Does Norepinephrine Play a Role in the Genesis and Progression of Ascending Aortic Aneurysms?

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ABSTRACT: Ascending aortic dilatation (AAD) affects a significant percentage of subjects over 55 years of age and causes a high mortality, and more than 80% of cases of AAD are not associated with a previously detected hereditary syndrome. There is a real need to learn more about its etiopathogenesis in order to help prevent it. The methodology used by us to address the role of norepinephrine in the genesis and progression of AAD was systematic review. The hallmark histological features of aortic disease are cystic spaces filled with mucoid material (CSMM) and the release of matrix metalloproteinases (MMPs). It is interesting to note that there are no histological differences between subjects with syndromic AAD (SAAD), eg, Marfan syndrome, nonsyndromic AAD (NSAAD), and cases of CSMM in the elderly. Moreover, there are no histological differences between AAD and ascending aortic dissection (AD). This paper assesses whether norepinephrine plays a significant role in the genesis of these aortic diseases by modulating MMP expression, elastic fiber fragmentation and the formation of CSMM, and finally participating in the subsequent ascending aortic dilatation, which would have major therapeutic and preventive implications.

KEYWORDS: ascending aortic aneurism, cystic spaces, the hallmark histological feature, etiopathogenesis, norepinephrine, experimental models

CITATION: Fantidis et al. Does Norepinephrine Play a Role in the Genesis and Progression of Ascending Aortic Aneurysms?. *Clinical Medicine Reviews in Cardiology* 2016:4 7–12 doi: 10.4137/CMRC.S41065.

TYPE: Review

RECEIVED: October 03, 2016. **RESUBMITTED:** November 21, 2016. **ACCEPTED FOR PUBLICATION:** November 23, 2016.

ACADEMIC EDITOR: Garry M. Walsh, Editor in Chief

PEER REVIEW: Three peer reviewers contributed to the peer review report. Reviewers' reports totaled 1355 words, excluding any confidential comments to the academic editor.

FUNDING: Authors disclose no external funding sources.

COMPETING INTE RESTS: Authors disclose no potential conflicts of interest.

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Introduction

Thoracic and abdominal aortic aneurysms are a significant health problem that affects a considerable percentage of subjects over 55 years of age and has a high mortality.[1–4] It is therefore obvious that there is a need to improve diagnostic criteria and to know the risk factors and the prognosis and clinical management of patients with aortic aneurysms. Further, the role of bicuspid aortic valve in this illness and its relationship with circulating levels of norepinephrine need continuous evaluation. It is not the objective of this review to analyze each of these items related to aortopathies.[1]

Earlier studies have highlighted the need to learn more about the etiopathogenesis of aneurysms in order to help prevent them.[1–4]

Ascending aortic dilatation (AAD) associated with hereditary syndromes is only a fraction of the total of AADs.[1,3,4] Different agents, including genetic mutations,[1] bacterial and viral infections,[5] smoking,[4,6] bicuspid aortic valve,[7] and mechanical factors,[8] among others, have been associated with the genesis and progression of AAD. But more than 80% of ascending aortic aneurysms is not associated with a previously identified syndrome.[1,3,4]

Based on clinical and experimental studies, which will be discussed subsequently, it seems that norepinephrine, a stress hormone, could be involved in the genesis of AAD by causing histological changes to the aortic wall.

In view of this, the purpose of this review is to assess whether norepinephrine plays a significant role in the genesis of these aortic diseases by modulating metalloproteinase expression, causing fragmentation of the elastic fibers and the formation of cystic spaces filled with mucoid material (CSMM), and finally participating in the subsequent ascending aortic dilatation.

