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Integrative Approach of Venous Return And Cardiac Output in the Context of Skeletal Muscle Atrophy

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Abstract

The progression of venous return impairment is related to the evolution of muscle atrophy. Venous return is influenced by factors such as blood volume, pressure gradient between the veins and atrium, and venous resistance determined mainly by vascular diameter, which might all work in a compensatory manner in the event of loss of skeletal muscle mass to prevent the progression of vascular problems. It is expected to occur a continued progression in the loss of venous return, and in the loss of muscle mass. The latter represents the main factor of influence on this hemodynamic mechanism and on cardiac output. There are significant data on venous return, exercise and muscle atrophy, but few are associative data between these subjects. In this sense the literature gap hinders the development of and/or therapeutic application to subjects with muscle atrophy. The proposed manuscript addresses the relationship between loss of muscle mass and impairment in venous return and, consequently, in cardiac output. In this context, the present review also brings some perspectives on the viable biomarkers used to indicate the integrative function of the venous return and cardiac output.

Keywords: Venous return; Cardiac output; Skeletal muscle atrophy; Biomarkers; Reactive oxygen species

Introduction

The main function of the cardiovascular system is to supply cells with nutrients and oxygen and to remove excretes from their metabolism. This function, along with the general constitution of the cardiovascular system, has been known since Harvey's findings in the 17th century. He demonstrated that the heart was the central organ of the cardiovascular system, and that it was responsible for propelling the blood to the arteries and veins and back to its starting point. This unidirectional blood flow was ensured by Harvey's description of valves in the venous system, which allows blood to flow toward the heart preventing it from going in the opposite direction [1,2].

In the 19th century, Bayliss and Starling broadly described function and control of the venous system [3]. Afterward, in the 1950's, Guyton et al. [4-8] further explored the venous system control and its relationship with right atrial pressure. Nevertheless, during the years, the venous side physiology has not been as appreciated as the arterial side; hence it being left out of the circulatory system physiology. Currently, the two basic known functions of the venous system are to return the blood from the periphery to the right atrium and to store large amounts of unneeded blood serving as a reservoir [9].

This system contains about 70% of the total blood volume while only 18% are in the arteries [10-12]. Approximately three-fourths of the 70% are in small veins and venules, especially in the systemic venous circulation [12-14]. Such difference is due to the much higher compliance of veins when compared to the arteries (30 times greater) enabling the venous system to alter its blood volume without producing any significant changes in venous pressure [9,10]. For this reason, veins are usually called capacitance vessels, undoubtedly the most important blood reservoir within the circulation, and they play an important role in maintaining filling pressure in the right heart [13-15]. The most important blood reservoir within the venous system is the splanchnic region (liver, spleen, and small and large intestine) for two reasons: it has the highest compliance, holding about 30% of the total blood volume, and is richly innervated by the sympathetic nervous system [14-16].

The hemodynamic mechanism that involves the rate of venous blood return to the right heart through the venous system is defined as Venous Return, and is equivalent to the Cardiac Output at steady-state conditions [13,14,17].

The functionality of the venous system depends on valves or valve-like structures, which are more prominent in deep limb veins and in the legs [18,19]. Skeletal muscles surround these structures, and, therefore, serve as an external pump that compresses the veins to ensure the unidirectional blood flow back to the heart [13,14,20].

Venous Return Determinants

Hemodynamic parameters that determine venous return and, consequently determine cardiac output include: blood volume (unstressed and stressed volume), mean circulatory filling pressure, right atrial pressure, and venous resistance [9,21,22]. Furthermore, venous return from lower extremities can be profoundly influenced by the skeletal muscle pump and by valve function; these are important mechanisms during exercise performance [19,20]. Thus, effective venous return depends on adequate interactions between the central pump, the pressure gradient (peripheral and central pressure), a peripheral venous pump, and on competent venous valves [19]. Hemodynamic factors affect or can be affected by vascular capacity.

Since the venous system is the body's main blood reservoir, any change in its capacity greatly influences venous return (altering

preload) and, in turn, affects cardiac output and blood pressure [13,14,22]. Therefore, in physiological conditions, we can assume that cardiac output depends entirely on venous return and on all its determining factors [15,21].

Unstressed and Stressed Volume

The total blood volume contained in the circulation at a specific distending pressure, e.g., the baseline distending pressure, is named vascular capacity. This volume can be divided into unstressed and stressed volumes [13,14,22,23]. The former is the volume of blood that fills the vessels to capacity without increasing transmural pressure, the difference between the pressure inside the vessel and outside the vessel wall [9,14,15,22]; it represents about 70% of the total volume and is hemodynamically inactive [14,15,24]. Conversely, the latter is the volume of blood that stretches the vessels and generates a positive transmural pressure [9,14,22]. Due to the pressure, stressed volume is considered hemodynamically active; it represents approximately 30% of total volume [9,14,15].

