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Exercise prescription for the heart

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Abstract. It is universally known the link between physical inactivity and coronary heart disease. It is estimated that over 30% of coronary heart disease worldwide is due to physical inactivity. This evidence draws attention to the importance of exercise in primary prevention of heart disease and in secondary prevention measures, such as cardiac rehabilitation. International guidelines started to include exercise training beside pharmacological therapies, developing a specific type of training modality tailored for each subpopulation of cardiovascular patients and their risk factors. Many different types of exercise protocols, arranged for intensity, method, type, application, control and setting, exist and cardiopulmonary exercise test represents the gold standard for the assessment of functional evaluation in exercise prescription. In clinical practice, it is not always feasible to group patients into a specific category, due to the variety of their co-morbidities and risk factors: in secondary prevention, exercise intensity must yet be safe but also tailored to achieve the outcome goal of rehabilitation. The purpose of this report is to introduce the innovation of recent notions published in the scientific literature, trying to insert them into clinical practice giving a simple, but yet effective, instrument to the health care professionals.
Key words: *exercise prescription, sport medicine, heart*.

Introduction

Strong evidence shows that physical inactivity increases the risk of many adverse health conditions, including the world's major non-communicable diseases (NCDs), such as coronary heart disease (CHD), type 2 diabetes, breast and colon cancers, shortening life expectancy (1). Cardiovascular diseases account for most NCD deaths, or 17.7 million people annually, followed by cancers (8.8 million), respiratory diseases (3.9million), and diabetes (1.6 million) (2). It is estimated that over 30% of coronary heart disease worldwide is due to physical inactivity (2). This evidence draws attention to the importance of exercise in primary prevention of heart disease and in secondary prevention measures such as cardiac rehabilitation.

Even though exercise prescription has become a popular topic not only in cardiac rehabilitation and it started to appear on current guidelines, many clinicians experience difficulties in prescribing exercise. *The Exercise is Medicine Canada* (EIMC) workshop studied the impact of physical activity counselling and exercise prescription within health care professionals before and after EIMC training. The study pointed out the difficulties referred by physician in providing physical activity information compared with exercise professionals, also due to the lack of patients interest, resources and time. The majority of physicians (85%) provided a written prescription for exercise in <10% of appointments. Following the workshop, 87% of physician attendees proposed at least one change to practice; 47% intended on changing their practice by prescribing exercise routinely, and 33% planned on increasing physical activity and exercise counselling, measured through open-ended responses (3). One of the major adversity perceived by health care professionals in prescribing physical activity is the presence of concomitant cardiovascular diseases and risk factors within the same patient. Hanses et al. recently developed an interesting and useful digital training and decision support (EXPERT TOOL) which promise to overtake the barriers in exercise implementation (4).

Purpose of this review is to focus on published clinical guidelines, implemented with the most recent scientific notions, with the aim of overcoming the obstacles that prescription of physical exercise for the heart meets by professionals providing an easy tool consultation and quick access.

Material and Method

A comprehensive literature review was employed to identify relevant articles on this topic using PubMed as the main database.

Definition and measures of the Physical Activity

The expression ''physical activity'' (PA) refers to any bodily movement produced by the skeletal muscles that results in energy expenditure above the basal metabolic level. PA is usually described in terms of duration, frequency and intensity in order to refer to a dose useful to obtain particular physiological response and outcomes. Duration can be defined as the amount of time accrued in a single exercise session (expressed as minutes or hours). Frequency captures the number of exercise sessions over more extended periods (i.e. days, weeks or months) (5). Intensity or demand/to quantify energy expenditure can be expressed with many approaches: the two traditional ones are metabolic equivalent unit (MET) and the kilo calorie (kcal) utilization (6).

MET is a unit used to estimate the metabolic cost (oxygen consumption) of physical activity. One MET equals the resting metabolic rate, approximately 3.5 mL O_2 per kg per min, and corresponds to the amount of energy expended during one minute of seated rest (7).

With the Kcal utilization instead, energy cost is expressed as the total energy yield for the activity. If PA is related to the movements that people perform, ''physical fitness'' (PF) can be described as the amount of attributes that people have or can achieve that relates to the ability to perform PA. To define individual fitness, it is possible to refer to indexes of relative exercise intensity defining intensity as a percentage of some peak or maximal physiological parameters (for example, percent of VO_2, percent of maximal heart rate, rate of perceived exertion) (5).

Exercise is a subcategory of PA defined as a planned and structured action with the purpose of improving or maintaining physical fitness or health. Exercise involves some combination of isometric and isotonic stress. Training protocols vary in a number of variables: intensity (aerobic and anaerobic); type (endurance, resistance, and strength); method (continuous and intermittent/interval), application (systemic, regional and respiratory muscle), control (supervised and non-supervised), and setting (hospital/centre and home-based) (8).

The gold standard for the assessment of functional evaluation in exercise prescription in everyone who needs to undergo an aerobic training program is a ramp incremental cardiopulmonary exercise test (CPX) with respiratory gas analysis. Trough CPX, physiological descriptors of aerobic energetic yield during incremental exercise can be derived: VO_2 at the first and second ventilatory thresholds and peak VO_2. CPX allows to match the unique physiological responses of different exercise intensity domains to the individual patient pathophysiological and clinical status, maximizing the benefits in relation to the risk assessment (9).

