

Segmental Arterial Mediolytic - a Vasospastic Arteriopathy: A Morphologic Survey and Proposed Role of Norepinephrine Coupled with Hyperdense Alpha-1 Adrenoceptor in its Pathogenesis

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Abstract

Segmental arterial mediolysis (SAM) is a rare arteriopathy involving the large muscular arteries innervated by the peripheral sympathetic nervous system. SAM's proposed pathogenesis is reviewed in this article. It is initiated by stimuli from sympathomimetic agonists, some Beta agonists and the adrenal medulla that signals the release of norepinephrine from innervating sympathetic nerves. Norepinephrine forms ligands with dynamically created hyper dense foci of alpha-1 adrenoceptor located on the smooth muscle cell membrane. These undergo conformational changes and couple with Gq heterotrimeric G protein to unleash a series of perturbed biochemical events causing a cytoplasmic overload of calcium ions and spastic vasoconstriction producing mediolysis from mitochondrial hydropic degeneration, intrinsic apoptosis of the medial muscle and a shearing separation of the outer media from the adventitia. A norepinephrine driven reparative response develops in areas of medial muscle loss and in the adventitial medial tear site creating sequelae- dissecting hematomas, arterial stenosis, persistent aneurysms and fibromuscular dysplasia forerunners of a number of arterial lesions of uncertain or multiple etiologies. Norepinephrine is also implicated in the genesis of mesangial hyperplasia. Beta agonists releasing norepinephrine to initiate SAM can cause intrinsic apoptosis in hearts of subjects undergoing hemodynamic stress. Dynamically uploaded cardiac beta-1 receptors coupled with supra physiologic released norepinephrine results in Ca²⁺ overload causing mitochondrial hydropic change and intrinsic apoptosis of cardiac myocytes. Conclusion: Supra physiological levels of norepinephrine coupled with hyper dense foci of arterial alpha-1 and cardiac beta-1 adrenoceptors can generate intrinsic apoptosis in arteries and heart - sources of a variety of non-inflammatory arterial diseases and myocardial non-ischemic fibrosis.

Keywords: Norepinephrine; Alpha-1 and Beta-1 Adrenoceptors; Intrinsic Apoptosis; Fibromuscular Dysplasia; Dissecting Hematomas of Coronary and Vertebral Arteries; Stenosis and Aneurysms of Intestinal and Renal Arteries

Abbreviations

SAM: Segmental Arterial Mediolytic; FMD: Fibromuscular Dysplasia; SCAD: Spontaneous Coronary Artery Dissection.

Introduction

Catastrophic haemorrhages occurring in the abdomen, retroperitoneum or brain base are the principally recognized diagnostic presentations of segmental arterial mediolysis (SAM) a rarely reported vasospastic arteriopathy involving large and medium sized muscular arteries innervated by the peripheral sympathetic nervous system [1]. SAM can also initially present with ischemic symptoms and/or evidence of abdominal organ injury such as pancreatic haemorrhages or renal infarcts [2-5]. SAM also may be asymptomatic discovered serendipitously on radiologic examinations, in surgical resections or at autopsy [6]. Collateral mesangial cell hyperplasia and rarely foci

of myocardial necrosis have been described in patients, dogs and pigs with SAM [7-10]. This article, prompted by SAM's unique pathology, will formulate a pathogenesis explaining how SAM and its engendered arterial sequelae are created and how this pathogenesis is germane to SAM's accompanying collateral lesions in the glomeruli, large abdominal veins and myocardium.

Methods and Materials

The photographs used in this article were garnered from the multiple cases of SAM previously reported by the authors in references [1,2,5-14]. Their journal origins are included in the microscopic descriptions of the figures. Those without journal origins are derived from unpublished photographs from these papers. The photographs were chosen to support the author's proposed pathogenesis of SAM, its sequelae and its collateral lesions.

Results and Discussion

Injurious Phase

Norepinephrine is the hormone instigating SAM. The following evidence supports this hypothesis: 1) SAM's vasopressor characteristics - a vasospastic histologic appearance and its segmental distribution [8]; 2) the discrete localization of SAM to arteries innervated by the peripheral sympathetic nerves; 3) the initial arterial medial lesions always form at or are restricted to the adventitial medial junction and the outer medial smooth muscle the precise site that norepinephrine is produced in varicosities and released from the efferent sympathetic nerve fibers innervating the involved arteries; 4) SAM rapid development following the iatrogenic administration of alpha-1 adrenoceptor agonists and Beta-2 agonists capable of releasing norepinephrine from the peripheral sympathetic nervous system [6,11-14] and 5) SAM's occurrence in clinical conditions in which supra physiologic levels of norepinephrine are released from the adrenal medulla [8].

Norepinephrine causes vasoconstriction but how is SAM created from this response? To provoke vasoconstriction following stimulation by iatrogenic sympathomimetic agonists or endogenous supra physiologic levels of catecholamine's the norepinephrine produced and released as neurotransmitters from the varicosities located on the efferent branches of the sympathetic nerves innervating the target arteries forms a ligand with alpha-1 adrenergic receptor aggregates on the cell membrane of the medial smooth muscle to induce conformational change in this receptor. The inner intracellular domain of the conformational altered receptor activates a heterotrimeric G protein which sets into motion a cascade of biochemical events leading to smooth muscle contraction powered by energy released by the hydrolysis of guanosine triphosphate to guanosine biphosphate. Cytoplasmic calcium is necessary for contraction and these ions are released into the cytoplasm from the sarcoplasmic reticulum and by the opening of calcium channels on the sarcolemma permitting the cytoplasmic entrance of extracellular Ca^{2+} events signalled by the activation of phospholipase C and IP3 (triphosphoinositol).

Perturbations in this biochemical chain of events orchestrated by the alpha-1 adrenoceptors are suspected of converting smooth muscle contraction to SAM [1]. There are two features of SAM that convincingly support this hypothesis. The first is the plasticity of this receptor: Arterial alpha-1 adrenoceptor distribution is in a dynamic state influenced by a variety of exogenous or endogenous factors that can override its normal genetic programming to create new zones of hyper density. This explains how SAM's wide age distribution ranging from the fetus to the elderly can occur and which arterial bed will be targeted in these different age groups. Estrogen can increase this receptors density [15], a finding that may account for the higher incidence of fibromuscular dysplasia (FMD), a sequela of SAM, in premenopausal females than men of the same age. Aging uploads the density of alpha-1 adrenoceptors and is putatively responsible for the increased incidence, intensity and equal sexual redistribution of injurious phase SAM in the elderly [16]. Fetal cerebral arteries have a lower density of alpha-1 adrenoceptors than adults [17] a feature accounting for the absence of cerebral SAM in neonates and children with coronary artery SAM. Indeed, lesser alpha-1 adrenoceptor density aggregates also putatively are responsible for the absence of SAM in the abdominal arteries in these patients and contrariwise coronary artery SAM is not detected in mature adults and the elderly because

of the proposed decreased density of this receptor in the pericardial arteries. Prior exposure to sympathomimetic agonists also may promote increased density of this receptor sensitizing these arteries to these agents. This point is putatively substantiated by the occurrence of SAM in the distal renal arteries in a 38 year old female 10 years following 17 weeks of tocolysis with ritodrine [5] and the development of SAM causing an aneurysm in the celiac trunk, dissection of the superior and inferior mesenteric arteries with thrombosis and aneurysms of both distal renal arteries in a 56 year old female who took a triple dose of a “thermogenic” supplement containing ephedrine 10 days prior the onset of ischemic induced abdominal pain (chronic splanchnic syndrome) preceded by a 30 year history of nasal congestion treated with naphazoline and the intake of this “thermogenic” supplement [Dr Luiz Lanziotti personal communication]. This event may also occur more acutely in a “sensitized” artery with new lesions of SAM developing within 3 hours following the administration of vasopressor agents for the treatment of hemorrhagic shock caused by a ruptured gap-aneurysm [18].

The second feature implicating a hyper density of the alpha-1 receptor in the genesis of SAM is the character of SAM’s morphologic lesion in its injurious phase. This phase consists of two components - mediolysis or less frequently apoptosis of the medial muscle and a shearing lesion that tears the adventitia from the outer medial muscle. These changes are unleashed by the intense or prolonged activation of Gq heterotrimeric G protein by hyper dense zones of conformational altered alpha-1 adrenergic receptor. This would cause exaggerated biochemical responses creating a greater flux of calcium ions into the smooth muscle cytoplasm and a more intense smooth muscle contraction. The former results in a cytoplasmic Ca^{2+} overload that creates mitochondrial dysfunction that signals the excessive step wise reduction of O_2 to water by reactive oxygen species (ROS) and an interference with the mitochondrial permeability transition pore [19]. The hydropic mitochondria dilate, lose structural integrity and liberate water into the cytoplasm by rupturing. The release of water from multiple injured mitochondria floods the cytoplasm with water creating large intracellular non-stainable distended cytoplasmic vacuoles some containing membranous residues (Figures 1 and 2) These vacuoles, first forming in muscle cells located in the outer media, become confluent through cell membrane disruption. The watery cytoplasm of these coalesced cells loses cellular definition but retain a foamy appearance generated by organelle and membranous fragments (Figure 3) The added cytoplasmic water that floods into the adjacent interstitial tissue often distends the adventitial and/or intimal medial boundaries (Figure 4). Mediolytic is the histologic end result of this process. Another consequence of the mitochondrial injury is the release of cytochrome C into the cytoplasm from the inner mitochondrial membrane where it signals a caspase cascade resulting in apoptosis (Figure 5). This event explains how both mediolysis and apoptosis can be encountered in cases of SAM.

