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# Segmental Arterial Mediolysis: A Review of a Proposed Vascular Disease of the Peripheral Sympathetic Nervous System – A Density Disorder of the Alpha-1 Adrenergic Receptor?

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## Abstract

Segmental arterial mediolysis (SAM) is an uncommon arteriopathy that causes catastrophic abdominal hemorrhages, ischemic vascular changes and organ injury. Morphologic changes have suggested that SAM is a vasospastic disorder and that the responsible pressor agent is norepinephrine. This premise was strengthened by the finding of SAM in greyhound dogs administered ractopamine, a Beta-2 agonist capable or releasing norepinephrine from the peripheral sympathetic nervous system. This article will fortify this hypothesis by fitting the morphologic features and clinical presentations of SAM into events occurring in a stimulated peripheral sympathetic reflex arc. SAM is activated by non-physiological stimuli supplied by indirect acting sympathomimetic agonists. The stimulus is discrete usually limited to one vascular bed. A possible excessive quantity of norepinephrine is released which combines with hyper dense areas of alpha-1 adrenoceptors on the cell membranes of the medial smooth muscle. The alpha-1 adrenoceptor density is in a dynamic state influenced by a variety of exogenous and endogenous factors such as age, sex and prior exposure to sympathomimetic agonists all important components of SAM's clinical presentation. There is a plasticity to these hyper dense areas accounting for the variable targeting of SAM in the stimulated arterial bed. The hyper dense zones of conformed alpha-1 adrenceptor intensely activates the smooth muscle intracellular Gq heterotrimeric protein setting into motion a perturbed cascade of biochemical events directed to causing vasoconstriction. These events create SAM's pathology by 1) overloading the cytoplasm with $Ca^{2+}$ causing mitochondrial dysfunction that terminates in mediolysis and/or apoptosis, 2) launching a powerful vasoconstrictive response that shears the outer media from the adventitia and 3) inaugurating an exaggerated reparative response that may angiographically resolve injurious arterial lesions or create sequelae including fibromuscular dysplasia. In conclusion evidence garnered from clinical and morphologic findings in SAM support the hypothesis that SAM represents a disorder of the peripheral sympathetic nervous system effectuated by a hyper density of the alpha-1 adrenoceptor.

## Introduction

Calamitous abdominal hemorrhage is the hallmark presentation of segmental arterial mediolysis (SAM) an uncommon arteriopathy of the large and medium sized muscular arteries distributed in the abdomen, retroperitoneum, heart, and brain base. Slavin and Gonzalez first described it as a distinct clinical entity involving the abdominal arteries in elderly patients in 1976 but the disease was appreciated earlier in the vertebral and posterior inferior cerebellar arteries in immediate post-operative patients and in the epicardial coronary arteries in newborns [1-3]. As new cases were uncovered, it became apparent that this entity had other presentations. It could be introduced as an ischemic disorder caused by reparative sequelae to its initial injurious phase with in some, lesion evolution to fibromuscular dysplasia (FMD) [4-7]. Organ injury, as renal infarcts or pancreatic hemorrhages was another reported presentation [8,9]. Finally it could be entirely subclinical discovered serendipitously in surgical specimens or angiographic studies [6]. Such subclinical lesions on angiographic follow-up could resolve [6,8]. SAM's multifaceted pathology caused by the varying intensities of injuries and subsequent repair in the media and at the adventitial medial border explains its heterologous presentations [6-8]. First named segmental mediolytic arteritis it soon became apparent that this was a misnomer since inflammatory alterations were inconstant and laboratory evidence of an immunologic or infectious assault were absent [1,4,10]. SAM's etiology at first was unknown since it did not appear to be of degenerative, congenital, developmental, immunologic,

toxic or infectious in origin. Slavin and coworkers suspected that SAM represented a vasospastic disorder because of its segmental distribution and medial morphologic features and renamed it SAM a descriptive term drawn from its most characteristic morphologic features [4]. They proposed that norepinephrine was the responsible pressor agent since the earliest lesions formed at the outer arterial wall the precise site where norepinephrine is produced in varicosities and released from the efferent sympathetic nerve fibers innervating the muscular arteries [5]. This hypothesis was strengthened with the discovery of SAM in the large renal, intrahepatic and coronary arteries of greyhound dogs administered a single dose of ractopamine an agent used in animal husbandry for its repartitioning properties and illegally to enhance athletic ability in racing animals [11]. Ractopamine is a Beta-2 adrenergic agonist believed capable of releasing norepinephrine