Despite unstressed volume not being considered hemodynamically active, in some situations, e.g. alterations in blood vessel capacity and in the smooth muscle activity, it can be reduced or enlarged [14,22]. The unstressed volume can be reduced by venoconstriction through diminished inflow or decreased transmural pressure; on the contrary, it can be increased by venodilatation through increased inflow or augmented transmural pressure [14]. Unstressed volume can become stressed volume, acting as a blood volume reserve, which is quite important under various conditions such as hemorrhage and exercise [13-15]. Therefore, alterations in stressed volume can directly affect cardiovascular hemodynamics through changes in venous pressure and, consequently, in venous return and cardiac output [15].

Mean Circulatory Filling and Right Atrial Pressures

The mean circulatory filling pressure is the hypothetical mean vascular pressure in the systemic circulation that would be observed if the heart were stopped and the pressure in all parts of the circulation, from the aorta to the right atrium, were equilibrated [14,17,25]. This concept of "mean systemic pressure" at zero flow was established in 1850 by E.H. Weber [apud 21] and was further linked to the cardiovascular system by Bayliss and Starling [3]. After having performed a sympathectomy to induce cardiac arrest, by vagal stimulation in a dog model through the insertion of a cannula in the femoral artery and vein, portal vein, inferior vena cava and aorta, Bayliss and Starling [3] demonstrated that under these circumstances, the pressure at these points reached an equilibrium with values about 5 to 10 mmHg. Additional studies have observed that the mean circulatory filling pressure measured in patients in the intensive care unit is approximately 18 mmHg (or 12 mmHg, considering central venous pressure zero) [26]. Therefore, it can be assumed that this pressure is a reflection of how tightly the blood volume fills the venous and arterial systems [23].

Normally, when the heart pumps blood, the arterial pressure rises and the venous pressure reduces compared to the mean pressure of the system. This pressure gradient between the vessels allows that blood to be pushed through the arterial system, capillaries and venous systems and, subsequently, back to the heart. Nevertheless, the pressure within venules and small veins, the primary sites of compliance, is the same during active circulation and cardiac halt [15,25]. For this reason, this pressure is considered to be the equivalent of mean circulatory filling pressure. Therefore, it can be postulated that, under normal conditions, mean circulatory filling pressure resides in small venous territory, and is the main driving force (the upstream pressure) that determines the rate of venous return and thus cardiac output [4,5,22,23,25].

The total stressed blood volume primarily determines the mean circulatory filling pressure. Other factors, however, such as venous compliance, ventricular contraction and relaxation, venous valve function and skeletal muscles can alter it as well [14,15]. An increase in stressed blood volume, by means of infusion of additional volume, and/or by a decrease in venous capacity by venoconstrictors, or skeletal muscle contraction, raises mean circulatory filling pressure and consequently increases the venous return [9,15,21]. Similarly, a reduction in venous compliance, in the absence of a change in blood volume, also evokes an increase in mean circulatory filling pressure and in venous return [14]. For this reason, the mean circulatory filling pressure is considered to measure the effective volume status (theoretically) independently from cardiac function [22].

The cardiac function can only affect venous return indirectly by changing right atrial pressure (the downstream pressure), and consequently altering the driving pressure gradient [9]. Guyton et al extensively demonstrated this relationship through the venous return curve [4,5,7]. This curve represents the steady-state relationship between stepwise changes in right atrial pressure and the resulting changes in venous return, which is a function of the circulating blood volume, vasomotor tone and blood flow distribution [22]. When the right atrial pressure is 0 mmHg, the gradient between the upstream and downstream pressures is the greatest and the venous return reaches a maximum. If the right atrial pressure falls below 0 mm Hg, it produces a suction force that initially increases venous flow but, shortly after, limits the venous return at a plateau due to extrathoracic veins collapse [27]. On the other hand, if right atrial pressure rises, venous return is reduced. It is noteworthy that venous returns can only be zero when there is no pressure gradient between the upstream and downstream pressures. This occurs when the venous return curve intercepts the X-axis and, at this point, right atrial pressure reflects the mean circulatory filling pressure [25]. Furthermore, the derivative of any point of this curve describes the resistance for venous return, also referred to as venous resistance [9,22].