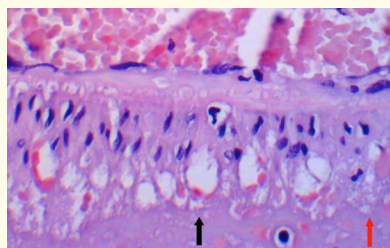


Figure 1: Segmental arterial mediolysis injurious phase, early injurious phase in pig renal artery. Outer media shows large (black arrow) and smaller (red arrow) cytoplasmic vacuoles containing non-staining clear contents (water) representing different sized enlargements of swollen mitochondria. Scattered red cells border some vacuoles. Hematoxylin and Eosin x400.

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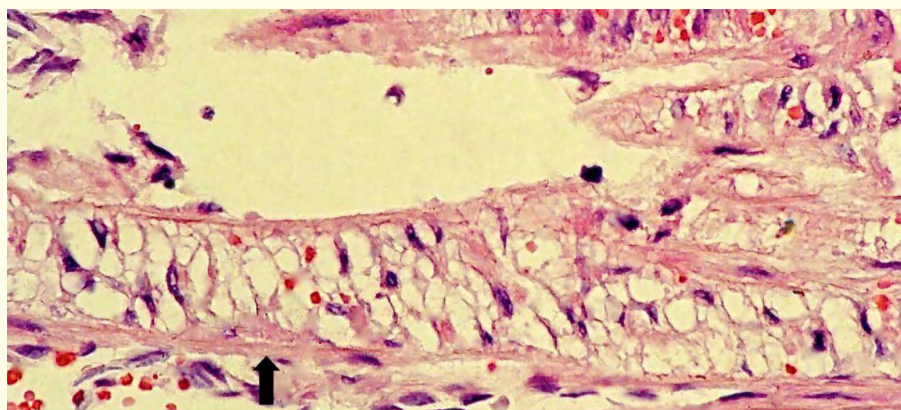


Figure 2: Segmental arterial mediolysis injurious phase. Arrow points to a longitudinal section of arterial wall showing trans mural cytoplasmic vacuolar change caused by hydropic mitochondria. Many cell membranes outlining the swollen muscle cells are still intact although some disrupted membranous fragments are evident. Note the patchy sparing of individual smooth muscle cells and the presence of occasional red cells. Hematoxylin and Eosin. x200.

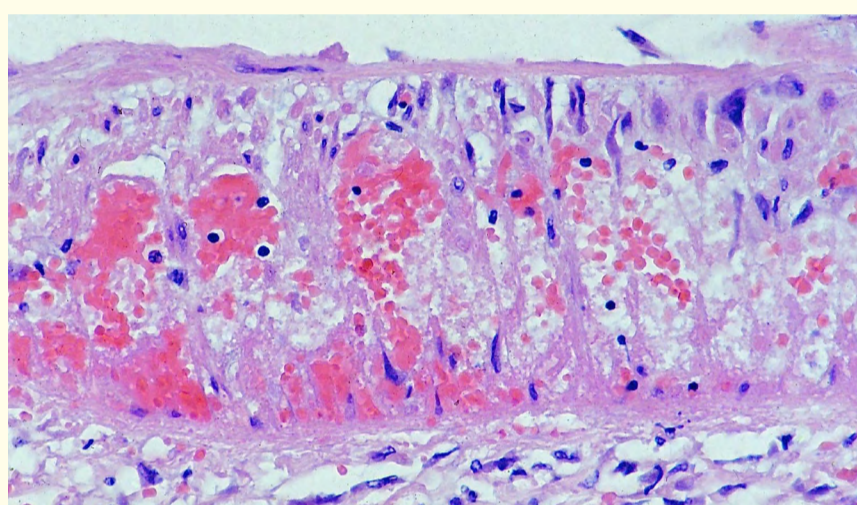


Figure 3: Segmental arterial mediolysis injurious phase. Arterial wall shows confluent mediolysis caused by cell membrane disruption with foamy contents diffusely involving the outer and mid media with focal extension into inner media. Scattered foci of hemorrhage with sparse inflammatory cells are evident in the media. Note occasional sparing of muscle cells in mediolytic areas. A linear deposit of fibrin focally lines the adventitia. Hematoxylin and Eosin x200. Adapted from the WJCD, 2013(1), On-line publication.

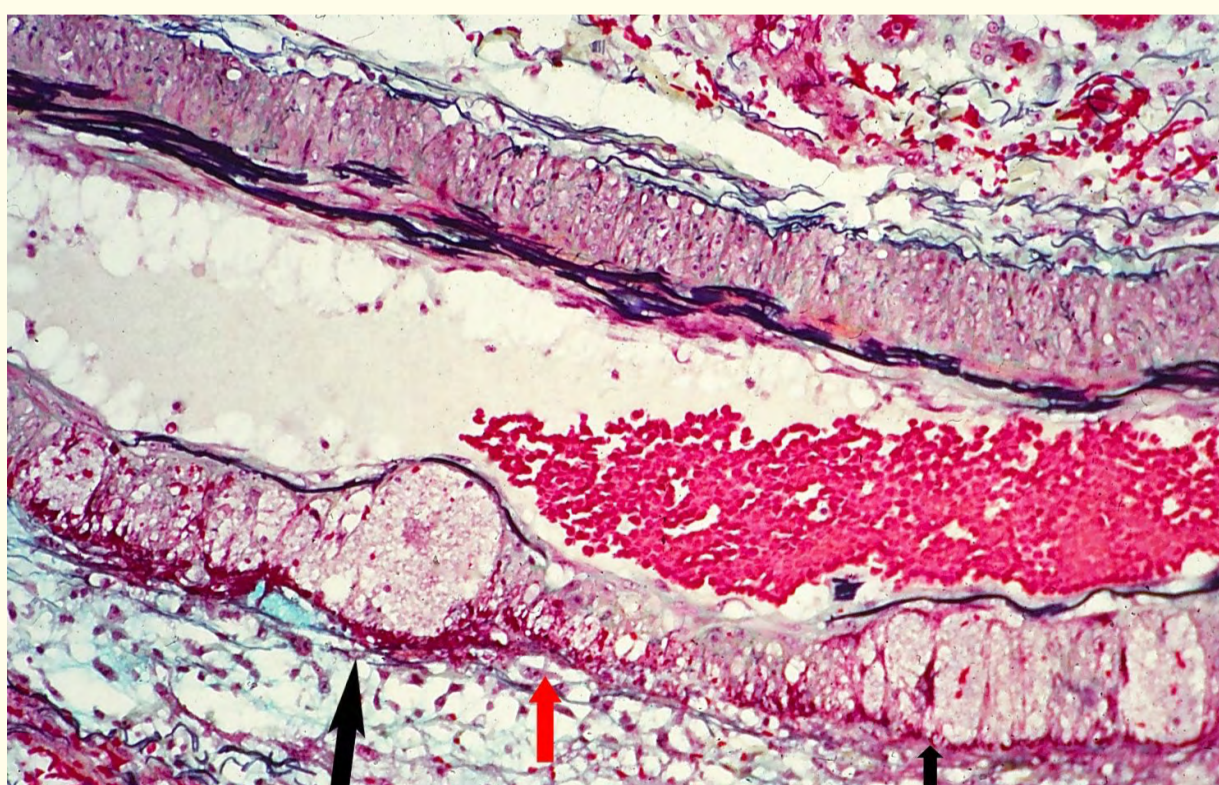


Figure 4: Segmental arterial mediolysis injurious phase. Large black arrow points to a distended area of total mediolysis caused by water that has created an outward bowing of both the preserved inner elastica (black stained membrane) and the fibrin lined adventitia (red stained membrane). Smaller black arrow designates another focus of distended trans medial confluent mediolysis contained by the inner elastica and fibrin lined adventitia. Note the foamy appearance of the confluent mediolytic zones. Red arrow points to a focus of beginning gap formation created by the incipient loss of the watery medial contents through an intima depleted of its internal elastica. Movat stain x100. Adapted with permission from the American Journal of Surgical Pathology, 13(7), copyright 1989 Lippincott, Williams and Wilkins.

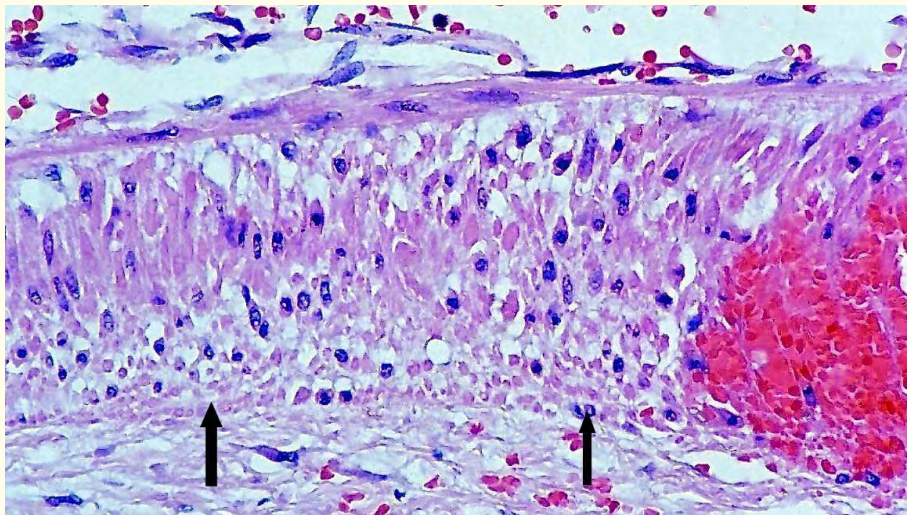


Figure 5: Segmental arterial mediolysis injurious phase. Arrows point to areas of apoptosis diffusely involving the outer media with patchy extension into the mid and inner media. Focal medial hemorrhage also is evident. Hematoxylin and Eosin x200.

