Integrating the theories of Darwin and Bernoulli: Maladaptive baroreceptor network dysfunction may explain the pathogenesis of aortic aneurysms

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Summary Current treatment options for aortic aneurysms are suboptimal and their pathogenic mechanisms remain unclear. We propose the existence of a coordinated multi-node baroreceptor network that measures pressures at all vascular bifurcations and enables system-wide hemodynamic coordination and vasomotor regulation, in accordance with the principle of Bernoulli. While the presence of baroreceptors at bifurcations remains unknown, behavior at the level of systems predicts their existence, possibly as glomus cell derivatives. We propose that pressure misregistration among sensor nodes at different vascular bifurcations can precipitate feed-forward dysfunctions that promote thrombosis, inflammation, and vasomotor dysregulation resulting in aneurysm formation. One example of this phenomenon is aortic aneurysm, which is currently attributed to focal anatomic defects. As plaque builds in the infrarenal aorta, the increased blood velocity through this segment can widen the difference between pressures sensed at the iliac and the renal artery bifurcations. Due to the Bernoulli effect, this change creates an incorrect impression of reduced dynamic pressure at the kidneys. The erroneous perception of hypovolemia can induce a pernicious cycle of maladaptive adrenergia and associated coagulation and thrombosis, particularly in the infrarenal aortic segment as the body attempts to normalize renal perfusion. Atherosclerosis can further exacerbate baroreceptor dysfunction by interfering with sensor biology in feed-forward fashion. Hypertension may be a consequence as well as a source of atherosclerosis and aneurysm. The described system may have evolved when trauma-related hypovolemia was a far more prevalent driver of natural selection but may be rendered maladaptive in the setting of modern stressors. Failure to address these factors may explain the suboptimal long-term outcomes with current surgical and endovascular treatments for aneurysms. Implications for other potential sensor networks including chemoreceptors and lymphoid tissues at bifurcating biologic branch-points such as vessels, airways, nerves, lymphatics, and ducts are discussed.
framework may also provide a new basis for understanding thoracic aneurysm, renovascular dysfunctions, coronary artery disease, carotid artery disease, pulmonary embolism, portal hypertension, venous thrombosis, biliary disease, pancreatic disease, and neurologic disease. Novel treatment paradigms based on drugs or interconnected networks of devices that modulate sensors are envisioned. Improving the interface between sensors and their substrate information by techniques such as minimally traumatic atherectomy or thrombectomy may also restore appropriate sensor function. Lessons learned from bifurcation sensors and their potential maladaptations may generalize to other types of branching systems including botany, civil engineering, and Pitot tube aeronautics.

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Hypothesis

Aortic aneurysms are a major cause of mortality. Death typically occurs due to hemorrhage from rupture, often secondary to progressive enlargement. The yearly risk of rupture at an aortic diameter greater than 5 cm exceeds 50% [1]. The majority of these aneurysms occur in the abdominal aorta below the origin of the renal arteries and above the iliac bifurcation [2]. The reason for this tendency remains unclear. Various studies have focused on the possibility of local weakening of the aortic wall through inherent defects in structural composition [3], increased local inflammation [4], or aberrant enzymatic activity [5,6]. Atherosclerosis tends to occur in conjunction with these aneurysms [7], and thrombotic material is often found in their lumens [8].

We describe a coordinated multi-node baroreceptor network that measures pressures at different locations to regulate hemodynamic response in the arterial vascular system. We propose that pressure misregistration among sensor nodes at different vascular bifurcations can precipitate feedforward dysfunctions that promote thrombosis, inflammation, and vasomotor dysregulation resulting in disease. Aortic aneurysms may exemplify this phenomenon.

Evidence

Theoretical existence of a baroreceptor network

Baroreceptors, or pressure sensors, are best known for their existence in the carotid sinus at the bifurcation of the external and internal carotids, and in the aortic arch [9]. These baroreceptors presumably detect stretching of the vessel walls. Baroreceptor activity normally leads to constitutive inhibition of sympathetic efferent activity from the medulla [10]. A decrease in arterial pressure at these sites dampens baroreceptor activity which subsequently triggers efferent sympathetic activity [11].