Six minutes walking tests and sub-maximal exercise evaluations are presented as alternatives to symptom-limited stress testing. In clinical practice, cardiopulmonary exercise testing is not always available, and it is necessary to admit the use of alternative indirect methods to assess exercise intensity: heart rate, heart rate reserve and rating of perceived exertion. Moderate-intensity PA is usually defined as any PA level at which a person experiences some increase in breathing or heart rate and a rate of perceived exertion (RPE) of 11-14 on the Borg scale. The person should be able to carry on a conversation comfortably during the activity. It is typically characterized as energy expenditure of 3-6 METs (i.e. brisk walking). Vigorous-intensity is any type of activity that is intense enough to represent a substantial challenge to an individual and results in a significant increase in heart rate, breathing frequency and sweating. In terms of energy expenditure, it is equivalent to any activity that corresponds to more than 6 METs (i.e. jogging). Activities corresponding to less than 3 METs are characterized as light activities, but can, if the duration is sufficiently long, contribute to health (6).

Keeping all these notions in mind, it is mandatory to shift from a ''range based'' to a "threshold-based'' aerobic exercise intensity prescription in which the first ventilatory threshold marks the limit between the moderate-intensity and the high-intensity efforts domains (representing the highest exercise intensity performed without lactate accumulation) while the second ventilatory threshold has been proposed to be related to the so-called ''critical power'', the upper intensity limit for prolonged aerobic exercise (critical

power represents the highest power sustainable in conditions of both VO_2 and lactate steady-state) and it demarcates the limit between the high-intensity and severe intensity domains of effort (10).
Weatherwax and al. developed a study protocol, which will end in mid-2018, to demonstrate that an individualized approach (set on an individual's threshold such as the ventilatory one, monitoring changes in VO_2 max) should take into consideration metabolic responses to exercises to increase responsiveness to training as opposed to a standardized approach (%HRR) (11).
Considering this perspective, it is essential to know how the key concepts of exercise dose can be integrated into clinical practice.
Training modalities. General recommendation in application of resistance training in secondary prevention of cardiac patients suggest to use 30-40% of the 1-RM (one-repetition maximum) for the upper body and 50-60 % of the 1-RM for lower body exercises, with 8 to 15 repetitions in 1 set repeated two to three times weekly with a minimum of 48 hours of rest between each session (1 RM, or one-repetition maximum, corresponds to the heaviest weight which can be lifted with maximum effort in a single repetition). A single set of 8-10 exercises typically takes 20-25 minutes. Patients should increase the number of repetitions performed in each set and the number of sets before increasing resistance or weight. When three sets of 10-15 repetitions is reached, patients can increase weight load by approximately 5% and repetition reduced again. Borg Scale must be set between 11 and 14 (12).
Absolute contraindications to resistance training are unstable angina, first week after acute myocardial infarction, decompensated heart failure, uncontrolled arrhythmias including sinus tachycardia, severe pulmonary hypertension, severe and symptomatic aortic stenosis, acute myocarditis, endocarditis or pericarditis, acute systemic illness or fever, uncontrolled hypertension, postural hypotension, aortic dissection, Marfan syndrome, recent embolism, thrombophlebitis, high-intensity resistance training in patients with active proliferative retinopathy or moderate to severe non-proliferative diabetic retinopathy.
High intensity interval training (HIIT) model consists of 10 minutes warm-up followed by 4x4 minutes intervals at 85-95% peak HR, with active recovery phases of 3 minutes at 70% peak HR; this model is used both in healthy and in cardiac subjects. In contrast, shorter, sprint-type intervals of all-out severe to extreme-intensity exercise have been shown to induce rapid changes in exercise capacity, improving work performance due to enhanced skeletal muscle energy metabolism with modest effects on peak VO_2 (9).
Considering three types of models (long intervals, medium intervals and short intervals), it emerged that HIIT with short intervals, compared with continuous aerobic exercise training, was associated with lower VO_2 peak achieved. Medium to long HIIT protocols instead produced higher intensity, were less tolerated and associated with lower compliance. They can be used preferably in patient with higher aerobic fitness and would be ideally used in the improvement and maintenance stages due to their high physiological stimulus (13).
When the target is weight loss, higher intensity and duration of PA conducted on regular basis, are both associated with greater weight loss and less long-term weight gain compared with lower intensity and shorter duration. At least 10 METs h/week of aerobic exercise are required for visceral fat reduction. A minimum of 30 minutes of light to moderate activity should be sufficient in order to lose weight and prevent weight gain, with greater benefits when it lasts 45-60 minutes or the intensity rises up to moderate to high levels, with improvement also in cardiorespiratory fitness (9).
Carnethon et al. studied the impact of low cardiorespiratory fitness in young adults (18 to 30 years old) estimated by shorter duration of exercise treadmill test and how it was associated with the development of cardiovascular disease (CVD) risk factors. Cardiorespiratory fitness was inversely associated with the risk of developing hypertension, diabetes and metabolic syndrome, and hypercholesterolemia in middle age, showing the independent protective role which fitness plays. Among those who become obese earlier in life, fitness does not protect against diabetes or metabolic syndrome. Increasing treadmill test duration between visits was associated with a lower risk for developing both diabetes and the metabolic syndrome: this means that two of the most important risk factors for CHD and mortality could be modified by improving fitness over time. A modest association between fitness and plasma LDL levels is probably due to the role of genetics and diet much more remarkable (14).
Thompson et al. focused on the use of exercise prescription in clinical practice: placing the risks into perspective. Although habitual physical activity reduces coronary heart disease events, vigorous activity can also acutely and transiently increase the risk of sudden cardiac death and acute myocardial infarction in susceptible persons. Exercise-associated acute cardiac events generally occur in individuals with structural