Venous Resistance

Different from arterial resistance, venous resistance is lower, but is an important determinant of venous return due to the low pressure and the high capacity of the venous circulation. Whereas altering the tone of arterioles mostly affects resistance, in veins it mostly affects capacity. Thus, it is volume rather than resistance that is controlled in order to regulate the circulation [28]. In this context, it is postulated that venous resistance depends on the combination of resistance and capacitance (the relationship between contained volume and distending pressure of a segment) in different portions of the peripheral circulation. Small veins and venules have very large cross-sectional areas with high capacitance and, thus, they have little contribution to venous resistance, serving mainly as a blood reservoir. On the other hand, large central veins such as the vena cava, and peripheral large and medium-sized veins have small cross-sectional areas with little capacitance, acting primarily as a conduit and having small contribution to the blood reservoir. Therefore, venous resistance is mainly determined by these conducting veins, which can be passively affected by blood volume alterations in the reservoir

compartment, by autonomic stimulation, and by vasoactive mediators [9,14,21].

Many factors, such as the diameter of vessels and blood viscosity can alter venous resistance [9,22]. Constriction of conducting veins can directly increase venous resistance, although it causes only a minimal effect when compared to the arterial side as mentioned before. An increase in blood viscosity (polycythemia) can also increase venous resistance. Nevertheless, the main mechanism by which venous resistance is altered is by redistribution of blood between different vascular beds through vasoconstriction mainly in the splanchnic region [21,22]. Venoconstriction and venodilation in different parts of the systemic circulation is controlled mainly by a counterpoise between α-adrenergic and β2-adrenergic activation. α1- adrenergic activation of a vascular bed produces venoconstriction and, thereby, decreases its unstressed blood volume while increasing its stressed volume. These alterations evoke a brief rise in upstream pressure and expel blood into the systemic circulation [22]. Most of the venoconstriction occurs in the splanchnic circulation due to a more prominent innervation and a greater sensitivity to sympathetic stimulation than arterial resistance vessels [15,19,21]. Still, it is important to point out that the splanchnic venoconstriction does not significantly affect venous resistance, but has a great capability to increase mean circulatory filling pressure secondary to an increase in stressed volume [15,22]. Conversely, other vascular beds, such as the hepatic one, are venodilated through β2-adrenergic activation, and facilitate the blood flow and volume shift from the splanchnic vasculature to the inferior vena cava and afterwards to the right atrium, thereby increasing venous return [15].

Skeletal Muscle Pump

The skeletal muscle pump is considered one of the most important factors that increase venous return mainly from the lower extremities acting as a "peripheral heart" [19,29,30]. Although in accordance to the classic muscle pump hypothesis, increased venous pressure caused, for example, by a head upright tilt, would produce increased blood flow, different insights about skeletal muscles have been brilliantly elucidated [31]. Laughlin et al. proved that the peak venous outflow is directly related to the total tension produced during skeletal muscle contraction [32]. The authors also established the duration of muscle contraction as an important determinant of venous outflow dynamics. Both the amount of venous outflow per contraction and the time course of outflow during contraction are altered by changes in stimulation patterns.

Competent venous valves, that divide the hydrostatic column of blood into segments, assist the muscle pump to avoid gravitational venous reflux [30,33]. It happens mainly during walking and dynamic exercise when the rhythmic contraction of the peripheral skeletal muscles increases and causes intramuscular veins to suffer greater compression [20,34,35]. In turn, this compression increases the mean circulatory pressure about three times the normal value and expels large amounts of blood from the venous vasculature toward the heart. Thus, this muscle pump mechanism is one of the main factors that increases the cardiac output at the onset of muscular activity (in conformity to Frank-Starling mechanism), and it is mostly dependent upon muscle mass and pump activity intensity [32,34,36,37].

The ability of the skeletal muscle pump to empty the venous vessels has been widely demonstrated in animal and human studies [20,32,34-38]. The main skeletal muscles responsible for this pump function are the lower limb muscles including those of the feet, calves, and thighs. Among these, the most important is the calf muscle pump due to its large capacitance, and to the highest pressure generated [19,35]. Studies have demonstrated that over 60% of the venous volume can be moved centrally with a single calf muscle contraction [19,37,39]. At least two mechanisms are responsible for this circulatory pump role played by lower limb muscle contraction. First, during muscular compression of intramuscular venous vessels, a considerable amount of kinetic energy is transmitted to the venous blood that facilitates its return to the heart (assisted by the venous valves). Second, during muscular contraction, venous pressure is reduced to very low values or even negative values, which generates a greater arterial-venous gradient just after the end of muscle contraction that contributes to the venous flow. As a result, venous return is augmented, and it contributes to most of the increase in cardiac output during exercise [17,20,32].