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from the peripheral nervous system. With the realization that SAM was putatively initiated by norepinephrine, review of available detailed histories of patients with SAM revealed recent exposure to tocolytic drugs, presumably a Beta-2 agonist, and the alpha-1 agonists' metaraminol and dopamine [1,4,5,12]. On the basis of these findings it was proposed that SAM was primarily an iatrogenic vascular disorder induced by alpha-1 adrenergic receptor agonists or Beta-2 agonists capable of releasing norepinephrine from the peripheral sympathetic nervous system [11]. SAM therefore, may be considered as a disease of the peripheral sympathetic nervous system. This article will reinforce this hypothesis by matching SAM's pathology and clinical presentations to features and biochemical events occurring in the stimulated peripheral sympathetic reflex arc.

## Materials and Methods

Photographs presented in the manuscript are taken from cases of SAM previously reported by the author and coworkers in the literature [1,4-8,10].

### SAM and the sympathetic reflex arc

**Arterial involvement:** The agents activating SAM are indirect acting sympathomimetic agonists that initiate non-physiologic stimuli to the peripheral sympathetic nervous system. The response to these stimuli is rapid being morphologically evident within one day after a single dose of these agonists. It is also discrete, an inherent characteristic of the autonomic nervous system, restricted to a single or a few large or medium sized muscular arteries located in the abdominal cavity, epicardium or brain base [13]. Any of the large intra-abdominal muscular arteries may be targeted but those most frequently involved are the celiac artery and its splenic and hepatic branches and the distal renal artery [6]. The large branches of the targeted arteries entering the pancreas, liver, stomach, intestines and kidneys also may be assaulted. SAM in the heart involves the epicardial coronary arteries and they're large penetrating branches. Targeted in the brain base are the vertebral and posterior inferior cerebellar arteries, those in the Circle of Willis and the internal carotid [2,7]. The most frequently involved cerebral arteries have yet to be tallied because the histologic diagnosis–the gold standard for the diagnosis of SAM-in some reported cases either couldn't be accurately assessed, was questionable or even incorrect [7]. Rarely, SAM has been reported in arteries in more than one site, i.e., the intra-abdominal and cerebral arteries in humans and abdominal and coronary arteries in greyhounds [11,14,15].

**Alpha-1 adrenergic receptor:** Multiple post ganglionic branches leave the plexuses-the celiac for the intra-abdominal arteries, the cardiac for the coronary arteries, and the vertebral and internal carotid innervating the cerebral arteries-to conduct the agonists to the SAM targeted arteries where they displace norepinephrine, the endogenous neurotransmitter, from varicosities clustered at the adventitial medial border-the advent site of SAM. As ligand the norepinephrine couples with the alpha-1 adrenoceptor (a G-protein-coupled receptor) aggregated on the cell membrane of the smooth muscle cells to induce conformational change. This alteration enables the receptor to activate a heterotrimeric G-protein that initiates a cascade of biochemical events opening calcium channels and provoking vasoconstriction. SAM is suspected of occurring in arterial segments possessing a hyper density of this receptor. There are 3 subtypes of alpha-1 adrenoceptors: alpha-1A, alpha-1B and alpha-1D but available literature regarding their roles in vasoconstriction in humans has not been definitively established [16]. Although an inverse relationship exists between the concentration of available sympathomimetics and the number of