cardiac disease. Hereditary or congenital cardiovascular abnormalities are predominantly responsible for cardiac events among young individuals, while atherosclerotic disease is primarily responsible for these events in adults. A key role is played by maintaining physical fitness through regular physical activity: this can help to reduce events because a disproportionate number of them occur in least physically active subjects performing unusual physical activity. Other strategies, such as screening patients before participation in exercise, excluding high-risk patients from certain activities, promptly evaluating possible prodromal symptoms, training fitness personalized for emergencies, and encouraging patients to avoid high-risk activities, appear prudent but have not been systematically evaluated (15).

Effects of exercise training on Autonomic Nervous System (ANS)

Regular exercise promotes functional and structural changes in the central and peripheral mechanisms of the cardiovascular system. The resting bradycardia observed in athletes is a marker of the effect of exercise training, which is related to cardiac autonomic and non-autonomic (molecular) adaptations. The balance between sympathetic and vagal arms in athletes is characterized by the predominance of parasympathetic on sympathetic drive (nominally 4:1). The cardiac autonomic control can be assessed with various techniques. A convenient non-invasive approach is based on monitoring heart rate variability (HRV). This technique evaluates the instantaneous variation of the intervals between R waves (RR interval) of the electrocardiogram. Changes in the HRV indices reflect the ability of the autonomic nervous system to respond to multiple physiological and environmental stimuli, such as breathing, physical exercise, mental stress, hemodynamic and metabolic changes, and sleep and posture changes, as well as compensating for disorders resulting from illness. Fitness level, experience, intensity, training schedule, and the athlete's daily routine can influence physiological and emotional aspects related to changes in the autonomic responses during training, and consequently the HRV indices. In sports, the HRV is proposed as a tool for temporal adjustments of the training load, diagnosis and prevention of tiredness, potentially evaluation of overtraining and aerobic capacity, and characterized by emotional aspects such as anxiety and precompetitive stress (16).

Patients with cardiovascular disease show autonomic dysfunction, including sympathetic activation and vagal withdrawal, which facilitates serious, even fatal events. Pharmacological treatments for CVD comprises a restraint of the over-activity of the sympathetic nervous system (SNS) and simultaneously an increase of parasympathetic drive. Additionally, different non-pharmacological techniques have a similar goal, such as vagal stimulation, renal denervation and carotid baroreceptor stimulation. Among the non-pharmacological techniques, exercise training (ET) is of growing interest. The therapeutic potential of restoring or enhancing the cardiac vegetative balance with ET is very promising. Therefore, the sports science concept of the heart rate variability-vagal index used to manage exercise sessions (for a goal of performance) could be extended to cardiac rehabilitation to improve cardiovascular fitness and balance autonomic nervous system regulation.

Besnier et al summarize in a recent report the beneficial effects of aerobic ET on CVD and place autonomic balance as an essential element to be considered in management for patients who benefit from a cardiac rehabilitation program (17).

The effect of ET on the autonomic nervous system can be assessed with four different measurements: muscle sympathetic nerve activity (MSNA), HRV, arterial baroreflex gain, resting heart rate (HR) and HR recovery.

MSNA, an invasive measure of sympathetic nerve traffic (usually from the peroneal nerve), is increased in patients with hypertension and chronic heart failure (CHF) as compared with healthy controls, but it can be decreased by ET.

HRV (usually considering its time domain proxies) is markedly decreased in CVD patients and predicts poor outcomes. This information is additional with reduced left ventricular function and predicts sudden cardiac death.

Defective arterial baroreflex is usually associated to sympathetic over-activity and it is also a powerful predictor of cardiovascular death. It is improved with ET in animal studies and in CHF patients; ET seems to improve baroreflex function or prevent its deterioration. In the same way, baroreflex gain is decreased after myocardial infarction (MI) but ET seems to improve its sensitivity on a long term period.

Epidemiological studies have confirmed that an elevated resting HR reflects greater neuro-hormonal activation and it is an independent predictor of cardiovascular and overall mortality in the general population and in patients with CVD. Moreover, a high resting HR affects ischemic episodes that may trigger (reflexly) arrhythmias. Keeping HR under 60 beats/ min with pharmacological treatments reduced overall and cardiovascular-related mortality. ET in patients with CVD appears to be efficient in lowering resting HR and