Histology

The histological changes that characterize AAD are smooth muscle cell apoptosis and the fragmentation of elastic fibers. The hallmark histological features are CSMM and the presence of inflammatory infiltrate and release of matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9.[2–4,7,9]

Calcium, which is very common in abdominal aortic aneurysms, is not normally found in ascending aortic aneurysms.[2–4,7,9]

One very intriguing aspect of aortic disease is that there are no significant differences in histological findings between young subjects with syndromic AAD (SAAD; eg, Marfan syndrome), adult subjects with nonsyndromic AAD (NSAAD), and the spontaneous cystic medial degeneration

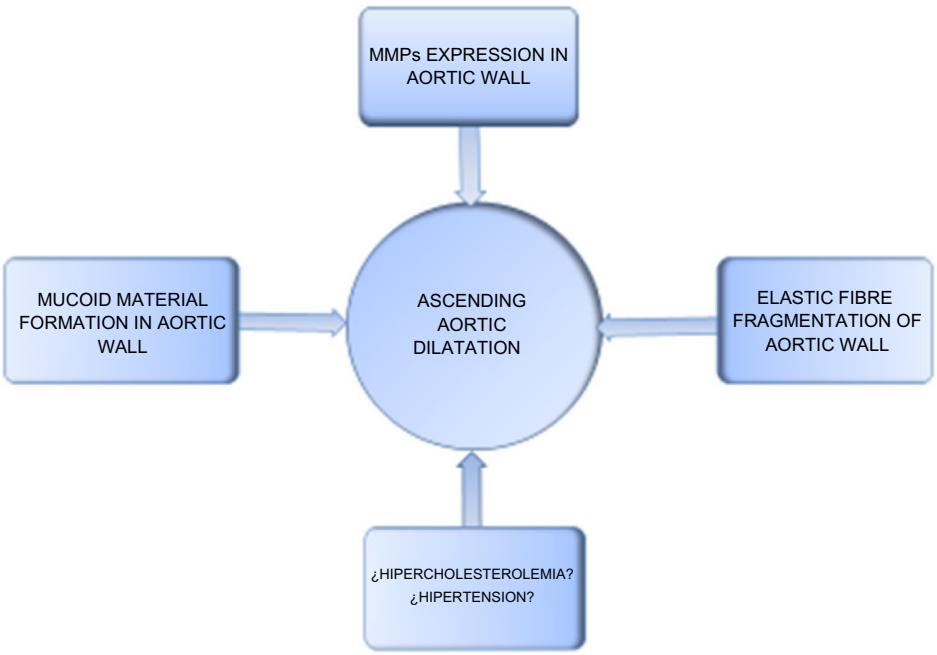

Figure 1. Factors modulating of ascending aortic dilatation. MMPs, matrix metalloproteinases.

found in the elderly.[1,3,7,9] Likewise, there are no histological differences between AAD and aortic dissection (AD) or between AAD and noninflammatory tendinopathies, including those of the mitral chordae tendineae.[9]

This might suggest that all these aortic diseases may be caused by a common mechanism.

Norepinephrine and Histological Changes in the Wall of the Ascending Aorta

The mucoid substance that occupies areas of cystic degeneration primarily consists of mucopolysaccharides, which do not break down and therefore accumulate in the extracellular matrix.[9]

The polysaccharide chains are very rigid and hydrophilic, which means that they tend to occupy large volumes in relation to their mass, forming gels. Furthermore, their strong negative charge means that they essentially attract large amounts of sodium and potassium (calcium, to a lesser extent), which results in the retention of large amounts of water in the extracellular matrix due to their osmotic properties.

The production of hyaluronan, the main glycosaminoglycan (GAG) found in cysts filled with mucoid material in the wall of the aorta, is positively modulated by catecholamines produced by the endogenous endocrine system or sympathetic innervation.[10,11]

On the other hand, Bolande et al.[12] used intravenous infusion of norepinephrine to induce hypertension in experimental animals (piglets). The histological findings in the animals used with this model are similar to those found in subjects with AAD. The authors found fragmentation of the internal elastic, invasion of the intima by platelets and monocytes/macrophages, and in later stages collagenization of the media.[12] But, as was the case with the formation of aneurysms caused by simple periarterial application of calcium chloride to the wall of the abdominal aorta or the carotid arteries,[13] in the short term at least, no formation of degeneration cysts filled with mucoid material was found with the model used to induce hypertension in the piglets.[12]

