this study 116 patients (67.8 \pm 9.5 years; 81% male) with stable CAD and preserved left ventricular ejection fraction $>$ or \geq 45% were studied. Interestingly, only flow-mediated dilation significantly correlated with increased physical activity, but not EPCs, suggesting that physical activity improves endothelial function not only through EPCs recruitment, but also through other mechanisms, such as sirtuins activation and overexpression (76).

4.5. Physical activity and CSCs

Data on the effect of physical exercise on CSC number is scarce. Brehm *et al.* (77) analyzed the effect of regular exercise in promoting the mobilization and improving the functional activity of CSCs in patients with recent myocardial infarction. Patients undergoing a physical exercise program demonstrated that the number and migration capacity of cardiac progenitors cells increased significantly whereas the BNP level decreased.

5. EFFECTS OF PHYSICAL ACTIVITY ON AGEING RELATED CARDIAC DYSFUNCTION

5.1. Cardiac remodelling

With ageing a moderate increase in the thickness of the left ventricular (LV) wall (78) and concentric hypertrophy of myocytes (79) occur. Mild hypertrophy may be due to an increase in systolic blood pressure, and neurohormonal or other trophic factors. Hypertrophy involving interventricular septum leads to LV

outflow obstruction and thus to a further increase in afterload. The wall thickening of LV and its reduction in length produces a more spherical ventricle. Dextral shift of the ascending aorta also contributes to this remodeling (80). Systolic function and cardiac output may remain normal (81). In contrast, LV diastolic function may be abnormal in older people.

The aforementioned changes in the calcium cycle influence myocardial relaxation and explain the deceleration of the premature diastolic filling rhythm, typical of aging. Ultrasound and radionuclide analysis have shown a 50% reduction of velocity of the early phase of LV filling, between the third and ninth decades of life, with an equivalent increase in the late diastolic filling phase (82). The delayed relaxation, combined with the decreased compliance of aged myocardium, leads to an increase in end-diastolic pressure, a decrease in the early passive diastolic filling phase, and an increase in the late active phase of diastolic filling. Possible mechanisms that explain the reduction of velocity of the early diastolic filling include the accumulation of ECM, fibrosis and the deceleration in calcium activation from preceding contraction (83). The combination of decreased diastolic pressure and LV hypertrophy predisposes the individual to subendocardial ischemia and to fibrosis in the intermediate tissue. Ischemia further worsens the LV contraction (left and up shift of pressure-volume curve).

Consequently, compliance, and filling of the LV are reduced, with an increase of the pressure in the left atrium and pulmonary veins. Thus, a vicious circle exists that leads to diastolic heart failure, the most common form (40-80%) of heart failure in elderly people (84). These changes can be prevented with prolonged and sustained endurance exercise. Recent evidence demonstrated that age-related impairment in LV function could be partly prevented by regular endurance training (85). The mechanism(s) include preservation of viscoelastic myocardial properties and pericardial size, as well as optimization of chamber geometry. Prolonged endurance exercise is known to result in eccentric ventricular hypertrophy, ie, a balanced enlargement of ventricular mass and dimensions. These adaptations lead to improved cardiac performance without apparent change in contractility and are largely explained by enhanced diastolic function (86).

Prolonged exercise training may also elicit its effect through the maintenance of vascular elasticity and thus smaller arterial load. Arterial elastance is inversely related to vascular compliance and is a more sensitive marker for arterial load than total peripheral resistance (87). Decreased vascular compliance is associated with ageing and hypertension (88,89) and, recently, has been associated to heart failure with preserved ejection fraction (90) and to cerebrovascular events (91). Endurance training preserves vascular elasticity with ageing (92), thereby preventing cardiac adaptive changes, including myocyte ultrastructural degradation and focal proliferation of matrix, preventing myocardial stiffness. Therefore, preserving ventriculo-vascular coupling is a key component in the fight against hypertension and heart disease (88).