alpha1-adrenergic receptors this association is lost in SAM [17]. The adrenoceptor density is in a dynamic state influenced by a variety of exogenous or endogenous factors that can override its normal genetic programing to create zones of plastic hyper density. This changeability influences the pharmacological responses to sympathomimetic agonists in different people or animals or in the same individuals at different times. It accounts for SAM's seemingly capricious arterial distribution in arterial beds and offers an explanation for its wide age distribution ranging from the fetus to the elderly. Estrogen can increase alpha-1 adrenoceptor density [18]. This may be the principal reason why FMD, a sequela of SAM, is more common in premenopausal females than in males of the same age. The density of alpha1-adrenergic receptors is uploaded with aging putatively causing the increased incidence, intensity and equal sexual redistribution of injurious phase SAM in the elderly [19]. Reported is a lower density of alpha-1 adrenoceptors in fetal cerebral arteries than in adults a determination possibly accounting for the absence of cerebral SAM in neonates [20]. Prior exposure to sympathomimetic agonists may promote increased arterial density of this receptor a mechanism possibly accounting for the sensitization to these agents. The development of SAM in the large intrarenal arteries in a female 10 years following 17 weeks of tocolysis with ritodrine illustrates this point [8]. The hyper density of the alpha-1 adrenoceptors on the smooth muscle in SAM lesions may not be uniform clarifying why smooth muscle cells or islands are often spared in zones of mediolysis and why mediolysis is restricted in some arteries to the outer media, while in others it involves the outer and mid-media or entire media (Figure 1). However, the quantity of released norepinephrine influenced by the relative strength of the sympathetic discharge is of equal importance in determining the extensiveness of mediolysis. Only the outer medial smooth muscle cells receive sympathetic innervation. This explains why the outer media is always injured in SAM and may be the only site of mediolysis while the smooth muscle cells in the inner portions of the media exposed to varying quantities of diffused norepinephrine may be targeted or spared. These differences, by varying the morphologic intensity of the injurious phase, alter SAM's pathology and subsequent clinical presentations. This is best exemplified by arterial gap-aneurysms the cause of SAM's catastrophic hemorrhages. This lesion is created in
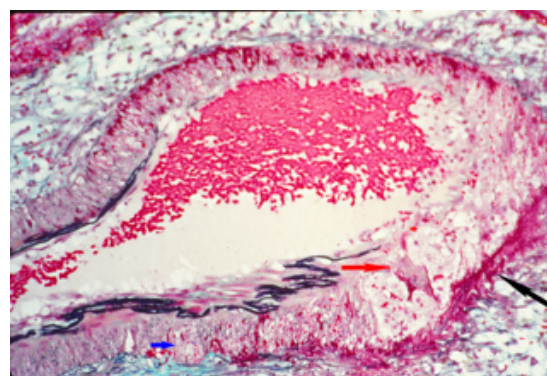


**Figure 1:** Injurious phase of segmental arterial mediolysis. Red arrow points to a peninsula of intact smooth muscle projecting in a sea of confluent mediolysis. The mediolysis exhibits a foamy appearance caused by membranous and organelle debris. It's watery content has expanded the medial space, contains scattered red cells, and is externally bordered by a circumferential linear band of fibrin( dark red). The internal elastica (linear black membrane) bedecking this zone of mediolysis is lost, a prelude to gap formation. Blue arrow points to one of several smaller foci of mediolysis involving the outer and mid-media. Movat stain x100.

areas of extensive transmedial mediolysis with gap formation (Figure 2). The gap is produced by accompanying intimal and internal elastic medial loss caused by the rending of muscular stromal connections from the subintimal lysed smooth muscle cells (Figure 1).

**Mitochondrial dysfunction, mediolysis, apoptosis and spastic vasoconstriction:** The inner intracellular domain of the conformationally altered alpha-1 adrenergic receptor activates the Gq heterotrimeric G protein that 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. Contraction requires cytoplasmic calcium ions. Activation of phospholipase C and IP3 (triphosphoinositol) increases intracellular $Ca^{2+}$ concentration by opening $Ca^{2+}$ channels in the endoplasmic reticulum, a storage site of $Ca^{2+}$, and $Ca^{2+}$ channels on the cell membrane of the smooth muscle allowing entrance of extracellular $Ca^{2+}$. In SAM the densely distributed conformationally altered alpha-1 adrenoceptors intensify or prolong the activation of the Cq heterotrimeric G protein and/or its activated biochemical events leading to a greater flux of the much higher extracellular concentration of calcium ions into the smooth muscle cells. The produced cytoplasmic $Ca^{2+}$ overload causes mitochondrial dysfunction by triggering permeability of the mitochondrial permeability transition pore and the excessive stepwise reduction of $O_2$ to water by reactive oxygen species (ROS) [21]. The water laden mitochondria swell and rupture inundating and distending the cytoplasm with watery contents that further disrupts the cell membrane (mediolysis) — so called "mitochondrial apoptosis" [22]. These events mirror the ultra-structural and histologic features of mediolysis, which show incompletely, bordered edematous zones of non-stainable cytoplasm (water), containing dilated vacuoles and membranous debris (Figure 1) [5-7,10]. Mitochondrial injury is also linked to cytochrome C release a key event in apoptosis (Figure 3) [21]. Both types of programed cell death can be identified in the injurious phase of SAM [7]. Mediolysis therefore represents a unique type of vasospastic alteration caused by mitochondrial injury and apoptosis without either endothelial or inflammatory cell participation. It is accompanied by a powerful vasoconstrictive response also initiated by the intense activation of the Cq heterotrimeric G protein that shears the outer media from the external elastica and adventitia (Figure 4). This elicits micro hemorrhages derived from torn capillaries and vasovasorum in and around the adventitial-medial border and fibrin deposits along the plane of the tear – SAM's earliest morphologic alterations (Figure 1). This series of events explains the genesis of injurious phase SAM, a unique arterial lesion, created by the combination of mediolysis and/or apoptosis with a shearing injury.