The other lesion generated in injurious phase SAM is provoked by excessive vasoconstriction propelled by the intensely activated Gq heterotrimeric G protein. This shears the outer media away from the external elastica and adventitia causing fibrin deposition along the plane of the tear associated with micro hemorrhages around the adventitial medial border derived from torn capillaries and vasovasorum (Figure 6). More intense vasoconstriction with detachment of the stromal connections to the adventitia causes significant single, multiple, or circumferential separations of the outer media from the adventitia (Figure 7). Arteries showing this change may also exhibit mediolysis although the two injurious type lesions may separately occur.

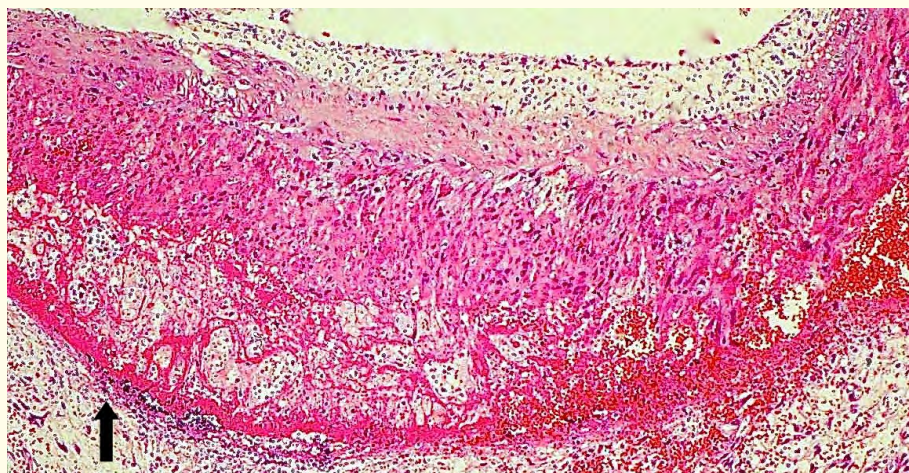


Figure 6: Segmental arterial mediolysis injurious phase. Adventitial - medial tear with arrow pointing to the fibrin lined adventitia. Tear space expanded by edema fluid, fibrin and recent hemorrhages. Fibroblasts mixed with leukocytes liberated and responding to bleeding from the torn capillaries in the adventitia are evident in the tear space and adventitia. Hematoxylin and Eosin x100. Adapted with permission from *Modern Pathology*, 8(3), copyright 1995, Nature Publishing group.

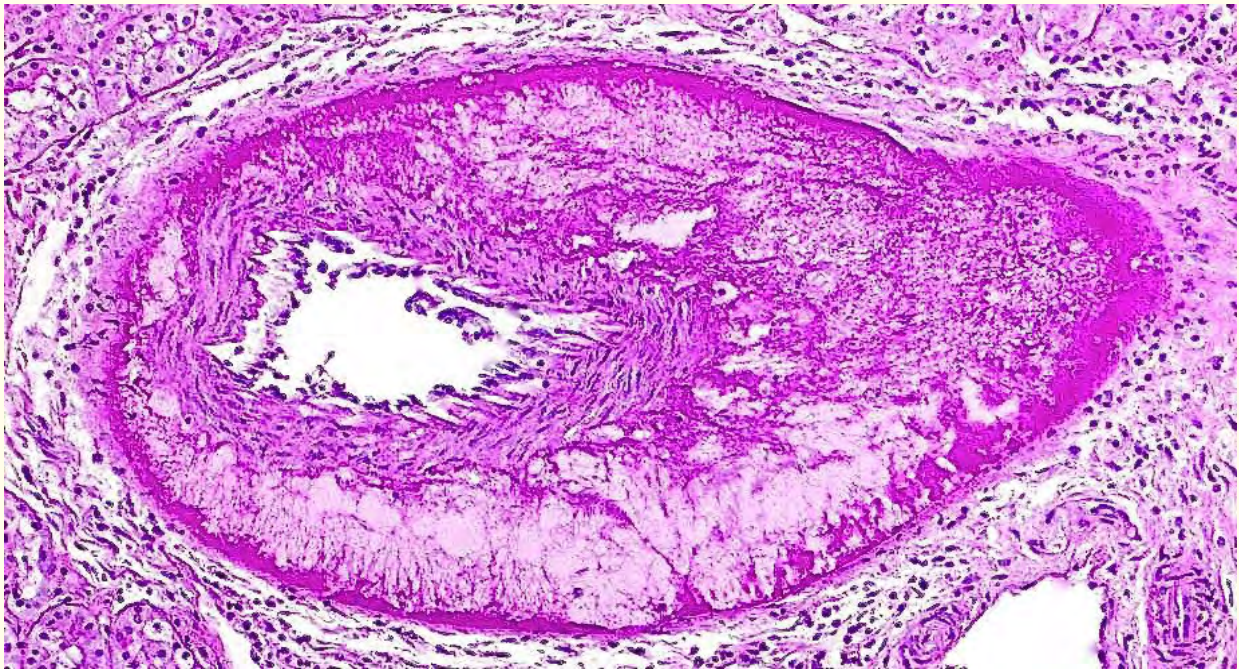


Figure 7: Segmental arterial mediolysis injurious phase. Pig renal artery showing an almost circumferential tear separating the outer media from the fibrin lined adventitia. The tear space is distended by edematous fluid containing fibrin strands that outwardly pushes the fibrin-lined adventitia away from the media. PAS stain x100. Adapted from *Interventional Cardiology* 2017, 9(5). On-line publication.

The causes of the dramatic hemorrhages in injurious phase SAM are gap-aneurysms (Figure 8). These develop from arterial gaps created in areas of trans medial mediolysis combined with internal elastica and intimal loss by the disruption of muscular stromal connections (Figure 9). Large gaps will dilate to form aneurysms but often the aneurysms form when islands of uninvolved arterial wall distributed between smaller gaps become detached from the adventitia by dissections beginning at the interface of the gap with the arterial wall and by hemorrhages at the adventitial medial junction caused by the tearing of the vasovasorum or capillaries by the shearing of the outer media from the adventitia (Figure 10). Medial island detachment in the elderly is aided by aging degenerative changes of the stromal adventitial connections [20].

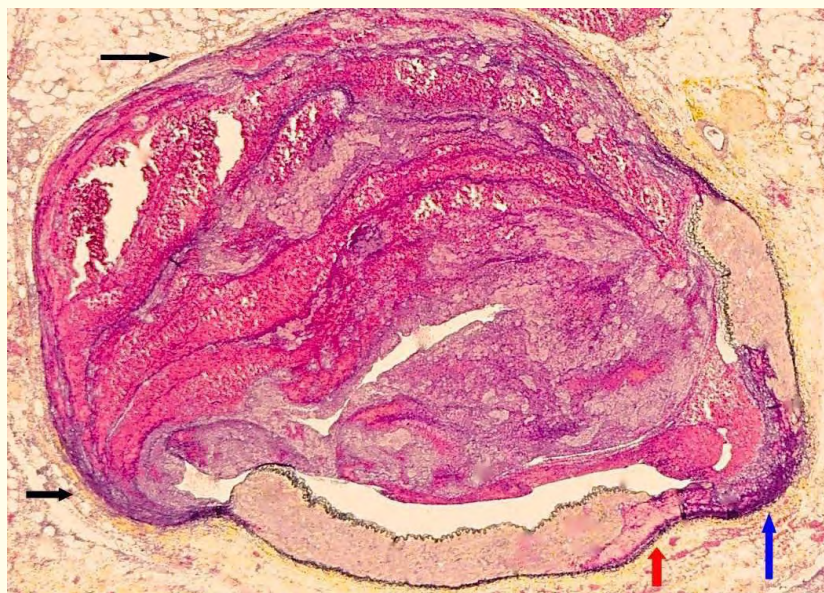


Figure 8: Segmental arterial mediolysis injurious phase. Artery showing a multiplicity of lesions - a large gap-aneurysm containing a recent thrombus (black arrows), a gap with a fibrin border (blue arrow) and an early dissecting hematoma tracking between the fibrin lined adventitia and the outer media (red arrow). Movat stain x50.