increasing chronotropic reserve. HR recovery after a maximal exercise stress test can be considered a proxy of vagal function. During exercise bouts, the initial increase in HR is due to withdrawal of the predominant parasympathetic activity, then, with moderate and high intensity, the effects of combined sympathetic activation become apparent (18).
Just after peak exercise, HR drops during the first few seconds and minutes because of parasympathetic reactivation combined with the decrease of sympathetic drive. HR recovery is considered an indicator of vagal function and a strong prognostic factor of cardiovascular events and death in healthy people and CHF patients (19) as well as patients with coronary artery disease (20).
Resting HR decrease and HR recovery are enhanced with an ET, presumably because of improved vagal function. In consequence, with a lower resting HR and a better HR recovery after exercise, HR reserve is increased, thanks to a better sympathovagal balance leading to improved survival in CVD patients.
Most of the studies investigate the effect on ANS of continuous moderate aerobic exercise, but also alternative interventions to traditional ET have shown their valuable effects (17).
Regarding training modalities, HIIT seems to increase parasympathetic tone and decreases premature ventricular contractions very efficiently. Passive recovery periods which characterises this exercise modality have led to a "vagal training stimulation" leading to a resetting in sympathovagal balance, as suggested by the effects on HRV. Breathing exercises or relaxation also have shown beneficial effect on increasing baroreflex gain and reducing cardiovascular risk. Transcutaneous electrical nerve stimulation (TENS) of negative feed-back afferents could reduce sympathetic activity (measured by MSNA) probably by enhanced spontaneous negative feedback (e.g. baroreflex) sensitivity, stimulating the nucleus tractus solitarius and the release of mediators (e.g. substance P), which could interact with baroreflex circuitry and decrease sympathetic outflow.
Nevertheless resistance training seems to provide a less consistent reduction of CV risk, appearing to carry smaller influences on vagal regulation (21).
The influence of respiration can be very easily deduced from perusal of the tachogram obtained from a continuous ECG. In healthy individuals, observed under resting conditions the tachogram shows periodic variation consisting of a rhythmic phenomenon known as respiratory sinus arrhythmia (RSA). RSA fluctuates with the phase of respiration with cardio-acceleration during inspiration and cardio-deceleration during expiration. Vagal efferent trafficking to the sinus node occurred primarily in the phase with expiration, and absent or attenuated during inspiration. As a dynamic marker of loads, HRV appears to be sensitive and responsive to acute stress (and also mental load). Aging process decrease HRV at rest possibly through a decrease in efferent vagal drive and reduced adrenergic responsiveness. On the other hand, molecular age remodeling cannot be excluded. Conversely regular physical activity retards the aging process, increasing HRV, presumably by increasing vagal tone (22).
The clinical applications of HRV are still in their infancy, because in spite of the abundance of studies, of several aspects of HRV that still require clarification (23).
A convenient summary of the methodologies and of the indices employed to assess either in time or frequency domain the beat by beat variations of the RR interval is provided by the Task Force standards proposed in 1996, that discuss both short (few minutes) and long term (24 h) recordings. In brief summary: The period between the individual QRS complexes resulting from sinus node depolarization's is termed the normal-normal (N-N) interval. HRV is the measurement of the (time domain) variability of the N-N intervals. Frequency-domain analysis describes high and low frequency (LV) components of the variability changes, reflecting the activity of different branches of ANS. Still debated is the relationship between HRV parameters and underlying neural activity (peripheral, i.e. vagal and sympathetic, and central oscillations).
In particular, it is not fully appreciated that absolute and normalized powers of spectral components may carry a different meaning. Likewise absolute and higher order modulation codes might be necessary to unravel the meaning of neural (vagal and sympathetic) activity and hidden modulation (such as LF and HF, better expressed in nu) (23). An important element for the clinical applications of HRV is the time-domain parameter reflecting the standard deviation (SD) of all N-N intervals (SDNN) that reproduce the total variability and the root mean square of SDs between adjacent N-N intervals (RMSSD), which reflect parasympathetic activity. Another model that may be considered is the Pointcaré plot, calculated as follows: an individual's R-R intervals plotted over time and SD used to interpret changes are evident in the plot. The standard descriptor 1 (SD1) is the fast beat-to-beat variability in the R-R intervals, while the standard

