

The Mammalian Stress Mechanism (MSM) Explains Radial Artery Spasm (RAS)

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Abstract:

Objective: Based on stress theory, this paper proposes a fresh explanation of Radial Artery Spasm (RAS), the nature of which remains unclear.⁽¹⁾

Data Sources: Published research papers accessed via PubMed

Study Selection: Abstract review

Data Extraction: Computerized Internet Search

Data Synthesis: Fresh information relevant to stress theory derived from unrelated research enabled the description of a testable “mammalian stress mechanism” (MSM) that explains the stress theory proposed by Hans Selye.

Conclusions: MSM activity explains the nature of RAS.

Keywords: Stress; Hans Selye; Coagulation; Radial artery spasm; RAS; Thrombosis; Angioplasty; Invasive monitoring

Introduction

Radial artery spasm (RAS) occurs after multiple unsuccessful attempts to cannulate the radial artery using small, short catheters for monitoring and blood sampling, where upon the radial pulse becomes impalpable and cannulation becomes futile. Persisting ulnar circulation presumably prevents ischemia, and the artery recovers if left unmolested, but sometimes hours after successful cannulation the pulse wave degenerates and the pulse becomes impalpable as far proximal as the elbow, particularly in the presence of pathology. Diverse treatments relieve RAS including radial nerve blockade, sympathetic ganglion blockade, warming the extremity, aspirating thrombus from the catheter tip, and flushing the artery with local analgesics, vasodilators, and anticoagulants^[1,2].

Interventional radiologists have embraced the RAS acronym to explain the “entrapment syndrome” that occurs after the installation of larger and longer angioplasty catheters via the radial artery, causing painful arterial damage in accord with larger catheters and lesser arterial diameter. RAS can also prevent catheter insertion. Angioplasty RAS is routinely relieved by flushing the artery with heparin or cocktails of nitroglycerin and verapamil that lack neuromuscular effects^[3].

As its name implies, RAS is attributed to neuromuscular vasospasm. This seems reasonable because arteries visibly spasm during angioplasty and surgery; sympathetic blockade relieves RAS; and medical physiology presumes that opposing forces of cardiac contractility and muscular vasoconstriction governs blood flow^[4]. However, muscular spasm offers a weak explanation of RAS, because intense muscle contraction rapidly depletes ATP, causing obligatory muscle exhaustion and relaxation.

Like other intracellular activities, muscle contraction is energized by ATPase enzymes that require Ca^{+} and ATP^[5]. The sarcoplasmic reticulum releases Ca^{+} into myocyte cytoplasm to initiate contraction. ATPase then energizes the movement of fibrillar actin strands relative to adjacent myosin strands via a “ratcheting mechanism” to contract the muscle^[6,7]. A calcium pump mechanism removes Ca^{+} from the cytoplasm and sequesters it within the sarcoplasmic reticulum to release the ratcheting mechanism, halt ATPase activity, and enable muscular relaxation. ATP depletion accordingly under mines muscle contraction.

The mitochondrial Krebs Cycle efficiently generates ATP in eukaryotic animal cells, but this necessitates oxygen and glucose, so that ATP generation is limited by tissue perfusion and oxygenation. This is readily observed during intense exercise, where cellular oxygen starvation causes skeletal muscle cells to revert to inefficient anaerobic ATP generation, causing muscle fatigue. Exercise conditioning induces angiogenesis (capillary proliferation) in muscle tissues that enhances oxygen delivery,

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increases ATP generation, and improves exercise tolerance, but only up to a point^[8-11].

Unlike skeletal muscle, vascular smooth muscle contracts slowly and enjoys close proximity to oxygenated blood, but its function nevertheless remains dependent on ATP generation. This is illustrated by Rigor Mortis, where the circulatory failure of death disrupts oxygen transport and delivery, causing cellular anoxia that halts ATP generation by the Krebs Cycle, so that universal muscle flaccidity ensues in the immediate aftermath of death, including vascular smooth muscle. The resilience of the calcium pump prevents rigor mortis in life. Anaerobic metabolism generates enough ATP to sustain the calcium pump for a few hours after death, but as the failing sarcoplasmic reticulum releases its calcium into the cytoplasm, the ratcheting mechanism locks in place for lack of ATP, causing rigor mortis in all types of muscle, including vascular smooth muscle.

Muscular spasm fails to explain why anticoagulants, which lack neuromuscular effects, can successfully prevent and relieve RAS, or why the incidence of RAS is exaggerated by seemingly unrelated diseases including congestive heart failure, hypertension, diabetes, obesity, and cancer.