5.2. Physical activity in preventing arrhythmias

Hypertrophy is one of the possible mechanisms underlying arrhythmias that occur in both trained and sedentary subjects. Normally, the cardiac rhythm is regulated by the autonomic nervous system (ANS), and the age-related malfunction of the ANS is reflected by the decreased variability of cardiac rhythm (93). Changes in parasympathetic and/or sympathetic regulation of the heart can contribute significantly to the induction of different kinds of arrhythmias, particularly ventricular tachyarrhythmias. Heart rate variability is considered a valid index of cardiac vagal activity (94-96). A wide range of cardiovascular risk factors have been linked to a reduction in heart rate variability. These include hypertension (97-99), diabetes (100-103), carotid atherosclerosis (104), smoking (105-107), heart failure (108,109) and myocardial infarction (110-112). Subjects who show the greatest reduction in heart rate variability also have a higher risk of sudden death following an infarct (113). In contrast, in patients who exhibit a high heart rate variability, mirroring a well preserved vagal tone the risk of sudden death is sharply reduced (110,111). These results suggest that parasympathetic tone plays a protective role, contrasting to the development of sudden cardiac death. An enhanced cardiac sympathetic activity increases the risk of sudden death provoked by a lethal cardiac arrhythmia (114,115). Therapeutic interventions to augment parasympathetic tone, at least in animal models, have been shown to be useful in reducing possible lethal arrhythmias (116). The use of this strategy in humans is strongly hampered by the gastrointestinal side-effects of cholinergic agonists. Finally, interventions that reduce cardiac sympathetic activity may play also a protective role against malignant arrhythmias (117-123).

Endurance exercise training induces an increase in cardiac parasympathetic tone combined with a reduction in sympathetic activity (124-131). Endurance exercise training increases cardiac parasympathetic tone and decreases sympathetic activity (132-136). Both in humans and animals, the heart rate at submaximal workloads was reduced in trained individuals compared with sedentary controls (136-140). A resting bradycardia is a well-established consequence of exercise training and is, in fact, used as a marker that the exercise-trained state has been achieved (134,136,139). Both acetylcholine content and choline-acetyltransferase were increased in the hearts of trained rats compared to the control animals (141,142). In humans, exercise training during recovery from myocardial infarction has been reported to increase heart rate variability (143). In a similar manner, exercise training has been shown to attenuate reductions in heart rate variability in patients with either hypertension (144) or heart failure (143). These data suggest that endurance exercise training can elicit changes in cardiac autonomic control that attenuate the cardiac autonomic remodeling induced by myocardial infarction.

Recent studies have analysed the effects of exercise training on both the parasympathetic and the β -adrenoceptor regulation of cardiac function in normal animals, aged animals, and animals with hypertension, in the presence of either a reduction in or no change in β 1-

adrenoceptor density (145-148). MacDonnell *et al.* (148) demonstrated that physical activity improves the inotropic response to β -adrenoceptor stimulation in spontaneously hypertensive rats. Abnormal repolarization (due to altered K^+ currents) or intracellular calcium regulation could act individually or in concert to decrease cardiac electrical stability and increase the propensity to arrhythmias and sudden cardiac death. Interestingly, hypertensive patients treated with beta-blockers do not show an impairment in the cardiovascular benefits of endurance training (149). Noteworthy, the right level of exercise seems to be important in order to produce a protective effect. In fact, an excessive strenuous exercise may have detrimental effects, increasing sympathetic activity and reducing parasympathetic tone (150). The role of physical activity in preventing lethal arrhythmias is particularly evident in high-risk populations, such as patients recovering from myocardial infarction (151-153). The cellular and molecular mechanisms responsible for causing arrhythmias and how exercise protects against them are not completely understood. Intracellular calcium dysregulation may play a role both in contractile dysfunctions and arrhythmogenesis (154-156). Intracellular calcium regulation, ion channels changes (157) and autonomic neural dysfunctions may also play a role, singularly or in concert, to decrease cardiac electric stability, leading to the development of lethal arrhythmias. Recent evidence suggests that various stimuli, through new gene expression facilitating myocardial repair and function, can have a central role in preventing arrhythmias and rescuing infarcted myocardium (158).