descriptor 2 (SD2) describes the longer-term variability. SD1 reflects mainly the parasympathetic input to the heart, while SD2 reflects the sympathetic and parasympathetic contributions to the heart (22).
Athletes exhibit a different HRV profile compared with sedentary control subjects, with an overall increase in HRV and parasympathetic cardiac modulation, while evidence suggests that high-intensity training can chronically lead to a shift vagal to sympathetic cardiac modulation. In recreational marathon athletes, the progressive sympathetic predominance at peak training load may predict performances in the race. However endurance elite athletes have an elevated parasympathetic tone compared to recreational athletes and non-athletes confirming that athletic conditioning is an important variable that in influences the autonomic control of the heart (22).
Athletes exhibit a different HRV profile compared with sedentary control subjects, with an overall increase in HRV and proxies of parasympathetic cardiac modulation, while evidence suggests that high-intensity training can chronically lead to a shift from vagal to sympathetic cardiac modulation. Endurance elite athletes have high values of parasympathetic markers compared to recreational athletes and non-athletes confirming that athletic conditioning is an important variable that is capable to set the autonomic control of the heart (22). In recreational marathon athletes, the progressive LF predominance at peak training load may predict performances in the race.
Enhanced markers of sympathetic regulation during an intensive training program suggests that this change in autonomic balance prior to competition may represent the sign of a neural adaptation enabling the cardiovascular system to prepare for demanding competition, enhancing athletic performance. Moreover, the HRV is a sensitive measurement of adaptation to physical and psychological stress, and also establishes a relationship between behavioral aspects such as attention and emotion. In competitive sports, the HRV is sensitive in detecting the autonomic changes caused by precompetitive anxiety. Generally, signs of low vagal drive suggest poor system adaptation, and it can be related to overtraining (24).
Literature survey recommends for short-term recording the use of frequency domain measurements. Notably, time domain measures are more consistent than frequency domain to describe the chronic cardiovascular autonomic adaptations in athletes. In addition other factors should also be considered such as changes in heart geometry that may be responsible for parts of adaptation (16).
The determination of HRV immediately post-exercise in different training regimens resulted in different changes in HRV. Indeed, HF values during the first hour after exercise resulted to be higher after constant intensity training when compared with interval training. The early recovery of autonomic modulation from 5 min to 1 h after termination of exercise were greatly dependent on the allocation of training of exercise load (25). In particular, Sala et al demonstrated that athletes showed a slower return of parasympathetic activity during short-term recovery after an interval (intensive) method of training relative to constant intensity of exercise (26). This suggests that the slower return may be due to less efficient recovery of the parasympathetic activity or for a more pronounced sympathetic involvement during the interval method relative to the stable method. By contrast, the late recovery of 24 and 48 h after termination of exercise did not depend on the type of exercise (interval training or constant identifying of exercise) (22).
Long-term HRV changes during a prolonged period, over 4 weeks of exercise has been shown to be a particularly good indicator of physiological adaptation in athletes able to assist in the planning training programs (22).
The usefulness of HRV measurements in prescribing exercise has also been identified in moderately active people: training (not only for highly trained but also inactive people) could be structured with weekly micro-cycles to improve cardiovascular fitness or cardiac recovery or induce an overload of training to progress fitness (27).
For example, to maximize recovery, the period of rest and low-intensity training sessions are increased and the frequency of high-intensity training sessions is reduced, each separated by at least 48 h of recovery to allow for beneficial compensation of the cardiovascular and autonomic systems. While improving cardiovascular fitness, the weekly micro-cycle is structured with consecutive high and moderate intensity training followed by a rest day to induce improvement. It has been demonstrated that in CHF the presence of a lower pre-training HRV index is associated with less improvement in physical capacity after a cardiac rehabilitation program. It is obvious that the pre-training HRV index could help identify patients who need specific individualized training to improve cardiovascular capacity and it could be helpful to distinguish ‘‘responders’’ and ‘‘non-responders’’ to an ET program. With the concept of a weekly micro-cycle described before patients could benefit from a session of HIIT or low intensity, or rest, depending on their HRV values. Daily HRV measurements may help determine the type of exercise session (low or high intensity or rest)

based on the status of apparent autonomic regulation. In cardiac rehabilitation centers, the optimal ET program to improve clinical values must consider individual characteristics of patients; exercise prescribers should be adequately trained to adapt the features of physical exercise sessions to each patient according to their needs, desires and physiological values. In this context, the use of HRV has become an approach to measuring fatigue well inspired by the concept derived from sports science, which uses the HRV-vagal index to manage exercise sessions (17).

However in athletes, HRV monitoring is frequently applied to prevent and diagnose overtraining (OT) syndrome which is associated with numerous syndromes such as ANS dysfunction and imbalance. It's possible to detect it through the measurement of the orthostatic HR change that occurs between sitting and standing. Athletes in an OT state may show a significant decrease in frequency domain (TP, LF and HF) and time domain (RMSSDD and SDNN) variables. Moreover, it has been demonstrated a hyper-responsiveness in the frequency and time domain in OT athletes. In this context, Sala et al observed that in world class Olympic athletes, a small subset of RR variability indices, related to sympathovagal balance, may be more appropriate than RR variance to assess excitatory sympathetic autonomic responsiveness of SA node and discriminating between two physiological conditions (laying rest and stand) related to posture and autonomic activation. These finding may have practical implications for the use of RR variability in guiding training and predicting success in competitions when added to RR value and time domain indices (variance or SD) (26).

HRV can also be used to detect the non-functional overreaching (NFOR) states, which are periods when athletic performance is substantially decreased, due to prolonged intensive training. The hypothesis behind the early detection of NFOR, OT and fatigue is the possibility of good recovery, involving the acquisition of rest before training continues to allow repair to the body and to strengthen it between workouts. The performance begins to decline if the recovery is not totally achieved as shown in the OT syndrome. In the OT syndrome, the training for an event or the event itself pushes beyond the body's ability to recover.

Sala et al have recently proposed a unitary cardiac autonomic nervous system index (ANSI), obtained combining multiple metrics from heart rate variability (such as RR interval, TP, LF and HF components in both absolute and normalized units, LH/HF and the stand-rest difference in LFnu) to provide an easily and more handy parameter to appreciate autonomic performance in a clinical setting (28). They end up stressing that ANSI does not evaluate underlying neural activity, but quantifies the ANS impairment associated with different clinical conditions (hypertension, obesity, smoking) and the greater impact of their combination if simultaneously present in the same subject. The conditions in which the unitary index can find the most interesting application are: monitoring the role of ANS in physical activity and training; detecting the role of ANS in development of diseases such as hypertension, CAD, heart failure and diabetes revealing its dysfunction before the onset of the disease; improving ANS profile by lifestyle interventions; exposing ANS as the only altered clinical parameter in functional syndromes or in particular situations like OT syndrome and overreaching in sport.

ANSI has also been tested in a population of elite athletes as a marker of quality cardiac autonomic regulation fine-tuned according to intensity of habitual physical exercise (it is remarkable lower in disciplines such as shooting, with low physical activity level, despite disciplines such as cycling in which physical activity level required is higher). Moreover a correlation between intensity of physical activity and biochemical values has been demonstrated, and thanks to the fact that ANSI seems to correlate with HLD, triglycerides and glucose levels, this suggests that better autonomic quality corresponds to better biochemical profile also in elite athletes (21).

