Arterial Aging, Metalloproteinase Regulation, and the Potential of Resistance Exercise

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Abstract: Background: Aging is a process that affects all living organisms. The transition through life elicits tissue specific alterations in the functional and structural capabilities of all physiological systems. In particular, the vasculature is vulnerable to aging specific adaptations which induces morphological changes and ultimately increases the risk of pathological states. Matrix metalloproteinases are a group of extremely active enzymes that regulate the age-associated structural changes of the vasculature which has been regarded as the hallmark of arterial aging. Although this process in unavoidable, the structural and functional changes to the vasculature that occur as a result of advancing age can be positively or negatively influenced by our lifestyle choices.

Conclusion: Exercise training has profound effects on the age-associated changes of the arteries which have been shown to be beneficial in offsetting the detrimental responses of aging. This review provides a brief synopsis of the matrix metalloproteinase induced alterations of the arteries during aging and highlights the potential of resistance exercise to influence such changes.

Keywords: Matrix metalloproteinase, resistance training, arterial, aging, extracellular matrix, enzymes.

1. INTRODUCTION

Aging is a process that affects all physiological systems. Beginning at conception and continuing through our entire life span, chronological advancement is a phenomenon that cannot be avoided. The relatively constant process is the same for every human being and normally presents itself in the third and fourth decades of life in the absence of pathological states [1]. Cardiovascular, gastro-intestinal, metabolic, muscular, respiratory, reproductive, skeletal, and vestibular changes are all succumbed by the effects of aging.

Exercise training has been shown to minimize the age-associated alterations in many physiological tissues. For example, aerobic exercise has been shown to protect and even reverse vascular aging through favorable modulation of age-associated oxidative stress, inflammation, and structural changes of the vessel walls [2]. In addition, Resistance Exercise (RES) has been reported to improve muscle function and attenuate the reductions in muscle mass in elderly populations, reducing the risk and symptoms of sarcopenia [3].

This review aims to give a brief overview of the current evidence on the effects of aging on the arteries and the potential of RES to modulate the age-associated modifications. The focus of this article will be directed to Matrix Metalloproteinase (MMP) regulation within the arterial wall, with specific emphasis on the influence of aging and RES on MMP regulation and the significance of potential alterations.

2. THE ARTERIAL EXTRACELLULAR MATRIX

The Extracellular Matrix (ECM) is a fundamental non-cellular constituent within all tissues that has several essential responsibilities for normal physiological functioning. Initially considered as a dormant material that provided structural support to tissues, our improved understanding has demonstrated that the ECM is a compelling organization that serves as a vital communication center that also generates adaptive biochemical and biomechanical signals that are essential for homeostasis, as well as morphogenesis and differentiation [4]. This 3-dimensional complex comprises several components including collagens, non-collagenous glycoproteins, elastin, and proteoglycans that express a tissue specific composition generated by the cellular microenvironment. Minor disturbances of the ECM can lead to alterations in the cellular phenotype of the cell-matrix interaction and consequently, lead to the development of disease states [5]. Therefore, the integrity and function of the ECM are of prime importance in a healthy physiological environment.

The vascular system is an extraordinarily dynamic and adaptable network of blood vessels. The arteries of this extensive arrangement are made up of three main layers, all of which include a substantial quantity of ECM components. The medial layer comprises the elastic lamellae which endothelial cells adhere. Proteoglycans, elastin and collagen fibers, as well as smooth muscle cells are contained within the...
intima layer. The adventitia layer consists of large type I collagen fiber bundles and fibroblast cells. As with many tissues, the ECM plays a pivotal role within the vasculature to accommodate the deformation associated with normal vascular functions [6]. The structural proteins of the arterial ECM allow for the even distribution of loads and reinforcement as protection against arterial rupture, in addition to the creation of a microenvironment that modulates cellular function. This microenvironment may be the primary driving force of cellular behavior, with subsequent changes in this driving force being held accountable or being associated with the onset of vascular disease [7].