Ultrasound detects thrombus in RAS; thrombus aspiration restores monitoring catheter function; and flushing the artery with anticoagulants prevents and relieves angioplasty RAS. These observations suggest that thrombus formation causes the RAS phenomenon, but this explanation is frustrated for lack of an effective hemostasis explanation. Such, however, may no longer be the case, because the recently discovered mammalian stress mechanism clarifies the nature of coagulation and its relationships with nervous activity, tissue repair, and disease^[12-17].

Methods

The author's curiosity about the recently discovered chimeric nature of coagulation factor VIII inspired a six-year review of published research via the Internet using advanced computer techniques. Factor VIII consists of enzymatically inert von Willebrand factor (VWF) and enzymatic factor VIIIc. The vascular endothelium manufactures VWF and releases it into blood circulation under nervous control, while VIIIc is continuously released by the liver. The two gigantic molecules bind together in blood circulation and exert their effects in concert. VWF stabilizes VIIIc and enables its enzymatic effects, which are otherwise so labile as to be nonexistent. Thus the factor VIII chimera links nervous activity to blood enzyme activity. Defects in VIIIc cause true hemophilia, a severe, sex-linked clotting diathesis. Defective VWF causes the von Willebrand coagulation diathesis, which is usually mild but in severe forms can mimic true hemophilia. VWF defects also cause angiodysplasia, because the VWF molecule maintains capillary structural integrity^[18-24]. The unique characteristics of factor VIII served as a "Rosetta Stone" that deciphered the relationships between and among coagulation enzymes, nervous activity, coagulation, capillary hemostasis, atherosclerosis, bleeding diatheses, sickle cell anemia, angiodysplasia, angioneurotic edema, hemodynamic physiology, tissue repair, disease, and stress^[25-30].

Results

The literature review successively identified testable mecha-

nisms of coagulation^[12,14], capillary hemostasis^[15], atherosclerosis^[31,32], tissue repair^[34], inflammation, apoptosis^[15], the surgical stress syndrome^[35], anesthesia, analgesia, allostasis^[35,36] and a capillary gate mechanism that explains hemodynamic physiology^[13]. These seemingly disparate mechanisms were ultimately comprehended as elements of the long-sought "mammalian stress mechanism" (MSM) postulated by Hans Selye^[16,16,37-43]. The MSM is testable, and it enables Selye's revolutionary "unified theory of medicine"^[42] that explains physiology, pathology, stress, and their relationships.

In retrospect, Selye was ahead of his time, like Jules Verne predicting trips to the moon before rockets were invented. He was an endocrinologist, and HPA hormone elevations and gross organ effects were the only recognized reactions to stress in his time^[43,44]. The intense international 30 year search for his putative mechanism that followed the discovery of DNA focused on hormones and failed to find the coagulation information needed to identify the elusive mechanism. However, the stress researchers were closer to success than they realized. They developed capillary gate theory and tissue repair theory to facilitate their search, and these hypotheses are embodied in the MSM. Another 30 years of fresh information from unrelated research was needed. Selye would have been surprised to learn that coagulation enzymes are the focus of his theory, that von Willebrand factor (VWF) is the prototypical stress hormone, and that his mechanism confers a unified theory of biology that exceeds the bounds of medicine. These implications will be elaborated in an upcoming book that is in the hands of its publisher.

This presentation will briefly review the MSM and its operation, which explains the nature of RAS.

The Mammalian Stress Mechanism (MSM)

The mammalian stress mechanism (figure 2) is analogous to the familiar coagulation cascade (figure 1), but it incorporates recent research that explains its relationships to nervous activity and tissue repair. It appears during the early stages of embryological development, and it converts chromosomal genetic information into cell specialization and cell organization that creates complex multicellular anatomical structures. It remains continuously active for the duration of life to regulate hemodynamic physiology, maintain the "internal milieu" that optimizes cell survival and function^[45], and maintain mature structures. Meanwhile, DNA resumes quiescence once embryological development is complete. Stress-induced MSM hyperactivity causes disease manifestations, and explains the relationships of diseases and stresses. For example, it explains why diabetes, hypertension, obesity, malignancy, and congestive heart failure are closely associated, and why seemingly disparate diseases commonly manifest fever, inflammation, edema, cachexia, and malaise. It explains the relationships of hemodynamic physiology, coagulation, atherosclerosis, tissue maintenance, and tissue repair, and thereby confers a fresh, simplified explanation of the puzzling RAS phenomenon^[16,17,34].