Likewise, the expression of MMP-2 and MMP-9 is increased in tissue from aortic aneurysms and carotid artery aneurysms. Both MMPs play a significant role in the progression of aneurysms; their pharmacological inhibition reduced the expansion rate of aneurysms in experimental animals and in humans.[4,14–18] Immunohistochemical studies colocalize both MMP-2, predominantly produced by smooth muscle cells and less often by macrophages, and MMP-9, predominantly segregated by macrophages, in these tissues.[15–18]

It has been reported that MMP-2 and MMP-9 are upregulated by the effect of noradrenaline.[19]

In patients with chronic heart failure, circulating norepinephrine levels are high,[20] which, among other effects, induce apoptosis in cardiomyocytes.[21] In vascular smooth muscle cells, norepinephrine can mediate its apoptotic effects via β-adrenergic receptors, just as it can in cardiomyocytes.[22] In fact, in dogs with chronic obstructive sleep apnea, in which the norepinephrine concentration was markedly increased, significant increases in the apoptotic rate of their ventricular myocytes were observed. With the use of metoprolol, a selective β_1 receptor blocker, there was a reduction in the rate of apoptosis.[23]

More importantly, experimental and clinical studies show that possible abnormalities in sympathetic nervous system (SNS) activity can modulate pathological changes in the thoracic aorta. Thoracic sympathectomy, which brings

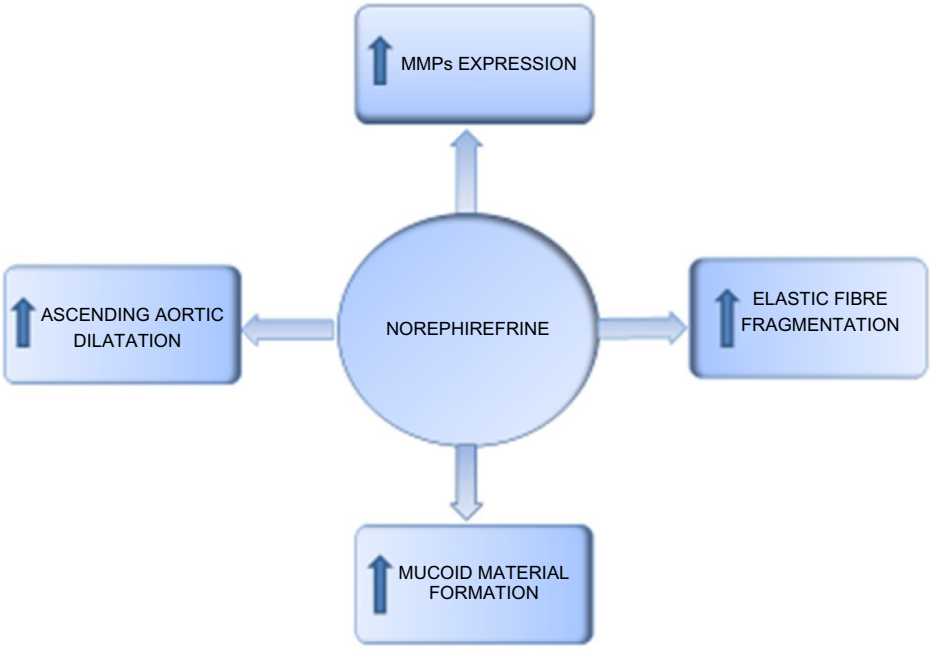

Figure 2. Effect of norepinephrine on the factors modulating aortic dilatation.

about a reduction in regional SNS activity, caused structural and biomechanical remodeling of the thoracic aorta including statistically significant increase in inner aortic diameter and wall thickness caused by extracellular matrix protein accumulation in that region.[24] More recently, a clinical study has shown increases in plasma norepinephrine levels in patients with thoracic AD. In these patients, there is an increase in both overall and regional aortic SNS activity.[25]

Risk Factors for Aortic Disease and Norepinephrine

Risk factors for histological changes to the wall of the ascending aorta, such as apnea syndrome, cocaine abuse, and hypertension, are usually accompanied by SNS hyperactivity, which suggests that abnormal SNS activity could play a significant role in thoracic ADs.[26,27]

Smoking has been associated with the genesis and progression of AAD,[4,6] and smoking mainly high-nicotine cigarettes activates the hypothalamic–pituitary–adrenal (HPA) axis,[28,29] while norepinephrine production is simultaneously increased.[30] This probable SNS hyperactivity induced by smoking could therefore play a significant role in the genesis of these aortic diseases.