6. ARTERIAL AGEING

With ageing, structural changes occur in the vessels, influencing cardiac function and the blood supply of peripheral tissues (159). Age-related arteriosclerosis macroscopic changes include: 1) dilation and convolution of large arteries (dilation is more severe in the aorta proximal to the myocardium and in its large branches, but smaller in the muscle arteries); 2) enlargement of the lumen and thickening of the vessel wall (160). However, precise factors and mechanisms involved in these age-related changes are not completely understood. Notably, the increased thickness of vessel wall constitutes an independent risk factor for cardiovascular events (160). Microscopically, endothelial cells become irregular in shape and increase in height (metaplasia). Hypertrophy, proliferation and migration of smooth muscle cells occurs in the intima and subendothelial space, with collagen accumulation, decrease and fragmentation of elastin, and deposits of hydroxyapatite, which leads to calcification. ECM is increased, containing more mature glycosaminoglycans and collagen polymers, which decreases vessel compliance, favouring peripheral resistance. The compliance of the common carotid artery decreases by approximately 40-50% from age 25 to 75 years. In the arterial wall of older people it is evident a chronic aspecific inflammatory process occurs. This is manifest with an increase in T lymphocytes, monocytes and activated macrophages, metalloproteinase activity, substantial presence of growth factors, Th1 cytokines and ACE (161). At the endothelial level, expression of

vasoconstrictive factors (such as endothelin-1 and angiotensin-II) increases, while vasodilator molecules (such as nitric oxide and estrogens) decrease (162).

Age-related arteriosclerosis is distinct from atherosclerosis associated to an abnormal homeostasis of cholesterol and saturated lipids. Arteriosclerosis results in stiffening of the large arteries and an increase of pulse wave velocity (PWV), which is a reliable and widely used index of arterial stiffening (163,164). The arterial waveform (165) shows an enhancement of the early systolic portion of the wave as a result of the earlier return of the reflected wave from the periphery due to the increased pulse wave velocity. This early systolic enhancement increases left ventricular afterload and predisposes to disturbed myocardial oxygen demand/supply balance (163,164).

7. EFFECT OF PHYSICAL ACTIVITY ON ARTERIAL AGEING

7.1. Structure and function (vascular remodeling)

The age-related increase in arterial stiffness is also responsible for changes in arterial pressure. Systolic blood pressure increases progressively, especially after the sixth decade, while diastolic pressure reaches a plateau after the fifth decade and decreases slightly after the sixth. These changes result in a widening of pulse pressure observable from the sixth or seventh decade onwards (163). The resultant pulsatile stretch of the large arteries endangers their wall integrity. Importantly, arterial stiffening (as indicated by its “gold standard” index PWV) is an independent predictor of cardiovascular morbidity and mortality, as well as of total mortality, in a wide array of populations, including patients with hypertension or CAD (coronary artery disease), as well as the general population (163,164). Arterial ageing may be slowed by adopting a healthy lifestyle. Any physical activity, including any form of recreational exercise, has favourable effects on retarding age-related arterial stiffening (163,164).

Physical activity activates sirtuins and resveratrol, provokes vasorelaxation *in vitro* and lowers blood pressure in obese Zucker rats and in various experimental models of hypertension. It is able to restore acetylcholine-dependent relaxation of aortas from both obese and aged animals: also this effect seems to be mediated by NO signaling (49,50). Resveratrol is able to upregulate the expression NADPH oxidase in vessel tissues, thereby protecting from oxidative stress and maintaining active NO signaling.

Resveratrol probably suppresses NADPH oxidase in vasculature activating SIRT1 and thus inhibiting NFκB. Overexpression of SIRT1, activating PGC-1α in endothelial cells, further suppresses NADPH oxidase expression.

Resveratrol inhibits platelet aggregation *in vitro* and *in vivo*, both in normal mice and hypercholesterolemic rabbits. It is well known that platelet aggregation is impaired by the inhibition of Mitogen-activated protein

kinase (MAPK) signaling, by phosphoinositol metabolism and by the high levels of cGMP due to NO signaling, however it is still unclear the precise mechanism by which an increased activity of SIRT1 is able to interfere with all these pathways.