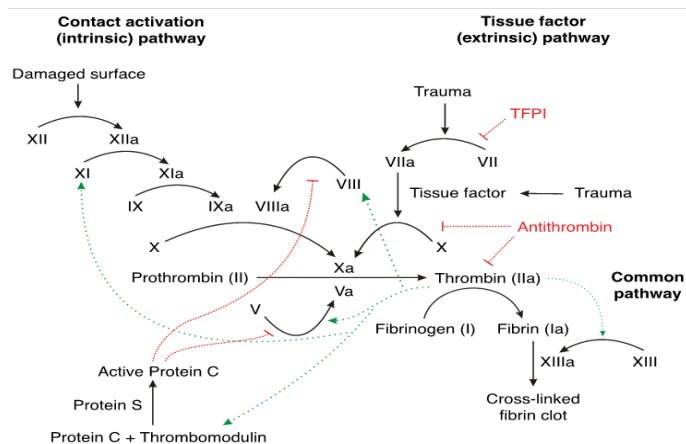


Figure 1: The Coagulation Cascade was described in the early 1960's. It explains coagulation as a "cascade" of enzymatic interactions that produces insoluble fibrin, but it fails to explain how the cascade is initiated, regulated, and concluded. It assumes that the sole purpose of coagulation is hemostasis. Conventional "vasoconstriction" theory fails to explain capillary hemostasis, because capillaries lack the ability to contract. The cascade consists of an "intrinsic pathway" consisting of factors VIII and IX, and an "extrinsic pathway" consisting of factor VII and tissue factor. Both pathways interact with factor X in a "final common pathway" to generate thrombin, soluble fibrin, and insoluble fibrin. By Joe D - Own work, CC BY-SA 3.0, <https://commons.wikimedia.org/w/index.php?curid=1983833>

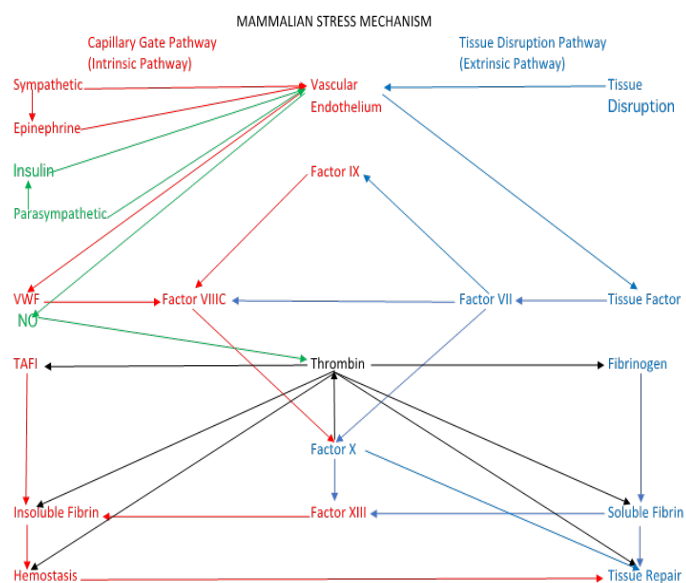


Figure 2: A simplified diagram of the "Mammalian Stress Mechanism" (MSM).

The MSM is analogous to the coagulation cascade, but it incorporates recent research that clarifies the relationships of stress, nervous activity, tissue disruption, tissue repair, hemostasis, and hemodynamic physiology. Sympathetic tone releases VWF from the vascular endothelium to activate the "capillary gate component" of the MSM, shown in red, which is analogous to the "intrinsic pathway" of the coagulation cascade. Parasympathetic tone, shown in green releases nitric oxide (NO) from the vascular endothelium to open the capillary gate. Tissue damage activates the "tissue disruption pathway," shown in blue that is analogous to the "extrinsic pathway" of the coagulation cascade, to enable tissue repair.

The Three Products of the MSM

Combinations of nervous activity and tissue disruption alter the enzymatic interaction of factors VII, VIII, IX and X to regulate the magnitude, location, and speed of production of the three MSM products, which are *thrombin*, *soluble fibrin*, and *insoluble fibrin*. This focuses MSM activity to regulate hemodynamic physiology, hemostasis, and tissue repair. Stress induces MSM hyperactivity that produces these three products in excess, which manifests as disease. The constantly fluctuating levels of the three products produces a bewildering blizzard of symptoms and manifestations that belie the relative simplicity of MSM operation.