Whereas the practice of physical exercise positively associates venous return and cardiac output, the disuse is the main mechanism to a negative relationship. Indeed, in aging underlies the comprehension of the disuse and of the cellular/biochemistry processes involved in muscle atrophy [40].

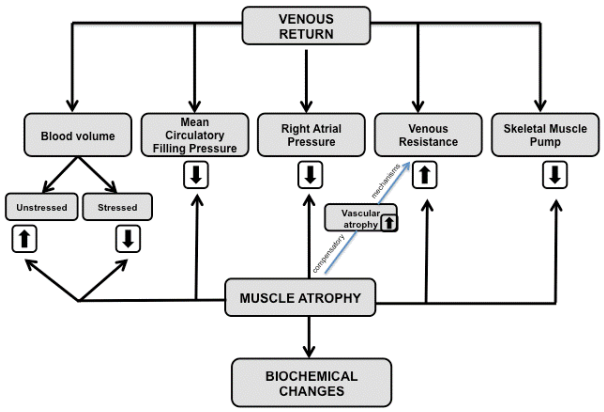

Figure 1: Schematic relationship of Muscle Atropy affecting the determinants of Venous Return. Briefly: Muscle atrophy causes venous blood pooling which favors an increase in the unstressed volume and a decrease of the stressed volume. As a result, the mean circulatory filling pressure decreases producing a reduction in right atrium filling and leads to extensive physical deconditioning, indicated through, e.g., the reduced demand of oxygen to the muscle leading to vascular atrophy. This compensatory mechanism will increase vascular resistance and contribute to a reduction in venous return. In the absence of skeletal muscle venous pumps, these hemodynamic changes promote an abnormal venous return that could compromise stroke volume and cardiac output.

Other causes of skeletal muscle atrophy may include: alcohol associated myopathy, Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's disease), BurnsGuillainBarré syndrome, injury, long-term corticosteroid therapy, muscular dystrophy, and other diseases with immobilization, like osteoarthritis, polio, rheumatoid arthritis, spinal cord injury and stroke. Among chronic diseases related to skeletal muscle there are: diabetes, uremia, cancer, and congestive heart failure [41-43]. A decrease in strength muscle will cause venous blood pooling

which favors an increase in the unstressed volume and a decrease the stressed volume.

As a result, the mean circulatory filling pressure will decrease producing a reduction in right atrium filling (Figure 1).

Moreover, as consequence of muscle atrophy and extensive physical deconditioning, the demand of oxygen to the muscle is reduced leading to vascular atrophy [44]. This compensatory mechanism will increase vascular resistance and contribute to a reduction in venous return [45-47]. Thus, in the absence of skeletal muscle venous pumps, these hemodynamic changes promote an abnormal venous return that could compromise stroke volume and cardiac output [47-49].

Indeed, some studies have reported cardiac output to be reduced after periods of inactivity induced by bed rest, spinal cord injury, and spaceflight [46,50-52]. Further, after 2 weeks of bed rest, Levine et al. [53] found decrease cardiac filling, which promoted a decrease in LV distensibility and impaired cardiac function. Despite some studies not reporting a decrease in cardiac diastolic and systolic function after spinal cord injury [45], it has been discovered that left ventricle mass index and cardiac dimensions were reduced by prolonged inactivity and short-term spaceflight [45,50,53].

Unquestionably, muscle atrophy caused by several conditions can impair cardiovascular hemodynamics and promote cardiac alterations.

Some important genetic muscle atrophy disorders, like Becker and Duchenne diseases [54,55], show progressive cardiac dysfunction. Both are clinically characterized by progressive muscle weakness, whose implications are [56] attributed as a cause or a consequence of cardiovascular complications and are thought to, directly or indirectly, affect the cardiac output and, consequently, the venous return. These dystrophies generally develop during the second decade of the patient's life [57-60]. Although cardiac dysfunction originates due to specific myocardial loss of dystrophin, extrinsic hemodynamic parameters may impact the development, as well.

In Becker muscular dystrophy patients, there is no correlation between cardiac involvement [61] and the severity of the cardiomyopathy. Cardiac involvement may manifest as electrocardiographic abnormalities, hypertrophic cardiomyopathy, dilation of the cardiac cavities with preserved systolic function, dilative cardiomyopathy, and cardiac arrest. On the other hand, taking [62] the organ into account, myocardial damage increases with age through progressive reduction of left ventricular ejection fraction as observed in patients over 20. Patients under 20 years of age do not present altered cardiac parameters such as ventricular dimensions, wall thickness, fractional shortening, and ratio of early (E) to late (A) ventricular filling velocities (E/A ratio); however, these young patients present lower systolic and diastolic intramyocardial velocity gradients, indicating the possible myocardial disease [63].