Physical exercise when performed at a regular basis in particular aerobic exercise/fitness, is associated with enhanced vascular function and reduced risk of CVDs. The beneficial effects of regular resistance exercise (i.e., strength training, weight lifting, etc.) on arteries and cardiovascular disease is less evident. These observations suggest that an exercise life-style may exert its beneficial effects on general physiological functions reducing age-related CVD at least in part by preventing adverse changes in the structure and function of arteries. The initial clue that habitual aerobic exercise might attenuate age-associated increases in large elastic artery stiffness came from the Baltimore Longitudinal Study of ageing, that showed older male endurance athletes had a lower aortic PWV, increased index and systolic blood pressure as compared to sedentary controls (166). Follow-up investigations showed that age-associated reductions in carotid artery compliance were ~50% as great in healthy men and women who performed habitual aerobic exercise compared to sedentary adults (167). Daily brisk walking for at least 3 months improved carotid artery compliance in previously sedentary middle-aged/older men (167) to levels observed in age-matched endurance exercise-trained adults, suggesting that even moderate aerobic exercise may produce beneficial effects. A substantial contribution to these beneficial effects of regular exercise came from the prevention of age-related structural changes of the arterial wall (168). Ascorbic acid (and other free radical scavengers) improves carotid artery compliance in sedentary, but not in endurance exercise-trained postmenopausal women (169), suggesting that a reduction in levels of oxidative stress is achieved in the habitually exercising subjects. Improvements in carotid artery compliance in response to regular moderate-intensity exercise are independent of baseline compliance and changes in conventional risk factors for CVDs, body composition, and aerobic fitness (167).

The increased vessel sclerosis results, not only from vessel structural changes, but also from reduced endothelium-dependent vasodilation, which usually is observed in humans with advancing age (170), as is also suggested by a decreased response to acetylcholine, which involves all peripheral vessels participating, including coronary arteries (170). The production of NO is decreased, favouring vasoconstriction (171). Ageing enhances the susceptibility of endothelial cells to apoptotic stimuli, reduces angiogenic and regenerative capacity of the endothelium, decreasing the number and the function of EPCs (172). The endothelial barrier (as determined by the integrity and strength of junctional complexes, especially zonula occludens), is abnormal in aged subjects as compared to younger subjects (171). A number of cellular and molecular mechanisms underlying age-associated are strictly associated with NO decline, produced by eNOS, but have not been fully elucidated. However, upregulation of inducible NOS (iNOS) has been reported, this may lead to

the formation of peroxynitrite radicals (ONOO⁻), thus contributing to oxidative damage of endothelium and other vessels (173).

Endothelium-dependent vasodilation is accentuated in middle-aged and older men who regularly perform aerobic exercise as compared with their sedentary peers (174-177), and it is similar to (174, 175), or slightly lower than (176) that of young healthy sedentary subjects. Three months of moderate-intensity aerobic exercise training improves endothelial function in previously sedentary aged healthy individuals (174) and in patients with asymptomatic metabolic syndrome (177). Aerobic physical activity improves endothelial function in middle-aged and aged-patients with CVD, but consistent effects have not been observed in healthy young men and women with normal baseline function (174). In aged rats aerobic training-induced improvements in endothelium dependent vasodilation and NO synthesis are associated with an overexpression of eNOS (178) and in patients with CAD a SNPs of eNOS having a phosphorylatable serine (179). In relation to this, no information is available in aged healthy humans. Acute administration of supraphysiological concentrations of antioxidants (vitamin C) improves endothelium dependent vasodilation in sedentary, but not in endurance exercise-trained, men (167). Trained middle-aged and older adults have lower malondialdehyde (a marker for lipoperoxidation) and a more efficient scavenging capacity as compared with age-matched sedentary adults (180).

7.2. Coronary heart disease

A large number of studies demonstrate that moderate and constant physical activity is associated with a decreased risk of death from coronary disease. A meta-analysis of 32 studies (181) demonstrated an increased risk of death from coronary heart disease (CHD) in subjects with a sedentary lifestyle as compared to those with an active one. Sesso *et al.* (182) followed 12,516 middle-aged and older men from 1977 through 1993 to examine the impact of physical activity on CHD risk, and other coronary risk factors. He showed a clear association between the level of physical activity and reduction in CHD risk. Lee *et al.* (183) analyzed the precise relationship between the intensity (duration and strength) of exercise and CHD risk, demonstrating that the accumulation of shorter sessions of physical activity seemed to have a more beneficial effect on reducing CHD risk than longer and stronger exercise. Similar results have been reported in a study examining the relationship between physical fitness and cardiovascular mortality in 4276 men, aged 30-69 years, with a follow-up of 8.5 years (184). The authors concluded that a lower level of physical fitness is associated with a higher risk of death from CHD and other CVD in clinically healthy men, and that this is independent of other coronary risk factors. Kim *et al.* (185) studied the effect of intensity versus frequency of exercise on lipid levels in patients with CHD. Exercise frequency appeared more important than intensity in improving HDL cholesterol, the LDL/HDL ratio and in lowering the total cholesterol/HDL ratio in these patients. More recently, a