3. ECM REGULATION AND THE ROLE OF METALLOPROTEINASES

The stringent regulation of the ECM molecules is maintained by the activity of several key aspartic, cysteine, metallo, serine, and threonine proteases [8-10]. The control of these proteases can determine the composition of the integrative components of the ECM and subsequently regulate functional capacity. MMPs, a group of highly active endopeptidases, are fundamental in maintaining the stability of the ECM due to their proficiency to degrade collagen, elastin and other extracellular molecules as part of the normal physiological function and pathological processes [11].

There are several categories of MMPs, which are dependent on their structure and substrate. MMP-1, MMP-8, MMP-13, and MMP-18 are categorized as collagenases due to their ability to cleave interstitial collagen type I-III as well as several other matrix proteins [9]. MMP-2 and MMP-9, the most widely studied MMPs within the vasculature, degrade collagens and gelatins which have been appropriately named as gelatinases. Several in vitro investigations in healthy and diseased vessels have demonstrated that vascular and inflammatory cells located in the vessel wall are capable of producing MMPs from subsequent normal physiological functioning or pathological states [9].

MMPs have a central role in the degradation of vascular ECM [9, 12, 13], therefore, it is essential that their activity is tightly regulated. Secreted MMPs remain dormant (also known as proMMPs or MMP zymogen) until activated via the cysteine-zinc interaction within the N-terminal of the propeptide, also referred to as the cysteine switch. This interaction occurs due to the release of a zinc ion from a cleaved MMP propeptide which binds to cysteine in the active site. Activation of proMMPs is established when the propeptide is cleaved from the assistance of other MMPs. However, the activation pathways are diverse within this group of enzymes which also include regulation at levels of gene transcription and interactions with Tissue Inhibitors of Metalloproteinases (TIMPs) [14]. The latter regulatory mechanism of MMPs by TIMPs is the primary governing system within the vascular wall [9]. Several TIMPs have been identified and are involved in the complex regulatory processes of MMP activity. TIMPs and MMPs possess a 1:1 stoichiometric relationship, with the primary mechanism of inhibition being the interaction of the N-terminal domain of TIMPs binding to respective MMPs active site cleft [15]. This interaction removes the ECM degradation potential of the MMPs which contributes to a homeostatic environment.

4. AGING CHALLENGES THE ARTERIAL ECM

Vascular aging is associated with the loss of function and adaptability to physiological stressors [16]. During aging and in the absence of disease, the composition of the arterial ECM undergoes dramatic changes which contribute to a reduction in arterial compliance and elasticity which consequently leads to the development of arterial stiffness. This remodeling process is facilitated by the migration and proliferation of Vascular Smooth Muscle Cells (VSMC) and Endothelial Cells (EC), in conjunction with an increased lumen diameter [16]. Although, the age-related changes are not limited to VSMC. The two primary proteins that provide the framework of the vessels, collagen and elastin, are also subjected to vast alterations.

Animal models have demonstrated a two-fold increase in the collagen content, in a combination of a relative reduction in elastin content in the aortas of 30-month old rats compared with 6-month old rats, resulting in decreased dispensability and compliance [17]. VSMC hypertrophy was also observed in the older rats, which consequently resulted in increases in medial thickness when compared with the younger animals. The phenotypical changes of VSMCs and modifications to the ECM also create a pro-inflammatory state [13].

Normally, tight regulation exists in the composition of collagen and elastin within the vessel walls. The age-associated increase in collagen content is mirrored by a reduction in elastin synthesis, giving rise to arterial stiffness and hypertension risk. These composition changes are accompanied by changes in their functional properties due to calcification of elastin and increased cross-linkage of collagen molecules [16]. The elastic lamellae also undergo structural change due to the age-associated increase in oxidative stress and give rise to the risk of rupture. These age-associated alterations in the ECM organization can severely compromise normal ECM function and promote an age-related disease environment [4].

The histological hallmark of arterial aging is MMP-induced remodeling [13] MMP activity is up-regulated with aging and contributes to a pro-inflammatory environment, endothelial dysfunction, enhanced intima-media thickness, in addition to the degradation of elastin proteins which consequently result in vascular remodeling and arterial stiffness. Vascular MMP-2 and MMP-9 activity is associated with collagen accumulation and heightened oxidative stress which consequently results in inflammation and increased vascular permeability [18].