Thrombin is the "universal enzyme of extracellular energy transduction." Like intracellular ATPase enzymes, it requires Ca⁺ and ATP, and it transforms ATP energy into action^[46-58].

Thrombin is generated when tissue factor, or TF (a glycoprotein in extravascular tissues), and Factor VII (a blood enzyme) meet in the presence of prothrombin. The selectively permeable vascular endothelium allows small quantities of TF to "leak" into blood circulation, and it allows small quantities of factor VII to "penetrate" into extravascular tissues. This generates small quantities of thrombin throughout the body (from its precursor, prothrombin). This "background" thrombin generation energizes ongoing tissue maintenance and a capillary gate mechanism regulated by autonomic balance that governs hemodynamic physiology^[59,60].

When trauma disrupts the vascular endothelium (even minor damage at the capillary level), the MSM accelerates thrombin generation in those damaged tissues to energize hemostasis^[61]. The MSM then maintains thrombin elevations within an optimal range to energize cellular tissue repair activities. It reduces thrombin generation to maintenance levels in healing tissues as the repair process nears completion, causing clot disintegration and apoptosis that shrinks granulation tissues to enable wound closure^[62,63].

Parathyroid glands regulate extracellular Ca⁺ within a narrow range that optimizes thrombin activity^[24,64-77]. Drugs and chemicals that elevate Ca⁺ levels exaggerate thrombin generation, and vice-versa. Mg⁺ competitively inhibits Ca⁺ and mitigates thrombin generation^[27,64,78-94]. Magnesium sulfate is used to treat eclampsia, a treatment readily explained by its thrombin inhibition.

Thrombin is essential for embryological development, tissue maintenance, tissue repair and for malignancy. Pharmaceutical effects and enzyme defects that inhibit thrombin generation also disrupt embryological development, tissue maintenance, tissue repair, and malignancy.

All cells thus far tested have PAR (thrombin receptors) on their outer surface that determine how they react to thrombin elevations. Four different types of PAR have been discovered. Individual cell types have characteristic PAR types and numbers that determine how the cell reacts to thrombin elevations. Like sails on tiny ships, these can be reconfigured by the cell to alter cell reactions to thrombin during embryological development, tissue repair, and malignancy^[57,62,63,95-102].

Ordinarily thrombin elevations energize cellular activities and inhibit apoptosis while thrombin starvation initiates apoptosis in fibroblasts, but cells react to thrombin differently at

different times and in different contexts. Thrombin can energize apoptosis, inhibit apoptosis, or be toxic to the cell. Additional research is needed to clarify thrombin effects, as present understanding relies on invitro studies that may not apply to living organism.

The following thrombin effects of thrombin reflect its universal role in extracellular ATP energy utilization.

- Chemotaxis of platelets, osteocytes, white blood cells, and other tissue repair cells^[69,103-105]
- Mitosis^[59,69,102,106]
- Metabolism^[69]
- Hypertrophy^[69,105,107-110]
- Angiogenesis^[47,111,112]
- Platelet activation, chemotaxis, and thromboxane release^[46]
- Proliferation, spreading and gap formation in the vascular endothelium^[117,118]
- Chemokine, cytokine, interleukin, bradykinins, caspase, and prostaglandin release^[96,104,109,119-127]
- Bone, muscle, collagen, and immune protein production by osteocytes, myocytes, fibroblasts, and immune cells^[54,63,66,105,106,108,110,118,128-131,132,133-139]
- Conversion of fibrinogen to soluble fibrin^[72]
- Conversion of fibrillar soluble fibrin to three-dimensional insoluble fibrin^[61,71,140-148]
- Stabilization of insoluble fibrin via “Thrombin-Activated Fibrinolysis Inhibitor” (TAFI) ^[145,149-152]
- Inflammation, which dissolves the “basement membrane” that binds cells in tight formation with one another and with the Vascular Endothelium to facilitate chemotaxis^[66,98].
- Astrocyte and glial cell proliferation in brain tissue^[102].
- Gelsolin activation^[153,154]
- Complement activity^[155] Complement cascade activity generates large amounts of thrombin.
- T-cell activation^[99,133]
- Blast transformation in lymphocytes^[131,133]
- Macrophage phagocytic activity^[67,99,111,112,131,136,156]
- Plasma (immune) cell and neutrophil activation^[136,147,157]
- “Tumor Necrosis Factor” release from microglial cells^[158]
- Tumor growth, malignancy, and fibrosis^[55,62,63,95,128,130,135,159,160,161]
- Inhibits apoptosis^[57,95,100,101,162,163]
- Intracellular gap formation in the vascular endothelium^[117]
- Defects in Factors VII, X and tissue factor lethally disrupt thrombin generation^[164]