meta-analysis has been conducted to quantify cardiorespiratory fitness (CRF) and its relationship with all-cause mortality and both CHD and other CVD, in healthy men and women (186). CRF was estimated as maximal aerobic capacity (MAC) expressed in metabolic equivalent (MET) units. This study showed that individuals with low CRF (<7.9 METs in MAC) had a substantially higher risk of all-cause mortality and CHD/CVD compared with those with intermediate and high CRF (7.9-10.8 and 10.9 METs in MAC, respectively).

Sedentary elderly subjects are characterized by the presence of age-related, oxidative stress-induced endothelial dysfunction (180). Long-term physical training appears to reverse endothelial dysfunction, presumably by preventing oxidative stress, preserving NO availability (187), and preventing the thickening of the intima-media and the fibrosis of the carotid artery wall (188).

Table 2 summarizes the principal age related changes (characteristics) which are positively affected by physical activity as well as the principal tests for each change (characteristic).

8. DISCUSSION

Ageing is characterized by biological, structural and functional changes of the cardiovascular system (Table 2).

To summarize, ageing is associated with:

- reduced resistance to oxidative stress, enlargement and hypertrophy of the remaining myocytes,
- thickening of the vascular wall leading to diastolic dysfunction, which predisposes to heart failure,
- increased pulse wave velocity and ejection time delay with increased systolic arterial and pulse pressure,
- endothelial dysfunction predisposing to atherosclerotic disease,
- decreased maximal heart rate, maximal cardiac output and maximal VO₂.

Human and animal data confirm an important beneficial role of exercise in the prevention of the age-induced cardiovascular modifications. In the present review we describe these changes and highlight the effects of exercise on oxidative stress, endothelial function, cardiac and vascular remodeling (Table2).

The antioxidant role of physical exercise in man is derived mainly from experimental studies. However, some evidence suggests that older athletes have higher antioxidant capacity and lower oxidative stress as compared to older sedentary subjects and that plasma antioxidant capacity and malondialdehyde levels were not different in older athletes when compared to the younger population (180). Although it has been suggested that acute exercise can cause oxidative stress by increasing LDL susceptibility to oxidation or vascular superoxide

Table 2. Principal age related pathophysiologic characteristics which are positively affected by physical activity as well as the principal tests for each characteristic

General mechanism	Laboratory and/or instrumental test	Clinical correlate
Oxidative stress	TOSC Telomere length MnSOD Gpx MDA	Impaired contractility Heart failure
Loss of cardiac stem cell, number of pacemaker and impulse transmitting cells	ECG	Impaired lesion repair Ventricular tachyarrhythmias Bradiarrhythmias
Reduced efficiency of the intracellular Ca ²⁺ cycle	Echocardiography	Diastolic dysfunction Systolic dysfunction
Myocardium remodelling	Echocardiography	LV and LA change: thickness, size End-diastolic diameter
Vascular remodelling	Augmentation index Pulse wave velocity IMT Integrated blackscatter analysis	Arterial hypertension Arterial stiffness Arterial wall thickness Echoreflectivity
Autonomic nervous system	ECG Heart rate variability	Sympatho-vagal imbalance

TOSC= total oxyradical scavenging capacity; MnSOD= manganese superoxide dismutase; Gpx= glutathione peroxidase; MDA= malondyaldehyde; LV= left ventricle; LA= left atrium; IMT= intima-media thickness

production, chronic exercise exerts a beneficial effect on oxidative stress by ameliorating the lipid profile, and/or by increasing antioxidant defenses (181-183).