## Reparative change

The hyper activated Cq heterotrimeric G protein and the surfeit of calcium ions also incite the proliferation of fibroblasts and smooth muscle. This induces the robust proliferation of reparative granulation tissue that often first appears in injurious phase SAM and smooth muscle nodules that occasionally concomitantly form in the arterial adventitia (Figure 5) [7,11]. The granulation tissue can repair the injurious arterial lesions with angiographic resolution or, depending on site of the arterial injury, create sequelae (Figure 6). These include dissecting hematomas produced from hemorrhages at the medial adventitial border tear sites or in its filling granulation tissue, arterial stenosis and occlusion formed from thrombi, ingrowth of luminal granulation tissue or medial compression by floridly proliferating granulation tissue, persistent aneurysms buttressed by granulation



**Figure 2:** Segmental arterial mediolysis. Artery exhibits a multiplicity of lesions. Black arrow points to a gap-aneurysm containing a thrombus, cyan arrow a dissecting hematoma and red arrow marks a gap. Movat stain x50. Adapted with permission from Modern Pathology, 18(3), copyright 1995, Nature Publishing group.
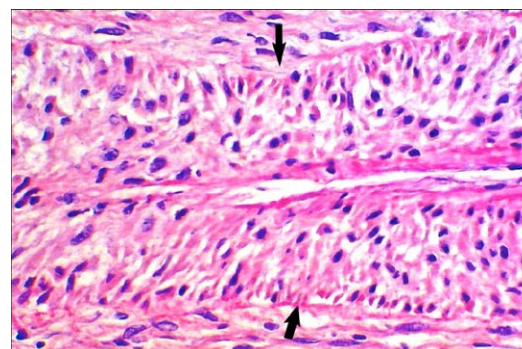


**Figure 3:** Injurious phase of segmental arterial mediolysis. Arrows point to areas of apoptosis of medial smooth muscle showing nuclear pyknosis, fragmentation and loss and densely eosinophilic cytoplasmic fragments. Hematoxylin and eosin x200.
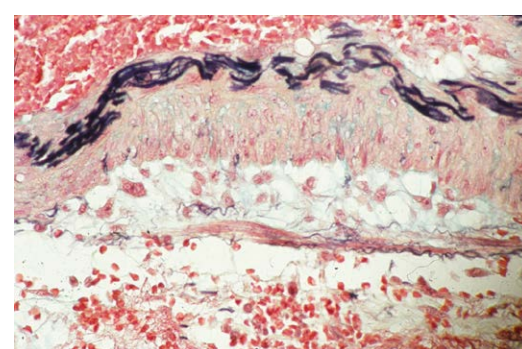


**Figure 4:** Injurious phase of segmental arterial mediolysis showing separation of the outer media from the adventitia. The tear space contains isolated intact smooth muscle cells in expanded extracellular matrix material. Scattered red cells are evident in the adventitia. Movat stain x100. Adapted with permission Cardiovascular Pathology 18(6) Copyright 2009, Elsevier Inc.