Soluble fibrin is the “*universal protein of tissue repair.*” Thrombin converts fibrinogen to soluble fibrin that appears in pus, exudates, scabs, scars, saliva, mucus, and milk^[165,166]. It escapes the vascular system via inflammatory gaps in the vascular endothelium and infiltrates damaged tissues to promote fibroblast proliferation and collagen production that facilitates tissue repair^[106,117,165]. Excessive insoluble fibrin causes tissue edema, organ dysfunction, fibrosis, and scar formation^[139,167-178].

Insoluble fibrin is the “*universal polymer of hemostasis.*” Factor VIII accelerates thrombin generation to energize its enzymatic conversion of soluble fibrin into strands of insoluble fibrin that entangle blood cells, reduce pulsatile turbulence below a threshold, and bind blood cells into a viscoelastic clot or thrombus^[12,33,56]. In capillaries, insoluble fibrin exaggerates flow

resistance to regulate hemodynamic physiology^[13]. Excessive insoluble fibrin exaggerates blood viscosity and coagulability, which decreases cardiac output, tissue perfusion, and tissue oxygenation, and invites infarction, thrombosis, embolism, and disseminated intravascular coagulation (DIC)^[35]. Excessive insoluble fibrin generation exhausts clotting precursors^[179,180].

Insoluble fibrin incorporates cross-links of plasminogen, which spontaneously degrades into plasmin that enzymatically disintegrates insoluble fibrin into “fibrin split products.” Thrombin-activated fibrinolysis inhibitor (TAFI) stabilizes plasminogen and preserves insoluble fibrin^[145,149-152].

The Interaction of factors VII, VIII, IX, and X

Hepatic enzyme factors IX and X have prolonged half-lives and circulate at stable levels, but factors VII and VIIC are labile, so that their fluctuating enzymatic activities alter the enzymatic interaction and determine the rate, magnitude, location and speed of production of thrombin, soluble fibrin, and insoluble fibrin.

Factor IX enhances factor VIII activity but lacks other effects.

Factor VIII links nervous activity to blood enzymes. It is a gigantic chimeric molecular complex consisting of continuously released hepatic enzyme factor VIIC and von Willebrand factor (VWF) that is produced by the vascular endothelium and released into blood in accord with sympathetic activity^[29]. These seemingly unrelated molecules bind together in blood circulation and exert their effects in concert, so that factor VIII fluctuates in accord with nervous activity, including emotion^[26,29,181-183]. Factor VIII interacts with factors IX and X to generate factor XIII that adds “cross links” of fibronectin, vitronectin and plasminogen to molecular strands of soluble fibrin to generate insoluble fibrin in capillaries and flowing blood.

Factor VII links tissue damage to blood enzymes. Tissue damage disrupts the vascular endothelium and exposes factor VII to tissue factor in extravascular tissues^[184]. Tissue factor stabilizes labile factor VII, where upon it generates small amounts of thrombin that enable the activities of factors VIII, IX, and X. Factor VII thus functions as a “trigger” that initiates and localizes the enzymatic interaction.

The pivotal activities of factor X have yet to be fully elucidated. It interacts with factor VII and tissue factor to enable embryological development and tissue repair, and it interacts with factor VIIC and VWF (factor VIII) to generate insoluble fibrin that enables hemostasis and capillary gate function.

The Vascular Endothelium

The vascular endothelium is a diaphanous layer of cells, one cell thick, that lines the inner surface of blood vessels and is the sole substance of capillaries. It regulates the enzymatic interaction of factors VII, VIII, IX and X to govern the rate, magnitude, and location of the production of thrombin, soluble fibrin, and insoluble fibrin.

The vascular endothelium insulates blood enzymes from tissue factor in extravascular tissues. Its traumatic disruption exposes tissue factor to blood enzymes and initiates coagulation and tissue repair. Harmful radiation and toxic chemicals increase its permeability to factors VII, X and tissue factor, which causes painful inflammation but does not induce coagula-

tion because the intact vascular endothelium remains impermeable to gigantic factor VIII. Abundant tissue factor exaggerates coagulability and malignancy in brain, nerves, lung, gonads, arteries, cervix, and placenta^[184].