Sirtuines can be considered as mediators of the beneficial effects of physical activity in cardiovascular physiology and pathology (table 1). A pertinent and important issue is the relationship between physical activity and quality or length of human life. Regular physical activity reduces the risk of cardiovascular disease, thromboembolic stroke, arterial hypertension, type 2 diabetes mellitus, osteoporosis, obesity, colon cancer, breast cancer, anxiety, and depression. Physical activity reduces the risk of falls and injuries from falls (189), prevents or mitigates functional limitations (190,191), and is effective therapy for many chronic diseases. Clinical practice guidelines identify a substantial therapeutic role for physical activity in coronary heart disease and arterial hypertension (192), peripheral vascular disease (193), type 2 diabetes (194), obesity (195), elevated cholesterol (192), osteoporosis (196), osteoarthritis (197), claudication (198), and chronic obstructive pulmonary disease (199). Finally, a role for physical activity exists in the management of depression and anxiety disorders (200), dementia (201) and pain (202). There is some evidence to suggest that physical activity prevents or delays cognitive impairment (203), disability (204) and improves sleep (205).

Recent epidemiologic studies support an independent and inverse association between physical activity (individual fitness status) and mortality in apparently healthy individuals and diseased populations (206-210). These benefits are realized at relatively low fitness levels and, in some studies, increase with higher physical activity patterns and/or fitness status in a dose-response manner. (208) The risk reduction is at least in part attributed to the favorable effect of exercise/physical activity on cardiovascular risk factors, namely, blood pressure, diabetes mellitus and obesity .

Table 3 summarizes the inverse relationship between physical activity and mortality/ heart attack risk.

However, the majority of these studies are prospective observational studies and no randomized trial has been conducted (211). Some considerations must be clarified. An exercise volume threshold can be defined beyond which a significant reduction in mortality risk occurs. Such thresholds appear to be at caloric expenditure of approximately 1,000Kcal per week was defined as the threshold for an average reduction of 20% to 30% in mortality risk (207,208). Further minor reductions in risk are observed with higher energy expenditure. Physical activity intensity higher than 3500 Kcal/week seems to be associated to a mild increase in mortality risk (207). The benefit of a moderate physical activity occurs also in twins, therefore it is recommended even in case of a relatively low genetic-familial risk (212). The independent contribution of the exercise components intensity, duration, and frequency to the reduction of mortality risk is not clear and the need for more research to better understand the contribution of each component is emphasized (209).

Although the physical activity-mortality relationship is now well established, information on the intensity, duration, and type of physical activity is still largely speculative. An exercise intensity threshold of about 6METs for a reduction in risk has been suggested by some (213). Others have shown an independent effect of exercise type, intensity, and duration on the risk for coronary heart disease. (214).

Finally, it is not yet clear whether physical activity is related to the risk of stroke as it is to the risk of CHD (211).

9. CONCLUSION

Many cardiovascular changes occur as a result of ageing. These changes predispose an individual to different diseases. Physical activity interacts with all the principal pathophysiologic mechanisms involved. New mechanisms

Table 3. Principal clinical studies on the inverse relationship between physical activity and mortality or heart attack risk.

Physical activity intensity or type	Mortality risk	Heart attack risk	Reference, n
< 2000 Kcal/week vs ≥ 2000Kcal/week		60% higher	207
≥ 2000 Kcal/week vs < 2000Kcal/week	25-33% lower		207
1000 to 2000 Kcal/week vs < 500Kcal/week	30-40% lower		207
> 3500Kcal/week vs 1000 to 2000 Kcal/week	30-40% higher		207
Active vs sedentary job		2-3 times higher	210
30 min walk 6 times per month vs twins with no leisure time activity	44% lower		212

like sirtuins related to this interaction have been described in experimental studies. It is likely that study translation to humans will improve the understanding and management of this interaction. Furthermore the validation of blood tests like TOSCA and telomerase length will help define the parameters of optimal physical exercise in each individual. At present a moderate intensity activity (1000 to 2000 Kcal/week) shows a clinical benefit. Because noninvasive and relatively cheap tests are available for detecting and monitoring the cardiovascular changes as well as the effect of physical exercise, each ageing patient undergoing an exercise regimen should be monitored to assess the progress of cardiovascular change.

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