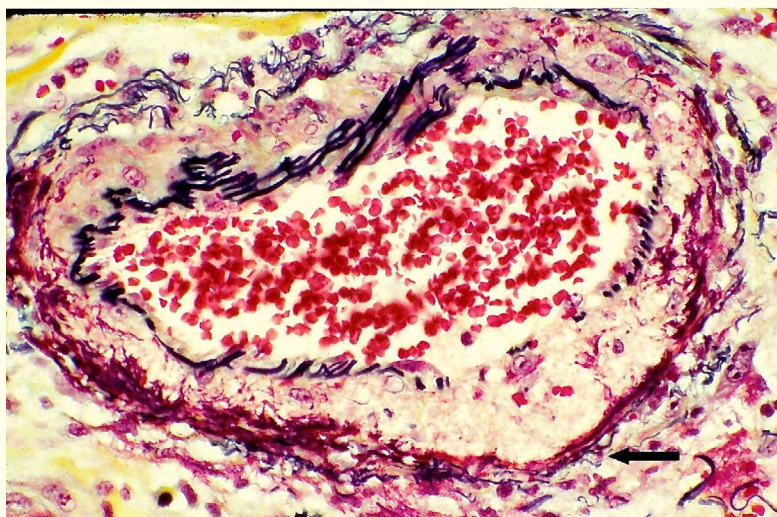


Figure 9: Segmental arterial mediolysis injurious phase. Arrow points to a focus of confluent mediolysis. Its foamy watery contents have bowed the fibrin-suffused adventitia outwardly. The internal elastica is fragmented and the intima is lost. These changes will allow the medial contents to be evacuated into the bloodstream creating the arterial gaps illustrated in figure 10. Movat stain x50. Adapted with permission from the American Journal of Surgical Pathology, 13(7), copyright 1989, Lippincott, Williams and Wilkins.

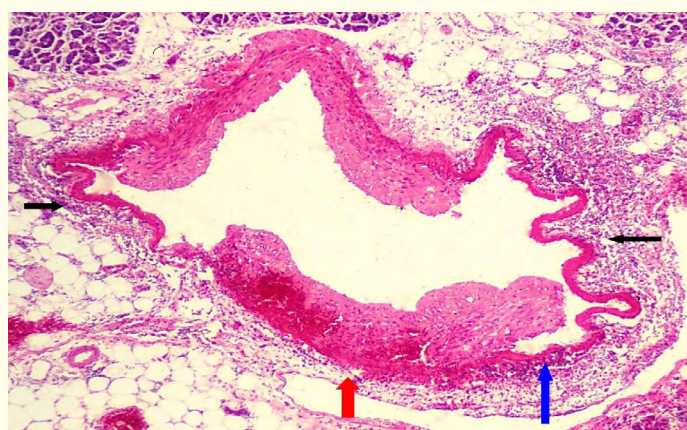


Figure 10: Segmental arterial mediolysis injurious phase. Black arrows point to two arterial gaps bordered by a thick linear band of fibrin. Lower medial island shows incipient detachment from the adventitia by a beginning dissection between the adventitia and media (blue arrow) and capillary bleeding in and around the adventitial medial junction (red arrow). Hematoxylin and Eosin x100. Adapted with permission from the International Journal of Surgical Pathology, 15(2) copyrights 2007, Sage Publications, Inc.

Arterial mediolysis can be of varying intensities in different arteries of the same case or even in different areas of the same artery. However, the outer medial muscles are participants in all cases since these muscles receive sympathetic innervation, whereas the mid and inner muscles are exposed to norepinephrine by diffusion. Thus, the presence or absence of mediolysis developing in the latter muscular areas depends on the relative strength of the sympathetic discharge. In zones of mediolysis isolated normal muscle cells are frequently found. This is putatively due to the non-uniformity of hyper density distribution of the alpha-1 adrenergic receptor on the smooth muscle cells in these areas.

Reparative Phase

Norepinephrine also incites the brisk development of granulation tissue that rapidly mends the injurious phase lesions (Figures 11, 12). This repair has several outcomes that are predetermined by the extent and type of lesions created in SAM's injurious phase.

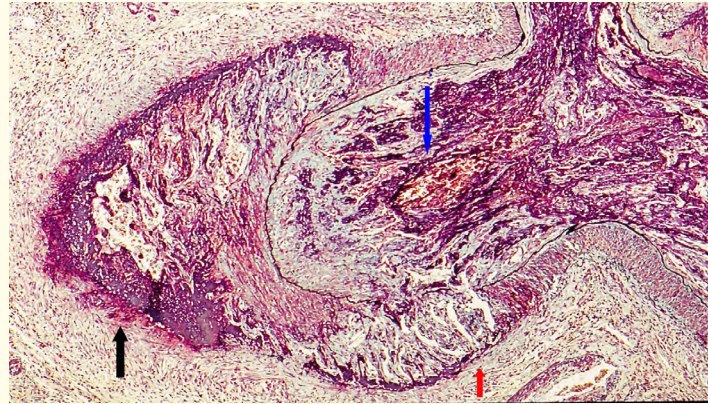


Figure 11: Segmental arterial mediolysis reparative phase (early). Red arrow points to granulation tissue filling and expanding a focus of transmural mediolysis and penetrating through the fragmented internal elastica to form an intimal plaque which severely narrows the lumen containing an early thrombus (blue arrow). Black arrow points to another focus of watery confluent mediolysis that bows the thick fibrin lined adventitia outwardly. The top of this area shows another focus of transmural granulation tissue. Movat stain x100. Adapted from the *Journal of Cardiovascular Disease and Diagnosis* 2015,32. On-line publication.



Figure 12: Segmental arterial mediolysis reparative phase. Black arrow points to a florid proliferation of granulation tissue in the space created by the tearing separation of the adventitia from the outer media. Bleeding from ruptured capillaries in the granulation tissue has initiated a dissecting hematoma (white arrow) tracking between the outer media and adventitia. Hematoxylin and Eosin x15. Adapted with permission from the *International Journal of Surgical Pathology*, 15(2), copyright 2007, Sage Publications, Inc.

Mediolytic Injury

Foci of mediolysis generally restricted to the outer and mid media with occasional extension to the inner media but with preservation of the intima and internal elastica will show on angiography varying degrees of stocking-like arterial dilatations. This lesion is generally asymptomatic. Its angiographic appearance can revert to normal following granulation tissue reparation (Figure 13).

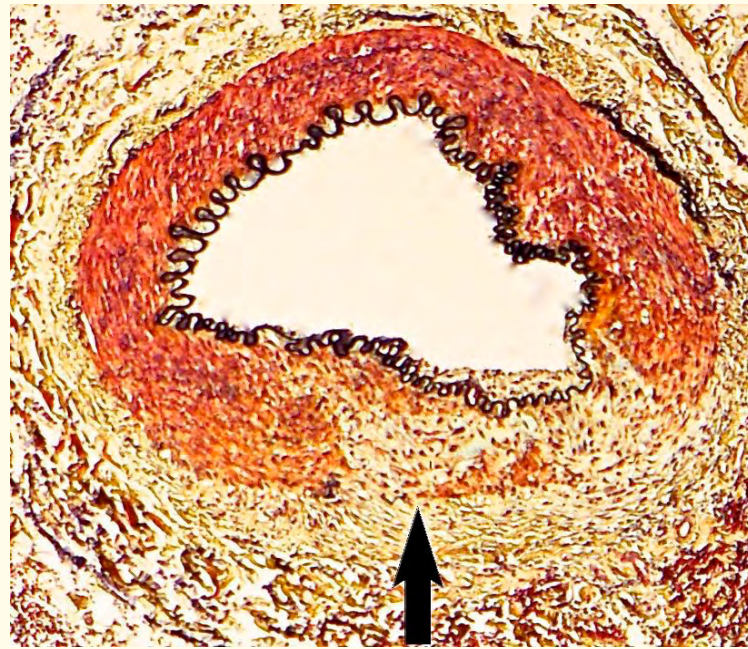


Figure 13: Segmental arterial mediolysis reparative phase. Arrow points to fibrotic granulation tissue (yellow stain) in the media, repairing 2 foci of mediolysis and in the adventitia as a crescent partially encircling the artery created as a response to prior injury at the adventitial-medial junction, an antecedent lesion to adventitial fibromuscular dysplasia. The internal elastica is intact but is bedecked by a thin layer of granulation tissue overlying the repaired media. This arterial lesion would be asymptomatic and would appear “resolved” on angiographic studies. Movat stain x100. Adapted with permission from *Cardiovascular Pathology*, 18(6), copyright 2009, Elsevier Inc.

The repairing granulation tissue also can create the following sequelae

Arterial stenosis: The arterial lumen can be compressed by circumferential proliferating granulation tissue replacing zones of trans medial mediolysis (Figure 14) or the lumen may be narrowed by intimal plaques formed by foci of trans medial granulation tissue extending through a fragmented internal elastica and intima (Figure 12). Thrombi may develop in these stenotic arteries or in other types of sequelae to worsen the stenosis or cause focal infarcts.

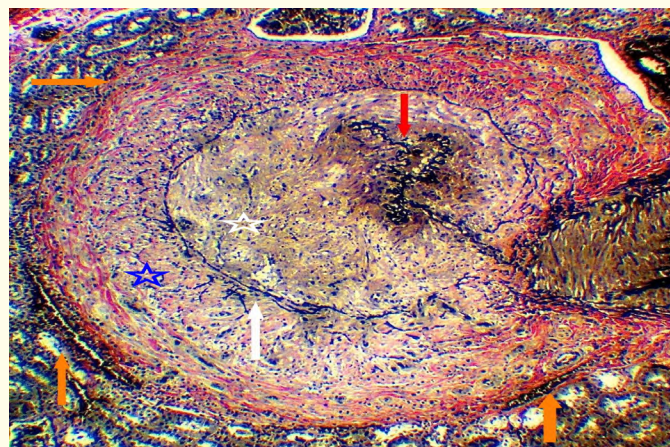


Figure 14: Segmental arterial mediolysis reparative phase. Renal artery stenosis in pig caused by luminal compression by expanded granulation tissue in the media (white star) and adventitial-medial tear space (blue star). Red arrow designates the compressed internal elastica (black membrane) surrounded by brown staining viable inner medial muscle. White arrow points to the external elastica (outer black membrane) and orange arrows to red staining adventitial connective tissue. Verhoef van Gieson x100. Adapted with permission from *Veterinary Pathology*, 52(6). Copyright 2015, Sage Publications Inc.