tissue and FMD (Figures 5,7-9). The principal sites of the granulation tissue either adventitial, perimedial or medial determine FMD type [7]. These sequelae often are asymptomatic and resolve, rarely they bleed but principally they create ischemic lesions. Symptoms stemming from the sequelae can be announced soon after the onset of SAM but dissecting hematomas may develop weeks, months or even years after
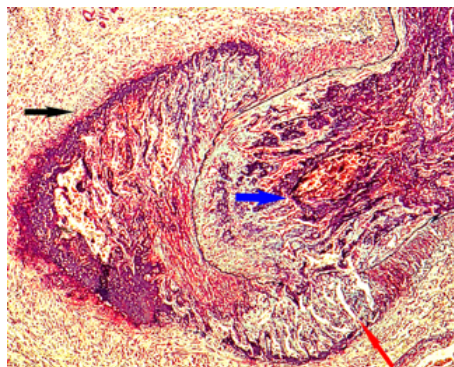
**Figure 5:** Early reparative phase of segmental arterial mediolysis. Red arrow points to granulation tissue filling and expanding a focus of transmural mediolysis and extending through the internal elastica to form an intimal plaque. This narrows the arterial lumen (blue arrow) that is partially occluded by a recent thrombus. Black arrow points to another focus of watery confluent mediolysis pushing the thick linear lined fibrin adventitia outward. The top of this area contains newly formed granulation tissue. Movat stain x100.
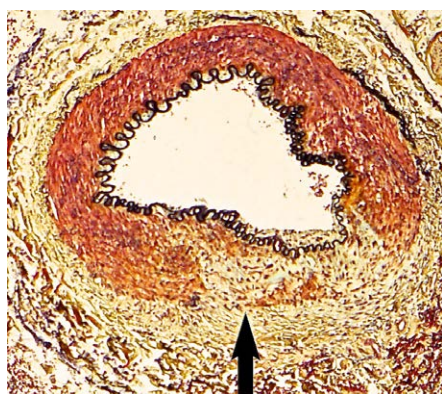


**Figure 6:** Reparative phase of segmental arterial mediolysis. Arrow points to an irregular focus of granulation tissue replacing an area of mediolysis. The internal elastica is intact and a thin intimal plaque of granulation tissue is evident overlying the repaired focus of mediolysis. Movat stain x100. Adapted with permission from Cardiovascular Pathology, 18(6), copyright 2009. Elsevier Inc.

the onset of SAM [6]. They have been provoked by the faulty placement of stents into the narrowed arteries [8]. Frequently more than one type of injury or sequela is identified in an involved artery and these may form unique pathologic lesions such as the double aneurysm of SAM (Figures 2 and 10) [6].

**Venous angiopathy in SAM - "Segmental venous mediolysis"**

Mediolytic vasospasm also develops in the large abdominal veins adjacent to arteries exhibiting lesions of SAM [5]. The morphologic changes are similar to those occurring in arterial SAM - medial muscle apoptosis admixed with vacuolar medial change followed by lysis and edema of the venous wall (Figures 11-13) [5,7]. This sequence suggests that the pathogenesis of the venous lesions is very similar to those occurring in the arteries both putatively representing a stereotypical vascular response to pressor induced vasospasm. As in SAM, robust fibrosis repairs areas of lysed venous muscle creating "venous fibromuscular dysplasia" (Figure 14) [23]. There are, however, morphologic differences between venous and arterial SAM. The venous medial changes do not always commence in the outer segment

of the venous wall and fibrin deposition is inconspicuous due to an absence of a shearing injury. Although norepinephrine causes venous vasoconstriction, the smooth muscle volume in veins is less than that of the accompanying artery and the veins receive a sparser sympathetic innervation [16]. These findings hint that other pressor agents may participate in or contribute to the development of the venous spastic angiopathy. This supposition was strengthened by the finding of Endothelin-1 (ET-1) distributed in endothelial cells and lining the cell membranes of the venous smooth muscle putatively forming ligands with ETA receptors [5]. The ET-1 could cross-talk with norepinephrine to convert venous vasoconstriction to a spastic injurious response or directly cause the venous angiopathy. The sites of venous ET-1 staining were not apparent in the adjoining artery but ET-1 was evident in the arterial adventitial capillaries and in adjacent nerves. This suggested that ET-1 may cross–talk with norepinephrine to contribute to SAM's development [7]. However, this adventitial arterial distribution of ET-1 was not evident in all of SAM lesions and the ET-1 also was found on the cell membranes of adjoining abdominal adipocytes. Based on this information it is more likely that the abdominal ET-1 release may be a response rather than a contributor to the norepinephrine induced arterial lesions.
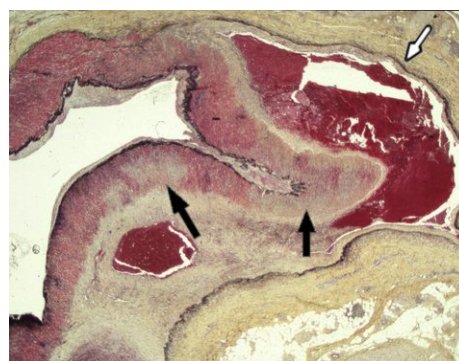