The vascular endothelium is “selectively permeable.” It allows the continuous “penetration” of factor VII from flowing blood into extravascular tissues, which generates small amounts of thrombin that energize tissue maintenance. It allows the continuous “leakage” of tissue factor into flowing blood, which enables the continuous “background” activity of factors VII, VIII, IX and X.

The cells of the vascular endothelium react to local factors and communicate with one another via electromagnetic signals^[185]. They release VWF in accord with sympathetic tone to generate insoluble fibrin^[26,186-190]. They release nitric oxide (NO) in accord with parasympathetic tone to disintegrate insoluble fibrin (nitergic neurogenic vasodilation)^[189,191-195].

The Tissue Disruption Pathway

The tissue disruption pathway is analogous to the extrinsic pathway of the coagulation cascade. Tissue damage disrupts the ubiquitous vascular endothelium, exposes tissue factor to blood enzymes, and triggers an intense enzymatic interaction of factors VII, VIII, IX and X that activates platelets, releases thromboxane, and generates strands of insoluble fibrin that entangle blood cells, reduce pulsatile blood turbulence below a threshold, and bind blood cells into a viscoelastic clot that restores the isolation of damaged tissues from flowing blood^[12].

The Tissue Repair Mechanism

Due to its gigantic size, factor VIII cannot penetrate the clot of its own manufacture, and factor IX interacts only with factor VIII, so that clot formation is limited to the vicinity of tissue damage. The selectively permeable viscoelastic clots regulates the penetration of factors VII and X into damaged tissues, where they interact with tissue factor to generate thrombin that energizes inflammatory gaps between the cells of the vascular endothelium that increase its permeability. Thrombin energized inflammation loosens cell connections to facilitate thrombin energized chemotaxis of repair cells that move from adjacent undamaged into damaged tissues, where they engage in thrombin energized tissue repair. Thrombin-generated soluble fibrin escapes the vascular system through thrombin inflamed tissues to enter damaged tissues, where it facilitates thrombin energized fibroblast proliferation and collagen production that fills empty spaces. Thrombin energized immune activity fights infection and removes debris. Thrombin energized cell differentiation replaces damaged bone and tissues. Thrombin generation declines as tissue repair restores the vascular endothelium, and thrombin starvation induces clot disintegration and repair cell apoptosis that draws wound edges together to conclude the repair process^[95].

The Capillary Gate Pathway

The capillary gate pathway is analogous to the intrinsic pathway of the coagulation cascade. Nervous activity releases von Willebrand factor (VWF) from the vascular endothelium into flowing blood to stabilize VIIIc and generate insoluble fibrin that increases blood viscosity and coagulability.

The Capillary Gate Mechanism

Capillary surface area is vastly greater than that of all larger vessels combined, and turbulence, flow rates and pressures are minimal at the capillary level. The capillary gate pathway regulates a submicroscopic “capillary gate mechanism” that governs capillary flow, capillary hemostasis, systemic vascular resistance, tissue perfusion, organ function, cardiac output, cardiac efficiency, blood pressure, and pulse rate. Autonomic balance and CO₂ tissue accumulation regulate the capillary gate mechanism^[196].

Sympathetic activity extrudes VWF from the inner walls of capillaries, next to binding sites for fibrinogen and fibronectin. Factor VIIIc binds to VWF and accelerates thrombin generation to convert fibrinogen to strands of soluble fibrin. Factor VIII then converts factor X to factor XIII that adds “cross-links” of plasminogen and fibronectin to molecular strands to soluble fibrin to generate insoluble fibrin that polymerizes into strands that “close” the capillary gate by increasing capillary flow resistance^[73,180]. Plasminogen spontaneously degenerates into plasmin that enzymatically disintegrates insoluble fibrin into “fibrin split products” unless plasminogen is continuously stabilized by “thrombin-activated plasminogen inhibitor” (TAFI). Parasympathetic activity releases nitric oxide (NO) from the vascular endothelium^[189,191-195]. NO is a gaseous molecule that diffuses into the capillary lumen and binds to Ca⁺, which inactivates thrombin, accelerates the disintegration of insoluble fibrin, and “opens” the capillary gate (aka “nitergic neurogenic vasodilation”).