Persistent thick-walled aneurysms: These are fabricated by the granulation tissue overlying gap-aneurysms, intervening medial islands and the intima of adjacent unaffected arterial wall (Figure 15). Organized thrombi may further add structural support to the aneurysmal wall. Follow-up angiographic studies has revealed the perseverance of these aneurysms for 2 or more years after the onset of SAM [6]. Since the fate of these aneurysms is as yet unknown periodic surveillance is recommended and it has been proposed that aneurysms, greater than 2 cm, be treated by surgical reconstruction or endoscopic embolization because of their potential to rupture [21].

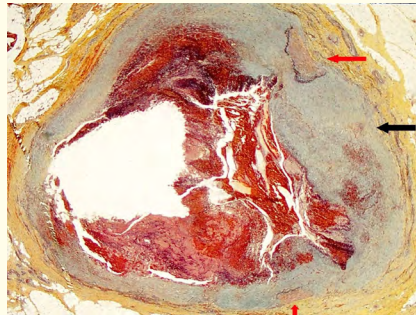


Figure 15: Segmental arterial mediolysis reparative phase. Black arrow points to a thick layer of mature granulation tissue filling a larger gap and extending over the intima of two medial islands (red arrows) to encircle a large gap-aneurysm. Presence of medial islands in the wall of an aneurysm is a histologic clue to a diagnosis of SAM as a cause of the aneurysm. Movat stain x25.

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Shearing adventitial -medial lesion

The arteries in the granulation tissue filling the adventitial-medial tear space can rupture causing the following sequelae:

Hematomas and dissecting hematomas (Figure 16): These may develop in the early repair phase of SAM but can also appear weeks, months or even as late as two years after the onset of SAM. Their growth can be provoked by the faulty placement of stents into stenotic arteries [5].

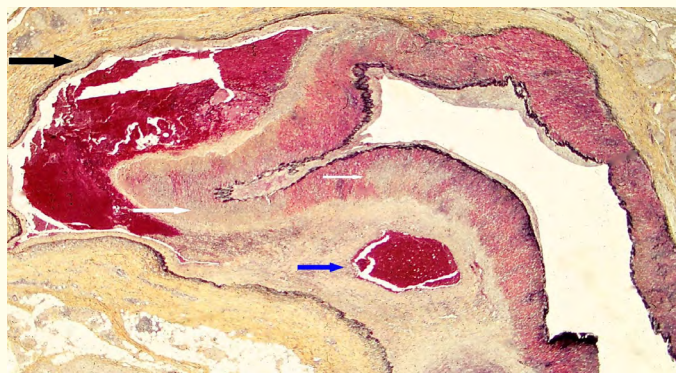


Figure 16: Segmental arterial mediolysis reparative phase. The mature granulation tissue filling and expanding the tear space between the outer media and adventitia exhibits a dissecting hematoma (black arrow) and a hematoma (blue arrow). White arrows point to areas of mediolysis repaired by mature granulation tissue, a clue to the diagnosis of SAM in cases of dissecting hematomas. Movat stain x15. Adapted with permission from the International Journal of Surgical Pathology, 15(2), copyright 2007, Sage publications Inc.

Fibromuscular Dysplasia (Figure 17): In 1995 Slavin and coworkers proposed that SAM was a precursor of FMD a disorder of unknown pathogenesis [12]. As new cases of SAM became available for study and its histologic evolution became clearer this hypothesis assumed greater validity [1,5,14]. The site and intensity of the injurious phase lesions and their repair determine the variant of FMD that will develop. Fibrosis of the granulation tissue primarily developing circumferentially in the adventitial-medial tear site will create Perimedial FMD, fibrosis of the granulation tissue repairing foci of medial muscle loss through mediolysis or apoptosis with concurrent fibrosis of the adventitial-medial tear space generates Medial FMD, Adventitial FMD originates from granulation tissue principally formed

in the arterial adventitia as a response to injurious phase lesions (Figure 13). Smooth muscle metaplasia of this granulation tissue can also occur creating leiomyomatous - like lesions. However, SAM is not a forerunner of intimal FMD, a vascular lesion occurring in children often involving the arteries of the extremities because these arteries are not innervated by the peripheral sympathetic nervous system and intimal plaques in SAM are only generated by the extension of medial granulation tissue into and through a fragmented intima (Figure 11) and/or the organization of overlying thrombi.

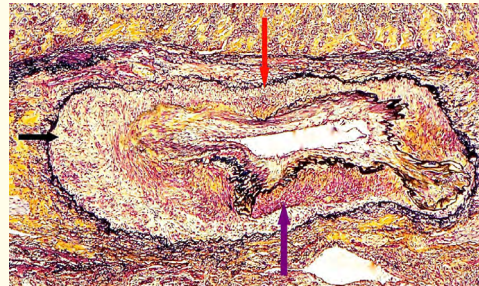


Figure 17: Segmental arterial mediolysis reparative phase evolved to fibromuscular dysplasia. Black arrow points to granulation tissue filling and expanding the tear space between the outer media and adventitia (outlined by black staining external elastic) and expanding into and replacing areas of medial loss through mediolysis (red arrow). Purple arrow points to residual medial muscle (reddish brown stain) showing patchy fibrosis (yellow stain). The internal elastic (inner black staining membrane) is missing in a zone of trans medial muscle loss. A circumferential plaque of granulation tissue bedecks the intima to significantly narrow the arterial lumen. Movat stain x25. Adapted with permission from *Cardiovascular Pathology*, 18(6), copyright 2009, Elsevier Inc.

Vascular considerations

SAM usually is restricted to one anatomic site, but concomitant cerebral and intestinal SAM has been reported [22,23] and co-existing abdominal and coronary artery SAM also recorded in greyhound dogs [9]. Although SAM can occur in any of the large abdominal arteries it most frequently targets the celiac artery and its main branches the splenic and hepatic arteries. The major tributaries of these arteries also can be implicated. Important involved side branches include the large pancreatic arteries, large intrahepatic arteries and the hilar branches of the renal artery. SAM can also be found in the serosal and submucosal arteries of the gastrointestinal tract and in the lobar and arcuate renal arteries. Arterial involvement in organs is focal and the renal cortex and hepatic periphery are spared since the SAM targeted larger arteries are absent in these areas. SAM can occur solely in one artery but generally more than one artery is attacked either in the same arterial system or in adjacent arterial beds. Concurrent involvement of gastrointestinal and distal renal arteries is common. Frequently, involved arteries will show several different SAM generated lesions that may occur together in one arterial section (Figure 8), distributed in different areas of one artery or its immediate tributaries or located in adjacent arterial beds. The double aneurysm of SAM, the side-by-side occurrence of a dissecting hematoma and gap aneurysm (Figure 18) is the most egregious example of this event. The injurious lesions develop very rapidly, may vary in intensity, and are quickly repaired. Aside for bleeding from gap-aneurysms, a finding generally restricted to the elderly, these rapidly disappearing injurious lesions are generally asymptomatic, can exhibit angiographic resolution and therefore may only be incidentally detected when accompanied by other serious disease states. This accounts for the purported rarity of reports of SAM in young adults. However, their reparative sequelae may become symptomatic as ischemic disorders or present as different vascular diseases caused by dissecting hematomas, splanchnic artery stenosis and aneurysms and FMD circumstances happening immediately after the injurious phase or weeks, months or even years after the onset of SAM. One example is SCAD (spontaneous coronary artery dissection). The epicardial coronary arteries are the arterial site of SAM specifically targeted in neonates, children, adolescents and young adults [24]. SCAD principally develops in young adult females [25], who as noted above, possess an increased density of alpha-1adrenoceptors. Usually an absence of coronary artery disease is noted, a feature explainable by a very recent or prior episode of asymptomatic injurious phase SAM. Concomitant FMD [26], another sequela of SAM (see below), is uncovered in many SCAD patients who often also present with a history of stress caused by delivery in pregnancy, strong emotions, and intense exercise - all stimuli that can provoke the supra physiologic release of norepinephrine from the adrenal medulla [27]. These facts support the hypothesis that reparative phase SAM is one precursor of SCAD.

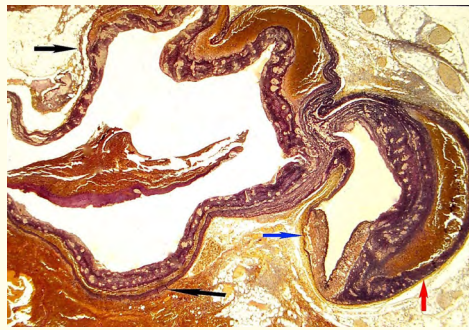


Figure 18: Segmental arterial mediolysis injurious phase. Double aneurysm - red arrow points to a dissection hematoma, black arrows to a huge gap-aneurysm and blue arrow to a gap media interface showing a beginning dissection between the outer media and the external elastica delineated adventitia. Movat stain X15. Adapted with permission Cardiovascular Pathology, 18(6), Copyright 2009, Elsevier Inc.