**Figure 7:** Reparative phase of segmental arterial mediolysis. Dissecting aneurysm (white arrow) and hematoma developing in the mature granulation tissue filling and expanding the tear space between the outer media and adventitia. Black arrows point to granulation tissue restoring foci of mediolysis. Movat stain x15. Adapted with permission from the International Journal of Surgical Pathology,15(2), copyright 2007, Sage Publications, Inc.
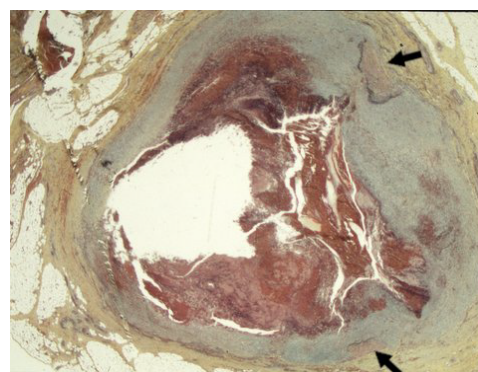


**Figure 8:** Reparative phase of segmental arterial mediolysis. Cross-section of a persistent gap-aneurysm repaired by a thick layer of granulation tissue. Arrows points to two surviving medial islands both partially encircled by the granulation tissue. Lumen contains a recent thrombus. Movat stain x25. Adapted with permission from Cardiovascular Pathology,18(6), copyright 2009, Elsevier Inc.
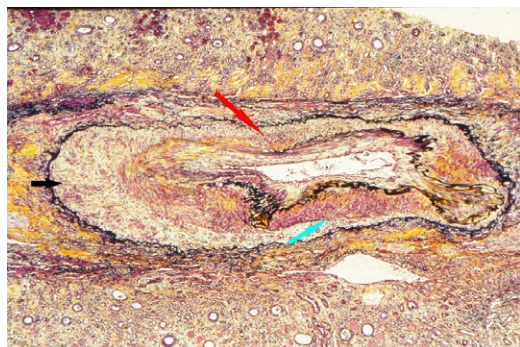
**Figure 9:** Reparative phase of segmental arterial mediolysis showing evolution to FMD. Black arrow points to mature granulation tissue filling and expanding tear space between outer media and external elastica (outer black circumferential band) and replacing a focus of total medial loss (red arrow). Cyan arrow points to preserved media (brown-red showing patchy fibrosis, yellow stain) The internal elastica ( inner black band) is largely intact and bedecked by a circumferential plaque of granulation tissue that narrows the arterial lumen. Movat stain x25. Adapted with permission from Cardiovascular Pathology,18(6), copyright 2009, Elsevier Inc.
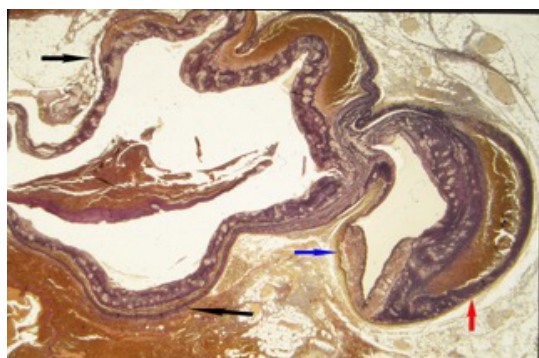


**Figure 10:** Segmental arterial mediolysis. The double aneurysm of SAM shows a dissecting aneurysm (red arrow) and large gap-aneurysm (Black arrows). Blue arrow points to an additional early dissecting hematoma. Movat stain x15. Adapted with permission Cardiovascular pathology, 18(6), copyright 2009, Elsevier Inc.

## SAM and FMD: Challenges and response

In 1995 Slavin and coworkers suggested that SAM was a precursor lesion to FMD a disorder of unknown pathogenesis [4]. Further reports of SAM clearly showed that reparative phase morphologic lesions in SAM were indistinguishable from FMD [6-8]. Despite the morphologic identically of reparative phase SAM and FMD this concept has been challenged because of marked differences in their clinical presentations. The following objections have been raised.

1) SAM in adults principally affects the elderly while FMD occurs in young adults. But, SAM is principally clinically recognized by bleeding from gap-aneurysms that generally only develop in the elderly because of the increased density of their alpha-1 adrenergic receptors, their increased sensitivity to adrenergic sympathomimetic agents and aging degenerative arterial changes that easily detach medial islands to increase gap size. Other injurious lesions may develop concomitantly but remain asymptomatic to resurface in the reparative phase as sequelae.