Ducceschi et al. [64] showed that in patients with Becker muscular dystrophy there is a tendency towards a straight relationship between the entity of cardiac sympathetic activity and the degree of left ventricular systolic dysfunction. The authors reported evolution of systolic impairment appearing somehow to be associated with the development of autonomic imbalance, a condition that contributes to increase ventricular propensity to arrhythmias. Further investigations, nonetheless, demonstrate no autonomic nervous system involvement as a key finding in Becker muscular dystrophy [65].

Lee et al. [60] demonstrated a reduction in left ventricle mass, combined with a decrease in stroke volume and no alterations in cardiac output in patients with Duchenne muscular dystrophy. To maintain the cardiac output, their hearts are forced to increase beating frequency to compensate reductions in left ventricle size. Consequently, the cardiac muscle encounters two major threats, i.e. mass reduction and overwork, that could evoke chronic cardiac fatigue and alter cardiovascular hemodynamics. Further, independent from additional genetic alterations in cardiac tissue, the widespread dystrophic damage of skeletal muscle concurrent with postural adaptation may also result in hemodynamic adaptation, which has been established as a risk factor for the development of cardiomyopathy [66,67]. Therefore, progressive skeletal muscle degeneration and weakness most likely contributes to progressive cardiac dysfunction.

Interestingly, animal studies with knockout mice have already demonstrated a potential causal link between skeletal muscle disease and cardiomyopathy. Normally, the mdx mice, a mouse model of Duchenne muscular dystrophy, do not show characteristic dystrophic cardiomyopathy until they reach 21 or more months of age [68,69]. Nevertheless, the mdx:MyoD-/- mice lacking dystrophin and the skeletal muscle-specific bHLH transcription factor MyoD display pronounced myopathic phenotype caused by marked reduction in skeletal muscle regeneration due to impaired satellite cells activity [70]. Using this mice model, Megeney et al. [70] observed that accelerated skeletal muscle deterioration caused cardiac dilation and myocardial fibrosis in the 5-month-old mdx:MyoD-/- mice heart. As MyoD is not expressed in the heart and plays no role in heart development, any myocardial changes evident in mdx: MyoD2y2 mice would be directly attributable to the level of skeletal muscle damage. Hence, the author suggested the progression of skeletal muscle damage as a significant contributing factor leading to the development of cardiomyopathy.

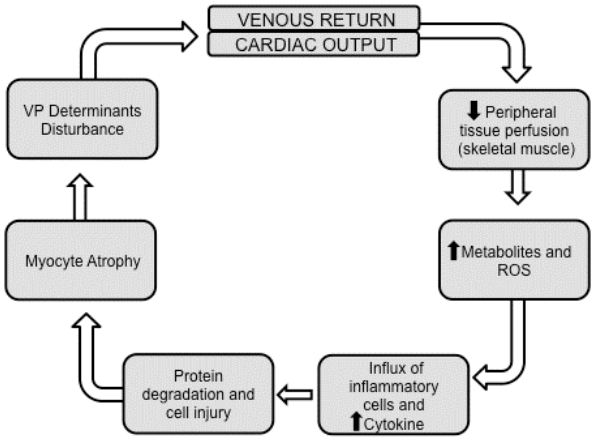

Figure 2: Integrative arrangement for venous return and cardiac output involving atrophy (of skeletal muscle and of cardiomyocyte). ROS: reactive oxygen species. VP: venous pressure.

Since in Becker and Duchenne muscular dystrophy cardiac impairment is not directly correlated with the severity of skeletal muscle involvement [71], the venous return is not directly a subject, but it is indirectly involved in cardiac manifestations. Cardiac involvement has been confirmed in cases preceding the onset of

skeletal muscle manifestation and in cases of wheelchair-bound patients who did not develop cardiac dysfunctions.

Skeletal Muscle Atrophy: Molecular pathophysiology

Studies concerning aging and skeletal muscle atrophy have contributed to the exploration of the relationship among myopathic changes, cardiac output, and venous return (Figure 2).

Neural, mechanical and metabolic factors coordinately keep integrative signalling between cardiac output and skeletal muscle perfusion [16,72-74]. It is well established that an increase in both the venous return as in cardiac filling pressure caused by peripheral vasodilatation is required to intensify cardiac output during heart rate pacing [75,76].