Effects of exercise training on Physical Fitness

Back to the definition of physical fitness, we can easily consider it as one of the most important health markers because it integrates most of the body functions (skeletomuscular, cardiorespiratory, hematocirculatory, psychoneurological and endocrine-metabolic) involved in performance of daily physical activity and exercise. When we test physical fitness, we indeed check the functional status of all these systems. The health related fitness components of a person include a cardiorespiratory component, a muscular component, a motor component, a morphological component and a metabolic component. Various tests can be performed to measure physical fitness: from self-assessment techniques over simple field test to more specific laboratory tests (29).

The World Health Organization (WHO), considered the maximal oxygen consumption (VO_2max) as the single best indicator of cardiorespiratory fitness and it can be estimated using a maximal or sub-maximal test (e.g. treadmill or bicycle tests, 2km. walk test, 20-m shuttle run, 6 min. walk test). According to muscular component, the handgrip strength test is one of the most used tests for assessing muscular fitness being a strong predictor of morbidity and mortality. For assessing power strength or muscular endurance jump, dynamic sit-up and bent-arm hand tests have been used with young, adult and older people. Agility, balance, speed or co-ordination is included in the motor component. Agility is a combination of speed, balance, power and coordination. Some tests used to measure motor component are 30-m sprint test and 4 x 10-m shuttle run test for young people and 30-m walk test and 8-foot-and-go, for older adults. For measuring static balance, single leg balance, with or without open eyes, is a good alternative test. Flexibility is a morphological component; chair sit-and-reach test and back scratch test are two validated tests for measuring this capacity.
Biomarkers have been of interest in sport in order to measure performance, progress in training and for identify overtraining (29).
Markers of chronic stress and fatigue are cortisol and testosterone. In some athletes, the stress response mediated by cortisol to an intensive exercise (as to any type of stress) can be activated so often that the metabolic pathways do not always are able to return to normal basal values. Salivary cortisol correlates with session-RPE (the load of training placed on an athlete) and countermovement jump (CMJ) (indicator of neuromuscular performance). Moreover it has been demonstrated that salivary cortisol levels are significantly different depending on the intensity of the exercise (the higher the intensity, the higher the elevation of the biomarker). In addition, it correlates also with training status of subjects (highly-trained subjects show an inverse and significant correlation with neuromuscular performance). When dosed at the start of the season, elevated values of cortisol may relate to significant reductions on performance during the season (however this relation is the opposite when shorter period of time are assessed). Cortisol is also capable of induce the inhibition of the testosterone synthesis (which increases muscle mass and strength reducing also the amount of muscle fat) and the cortisol/testosterone ratio is performed as an index of chronic fatigue in athletes (29).
Marker of overtraining are lactate, creatinine phosphokinase (CPK), creatinine, ammonia, lactate dehydrogenase (LDH), uric acid and urea. Lactate levels are the most utilized: they increase incrementally with exercise intensity, reaching the lactate threshold (4.0 mmol/L); fatigue onset appears fast above the threshold limit, while efforts just below the limit can be for hours if athletes are well trained. Too much training or above the lactate threshold can result in overtraining. So the blood lactate measurement is used to determinate not only the threshold but also the correct intensity of exercise and the time need to recover, detecting whether or not the training is producing the desired physiological effect. Ammonia is gaining increasily more importance, because rising levels are related to fast twitch muscle fibers and the effort intensity of exercise (29).
Markers of cardiovascular risk are homocysteine (Hcy) and cardiac troponin. The results regarding the first one are contradictory: theorically beacause PA contributes to reduce CV risk factors and Hcy is one of them, Hcy could be used as biomarker of CV health when PA is performed. However, it has been shown that an intensive and acute exercise tends to increase Hcy blood levels; effects of resistance training are controversial because while resistance training seems to reduce Hcy levels, intensive training increases them. cTnI and cTnT rises in case of muscular heart damage but in absence of cardiac symptoms, after intense or prolonged exercise, suggests muscle lesions, due to adaptation of training (29).
Parameters of oxidative stress are also gaining in importance. They are malondialdehyde (MDA) and protein carbonyls (PC), as indices of lipid peroxidation and abnormal albumin oxidation, superoxide dismutase (SOD) and glutathione peroxidase (GSH), as antioxidant enzymes which moderately increase when resistance training is performed, and reactive oxygen species (ROS), seen as something of beneficial rather than harmful, since free radical act as signals to improve the defences when cells are exposed to high levels of ROS (29).
Markers of inflammation are C-reactive protein (CRP), Interleukin-6 and leukocytes. CRP is reduced when continuous training is performed. Higher levels after training indicates lack of adaptation or overtraining, probably due to oxidative stress. After adaptation to training, however, values are normalized. IL-6 rise up to 100 times with intense ET, and it leads to up-rising lipolysis in adipose tissue and improvement insulin sensitivity in the liver. Finally: exercise causes a transient leucocytosis, which magnitude is directly related to the intensity performed and the training status (more pronounced in maximal exercise and poorly trained subjects). However, they reaches again basal levels after 24 hours (29).