This increase in MMP activity is mediated by Angiotensin II (Ang II) signaling [12, 13]. Ang II is a major mediator of vascular aging [19] and promotes MMP-2 expression in the arterial wall which disturbs the MMP: TIMP ratio. This results in the reduction of the endogenous mechanisms of MMP inhibition and consequent arterial remodeling characterized by increased collagen deposition and calcification [12]. These age-associated changes in the arterial wall also contribute to increases in systemic blood pressure.
5. RESISTANCE EXERCISE AND ARTERIAL REMODELING

RES has been shown to elicit beneficial responses for athletic performance, in addition to numerous preventive and therapeutic effects in patient populations. This has resulted in the prescription of RES being a fundamental component of current exercise guidelines [20]. However, studies that have explored the effects of regular participation in RES on arterial stiffness have provided conflicting results. A previous meta-analysis by Miyachi has suggested that RES is associated with increases in arterial stiffness in young adults, with no associations evident in middle-aged individuals [21]. These results may be discouraging as the magnitude of elevations in arterial stiffening in the younger participants was approximately 14.3%, suggesting substantial vascular remodeling. The clinical implications of these adaptations are yet to be clarified. Additionally, the results from this investigation show differing changes in arterial adaptation to varying levels of RES intensity. The collective results of the studies pooled in the analysis show that high-intensity RES is positively associated with an 11.6% increase in arterial stiffness, with no associations evident in studies that used moderate intensity RES. The authors acknowledge that the studies that used high-intensity RES also recruited younger participants, with the studies that used moderate intensity RES involved middle-aged adults. This may explain the age-associated discrepancies in arterial adaptation to RES. Nevertheless, the study provides evidence of potentially clinically relevant increases in arterial stiffness following RES in young adults.

A more recent systematic review and meta-analysis by Ashor et al. reported that RES has no effect on arterial remodeling [22]. This investigation included a total of 42 Randomized Control Trials (RCTs) which included participants aged from 19-72 years old, with the median age being 47 and 12 weeks being the median duration of RES interventions. The authors also performed subgroup and meta-regression analysis to determine the potential of participant and exercise characteristics on arterial stiffness, respectively. The data from these analyses show no significant differences in Pulse Wave Velocity (PWV) response to RES between subgroups and various exercise characteristics. The authors did report significant heterogeneity in the studies included in the analysis with studies showing improvements in arterial stiffness from varying forms of RES. The results from this meta-analysis oppose the data published by Miyachi [21]. This discrepancy is likely due to additional data from 9 published studies which were available to Ashor et al. [22].

Although these systematic reviews and meta-analyses provide imperative data regarding the potential for RES to influence the hallmark of vascular aging, they are limited by the availability of relevant literature regarding aged populations. Data concerning indices of arterial stiffness and older participants of RES may assist in determining the potential of RES to modulate molecular changes to the ECM and provide a mechanistic basis in which optimal exercise prescription can be achieved.

Figueroa et al. [23] investigated the effects of 12-weeks low intensity, lower body, progressive RES on arterial stiffness in obese postmenopausal women (mean age: 54 ± 6 years, body mass index: 33.8 ± 0.5 kg/m²). Forty-five women were recruited and were randomized to either a low intensity RES group (n=14), a diet-only group (n=13) and low-intensity RES and diet group (n=14). The data from this intervention are of interest. Low-intensity RES did not affect arterial stiffness, although the combination of RES with calorie restriction improved brachial-ankle pulse wave velocity (ba-PWV), a marker of central arterial compliance. The improvements of arterial function in the RES and diet group were mirrored by improvements in body composition. These data, in addition to the lack of body composition change in the low-intensity RES group, support previous findings that reductions in PWV are associated with reductions in body mass [24].