Challenges to the hypothesis that SAM is the precursor of FMD accrue from differences between these two entities in their clinical presentation, age, sex and sites of arterial involvement. These differences can be reconciled by the realization that SAM is a biphasic disorder, by the cognizance of the plasticity of the alpha-1adrenoceptor and the recognition that injurious phase lesions may be asymptomatic and with repair disappear on angiographic studies [1,5,14].

Venous Angiopathy in SAM: Venous mediolysis and fibromuscular Dysplasia

The abdominal and renal veins accompanying large SAM afflicted muscular arteries can also undergo mediolytic vasospasm (Figure 19) [13,14]. The lesions in these veins show a similar evolutionary sequence to those encountered in SAM - cytoplasmic vacuolization (Figure 20), followed by mediolysis and apoptosis (Figure 21) with release of water that widely separates surviving muscle bundles in the media and in the adventitia of large veins and expands into and disrupts the intima (Figure 22). These alterations result in a haphazard smooth muscle loss in the media and adventitia of large veins causing irregular outer wall contours (Figure 19), and a medial moth-eaten appearance in smaller veins. Zones of muscle loss are initially reinhabited by a sparse loosely formed edematous granulation tissue containing membranous remnants (Figure 19) that in large veins can significantly expand the muscle depleted media and adventitia (Figure 19). Like the arterial lesions in SAM, stenosing intimal plaques may also develop as well as gap-like lesions caused by areas of total medial loss with venous wall integrity preserved by an intact intima. Fibrosis of this granulation tissue creates venous fibromuscular dysplasia that may cause stenotic and obstructive lesions in the main renal and large intestinal veins (Figure 23).



Figure 19: Venous angiopathy accompanying segmental arterial mediolysis. Red arrow points to a vein exhibiting a ragged outer contour due to the irregular mediolytic loss of outer and mid media. Despite the muscle loss, the venous wall is expanded by membranous debris and edema fluid. The adjacent artery (magenta arrow) shows a gap (black arrow) occupied by granulation tissue that extends upward to partially fill an adventitial-medial tear (blue arrow), and downwardly into a zone of transmural mediolysis (orange arrow). Normal medial muscle stained reddish-violet. Movat stain x25. Adapted from the World Journal of Cardiovascular Diseases 2013,3 On-Publication.

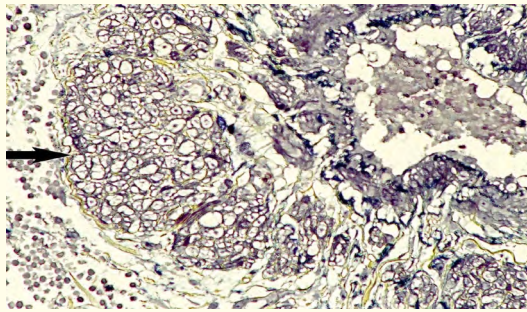


Figure 20: Venous angiopathy accompanying segmental arterial mediolysis. Black arrow points to a zone of outer media showing hydrops of the smooth muscle. Movat stain x200. Adapted with permission from the International Journal of Surgical Pathology 15(2), copyright 2007, Sage publications Inc.

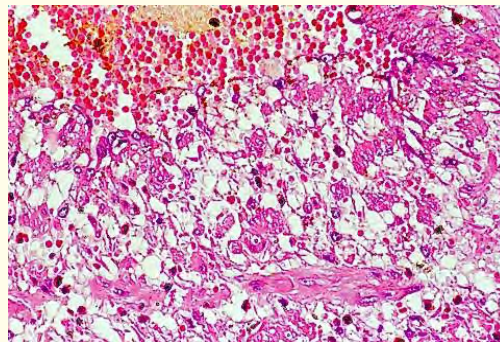


Figure 21: Venous angiopathy accompanying segmental arterial mediolysis. Microphotograph shows confluent mediolysis containing membranous and organelle fragments distributed in an edematous background created by the rupture of the cell membranes of hydropic smooth muscle cells. Scattered intact muscle cells are also evident some containing one or more cytoplasmic vacuoles (hydropic mitochondria) while others have been transformed into apoptotic bodies appearing as membrane bound markedly shrunken, densely eosinophilic cytoplasmic fragments some containing pyknotic nuclei. Hematoxylin and eosin x200. Adapted with permission from the International Journal of Surgical Pathology 15(2), copyright 2007, Sage publications Inc.

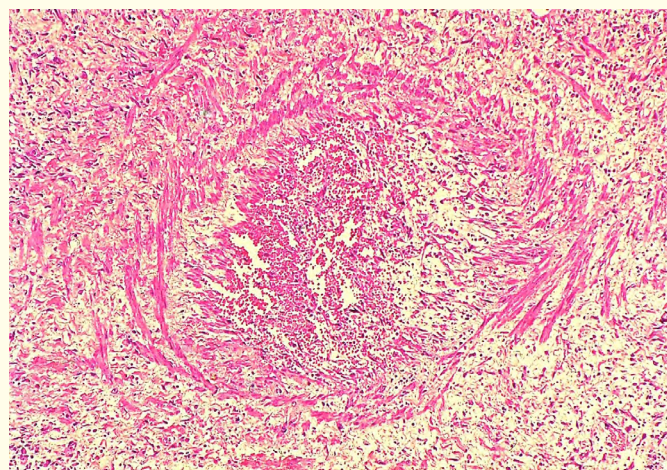


Figure 22: Venous angiopathy accompanying segmental arterial mediolysis. Watery fluid released from mediolysis containing forming granulation tissue widely separates surviving medial muscle and expands and disrupts the intima. Hematoxylin and Eosin x100. Adapted from the World Journal of Cardiovascular Diseases, 2013,3. On-line publication.

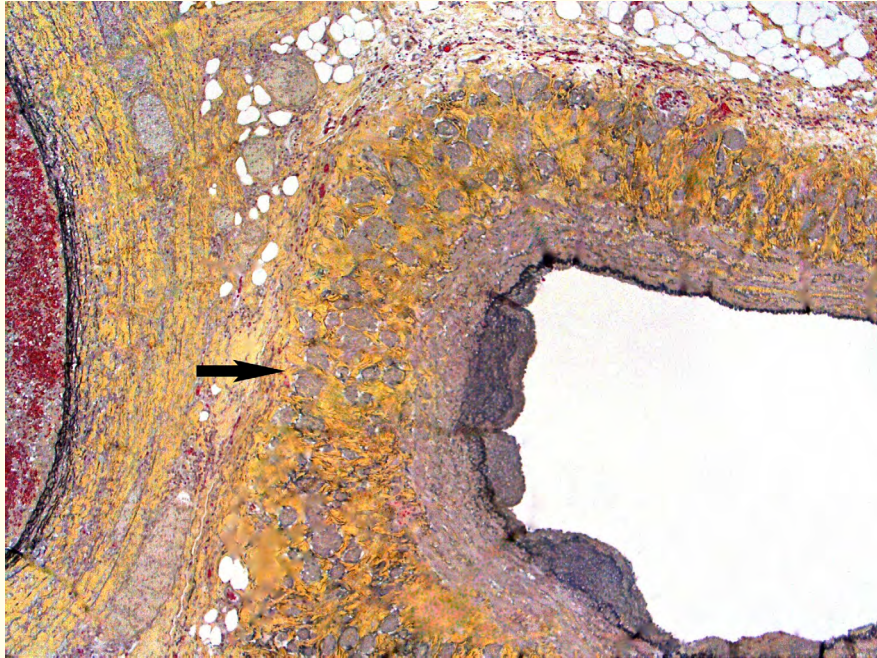


Figure 23: Venous fibromuscular dysplasia. Arrow points to a renal vein adjacent to a dissecting hematoma. The vein shows fibrous tissue (stained yellow) expanding the outer media, replacing and encircling surviving smooth muscle (stained brown) and extending into the adventitia. An irregular thin intimal plaque consisting of elastic fibers bedecks the intima. Movat stain x50, Adapted from World Journal of Cardiovascular Diseases, 2014,4, On-line publication.

Endothelin - 1 (ET-1) is identified by immunostaining in the intimal endothelial cells and staining the smooth muscle cell membranes and membranous fragments in this venous lesion [13]. SAM in the immediately adjacent arteries does not show ET-1 at these sites. ET-1 also is identified in the adventitial capillaries of both arteries and veins, in the capillaries of the adjoining mesenteric fat and in fat cells. These findings suggest that the ET-1 produced by endothelial cells represents a “field effect” stimulated by the pathophysiologic effects generated by SAM in the adjacent artery. ET-1 release would cause venous vasoconstriction but the ET-1 stained vein showed a spastic response. What was the genesis of this venous vasospasm? In physiologic vasoconstriction ET-1 produced in vascular endothelium binds to an ETA receptor on the cell membrane of medial smooth muscle. This couples with a Gq protein that activates a phosphatidylinositol calcium messenger system and protein kinase C via the formation of diacylglycerol (DAG) to stimulate muscular contraction. Essentially this is the same pathway that the norepinephrine conformed alpha-1 adrenoceptor takes to induce vasoconstriction. The cross-talk of norepinephrine coupled receptor with ET-1 coupled receptor is believed responsible for the genesis of the venous angiopathy [28]. This is accomplished through the activation of the Gq protein by both the coupled alpha-1 adrenergic and the ETA receptors. The high or prolonged intensity of this double activation creates a cytoplasmic Ca^{2+} overload. This incites mitochondrial dysfunction and the resultant pathophysiology, described above in the genesis of arterial mediolysis, creating lesions analogous to those described in SAM.