Changes in circulating CVD biomarkers and cardiorespiratory fitness (CRF) are useful indicators for the impact of exercise training on cardiovascular health. CRF can be added to traditional CVD risk factors in order to improve their prognostic power and it has been used as an indicator of habitual exercise. Moreover, it appears as an independent predictor of CVD risk, CVD mortality and total mortality. Beside the traditional markers of CVD, such as non-high-density lipoprotein cholesterol and high-sensitivity C-reactive protein, a plethora of new biomarkers appears into the risk assessment scenario, related to insulin resistance and inflammation. ET significantly lowers the levels of triglycerides and increases the levels of HDL-C and apolipoprotein A1 (this finding, though, strengthen the hypothesis that exercise may accelerate reverse cholesterol transport). The improvement in lipids profile may also be related to the effects on lipoprotein lipase expression and activity. Randomized controlled trials have shown lower levels of fasting insulin, homeostatic model assessment-insulin resistance and glycosylated haemoglobin A1c in exercise groups compared with controlled ones, and interleukin-18 and lower levels of leptin, fibrinogen and angiotensin II. Exercise could mitigate the chronic inflammation in adipose tissues (as presents in obese patients), resulted in improved insulin sensitivity. Moreover exercise effects are modulated by age, sex and health status such as age<50 years, men, type 2 diabetes, hypertension, dyslipidaemia or metabolic syndrome appeared to benefit more (30).

Edward et al. wanted to analyse if the independent associations between physical activity, sedentary behaviour and cardiorespiratory fitness with leukocyte telomere length (LTL) can be established also in association. Indeed, PA has demonstrated to extend LTL, which is, if shortened, a hallmark characteristic of aging process and it is associated with a number of chronic diseases. Moderate-vigorous PA (MVPA) seems to play the most important role in telomere preservation and probably different PA may impact in different ways on LTL. The study did not observed a as strong association between LTL and cardiorespiratory fitness as well as with moderate-vigorous PA, probably because there are many factors that can contribute to cardiorespiratory fitness, such as genetics ones. In conclusion participants who engaged in more PA, sat less, and had higher cardiorespiratory fitness had the longest LTL, but only moderate-vigorous PA was independently associated with LTL (31). MicroRNA (miRNAs) are small non-coding RNA molecules that regulate gene expression post-transcriptionally. Circulating miRNAs are involved in intercellular communication and can be used as biomarkers for disease and exercise-related traits. They can contribute to exercise screening, monitoring and developing of personalized exercise prescription. Denham and Prestes studied the impact of long-term strenuous aerobic exercise training and a single bout of maximal aerobic exercise on five muscle-enriched miRNAs implicated in exercise adaptations (miR-1, miR-133a, miR-181a, miR-486, and miR-494). Relative to controls, endurance athletes exhibited increased miR-1, miR-486, miR-494 content, while miR-1, miR-133a and miR-486 were decreased immediately after maximal aerobic exercise performed by 19 healthy young men. They found positive correlations between miRNA abundance and VO2max and an inverse correlation between miRNA-486 and resting heart rate. The whole blood muscle-enriched miRNAs are predictors of cardiorespiratory fitness parameters and can be considered as regulators of exercise-induced adaptations: it is possible that aerobic exercise training up-regulates miR-1 and miR-486 expression to promote myoblast differentiation and proliferation and enable the metabolic reprogramming of skeletal and heart muscle to promote adaptations leading to physical performance. Increased miR-486 and miR-494 could encourage exercise-induced physiological left ventricular hypertrophy and subsequent augment VO2max and endurance performance by deregulation PTEN. miRNAs seem also to reflect exercise status. Non-fasted, healthy individuals with relatively low VO_2max possessed increased plasma miR-21, miR-210 and miR-222 content compared to those with high VO2max (32).

Exercise prescription in selected cardiac patient groups

At the population level the most recent guidelines by US Department of Health and Human Service (HHS) in 2008 and WHO in 2010 suggest a total of at least 150 minutes of weekly moderate-intensity activity (3-6 METs) or 450 to 900 MET-min/wk (33-34). The American Heart Association and American College of Cardiology recommended the same total amount of exercise but divided into sessions of longer duration (40 instead of 30 minutes) performed less frequently (3-4 rather than 5 sessions per week) (35). This appears to be the minimum amount of exercise required to reduce the all-cause mortality rate.

In addition, every adult should perform activities that maintain muscular strength and endurance a minimum of two days per week. 8-10 exercises should be performed on two or more non-consecutive days each week using the major muscle groups. To maximize strength development, a resistance should be used that allows