This has profound implications when considering vascular adaptations to RES during aging. Previous reports have noted inverse relationships with muscle mass and arterial stiffening in older adults [25, 26], suggesting that the age-associated reductions in arterial functioning may be offset by improvements in muscular strength and body composition induced by RES. Jefferson et al. [27] determined the effects of 5 months moderate-intensity RES, independent and in combination with caloric restriction, on arterial stiffness in overweight and obese, older adults (BMI: 31.1 ± 2.7 Kg/m²; 68 ± 3 years). The investigators reported no differences in arterial stiffness following either intervention. Slight improvements were evident in arterial elasticity in the combined RES and caloric restriction group, who also presented improvements in body composition and muscular strength. The lack of improvements in muscular strength in the RES group may indicate that the exercise protocol may not have been adequate to promote muscular or arterial adaptation. Therefore, the question still remains as to whether there is an association with RES induced improvements of muscular strength and body composition and age-associated arterial stiffness.

6. THE INFLUENCE OF RESISTANCE EXERCISE ON MMP REGULATION

There is evidence to suggest that RES can modulate MMP regulation in several tissues, however, the literature concerning RES and MMP induced regulation of arterial ECM is scarce. Although, there are several studies that have investigated RES and MMP regulation in cardiovascular tissues. Lettie et al. [28] used an animal model to investigate the influence of RES on left ventricular MMP-2 activity in a high-fat fed state. The rats were randomized into training or sedentary groups, which were further divided into receiving a high-fat or standard diet. The training groups were subjected to vertical load carriage 3 times per week for a total of 12 weeks. The data show higher MMP-2 activity in the left ventricle of the trained rats independent of diet, with concomitant improvements in body composition and blood pressure. Although these results provide evidence that RES has the potential to modulate myocardial MMP-2 activity, they are limited in the provision of details regarding MMP-2 regulation and associated ECM alterations, in addition to the consequence of increased MMP-2 activity.

A later systematic review aimed to explore the literature on the effects of different exercise interventions and training
effects on MMP-2 and MMP-9 activity within humans [29]. The review contained several studies which employed an RES methodology and reported varying results. One study included in the review [30] recruited an elderly female population (62-73 years old) to participate in a progressive 24-week exercise protocol involving synchronization, dexterity, flexibility, strength, and steadiness exercises. The authors reported a reduction in plasma MMP-9 levels with no change being observed in plasma MMP-1 levels. Although there was a limited number of MMPs investigated, these data may suggest that exercise-induced MMP expression may be modality specific in postmenopausal females due to the varying response in measured MMPs. The alterations in plasma MMP-9 levels have been speculated to be associated in the remodeling process of skeletal muscle ECM as a consequence of strength improvements.

These data suggesting exercise modality specific responses of MMPs are consistent with other studies included in the review of Nascimento et al. [29] Urso et al. [31] investigated the effects of 8-weeks of callisthenic exercises (n=8, 29.6 ± 0.7 years old) or RES (n=8, 26.6 ± 0.7 years) on MMP response in males. The authors measured the MMP response to an acute bout of RES (6 sets of 10RM, 2 minutes’ rest between sets) in both groups before and after exercise training. The results showed that MMP-1 and MMP-3 concentrations increased following the acute bout of RES in both groups, however, following 8-weeks of prescribed exercise, this MMP increase in response to acute RES was only evident in the callisthenic group. Different responses were also evident in other MMPs, supporting previous data that suggest circulating MMP response is exercise modality specific. Although these data contribute a substantial piece of the MMP response to exercise puzzle, they lack RES specific responses as the investigators reported significant increases in VO₂ following the prescribed exercise, which questions the response of such MMPs independent of improvements in cardiorespiratory fitness.

The review by Nascimento et al. [29] highlights the limited knowledge we have regarding RES induced modulation of MMP regulation. The quality of the studies included in the review achieved only moderate status which was assessed by the PEDro scale [32], highlighting the need for more controlled studies. Although these data provide considerable contributions to our understanding of MMP alterations following RES, the varying results maintain the curiosity of how RES can modulate MMP regulation and what consequences to the arterial ECM occur.