Concerning the molecular aspects, a relevant cause of disuse atrophy is an elevation in protein degradation rate relative to the synthesis rate [77]. Taking a step back, a way to better understand atrophy mechanisms is through investigative studies about hypertrophy.

Mechanisms underlying muscular hypertrophy of externally applied occlusive stimulus have been interpreted as follows: 1) Additional recruitment of fast-twitch fibers in a hypoxic condition [78]; 2) Moderate production of ROS, which promotes tissue growth [79-81]; 3) Stimulated secretion of catecholamine and growth hormone [82].

All of these processes are also thought to be associated with conventional, heavy-resistance exercises, because strong muscular contractions produce large amounts of metabolic products and cause transient intramuscular ischemia [83]. If the last two processes above play roles in muscular hypertrophy, the occlusive stimulus per se is expected to have an effect in either promoting hypertrophy or attenuating atrophy. In addition to these mechanical, neural, and hormonal factors, changes in the intramuscular oxygen environment may play a role in the present effect of occlusive stimulus.

As is widely known, heart inotropism is important to cardiac output. Reduced inotropism certainly contributes to reduced functional capacity; impairments in skeletal muscle physiology, including muscle atrophy, weakness, and reduced oxidative capacity have well-accepted influence in such cardiac performance [84].

In a healthy individual, who presents elevated cardiac output during submaximal or adenosine triphosphate (ATP) challenge, heart rate response appears to be secondary to the regulation of cardiac output due to a compensatory mechanism of reduction in stroke volume [85]. On the other hand, cardiac output is mainly regulated by an increase in venous return that occurs in parallel to the increase in skeletal muscle blood flow [85]. This suggested that peripheral O2 demand and vasodilatation are the main determinants of cardiac output during steady-state conditions.

Cardiac function is impaired in athletes with complete lesions above T1. Undeniably, these individuals lack sympathetic innervation to the heart and rely solely on parasympathetic withdrawal and circulating catecholamines to increase their heart rate. Heart rate responses during maximal exercise or high-intensity submaximal performance will therefore hardly exceed 110–130 beats/min [86]. Athletes with spinal lesions in levels down to T6 are also likely to achieve lower than anticipated maximal heart rate values, while those with lesions below that level will have normal responses [87-89].

Muscle ischemia also increases norepinephrine release from sympathetic nerves [90]. Subsequent activation of α1-adrenoreceptors exerts growth factor-like activity on arterial smooth muscle cells by a ROS-dependent mechanism; also, it induces leukocyte accumulation. This results in collateral growth and angiogenesis in the ischemic region, providing a means to increase nutritive perfusion [90].

Muscle Atrophy: Molecular Approaches

Non-stimulated or poorly stimulated muscle fibers will have their functional properties changed [91] leading to issues in co-factors such as spasticity and microvascularity, which constitute important morphological, molecular, and biochemical alterations. Bulks of biomarkers have been used to detect cardiac and skeletal muscle impairment, and to find a relationship between their integrative functions.

Myotoxicity and biomarkers

There are some important approaches in studies about myotoxicity [92]. Measurements of enzyme activity like of aspartate transaminase (AST), lactate dehydrogenase (LDH) and creatine kinase (CK) have long been used to detect cardiac and skeletal muscle injury. These three biomarkers, however, present low sensitivity and specificity [93,94]. Cardiac troponin I (cTnI) and T (cTnT) have been used as the preferred biomarkers for myocardial infarction in clinical examination as proposed by the American College of Cardiology and the European Society of Cardiology [95-97]. Troponins and myosin light chain 1 (MLC1) [98] are considered, mainly in pre-clinical conditions, useful biomarkers of cardiotoxicity; while plasma fatty acid binding protein 3 (Fabp3), as a biomarker of skeletal myotoxicity [99].

Tonomura et al. [100] properly demonstrated proteins Fabp3 and MLC1 as effective biomarkers due to their specific skeletal muscle distribution, although the rapid blood clearance of these markers should be taken into account when considering their use. An important contribution of Tonomura et al. [100] was the higher positive predictive value from combinatorial measurements of Fabp3, MLC1, cTnI, cTnT, AST, LDH and CK, as well as a comparison of their usefulness as drug safety biomarkers of myotoxicity (skeletal and cardiac).

