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Commentary OMICS International

A Changing Paradigm for Understanding the Behavior of the Cardiovascular System

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Abstract

The prevailing view of the behavior of the smooth muscle wall of large arteries is described by the Windkessel hypothesis, in which the wall does not actively contract in synchrony with the cardiac cycle. This hypothesis has predominated for well over a century. By contrast, several lines of evidence show that the smooth muscle wall of the aorta and other large arteries is capable of undergoing contractions at the rate of the heartbeat and that these contractions are neutrally-mediated (i.e., pulse synchronized contractions [PSCs]). The pacemaker for PSCs resides in the right atrium, and direct electrical stimulation of the aorta results in similar contractile activity. PSCs represent a modified platform to understand the etiology of cardiovascular diseases and may allow for the development of new therapeutic targets.

Keywords: Aorta; Pulse synchronized contractions; Vascular smooth muscle; Windkessel hypothesis

Commentary

Cardiovascular diseases are a prominent cause of death [1]. One of the key platforms by which the cardiovascular system is understood is the Windkessel model, in which the smooth muscle wall of large arteries does not undergo rhythmic activation during the cardiac cycle, but, rather, the elastic components are rhythmically distended by the pulse wave [2]. The Windkessel behavior of arteries has been understood as the prevailing view for over a century. If the Windkessel explanation is not correct, then alternative explanations for the development of certain cardiovascular diseases and, therefore, new paradigms for the development of therapeutics need to be considered.

The platform for the Windkessel description of the aortic smooth muscle wall resides principally in the belief that the dynamics of vascular smooth muscle contractions are sufficiently slow that they could not support rhythmicity at a frequency as fast as the cardiac cycle. Even when hysteresis in pressure-volume relationships [3] provided evidence of "energy gain in the aortic segment during each cardiac cycle," suggestive of an active contraction, this was ignored in favor of the explanation that there is inadequate smooth muscle in the wall and its kinetics are too slow to produce rhythmic tension changes during the cardiac cycle [3].

In contrast to the above, several lines of evidence have supported the notion of rhythmic contractile activity occurring in the aorta and other large arteries in synchrony with the heartbeat. Heyman, in a series of papers in the 1950s and 1960s [4-8], concluded that (1) the arterial wall demonstrates pulse synchronous movements; (2) these contractions are coupled to the P-wave and precede the pulse wave; and (3) the waves are neutrally-mediated and eliminated by ganglionic blockade. These waves were recorded in humans and canines. This series of papers has largely been ignored.

Mangel et al. [9], Ravi and Fahim [10], and Sahibzada et al. [11] performed a variety of experiments in which the blood flow was either bypassed or occluded from segments of large vessels. Recordings of tension changes in these segments, devoid of luminal blood flow, showed rhythmic tension oscillations occurring at the same frequency as the heartbeat (denoted pulse synchronized contractions [PSCs]). PSCs were blocked by application of neural blockers. Considerable effort has been expended to test whether PSCs were due to a mechanical artifact [9]. To eliminate the pulse wave as a potential source of artifact-producing PSCs, animals were bled. Following bleeding, pulse waves were eliminated, but PSCs persisted [9,11]. A second potential source of movement artifact yielding the appearance of rhythmic tension changes comes from cardiac contractions. Two lines of evidence dissociated arterial and cardiac contractions. The pacemaker for PSCs resides in the right atrium [9-11], and stimulation of the right atrium during cardiac refractory periods resulted in ectopic PSCs without any cardiac contractions [10]. Thus, PSCs occurred while the heart was at rest. Furthermore, appearance of PSCs in bled animals, as well as following right atrial stimulation during the cardiac refractory period, strongly supports induction of PSCs by a neurogenic signal and either a limited or no role for a myogenic response secondary to stretch. A second type of experiment dissociating cardiac contractility and PSCs also involved right atrial stimulation. During right atrial stimulation, aortic PSCs were entrained to the atrial stimulation rate. In some animals, heart block develops during stimulation, and large ventricular contractions occurred. During this time, aortic PSCs were still locked to right atrial stimulation frequency and not distorted by the large ventricular contractions [9].

As mentioned previously, there is a prejudice that smooth muscle cannot contract as fast as the cardiac cycle. To test that notion, Sahibzada et al. [10] directly stimulated the in vivo aorta in segments with occluded blood flow. Using stimulation frequencies similar to that of the heart rate, tetrodotoxin, a neural blocker, abolished tension changes. These experiments revealed that (1) that the aortic smooth muscle may contract as rapidly as the heart rate; and (2) this activity is

secondary to neural stimulation. The stimulated contractility activity is at least partially driven by stimulation of the sympathetic nervous system, as contractions were partially blocked by the alpha-adrenergic antagonist phentolamine [11].

As indicated earlier, the pacemaker for PSCs appears to reside in the right atrium. In baddition to the aforementioned experiments studying right atrial stimulation, excision of the right but not left atrium resulted in abolishment of PSCs [9]. This location for the PSC site of origination may allow precise coordination between cardiac and arterial contractile activity.

The Windkessel model has been the platform for understanding the behavior of the large conduit arteries for over a century. However, significant evidence is in contradistinction to that hypothesis. Some of the important questions to address with respect to PSCs include: a. what are the clinical/physiologic roles of the PSCs? Do they have an effect on the hemodynamics of blood flow? Our suspicion is they don't but, rather, they serve a protective role to limit vessel distension during the upstroke of the pulse wave, thus reducing the Laplacian Forces on the vessel wall. However, this remains to be proven; and b. to understand the conduction pathway from the SA node to the aorta and other large vessels. Once this is understood, selective lesions may lead to elucidation of the physiologic and clinical significance of PSCs.

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