Subsequent work by the same group evaluated the efficacy of acute eccentric RES on MMP activity in obese elderly women [33]. Ten community-dwelling women (67.4 ± 7.4 years; 44.7 ± 4.8% body fat) performed 7 sets of 10 repetitions of eccentric leg extension of a load corresponding to 110% of 10 repetition max. The data show significant reductions in serum MMP-2 and MMP-9 following RES. As with the previously described studies, data regarding possible MMP regulation mechanisms may have provided insight into the observed results. Additionally, although studies have presented data showing altered circulating MMP concentrations in response to RES, this may not reflect the MMP activity within other tissues as an adaptation to RES varies within physiological structures.

This issue has been addressed by more recent work that has investigated the effects of RES on muscle, systemic, and adipose tissue MMPs using an animal model [34]. Wistar rats performed vertical load carriage at 3 times per week for 8 weeks. Eight ladder climbs per session resulted in a 47.1% increase in active MMP-2 activity in the gastrocnemius muscle compared to sedentary controls, with decreases of 67.8% of active MMP-2 activity in adipose tissue in the training groups compared to sedentary controls. The varying response of MMPs in different tissues resulting from RES highlight the complexity of the MMP system, but also support previous data reporting extracellular remodeling induced by MMPs is modulated by RES. Data regarding MMP regulation was limited which may have given insight into the mechanistic properties of the RES induced modulation.

More recent work has provided evidence that RES has the potential to reduce the age-associated collagen deposition in the myocardium. Guzzoni et al. [35] investigated the effects of chronic high-intensity RES on left ventricular structure and function, as well as MMP and TIMP activity using an animal model. Young and old rats were randomized into a training or sedentary group. The trained group was subjected to vertical load carriage 3 times per week for 12 weeks, at intensities of 65-100% maximum carrying capacity, with 4-9 ladder climbs per session. The authors report significant increases in load carried by both young and old training groups in addition to reduced collagen accumulation within the left ventricle. Interestingly, the percentage of collagen deposition observed in the old trained animals were reduced to values similar to that observed in the young trained group. The sedentary groups presented higher collagen deposition in the left ventricle. This attenuated collagen deposition in the RES groups was associated with higher MMP-2 activity and TIMP-1 gene expression. Although this investigation did not investigate the vasculature, the reported data is the first to demonstrate an anti-aging response to RES in the myocardium ECM associated with MMP modulation. These data not only provide the critical knowledge of ECM turnover in response to RES, it also reinforces the protective potential of RES to age-associated tissue remodeling. It may be plausible that the beneficial responses to RES observed in the ECM of the myocardium may also translate to the arterial ECM.

7. FUTURE DIRECTIONS

From the available animal and human data, it is clear that RES can modulate MMP activity. However, the consequence of altered arterial MMP levels as a response of RES, especially within aging populations, is lacking. The primary goals of exercise are to provide preventative and therapeutic advantages to the many physiological systems that maintain the balance of homeostasis for normal physiological function. Improving our understanding on the potential of RES on the regulation of MMPs and their endogenous inhibitors within the arterial ECM will provide the necessary foundations to develop optimized, personal exercise guidelines to promote healthy aging. The lack of data involving aged populations is a major contributor to our limited knowledge of the potential of RES on arterial aging. The current litera-
ture indicates that RES may induce changes in arterial ECM through altered MMP expression, which may offset the age-associated detrimental changes in vascular function. Although, this still needs to be established. RCTs investigating arterial-specific responses to RES in older populations are necessary to improve our understanding on the potential of RES to regulate MMP induced remodeling, the hallmark of vascular aging. It is also necessary for these RCTs to establish the effects of differing exercise intensities of RES as the nature of this exercise modality is highly varied.

CONCLUSION
RES is an integrative component of current exercise guidelines, yet our understanding of its full potential is limited. We understand the arterial ECM undergoes various MMP induced adaptations to specific stimuli starting from embryonic development until the end of life. Potential alterations in the arterial ECM induced by our lifestyle choices may enhance the longevity of the aging process. The participation in RES may be a promising method to reduce the age-associated vascular remodeling but, we are still a long way from understanding the full potential and limitations of this exercise mode and its ability to regulate normal physiological aging.

CONSENT FOR PUBLICATION
Not applicable.

CONFLICT OF INTEREST
The authors declare no conflict of interest, financial or otherwise.

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