2) SAM occurs with equal frequency in males and females while

FMD is more frequent in females. But premenopausal females have areas of estrogen induced increased adrenoreceptor density accounting for the prevalence of FMD in females and the increased sensitivity of their alpha-1 receptors to adrenaline [18,24].
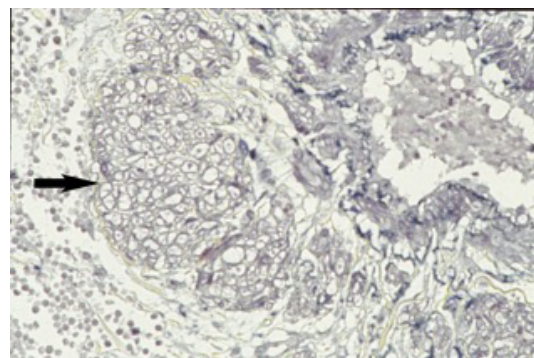


**Figure 11:** Segmental venous angiopathy. Arrow points to a focus of cytoplasmic vacuolization of the outer venous medial muscle with nuclear pyknosis and loss changes representing a precursor stage of mediolysis. Movat stain x100. Adapted with permission from the International Journal of Surgical Pathology, 15(2), copyright 2007, Sage Publications Inc.
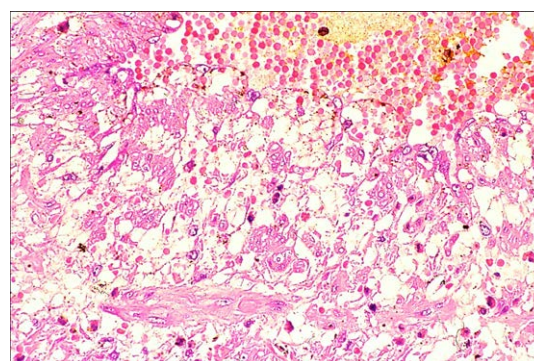


**Figure 12:** Segmental venous angiopathy. Mediolysis caused by the rupture of the large vacuoles in the cytoplasm of the medial smooth muscle. Scattered intact muscle cells contain small vacuoles while a few are tiny with dense eosinophilic cytoplasm and pyknotic nuclei. Hematoxylin and eosin x200. Adapted with permission from the International Journal of Surgical Pathology, 15(2) copyright 2007, Sage publications.
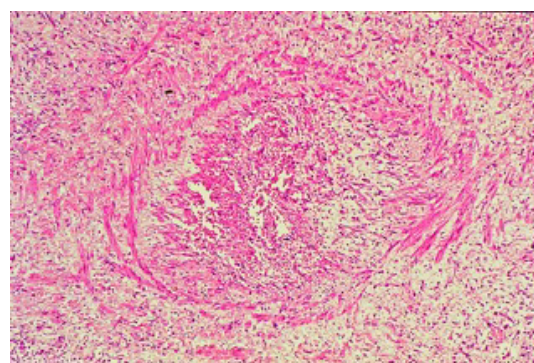


**Figure 13:** Segmental venous angiopathy. Watery fluid released by mediolysis containing cellular debris widely separates surviving medial muscle and expands and disrupts the intima. Lumen contains a recent thrombus. Hematoxylin and eosin x100. Adapted from World Journal of Cardiovascular Disease 3, 2013.
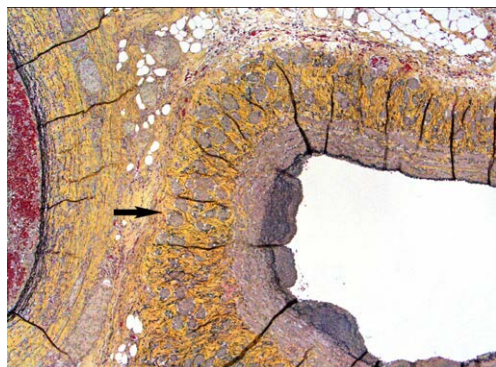
**Figure 14:** Venous fibromuscular dysplasia. Arrow points to renal vein adjacent to a dissecting hematoma showing fibrous bands (yellow tissue) replacing and encircling surviving muscle bundles (brown tissue) in the outer media. An irregular thin intimal plaque consisting of elastic fibers bedecks the intima. Movat stain x50. Adapted from World Journal of Cardiovascular Disease 4, 2014.