Although study of baroreceptors has been largely confined to the carotids and aortic arch, the capacity to detect stretch may not be limited to these locations. The glomus cell, a neurosecretory cell [12] in which the functions of pressure detection and transduction reside, occurs throughout the body, as evidenced by occurrence of glomus tumors in tissues as diverse as skin, bone, and colon [13–15]. Thus, one can infer the presence of glomus cell-derived baroreceptors in the peripheral vasculature. The complex nature of hemodynamic coordination also implies a need for a widely distributed baroreceptor network extending beyond the relationship between the medulla, carotids, and the aortic arch. The location of baroreceptors at the carotid bifurcation and the prevalence of atherosclerotic plaques at this site [16] provide evidence for just such a scheme.

Bernoulli’s principle in physiology

If one considers Bernoulli’s principle, the location of baroreceptors at points of bifurcation appears deliberate and strategic from a teleologic standpoint. A baroreceptor located at such a site would effectively measure the sum total pressure of the blood in the vessel upstream from the bifurcation, representing both its kinetic energy, in the form of dynamic pressure, and its potential energy, in the form of static pressure ($P_{p.total} = P_{p.dynamic} + P_{p.static}$) (Fig. 1). For a branch vessel extending perpendicularly from the axis of the parent vessel, a baroreceptor located at its subsequent bifurcation would do the same ($P_{d.total} = P_{d.static} + P_{d.dynamic}$) (Fig. 1). However, the sum total pressure of the blood in the daughter vessel would be equivalent to the static pressure, or the potential energy, of the blood of the parent vessel ($P_{d.total} = P_{p.static}$) (Fig. 1). Consequently, the difference between these two sum total pressures yields the dynamic pressure of the blood in the parent vessel ($P_{p.dynamic} = P_{p.total} - P_{d.total}$) (Fig. 1). This pressure then becomes a proxy for the velocity of the blood flow in the parent vessel.
As a result, distributed positioning of baroreceptors at bifurcations and integration of the collective information enables measurement of flow velocity in the vessel. Any changes in flow velocity at any one vessel could lead to compensatory upstream adjustments via either vasoconstriction or vasodilation to accordingly decrease or increase flow to that vessel. For example, determination of excessive flow might indicate downstream hemorrhage, invoking vasoconstriction of vessels further upstream.

Feed-forward cycles in the formation of aneurysms: Plaque at bifurcation

Given the complex interplay of upstream and downstream elements, any physical obstruction within the lumen or a functional compromise of a single baroreceptor could lead to dysfunctional response. For example, an atherosclerotic plaque at a bifurcation could dampen the pressure sensed by the baroreceptor \( (p_{p, total} < p_{d, total}) \) (Fig. 2). Consider the consequence if a similar process of atherosclerosis did not similarly dampen the baroreceptor located at the bifurcation of a branch vessel \( (p'_{d, total} = p_{d, total}) \). Since the sum total pressure sensed by that baroreceptor would represent the measure of the static pressure of the blood in the parent vessel \( (p_{p, static} = p_{d, total}) \), the overall system would then determine that the dynamic pressure of the blood in the parent vessel would be abnormally low, suggesting a low velocity of flow \( (p'_{p, dynamic} = p_{p, total} - p_{d, total}; p'_{p, dynamic} < p_{p, dynamic}) \) (Fig. 2). Effects further upstream to increase the volume of flow (combined with vasoconstriction of the parent vessel itself to maintain velocity of flow) would consequently occur in response to this perceived low flow state. However, in reality the velocity of flow would in fact be normal, resulting in a situation where a high volume of blood encounters a vessel that would likely already be filled to capacity. Static pressure would consequently increase, leading to heightened transmural stress. Higher measured static pressures with inappropriately dampened measured total pressures would mean the continued perpetuation of a vicious cycle, with eventual compensatory dilatation and aneurysm formation.