Furthermore, earlier studies have shown an association between bacterial and viral infections and the formation of aortic diseases, particularly AAD. It has also been shown that stress hormone secretion is activated during bacterial and viral infections,[6,31] which again suggests that SNS hyperactivity could play an important role in the genesis of these aortic diseases.

In any case, any injury to the endothelium and/or tunica media of arteries leads to an inflammatory process that essentially activates the HPA axis and SNS activity.

The Role of Norepinephrine in the Progression of AAD

The natural history of AAD is as yet largely uncertain and even confusing, and there is controversy regarding some aspects related to the mechanism that induces progression of the disease. Could the early stimulation of aortic wall healing affected by the disease prevent or decrease the subsequent formation of aortic aneurysms? It has been reported that in chronically stressed mice, stress impairs cutaneous wound healing and that wound healing was improved with catecholamine blockade in these mice.[32]

Although it is commonly accepted that high blood pressure and hypercholesterolemia are two of the factors that may most influence the progression of dilatation in ascending aortic aneurysms,[33,34] there is little evidence supporting the causal role of these two factors in the progression of the condition.[33,34]

Earlier studies showed that short-term hypercholesterolemia significantly increased the incidence of angiotensin II-induced abdominal aortic aneurysms.[35,36] However, a more recent study showed that when angiotensin II-induced ascending aortic aneurysms were compared in normal and hypercholesterolemic mice, equivalent ascending aortic dilatations were found in both groups of animals.[34]

Moreover, there is a widely recognized association between hypertension and cardiovascular disease, which is why blood pressure needs to be strictly controlled; however, it is not clear whether dilatation of the aneurysmal ascending aorta increases because of the increase in the individual's systemic arterial pressure per se.[37,38]

Earlier studies have shown that infusion of norepinephrine in mice led to increases in arterial pressure similar to those

induced by angiotensin II, but this norepinephrine-induced increase in arterial pressure did not have any significant effect on the dimensions of the wall of the thoracic aorta.[34,37,38]

Likewise, in a clinical study conducted on subjects with Marfan syndrome, the authors used Losartan, an angiotensin II receptor antagonist used primarily to treat arterial hypertension. The authors[39,40] found that the effect of this medicine in preventing significant dilatation of the aortic arch was independent of the systemic arterial pressure value.

This observation[39,40] suggests a specific molecular effect of Losartan on the progression of dilatation of the ascending aorta and aortic arch in patients with Marfan syndrome. This effect may be related to the fact that angiotensin II receptor expression and tissue concentration of angiotensin II are increased in the aorta of subjects with Marfan syndrome.[41,42] It could, therefore, be an effect that is specifically found in subjects with Marfan syndrome.

Furthermore, the most significant factor that highlights the importance of catecholamines in aortic disease is the histological findings of the aortic wall of piglets (internal elastic fragmentation, invasion of the intima by platelets and monocytes, and collagenization of the media).[12] In the medium- and long-term, these histological consequences may condition the progression of aortic dilatation. Effectively, it should be highlighted that the classic standard management of patients with AAD to protect against aortic dilatation involves, in particular, the use of β-blockers and reducing emotional stress to a minimum.[41]

Experimental Models

When assessing factors that modulate the genesis and progression of AAD, there are several that may confuse the results. Thus, the expression of angiotensin II and catecholamine receptors in the wall of the aorta may be different in young subjects with a known hereditary syndrome to adult subjects without any known syndrome. Moreover, to the best of our knowledge, it is not known whether an increase in systemic levels of circulating norepinephrine has the same effect on the wall of the ascending aorta as a local increase in norepinephrine levels (affecting a small part of the aortic wall).