The opposing effects of epinephrine and insulin extend autonomic balance to peripheral tissues where direct autonomic innervation is lacking. Sympathetic activity releases epinephrine from the adrenal glands, which releases VWF from the vascular endothelium, increases factor VIII activity, and generates insoluble fibrin^[197]. Parasympathetic activity releases insulin from the pancreas, which releases NO from the vascular endothelium, which accelerates insoluble fibrin disintegration^[198].

The Turbulence Mechanism

Familiar fluids such as water, oil, steam, and atmospheric gases are classified as “Newtonian” because they exhibit exponential *increases* in turbulent flow resistance when they are accelerated in pipes^[199]. (see figure 3) In contrast, blood is a “non-Newtonian” fluid that exhibits exponential *decreases* in flow resistance when it is accelerated in arteries. This is because mammalian red cells spontaneously form “aggregates” during blood acceleration that inhibit turbulent flow resistance, which enables the heart to efficiently eject its contents in less than a tenth of a second^[200]. The muscular arterial tree expands to accommodate cardiac ejection volume, and then functions as a “secondary heart” that propels blood toward capillary beds as it restores resting volume. However, blood flow momentarily reverses direction in the aorta at the outset of diastole, which closes the aortic valve. The reduced diameter of the distal aorta amplifies the momentary flow reversal, disrupts the aggregate patterns, and produces a burst of diastolic pulsatile turbulence that momentarily halts blood flow as it propagates toward the periphery of the arterial tree. Laminar blood flow resumes in the wake of the pulse wave. The pulsatile turbulence generates lateral forces that press on the inner walls of arteries. This explains blood pressure and the palpable pulse. The turbulence maintains arterial patency by dis-

integrating thromboses and mobilizing particulate deposits from the inner walls of arteries that would otherwise induce localized inflammation and tissue repair activities that cause atheroma formation. Decreasing arterial diameter exaggerates turbulence,

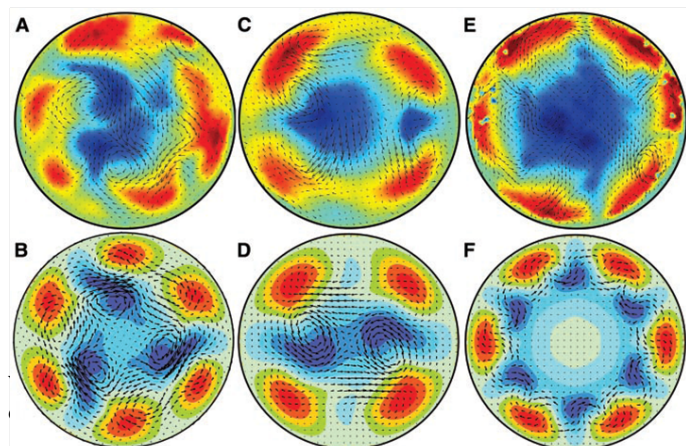


Figure 3: Newtonian Pipe Flow Turbulence.(199) Turbulent forward flow appears as fast-moving “jet streams” (shown in red) that form along the inner walls of pipes and force slow-moving fluid to the center, where it moves backwards (shown in blue), causing increased viscosity (flow resistance). A, C and E are laser photographs that reflect flow acceleration that exaggerates turbulent intensity. B, D and F are computer simulations. Similar diastolic turbulence inhibits atherosclerosis by mobilizing particulate deposits from the inner walls of arteries. Diastolic turbulence also generates lateral forces that explain blood pressure and the palpable pulse. The study of Hof et al has revolutionized the understanding of pipe flow turbulence and viscosity and refuted several older concepts that attempted to explain the manifestations of fluid flow in pipes and arteries. This includes systemic blood pressure (BP), pulmonary artery pressure (PAP), Pulmonary Vascular Resistance (PVR), the Hagen-Poiseuille Equation, Mean Arterial Pressure (MAP), Shear Stress, and Reynolds Numbers. (Reproduced with permission Science).

Accelerated Capillary Senescence

Capillary gate activity regulates tissue perfusion, but does not normally cause tissue oxygen starvation, as evidenced by the rarity of infarction in youth. However, inexorable capillary deterioration proceeds with senescence, which inexorably undermines tissue perfusion and glucose uptake, exaggerates flow resistance that causes essential hypertension, harmfully increases cardiac work that induces congestive heart failure, and alters pulsatile turbulence in favor of lateral forces at the expense of turbulent intensity that maintains arterial patency. Chronic stress, including toxic chemicals, smoking, fear, anxiety, obesity, and chronic illness, accelerates capillary senescence and promotes hypertension, diabetes, congestive heart failure, infarction, eclampsia, and multi-organ system failure. I call this “accelerated capillary senescence^[201-205].” Exercise conditioning mitigates capillary senescence by inducing angiogenesis^[8-11,206,207].