Differing from SAM is the absence of a venous shearing lesion between the outer media and adventitia missing for two reasons. Veins are not very muscular so that the exaggerated vasoconstriction generated by the cross-talk may not be powerful enough to create venous tearing lesions. Secondly, veins do not possess an external elastic lamina so that the tearing plane between the outer media and the adventitia is not sharply defined. This indistinctness is augmented in larger muscular veins by the presence of smooth muscle in their adventitia. The mediolysis of this adventitial muscle stemming from the cross-talk of ET-1 produced by the adventitial capillaries and the norepinephrine released at this site paired with ROS generated water causes the bizarre irregular outer contours in these veins.

Mesangial Cell Hyperplasia

The recognition of mesangial hyperplasia as a collateral lesion in SAM initially appeared in Slavin and Gonzalez-Vitale article defining SAM as a distinct entity (Figure 24) [2]. Thereafter there was little attention paid to the mesangium in cases of SAM until Leifsson and Slavin article reporting SAM in the kidneys of pigs slaughtered in a Danish abattoir examined to rule out septic emboli [7]. Half of the 36 kidneys with SAM showed mesangial hyperplasia (Figure 25). The development of SAM in these pigs was believed to be instigated by the liberation of supra physiologic levels of norepinephrine from the adrenal medulla as a consequence of a “fight-or-flight response”. Norepinephrine is also suspected of causing the mesangial hyperplasia [8]. The mesangial cell originates from hematopoietic stem cells [29]. Their contractile activity regulates blood flow in the glomerular capillaries the mesangial cell behaving as the glomerular homologue of vascular smooth muscle [30]. Norepinephrine can contract these cells and directly modulate the synthesis of extra cellular matrix protein [30,31]. Mesangial cells, innervated by the peripheral sympathetic nervous system, possess alpha-1 adrenoceptors and the biochemical events initiating contraction are similar to those occurring in smooth muscle [30,31]. Norepinephrine released from the sympathetic nervous system regulates their migration to glomeruli [32]. Therefore, the same stimuli causing SAM also may provoke the sympathetic nervous system innervating the bone marrow to produce mesangial cells and rapidly release them to colonize the glomeruli creating mesangial hyperplasia. The mesangial cells are then acted upon by the norepinephrine liberated from the peripheral sympathetic nervous system innervating the targeted renal arteries to couple with their alpha-1adrenoceptors forming conformational changes that activate the cytoplasmic Cq protein to contract these cells. The mesangial hyperplasia is generally discrete, not evident in all cases of SAM, and is dysfunctional since too few glomeruli exhibit the contracting hyperplasia required to significantly decrease the glomerular blood flow and filtrating surface areas of its capillary component. Mediolytic was not found in the hyperplastic mesangial cells but focal glomerular loop obliteration with stromal matrix replacement was evident, a change putatively caused by prior apoptosis of the mesangial cells with repair analogous to the injurious and repair cycle formed in SAM (Figure 24B). This response generated the glomerular lesions occurring in focal segmental glomerulosclerosis.

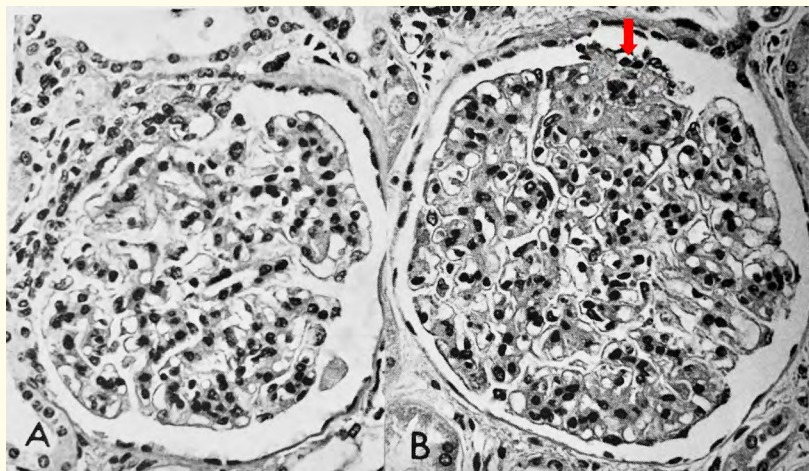


Figure 24: Human glomeruli in segmental arterial mediolysis. Glomerulus in A exhibits tandem-like arrangement of mesangial cells indicative of hyperplasia. Glomerulus in B shows increased numbers of mesangial cells and at arrow exhibits a segmental deposit of matrix material obscuring the adjacent peripheral capillary loop. Hematoxylin and Eosin. Figure A x350, Figure B x300. Adapted with permission from *Laboratory Investigation*, 35(1), copyright 1976, Nature Publishing Group

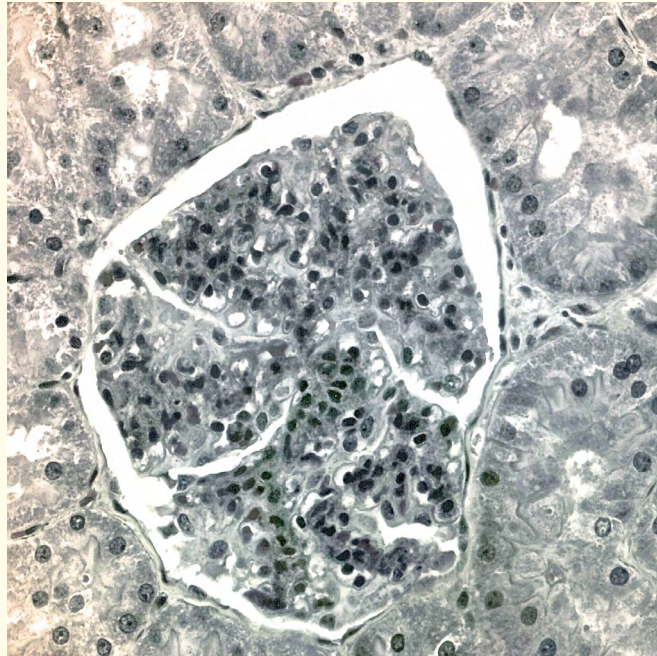


Figure 25: Pig glomerulus in segmental arterial mediolysis. The glomerulus shows an in tandem arrangement of hyperplastic mesangial cells forming the glomerular stalk. The cytoplasm of these cells and their matrix material has effaced many peripheral capillary loops. Movat x400. Adapt from *Interventional Cardiology*. 2017,9(5), On-line publication.

Beta-receptor Agonists, SAM and Myocardial apoptosis

Myocardial apoptosis accompanied SAM in instances of SAM's stimulation by Beta-receptor agonists. This occurred in a 28 - week old twin fetus, who died one day following tocolysis with a Beta receptor agonist [13] and in two greyhounds necropsied 4 and 17 days after a single dose of ractopamine administered to investigate the ability to detect this agent and its metabolites in urine by a pari-mutuel testing laboratory [9,10]. The latter is administered illegally in racing animals to enhance their athletic abilities. More importantly it also is utilized in animal husbandry as a repartitioning agent added to animal (cattle, swine and turkeys) feed in the finishing stage of growth before slaughter to foster animal growth by inhibiting fat production, increasing protein synthesis and reducing protein break down thereby increasing the monetary value of the carcass. It can be transferred to humans in the eaten meat products of these slaughtered animals.

How did these agonists cause SAM? Beta 2 agonists are drugs that bind with the Beta 2 receptor on the cell membrane of vascular smooth muscle to cause vascular dilatation. The Beta agonists causing SAM release high concentrations of norepinephrine from the varicosities of the sympathetic adrenergic nerves [33]. Since the liberated norepinephrine has a low binding affinity for the B2 receptors, it preferentially will form ligands with the alpha- 1 adrenoceptor. Their coupling unleashed the biochemical events leading to vasoconstriction; a response exaggerated in the hyper dense zones on the smooth muscle cell membranes, to cause SAM.

The heart lesions were best visualized in the myocardium of the grey hound necropsied four days after the administration of ractopamine. Multiple varying sized cytoplasmic vacuoles were discerned in groups of 20 or more myocytes in both right and left hearts (Figure 26). These vacuoles exhibited a clear content and developed in a linear arrangement parallel to the long axis of the myocyte. In areas the vacuoles dilated and anastomosed forming irregular tiny cytoplasmic lakes, some containing membranous spurs. This vacuolar change totally replaced and/or displaced the cytoplasm of some affected myocytes in other areas myocytes containing fewer vacuoles and lakes shrunk, lost their nuclei and acquired a dense eosinophilic cytoplasm that underwent fragmentation and budding creating circumscribed small islands of densely eosinophilic cytoplasm -apoptotic bodies (Figure 27). These degenerate alterations were accompanied by a vigorous reparative response consisting of fibroblasts and newly formed capillaries accompanied by edema and deposition of extracellular matrix material that developed in the interstitial tissue between individual and groups of apoptotic myocytes (Figure 27). Large interstitial coronary arteries nourishing the foci of degenerate myocardium showed foci of SAM without thrombosis. This reparative response was free of inflammation except for the presence of a rare eosinophil. By day 17 many zones of this granulation tissue were transformed into fine areas of fibrosis.