8-12 repetitions of each exercise resulting in volitional fatigue. Muscle-strengthening activities include a progressive weight-training program, weight bearing calisthenics, stair climbing and similar resistance exercises that use the major muscle groups (6).
For older adults, a combination of aerobic exercise training (AET) and resistance exercise training (RET) seems to be more effective than either form of training alone in defeating the effects of sedentary lifestyle on the health and cardiovascular and skeletal system. Such programs do not need to be go high intensity in order to reduce CVD and metabolic risk, but for some established diseases and geriatric syndromes a higher-intensity dose seems to be more effective. The chronic adaptations to repeated sessions of exercise is rapidly lost, even in more active older adults, when the training stops. Exercise prescription in older adults should include aerobic exercise, muscle strengthening exercise, flexibility exercises and, if the risk of falling is high, also balance exercise (36).
There is a significant link between low PA levels and an increase in cardiovascular risk factors also in children, and it is now demonstrated that those who engage in PA at young age are likely to continue this habit later in life. A Cochrane review shows the importance of school-based physical education program in decreasing in prevalence of obesity, reductions in blood lipids, increasing in PA levels and fitness (37-38).
Literature about exercise prescription in women is poor and not well developed. Lawton et al showed in a randomized control trial the effects of an existing primary care program, the green prescription, on 1089 women aged 40-74 relative inactive over a period of 24 months. Compared with the control group, the intervention group reached the target of 150 minutes of at least moderate intensity physical activity more than the first one, keeping it higher, despite the deterioration over time, than the control group not only at 12 but also at 24 months (39).
The first ventilator threshold, also known as anaerobic threshold, is with large consensus considered the target for all cardiac patients suitable for cardiopulmonary rehabilitation. Meyer et al first proposed it for chronic heart failure patients (40), while Tan et al studied it in a non-homogenous population who underwent cardiopulmonary exercise stress testing in order to demonstrate that the heart rate at ventilator anaerobic threshold would not exceed heart rate at ischemic threshold. They demonstrate that this benchmark can be applicable to patients with mixed cardiac lesions, ensuring the safety keeping the exercise intensity below the myocardial ischemia threshold but yet achieving the desideratum outcome of rehabilitation (41).
Chronic heart failure patients demand a specific structured exercise training (ET) which is recommended for stable NYHA class I-III HF patients. The key words are clinical stability and early but gradual mobilization in order to improve movement co-ordination and respiratory capacity. Three different training modalities have been proposed with different combination: the first one is endurance aerobic training (both in continuous and in interval setting), with the recommendation of starting low and going slow in more deconditioned patients, incrementing slowly the amount of exercise, the duration and the number of sessions if well tolerated. Recommended training intensities are 40-50% at the starting point, increasing to 70-80 of the percentage VO_2peak (corresponding to a heart rate reserve-HRR range of 40-70%) (8).
The SMARTEX - HF study disavowed the superiority of HIIT training in comparison with moderate continuous training in changing left ventricular remodelling or aerobic capacity, and its feasibility in HF patients remains unresolved (42). The second one is resistance/strength training (RST), clearly seen as a complement but not substitute of endurance exercise in CHF patients. To implement RST is suggested to go through 3 phases: instruction, resistance/endurance and finally strength phase going from 12-25 repetition at low intensity (30-40% of 1-RM) to higher intensity (40-60% 1-RM). Finally, the third one is respiratory training, suggested to start at a 30% of the maximal inspiratory mouth pressure and to readjust the intensity every 7-10 days up to a maximum of 60% (20-30 min/day with a frequency of 3-5 sessions per week for a minimum of 8 week). ICD and CRT patients should set a level of training keeping the maximal HR 20 beats under the ICD intervention zone (8).
Coronary Artery Disease (CAD) patients, if stable, should engage in regular physical activity. They should exercise 3 times per week for at least 30 minutes, including 5 minutes of warm-up and cool-down calisthenics and at least 20 minutes of exercise at an intensity requiring 70-85% of HR peak (43).
Stable angina pectoris (SAP) patients have one mandatory consideration during training: exercise safety. It is suggested exercising three to five times per week following a warm-up of five to 15 minutes, at moderate to high intensity (always below the ischemic threshold) for a period of 20 to 40 minutes followed by a cool-down period of 5 to 10 minutes (9).
The same evidence of SAP patients can be applied post-PCI: it has been found that high to severe-intensity interval training helped to reduce six month restenosis in the stunted segment, improves left ventricular

remodelling and increase endothelial NO production (44).
Pacemaker patients follow the same principles of non-pacemaker ones. If an exercising patient's chronotopic response exceeds the PM upper-rate limit, the device should usually produce a Wenckebach pattern to maintain a relatively high HR without risking rapid ventricular responses (9).
Chronic atrial fibrillation patients benefit of both light to moderate and moderate to high-intensity domains of dose exercise, monitoring it better with RPE than HR due to the highly variable ventricular chronotropic response (9).
Patients undergone traditional open chest coronary artery by-pass graft surgery (CABG) can start the rehabilitation program 2-3 weeks post-surgery, refraining the upper extremity aerobic exercise training for at least 4-6 weeks post-surgery to ensure the stability of the sternum wound (9).
Also valvular repair or replaced patient benefit of both light to moderate and moderate to high domains of exercise dose. Only not repaired less-severe aortic stenosis can exercise but the development of symptoms, index of inadequate cardiac output, suggest to keep the upper limit under the threshold that precipitate them (9).
Heart transplanted patient are better prescribed by the Borg scale: starting with a 10-12 RPE intensity, they can slowly increase the amount of exercise to higher intensity (9).
Peripheral artery disease patients show early benefit from the initiation of the training program (even in the first 4 weeks) (7). They should walk at least 3 times weekly to their maximal tolerable pain, rest and then resume the process for at least 30 minutes per session (43).

Conclusions

Field of exercise medicine is markedly improving in the recent years. New topic must be explored such as the effects of PA and sedentary behaviour on multiple health outcomes in youth, adult, women and seniors; strengthen the understanding of dose-response relationships between PA and multiple health outcomes especially during the life transitions between different ages; the role of demographic factors in influencing the relationship between PA and health outcomes; determining the role of light-intensity PA alone or in combination with moderate-to-vigorous PA to health outcomes.
New goal for the future is the acquisition of more information about the benefits of physical activity and the type and volumes needed to reach them, in order to develop guidelines able to be applied to everyone who needs. Also gains in the area of primary prevention and promotion of physical activity are requested.

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