Among all muscle atrophy promoting factors, cortisol is definitely one to focus on. Atrophy linked to cortisol action depends on metabolic processes due to amino acid breakdown to feed gluconeogenesis (distributing amino acids to the liver for glucose synthesis [101]. Indeed, glucocorticoids have been used to induce muscle atrophy, and to study the mechanisms in which it regulates muscle protein degradation. It has been demonstrated that atrophy triggered by synthetic glucocorticoids is dependent on alterations at muscle gene expression [102]. The synthetic glucocorticoid dexamethasone was shown to induce atrophy and trigger changes in muscle gene expression ('atrogenes'). The main gene involved is a Ubiquitin-ligase (E3), called atrogin 1 (MAFbx), a muscle-specific F box protein that is induced many-fold in fasting, diabetes and cancer [103]. Another muscle-specific E3, MuRF1, is also highly induced in atrophying muscle [104]. Both of these genes have been shown to be upregulated in human muscle atrophy induced by lower limb immobilization [105]. In this sense, the potential findings of Tonomura et al. [100] are clinically applicable when taking into account a cortisol long-term treatment and its toxicity.

Myofibrils and biomarkers

Apart from myotoxicity concerns, metabolic adaptations are another point of focus. They are found in a vast group of muscles and cause a direct impairment in the activity towards cardiac output. These adaptations are not always associated with contractile myofibrils, such as the myosin heavy chain (MHC) isoforms.

The formation of the myosin-actin interaction (cross-bridge) culminates in muscle contraction. In peripheral skeletal muscle, distributions of isoform MHC IIA in single fibers tented to show a greater expression of MLC 1f in patients who had suffered heart failure [88], however this was not associated with differences in single fiber function. Although measured indirectly, variations in Ca^{2+} sensitivity were noted in MHC IIA fibers, which could reflect adaptations in actin-associated regulatory proteins.

Considering diagnostics, a relationship between impaired cardiac function and reduced tension has been demonstrated in heart failure patients and in experimental models with both MHC I and IIA fibers [107,108]. On the contrary, Miller et al. [106], found no diminution in single fiber tension, arguing that prior results of reduced tension with heart failure were explained more by muscle disuse and/or aging than by heart failure per se. Since the authors concluded that adaptations in myosin kinetic properties compensate for the loss of myosin protein content to preserve isometric contractile strength, myofibril evaluation may have a low predictive value as a biomarker of cardiac output.

Cellular activity, metabolism, and biomarkers

There seems to be an orchestrate-like regulation, mainly under neuroendocrine control, involving systemic blood flow and oxygen delivery to peripheral tissues and organs. Take blood pressure for example: compensatory mechanisms promptly act to correct any decreases in blood flow or pressure. These mechanisms provide short-term benefits to metabolically active cells, but trigger long-term injury to the cardiovascular and, ultimately, to systemic body systems when chronically activated [109].

In general, peripheral tissues function as “sensors” of metabolic alterations, and their activities count with an integrated function of the cardiac output. In this sense, conditions of metabolic deficit lead the peripheral tissues, like skeletal muscle, to push for an increase in cardiac output [110].

The intramuscular accumulation of metabolites has been shown to stimulate the sympathetic nerve and the hypothalamus-pituitary system through actions of muscular metaboreceptors, and to cause an increase in plasma concentrations of noradrenaline, adrenaline [78,83,111,112] and growth hormone [78]. In addition, the application of strong occlusive pressure may directly stimulate the sympathetic nerve through the intramuscular pressure-sensitive mechanoreflex [113,114]. These nervous and hormonal responses may be involved in the mechanisms underlying the present atrophy-attenuating effect of occlusive stimulus. It should be noted, particularly, that stimulation of β2- adrenergic receptors in rat muscles promotes a selective hypertrophy of fast, Type II fibers, by possibly suppressing protein catabolism [115,116].

Metabolically speaking, reactive oxygen species (ROS) are accepted to be core-contributing factors that link the biochemical and molecular pathways. According to Ozmen et al. [117] and Bachle et al. [118], ROS are the mediators between persistent ischemia and skeletal muscle necrosis, causing microcirculatory damage that results in irreversible deterioration and injury. It has been shown that muscular xanthine oxidase activity is elevated in hypoxic conditions, and that it produces ROS during subsequent reperfusion [119].

Several investigations about venous congestion and arterial ischemia have benefited studies of biomarkers. In the flap salvage model [120], for example, the pathophysiology of arterial occlusion results from an inadequate oxygen supply to affected tissues and from a simultaneous deficit in the clearance of toxic metabolites. As discussed by Nguyen et al. [120], there is accumulation of ROS, an influx of inflammatory cells including neutrophils, macrophages, and a progressive release of cytokines in a cycle of inflammation that ultimately leads to tissue necrosis [121-124].