Feed-forward cycles in the formation of aneurysms: Luminal thrombus

Development of thrombus in the lumen of the vessel in question would have similar consequences. Here the issue becomes not that of compromise at the site of the baroreceptor, but distorted readings from different sensors as a consequence of the obstruction and resultant nonlaminar flow. The baroreceptor at the bifurcation downstream from the thrombus would sense low sum total pressure \( (p'_{p, total} < p_{p, total}) \), whereas those situated on bifurcations of daughter vessels upstream from the thrombus would sense normal or increased
static pressure ($P_{d,\text{total}}^{III} = P_{d,\text{total}}$), leading to the calculation of low dynamic pressure ($P_{d,\text{dynamic}}^{III} = P_{d,\text{total}}^{III} - P_{d,\text{total}}$; $P_{d,\text{dynamic}}^{III} < P_{d,\text{dynamic}}$), and once again triggering positive volume provision upstream (and constriction of the vessel proper). In this case the vessel capacitance would have already undergone a fixed reduction by the presence of the thrombus, once again leading to an increase in static pressure and elevated transmural stress. Once again, the process escalates in an iterative fashion, with eventual compensatory dilatation and aneurysm formation.

Moreover, as the aneurysm begins to form, chemoreceptor behavior may further its progression. The developing thrombus in the lumen of the aneurysmal segment may cause downstream chemoreceptors to sense a hypoxic state via the proxy of pH. This signal would in turn also lead to a compensatory increase in upstream blood flow, thereby increasing transmural wall stress on the already taxed segment of vessel, and accelerating the expansion of the aneurysm.

Significance of infrarenal location

The predilection for aneurysm formation in the descending abdominal aorta, and specifically in the infrarenal portion, may arise from several anatomic factors. The renal arteries are situated perpendicular to the axis of the abdominal aorta and deliver high-value information to the kidneys, which act as both the sensor and the responder to hemodynamic status. Consider the following scenario: atherosclerotic plaque begins to narrow the infrarenal aorta, thereby increasing velocity through this narrowed segment in a persistent fashion. The total pressure in the renal artery sensed at its bifurcation would remain unchanged ($P_{d,\text{total}}^{III} = P_{d,\text{total}}$), but the total pressure in the infrarenal aorta sensed at the iliac bifurcation would increase ($P_{p,\text{total}}^{III} > P_{p,\text{total}}$) (Fig. 3). This measured total pressure would correspond to the static pressure in the renal artery ($P_{p,\text{total}}^{III} = P_{d,\text{static}}^{III}$). Consequently, the computed dynamic pressure for the renal artery would decrease ($P_{d,\text{dynamic}}^{III} = P_{d,\text{total}}^{III} - P_{p,\text{total}}^{III}$; $P_{d,\text{dynamic}}^{III} < P_{d,\text{dynamic}}$) (Fig. 3), even though in reality the true dynamic pressure remains unchanged.

Darwinian perspectives

Renal response as maladaptation

During prehistoric evolution, a decrease in renal dynamic pressure may have signaled hemorrhage, perhaps from trauma. Induction of vasoconstriction through an increase in adrenergic activity would produce an adaptive response and increase systemic pressure. In particular, adrenergia-driven increased vasomotor tone in the infrarenal aorta would equilibrate flow between the renal arteries and the infrarenal aorta. This adjustment would reestablish an appropriate difference between the pressures sensed at the iliac bifurcation and the renal bifurcation, which under normal circumstances would correspond to appropriate dynamic pressure and flow velocity.