Discussion

The MSM clarifies RAS, as follows:

Malignancy, obesity, smoking, emotional stress^[181,183,208], hypertension, and other illnesses induce MSM hyperactivity that exaggerates blood viscosity and coagulability, accelerates capillary

senescence, and promotes thrombus formation. Capillary senescence exaggerates flow resistance, which undermines turbulent intensity, causes essential hypertension, promotes thrombus formation, accelerates atherosclerosis, and exaggerates cardiac work, which causes congestive heart failure that further undermines pulsatile turbulent intensity. In reasonably healthy individuals, pulsatile blood turbulence maintains arterial patency in the aftermath of arterial cannula installation. However, co-existing disease inhibits turbulent intensity, which promotes thrombus formation and propagation that undermines the pulse wave and obstructs arterial flow hours later. This explains the close relationships of RAS and disease.

Nerve blockade promotes spontaneous thrombus disintegration by inhibiting sympathetic nervous activity that releases VWF from the vascular endothelium.

The unappreciated anticoagulant properties of local analgesics such as lidocaine^[209-211], calcium channel blockers such as Verapamil, beta-blockers such as propranolol^[212], furosemide^[213], and other pharmaceuticals explains their ability to relieve RAS.

Multiple arterial piercings increase tissue factor exposure and trigger thrombus formation that mimics spasm and obstructs arterial flow. Soon thereafter, pulsatile turbulence “tunnels” through the thrombus, restores arterial patency, and mimics spasm relief.

Blood is ordinarily transparent to both X-rays and ultrasound, but pulsatile turbulence reflects the Doppler ultrasound signal, which facilitates cannula installation. Doppler ultrasound detects mature thrombus formation but cannot detect immature thrombus formation that nevertheless undermines the palpable pulse and blood flow.

Angioplasty catheters disrupt the vascular endothelium along their entire length and cause far greater tissue factor exposure than small monitoring catheters. This induces thrombus formation along the length of the catheter in accord with small arterial diameter, large catheter diameter, and catheter length. The viscoelastic thrombus is tough, sticky, and flexible, and it bonds to the catheter, causing entrapment. The entrapment eventually resolves as plasmin degrades the viscoelastic clot, but ensuing tissue repair activity causes permanent arterial damage. Anticoagulant heparin, lidocaine, and verapamil infusions prevent and relieve catheter entrapment via hemolysis.

Cold exaggerates blood viscosity and coagulability^[214]. Warming the extremity reduces blood viscosity and coagulability, accelerates thrombus disintegration, and restores the waveform.

Ultrasound releases NO from the vascular endothelium, disrupts insoluble fibrin, disintegrates the thrombus, and restores the waveform^[215-217].

The MSM suggests simple, safe, inexpensive RAS treatments that can be synergistically combined. Ultrasound releases NO from the vascular endothelium and disintegrates insoluble fibrin. CO₂ supplementation of inhaled gas mixtures opens the capillary gate and optimizes pulsatile turbulence intensity. EDTA, trisodium citrate, and MgSO₄ are more potent than heparin, and they can be readily reversed with Ca⁺. They are inexpensive, and they have excellent safety records when used for chelation, dialysis, eclampsia, and blood preservation.

Conclusion

MSM activity here in does not refute spasm, but it offers an alternative explanation of RAS that invites further investigation. It is possible that a combination of spasm and coagulation causes the confusing manifestations of RAS. On the other hand, the Razor of Occam suggests that the simplest explanation is the one most likely to be correct. The coagulation hypothesis is simpler because it potentially explains all aspects of the RAS phenomenon.

The implications of the MSM exceed the bounds of medicine. In addition to enabling Selye's "unified theory of medicine" that explains physiology, pathology and stress, it confers a "unified theory of biology" that explains embryology, evolution, anatomy, ethology, intelligence, emotion, taxonomy, paleontology, dinosaurs, the Cambrian explosion, and the origin of life. It paves the path for understanding of the gene code, with implications that presently remain in the realm of science fiction. A book that discusses the extended medical and biological implications of stress theory is in the hands of its publisher and will soon be announced via my website: www.stressmechanism.com.

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Acknowledgment: The viewpoint presented in this paper is exclusively that of the author.

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