In venous congestion, arterial flow persists; this causes increased intravascular pressure and subsequent hemorrhage of the microvasculature into the extra-vascular space [125-127]. Increased extra-vascular pressure, in turn, causes external compression and collapse of the vessels.

Skeletal muscle has many potential modulators of cellular functions, which consequently deal with myofilament structure impairment; therefore, mitochondria are key organelles. A recent revision published by Hepple [128] presents a broad approach concerning controversial issues about the impact of mitochondrial function on skeletal muscle atrophy in aging muscles and on related disuse conditions. According to the authors, there are at least three postulated conclusions about mitochondria functions regarding the progressive skeletal muscle atrophy: i) it is reduced in aging muscle [129]; ii) there are no changes [130]; iii) it varies depending on the muscles [131].

What the researches above used to evaluate the aspects of mitochondrial content/function were mitochondrial enzyme markers (e.g., citrate synthase and cytochrome oxidase activities), specific mitochondrial proteins (e.g., porin, electron transport system complex subunits), mitochondrial DNA (mtDNA) copy number, and the gold standard, electron microscopic quantitation of mitochondrial volume density [132].

An important point that explains the disparities between results from the different approaches is physical activity levels that modulate mitochondrial activity. In other words, activity-matched subjects consistently show no decline in indicators of mitochondrial content and respiratory capacity, independent of the age.

Hepple [128] brought together important considerations about mitochondrial respiratory function and oxidative stress through ROS production among atrophy progression in different skeletal muscles, and through the benefit of maintaining physical activity to the organelle function.

In this sense, ROS and everything related to them must be prospective biomarkers. Lower cardiac stroke volume responses, potentially caused by the absence of the skeletal muscle venous pump in inactive legs, may involve ROS production.

In order to access the ROS and the mitochondrion metabolism involved, Servais et al. [133] used the thiobarbituric acid-reactive substance (TBARS) [134] as markers of reduced soleus muscle atrophy after antioxidant treatment (vit. E). Oxidative stress in the cellular environment results in the formation of highly reactive and unstable lipid hydroperoxides. Decomposition of the unstable peroxides derived from polyunsaturated fatty acids produces malondialdehyde (MDA), which can be quantified colorimetrically after a controlled

reaction with thiobarbituric acid. The measurement of these 'Thiobarbituric Acid Reactive Substances' (TBARS) is a well-established method for screening and monitoring lipid peroxidation [135,136].

Haemodynamic and coagulation biomarkers

Blood volume influences venous return to the heart. High plasma viscosity while total blood viscosity is lower than normal has beneficial effects in microvasculature haemodynamic. As the heart couples with the systemic vascular network, changes in plasma and blood viscosity during haemodilution determine both the vascular pressure drop and the flow rate, effecting cardiac function. When clotting mechanisms are stimulated in the blood, platelet aggregation and interactions with plasma proteins occur. This leads to an entrapment of red blood cells and clot formation, dramatically increasing blood viscosity [137].

As previously mentioned, blood viscosity modifies venous resistance [9,22] in the sense that increasing blood viscosity (polycythaemia) triggers an increase in venous resistance. This is related, either as a cause or a consequence, to skeletal muscle atrophy. In consideration, measurements of clotting mechanisms may represent an important biomarker. Actually, fibrinogen, a plasma glycoprotein synthesized by the liver, may indirectly indicate cardiac-skeletal muscle relationship. The conversion of fibrinogen to fibrin is catalysed by thrombin, and it plays a key role both in clot formation and in its stabilization. In addition, fibrinogen induces platelet activation and aggregation by binding to the platelet fibrinogen receptor glycoprotein GPIIb/IIIa [138,139]. Nikolaychik et al. [140] has demonstrated the importance of fibrinogen/fibrin as a dynamic indicator of optimizing the transfer of skeletal muscle-derived power to the heart as a mean of improving cardiac output in dynamic cardiomyoplasty.

Conclusion

The determinants of venous return are blood volume (stressed and unstressed), mean circulatory filling pressure, right atrial pressure, venous resistance, hemodynamic factors, pumping function of skeletal muscles and venous valves. A disturbance in any of these parameters significantly alters the venous return and consequently the cardiac output. Figure 2 represents a probable pathway of muscular atrophy in relation to the venous return.

Based on this review, muscular atrophy has an effective mechanism over venous return by neural, mechanical and metabolic deregulation. Measurements of specific molecular biomarkers have shown alterations in skeletal and cardiac muscles, which might account for changes seen in venous return and cardiac output.

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