However, the system may not have anticipated formation of atherosclerotic plaque as a potential source of persistent distortions in measurement, where the renal response becomes inappropriate. The system attempts to restore baseline pressures by increasing systemic pressure so as to correct its perception of an altered dynamic pressure, i.e. to normalize the difference between the measured total pressures in the infrarenal aorta and the renal artery. However, because of the persistence of the disparity in measurement caused by the atherosclerosis, the system progressively worsens the issue by continuing to increase the systemic pressure. In short, the system responds to a problem that does not exist, and in turn creates a problem of its own. In areas where limited capacitance of the vessel exists, such as sites of atherosclerotic
plaque, transmural stress increases, predisposing to aneurysm formation.

Adrenergia co-stimulates thrombosis and inflammation as part of a prehistoric adaptation to trauma [17]. In the setting of an abdominal aortic aneurysm, the adrenergia exacerbates the underlying inflammation and thrombosis that caused pressure misregistration in the first place. As the disease progresses, the thrombosis inside the infrarenal aortic aneurysm increases, the luminal flow hastens, the renal dynamic flow decreases, and the kidneys further upregulate adrenergia, inflammation, and thrombosis in the aorta in a nefarious cycle. One can see how hypertension can then become both a source and a consequence of aneurysm physiology. To test the validity of our proposed aneurysm model, one may experimentally modulate baroreceptors in their presumed location at the iliac and renal artery bifurcation and determine if such intervention can affect the formation of aneurysms.

The ability to perceive and respond to volume changes by integrating pressure information from a distributed network of sensors likely conferred substantial fitness advantage, especially during periods of hemodynamic instability as might occur after traumatic hemorrhage [17]. The aggregation of the functions of inflammation, autonomic response, and coagulation would allow for optimal coordination, because the responses for all of these systems to either of these situations would then occur in tandem.

Perspectives on therapy

The prevention and treatment of aneurysms may rely on the restoration of appropriate pressure monitoring and flow maintenance. Our model may also help explain the suboptimal long-term data of using endovascular stent-grafts in abdominal aortic aneurysm. Once thought to be the ideal replacement for highly morbid surgery, stents-grafts demonstrate a very high incidence of late-failures associated with so-called endoleaks, hardware dissociation, migration, kinking, and aneurysmal remodeling. While luminal expansion associated with stent-graft placement may temporarily reduce flow and pressure abnormalities inferred by our model, the reduced elasticity of the stent material compared to the normal aortic wall may both compromise baroreceptor sensitivity and artificially increase static pressure through reduced capacitance. While the network of sensors may be set to a new equilibrium with the introduction of a stent-graft, the underlying dysfunction may resume and the nefarious cycle may begin anew. Although aggressive treatment of atherosclerosis and appropriate institution of anticoagulation may reduce the risk of aneurysm development, the real key to prevention may lie with conserving baroreceptor response and autonomic mediation. Therapies that focus on maintaining the appropriate mechanisms of control from the standpoint of autonomic balance likely stand the greatest chance of success in this regard. Such approaches may have effects on retarding development of the associated risks contributed by atherosclerosis [18] and thrombosis as well [19].

Avionics analogy

The cycle of maladaptive response seen with vessels is similar to that seen with airplanes. The Pitot tube is a flow velocity meter that is capable of measuring flow velocities at a localized point. It yields a pressure measurement from which flow velocity can be obtained from the Bernoulli equation. This tube is used for measurement of airspeed on planes. If this tube becomes blocked, when the airplane goes from a region of high static pressure to low static pressure, as is the case during descent, the indicated airspeed will decrease regardless of the actual airspeed. When the airplane goes from a region of low static pressure to high static pressure during incline, the blocked Pitot tube will cause the indicated airspeed to increase regardless of the actual airspeed. In this scenario, progressive adjustments in response to a perceived increase in airspeed have led to situations where the nose of the plane became progressively more vertical in pitch, ultimately leading to stalling of the plane. Conversely, on descent, progressive adjustments in response to a perceived decrease in airspeed would lead to situations where airspeed would be far too high for a safe landing. The misregistration of the altitude of the aircraft due to Pitot tube blockage appears to correspond to the misregistration of systemic pressure in the body in response to atherosclerosis-related flow disturbances.