We, therefore, propose using an experimental model similar to the one used in our earlier study.[43]

With our experimental model,[43] the inoculation of a low concentration of *Staphylococcus aureus* into the wall of the thoracic aorta caused very different clinical symptoms and changes to the aortic wall compared to those it would probably have caused if the same concentration of the said bacteria had been injected directly into the blood stream.

By using this experimental model,[43] the inoculation of increasing concentrations of norepinephrine and angiotensin II into the aortic wall and subsequent histological and immunohistochemical evaluation provides direct information about the role of each of these two molecules in the genesis of AAD. Several papers have suggested the role of angiotensin in the formation of aortopathies.[44–47] However, it should be kept in mind that it has also been published that angiotensin II induces hyperplasia in the ascending aorta.[48,49] It has also been reported that angiotensin II increases the release of noradrenaline from sympathetic nerve endings, and that norepinephrine regulates MMP-2 activity in AD in patients with ascending AD.[50]

Final Considerations

The accumulation of GAGs that form cysts filled with mucoid material may be a consequence of increased GAG synthesis and/or the inactivity of the enzymes that usually degrade GAGs due to one of the factors being assessed.

Earlier studies showed that GAG metabolism may be under hormonal control and more specifically under the control of adrenocorticotropic hormone (ACTH).[51] It was also published that chronic treatment of cells with thyroid-stimulating hormone (TSH) increased the synthesis of heparan sulfate.[52] Therefore, in addition to catecholamines, β-blockers, and angiotensin II and their respective antagonists, it is necessary to know the role of ACTH and the hormones of the HPA axis in general, as well as of TSH, in the formation and progression of AAD.

The enzyme that, once activated, degrades excess hyaluronic acid, a major component of the extracellular matrix, is hyaluronidase. It may be of interest to experimentally assess the role of ligase and other enzymes that favor the degradation of GAGs in stabilizing the affected wall of the thoracic aorta and preventing its dilatation.

It has been reported that β-blockers are known to reduce the rate of aortic dilatation by reducing aortic wall stress through their negative chronotropic effect and that this is the only medical treatment to reduce aortic dilatation and clinical events and to improve survival.[53]

However, it has also been shown that propranolol has no beneficial effects on elastic fiber fragmentation, whereas losartan-treated mice show significant improvement in this sense.[54] More recently, in patients with Marfan syndrome, who underwent aortic root replacement, the addition of renin–angiotensin–aldosterone system blockade to β-blocker was associated with reduction of aortic dilatation and clinical events.[55] More experimental studies are needed to know which pharmacological agents prevent the fragmentation of the elastic fiber and the formation of mucoid material in the aortic wall.

Earlier studies suggest that increased levels of catecholamines (whether circulating or local or both have yet to be determined) play an important role in the genesis of these aortic diseases. This may occur because of catecholamines' capacity to fragment the elastic fibers, increase MMP expression, and modulate the accumulation of mucoid material in the medial layer of the aortic wall.

Experimental studies in pigs using a suitable experimental model[2,12–14,43,56] may shed light on the role of catecholamines in the genesis and progression of aortic disease. If these stress

hormones can be shown to play a role in aortic disease, this would be highly significant for the prevention and treatment of these conditions.

Author Contributions

Conceived and designed the experiments: PF. Analyzed the data: PF, JRG. Wrote the first draft of the manuscript: PF, JRG, IT, IK, ES, TP, JAC, DM. Contributed to the writing of the manuscript: PF, JRG, IT, IK, ES, TP, JAC, DM. Agree with manuscript results and conclusions: PF, JRG, IT, IK, ES, TP, JAC, DM. Jointly developed the structure and arguments for the paper: PF, JRG, IT, IK, ES, TP, JAC, DM. Made critical revisions and approved final version: PF, JRG, IT, IK, ES, TP, JAC, DM. All authors reviewed and approved of the final manuscript.

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