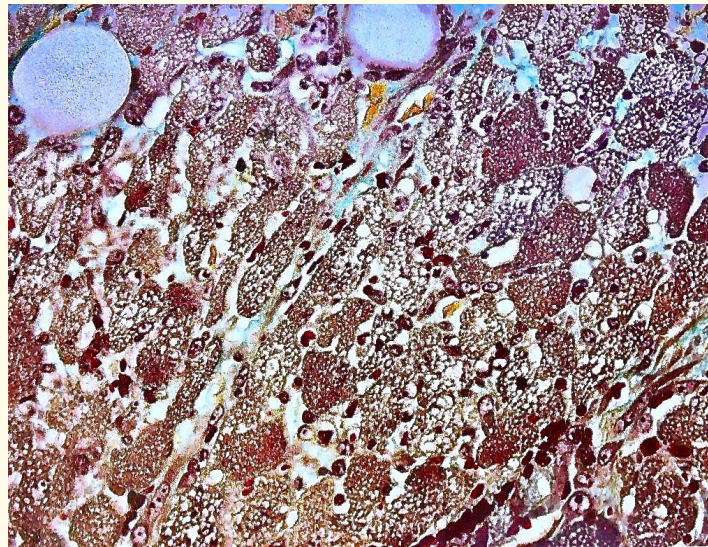


Figure 26: Grey hound myocardium in segmental arterial mediolysis. The cytoplasm of most of the myocytes is almost totally filled with alcian-blue negative cytoplasmic vacuoles (hydropic mitochondria). Fragmentation of the vacuolar membranes has resulted in their focal coalesce filling the cells with small lakes of water creating an almost identical picture to that observed in the smooth muscle in mediolysis. Edema fluid, derived from disrupted myocytes, and alcian-blue matrix material, supplied by the reparative granulation tissue, is evident in the interstitial tissue separating the degenerating myocytes. Movat x200.cation.

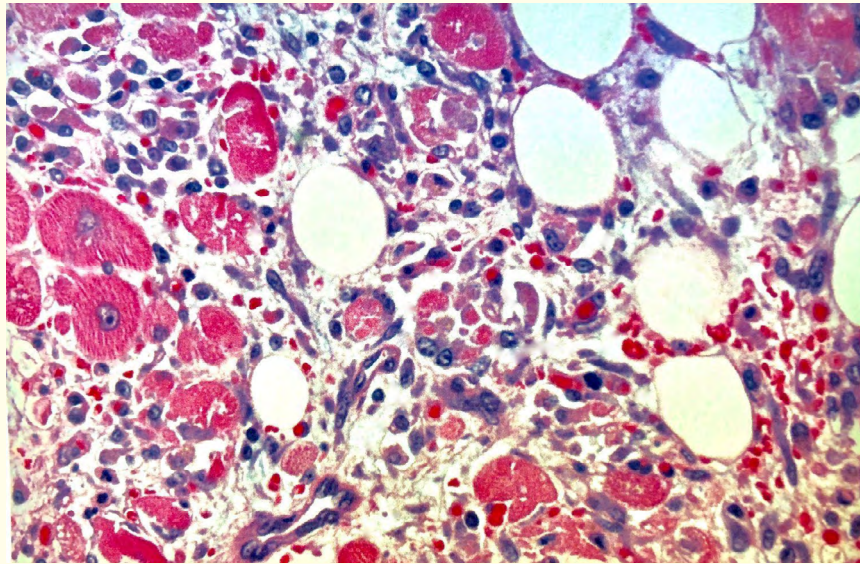


Figure 27: Greyhound myocardium in segmental arterial mediolysis. The myocytes show apoptotic degeneration - well-circumscribed densely eosinophilic fragmented cytoplasmic bodies showing budding and formation of apoptotic bodies. The apoptotic muscle cells are widely separated by edematous interstitial tissue containing granulation tissue - fibroblasts and newly formed capillaries. Hematoxylin and Eosin x400.

These pathologic changes are analogous to those occurring in the medial smooth muscle in SAM - intrinsic apoptosis putatively caused by an overload of cytoplasmic Ca^{2+} [34,35]. How could this occur in both fetal heart and greyhound myocardium? Both have markedly elevated heart rates. The fetal heart rate ranges from 120 to 159 beats per minute. This high heart rate is episodic in greyhounds whose extra-large hearts can beat at 310 - 340 beats/minute circulating the dogs entire blood volume between 4 and 5 times during a 30 second racing gallop [36]. The hemodynamic stress due to the increased myocardial contractility is the underlying condition promoting the apoptosis potential in these subjects. Cardiac beta-adrenergic receptors, like vascular alpha-1 adrenoceptors, are not static entities but are dynamically regulated by a variety of pathophysiologic states [37]. To meet the high physiologic cardiac demands of the fetus and greyhound it is likely that this receptor was upgraded creating foci of hyper density on the sarcolemma of the cardiac myocytes. The added stimulus for norepinephrine production by the Beta agonists could further signal the norepinephrine coupled hyper dense zones of beta-1 receptors to activate, in an exaggerated fashion, the quantity or quality of Gs-cytoplasmic protein or adenylyl cyclase. This would cause perturbations in cAMP production and signalling of protein kinase (PK-A) creating a dysregulated calcium influx through the L-type Ca^{2+} channel, the major Ca^{2+} channel in cardiac myocytes. The Ca^{2+} stores in the sarcoplasmic reticulum, the principal cytoplasmic repository of these ions would become overloaded. Their spontaneous release by the calcium activated ryanodine receptor would cause localized cytoplasmic overload of Ca^{2+} in the vicinity of the mitochondria due to their close or direct contact with the sarcoplasmic reticulum. The supra physiologic amounts of norepinephrine released by the B agonists also can couple with the alpha-1 adrenoceptor located on the nuclear membrane of the myocyte [38]. Its coupling of the Gq protein activates phospholipase at the plasma membrane. This cleaves phosphatidylinositol (PI) increasing inositol trisphosphate (IP3) that binds to the IP3-receptor in the sarcoplasmic reticulum to also liberate calcium. This doubled Ca^{2+} release may be prolonged contributing to a persistent cytoplasmic calcium ion overload because of the latency of the alpha-1 adrenoceptor response caused by their location on the nuclear membrane [38]. The varying toxic mitochondrial concentrations of calcium ions either signals the ROS to produce the water causing hydropic change and/or the biochemical events leading to the activation of cytochrome C from the damaged mitochondrial inner membrane that activates caspase 3 to initiate the caspase cascade leading to apoptosis [19,35,39]. The principality of these two intrinsic apoptotic steps possibly may depend in part on the toxic quantities of Ca^{2+} delivered to each mitochondrion from their bordering sarcoplasmic reticulum.

Conclusion

Evaluation of SAM's pathogenesis is introductory to understanding the steps required for the causation of norepinephrine induced cardiovascular disease. 1) The quantity of norepinephrine manufactured in varicosities on the efferent branches of the sympathetic nerve should be supra physiological and/or its release protracted events stimulated by iatrogenic administered sympathomimetic agonists and beta agonists capable of releasing norepinephrine or its release from the adrenal medulla. 2) This hormone must form ligands with hyper dense quantities of appropriate adrenoceptors distributed on the cell membranes of medial smooth muscle, cardiac myocytes and mesangial cells and cardiac myocyte nuclear membrane or cross-talk with other pressor agents such as endothelin-1 and their receptor. The hyper density of the adrenoceptors is created by their dynamic state, revealed and regulated by a number of pathophysiologic conditions such as age, sex, and prior contact with sympathomimetic agents in arteries and hemodynamic stress in the heart. 3) Conformational change of these dense ligands excessively couple with the Gq heterotrimeric G protein in large arteries and mesangium and the Gs protein in the myocardium to cause an exaggerated activation of the biochemical responses causing vasoconstriction or cardiac contraction. 4) A cytoplasmic calcium ion overload is created. This is toxic to mitochondria causing either the activation of the caspase cascade to cause intrinsic apoptosis in blood vessel smooth muscle, myocardium or mesangial cells and/or the activation of ROS with the produced water causing mitochondrial hydrops and rupture events ending as mediolysis in medial and heart muscle. The intense contractile signal also shears the outer media from the adventitia in arteries and closes glomerular capillary loops. These 4 events comprise the first phase of norepinephrine-induced injury. As response, a second phase of injury develops fashioned by a norepinephrine stimulated rapid and vigorous reparative response. This produces sequelae in involved arteries, fine myocardial fibrosis and focal segmental glomerulosclerosis. The sequelae are the forerunners of a number arterial diseases, many with unknown, uncertain or multiple etiologies, including FMD, spontaneous dissecting hematomas of the coronary, vertebral, intestinal and retroperitoneal arteries, stenosis of the renal and intestinal arteries, and aneurysms of the splenic, intestinal and renal arteries. In those arterial lesions with multiple etiologies a clue to SAM's genesis is the concurrent finding of more than one sequela in the involved arterial bed and the patchy histologic finding of foci of medial fibrosis as illustrated in figures 13 and 16 in or adjacent to the sequela lesion.

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Conflict of Interest

The author declares that there is no conflict of interest.

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