Implications

Bifurcation represents a ubiquitous feature throughout nature, and its functional significance is generally appreciated from the fractal, branching patterns of many natural processes. In this paper, we invoke the notion that bifurcations may also represent ideal nodes at which to acquire information as part of a coordinated intelligence network [20]. The concept bears similarities to
the router systems that parse the flow of electronic information on the Internet. If one presumes that a system can be better regulated by continuously integrating information including those derived from bifurcations, then numerous sensors may exist at biologic bifurcations that are yet unknown. If blood, lymph, bile, air, cerebrospinal fluid (CSF), and other bodily fluids are viewed as carriers of information, then one would anticipate the presence of sensors at the branch-points of the vascular, lymphatic, tracheobronchial, and CSF systems.

Potential nodal sensors that may read information include baroreceptors, chemoreceptors, or lymph nodes. Baroreceptors and chemoreceptors are examples of nodes that feed information to a central network such as the nervous system, while the lymphoid tissues are nodes that feed information to a distributed network [21]. Baroreceptors and chemoreceptors are known to occupy major bifurcations [22]. Lymph nodes are known to straddle tracheobronchial bifurcations such as the carina and hila, and also surround vascular branch-points such as the celiac axis and portal venous confluence. Sensor units of a corresponding magnitude may fractionally occupy each successive level of bifurcation in all systems.

Though less understood, many other types of sensors may potentially exist at bifurcations. For instance, anecdotal experience suggests that physical stimulation of bronchial branch points during bronchoscopy triggers the cough reflex. The body may use the same mechanism to clear mucus that is pushed up to branch points by ciliary motion. Systemic immune-mediated diseases can be reconsidered from the perspective of lymphoid sensor misregistrations. Asthma may involve both local immune sensor misregistration and airway baroreceptor dysfunction. Malfunction of sensors in the biliary tree may contribute to hepatic diseases, and that of sensors in the pancreatic duct may lead to diabetes and other pancreatic diseases. Diseases of the nervous system may also involve junction sensors that remain unidentified.

Besides aortic aneurysm, other vascular diseases may also arise from sensor dysfunction. Carotid artery plaques are currently thought to cause stroke by limiting cerebral flow or breaking off emboli. Based on our framework, carotid plaques may induce dysfunction of the baroreceptors and chemoreceptors situated at the carotid bifurcation. Subsequent perturbations in systemic and cerebral autonomic regulation may produce vasomotor dysfunction, inflammation, and coagulation that predispose to stroke. Renal artery stenosis is currently thought to cause renovascular hypertension by interfering with renal perfusion. Restoring flow by angioplasty or stent placement reduces hypertension, but embolizing the kidney produces similar relief [23]. By viewing renovascular hypertension as a sensor maladaptation of the renal arteries and kidneys rather than simply the underperfusion of the kidneys, this apparent contradiction could be reconciled. Pulmonary embolisms may produce their nefarious autonomic consequences in part due to the bifurcation sensor dysfunctions produced by thromboembolism. Bronchiectasis may equate to aneurysm formation in the pulmonary tree. Other common vascular conditions such as coronary artery disease, venous thrombosis, vasculitides, and portal hypertension may similarly involve dysfunctions of sensors at vascular branch points that produce maladaptive physiologic consequences.

At any place in the body where information has an opportunity to take one of two or more possible routes, a selective advantage exists in the ability to control this flow. The benefits of sensor existence at bifurcations and integration of information from a distributed network of sensors become readily apparent. Some elements of sensor systems are already known, but we believe that the study of sensor biology remains in its infancy. Better understanding of how sensors work, both locally and at the level of systems, may yield new insights into how they can produce diseases under maladaptive conditions. Our framework also portends new therapeutic approaches that specifically seek to treat disease by addressing sensor dysfunctions. Drugs or electromodulation techniques that modulate sensors can be envisioned. Improving the interface between sensors and their substrate information by techniques such as minimally traumatic atherectomy or thrombectomy may also restore appropriate sensor function.

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