3) SAM's clinical presentation of profuse bleeding is different from the ischemic lesions announced in FMD. This criticism fails to recognize the biphasic nature of SAM's clinical presentations caused by its changing pathology-bleeding in the injurious phase and ischemia in the reparative phase.

4) Abdominal arterial involvement in FMD is centered on the renal arteries while in SAM the intestinal arteries appear to be the principal targets. But in SAM the distal renal artery is also commonly targeted and intestinal artery involvement also is not uncommon in FMD [5,6]. Intestinal arterial lesions in SAM can be asymptomatic and disappear on angiographic studies [8]. This fact coupled with the capricious abdominal arterial targeting of intestinal arteries can explain their apparent scarcity or even absence in FMD.

5) FMD is also found in the large arteries supplying the extremities while SAM has not been described in these locations. The purely intimal type of FMD is probably not related to SAM since SAM does not cause intimal lesions without co-existing mediolysis. Moreover, the morphologic alterations of FMD in the arteries of the extremities in children do not closely resemble changes of reparative SAM [25]. These findings suggest that SAM is not the only cause of FMD. Indeed FMD may represent repair lesions of arterial disorders of diverse etiologies that induce medial apoptosis such as cystic necrosis of the muscular arteries [7]. However, SAM is suspected as being the major cause of FMD in intra-abdominal and renal arteries.

## Treatment

The current treatment of injurious phase SAM has been well summarized by Davron and et al. [26] and includes supportive treatment for the life-threatening hemorrhages and various types of surgery or transcatheter embolization to contain the bleeding arteries. Since the injurious lesions frequently develop in an asynchronous manner, a pharmacological approach with norepinephrine antagonists and calcium channel blockers that primarily act on arterial smooth muscle might be especially useful in suppressing the further development of mediolysis [27]. Treatment with ET-1 antagonists awaits further clarification of the role ET-1 plays in SAM. The management of FMD and its complications is beyond the scope of this review.

## Conclusion

SAM is suspected of representing a disorder of the peripheral sympathetic nervous system. Evidence supporting this hypothesis is garnered from its pathology and clinical presentation that match events in an activated peripheral sympathetic reflex arc. The following is a summary of this evidence.

1: The morphologic features of SAM in the injurious phase are consistent with vasospasm and the responsible pressor agent is released at the adventitial-medial junction the site of the initial lesion in SAM. 2: Identified agents suspected of initiating SAM are iatrogenic introduced indirect acting sympathomimetic agonists capable of releasing norepinephrine from the varicosities on the post-ganglionic branches of sympathetic plexuses. 3: The ability of the sympathetic nervous system to undergo discrete activation is mirrored in SAM where the pattern of activation is primarily limited to one arterial bed. The plasticity of this system accounts for the haphazard targeting of SAM in arteries in this one area. 4: The alpha-1 adrenergic receptors are in a dynamic state and their density can be increased by factors that also influence SAM's clinical presentations such as age, sex and prior exposure to sympathomimetic agonists. It is suspected that SAM is spawned from these newly created hyper dense areas possibly augmented by excessive norepinephrine release activated by non-physiologic stimuli provoked by iatrogenic sympathomimetic agonists. 5: The conformationally altered hyper dense alpha1-adrenoceptors intensify and/or prolong the activation of the cytoplasmic Gq heterotrimeric G protein. This initiates a cascade of augmented biochemical events. These induce a potent vasoconstriction that shears the outer media from the arterial adventitia and a prolonged opening of the cell membrane calcium channels causing an overload of cytoplasmic calcium ions. The latter creates mitochondrial dysfunction and injury terminating in mediolysis and/or medial apoptosis through the concurrent release of cytochrome C. 6: Medial and adventitial medial tear lesions are repaired by a robust proliferation of granulation tissue set into motion in SAM's injurious phase. The repaired arteries return to normal on angiograms, persist as sequelae or metamorphous into FMD. SAM in the abdominal arteries, therefore, acts as a bridging disorder for FMD both entities representing diseases of the peripheral sympathetic nervous system.

The recent recognition that SAM can develop in pigs as well as well as in dogs will hopefully provide experimental models that can be utilized to test, modify or alter the hypotheses developed in this article [11,27].

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