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Review Article

Pulse Synchronized Contractions: A Review

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Abstract

Significant morbidity and mortality remain attributed to cardiovascular diseases. A complete understanding of the functionality and behavior of the components of the cardiovascular system is paramount to facilitating the development of new therapeutics and procedures targeted toward the treatment of cardiovascular diseases. One aspect of the cardiovascular system that warrants more extensive evaluation is the behavior of the smooth muscle wall surrounding large conduit arteries. This review focuses on pulse synchronized contractions, or rhythmic mechanical activity in the smooth muscle wall of the large conduit activity *in vivo*.

Keywords: *Smooth Muscle; Pulse Synchronized Contractions; Neurogenic*

Abbreviations

EGTA: Ethylene Glycol Tetraacetic Acid; PSC: Pulse-Synchronized Contractions; TTX: Tetrodotoxin

Rationale for investigation of pulse synchronized contractions

A fundamental principle with respect to organs with a smooth muscle coat surrounding their lumens is whether the smooth muscle layer generates spontaneous rhythmic contractions, whether contractile activity is rhythmically activated by neural input, or whether the muscle is mechanically quiescent with tone being modulated by neuro-hormonal inputs. For example, most portions of the gastrointestinal tract show spontaneous electrical and mechanical rhythmic activity [1]. Classically, the smooth muscle walls of the large conduit arteries have been thought to behave as passive elastic tubes with tone being modulated by neuro-hormonal inputs. This description of the smooth muscle wall of the large arteries, reported over a century ago by Otto Frank, was denoted the Windkessel Hypothesis [2]. In other words, the smooth muscle walls of large conduit arteries behave as passive elastic tubes, rhythmically distended by pulsatile pressure changes.

Most gastrointestinal smooth muscles show spontaneous rhythmic changes in membrane potential, which classically drive an influx of extracellular calcium into the cells, resulting in initiation of contractions. We previously reported in gastrointestinal *in vitro* muscle segments incubated in solutions containing no added calcium plus ethylene glycol tetraacetic acid (EGTA) (EGTA chelates any remaining extracellular calcium) that subsequent changes in membrane potential induced contractions [3-5]. Thus, it was concluded that a depolarization-sensitive release of intracellular calcium occurs.

Based on the above observations, we also evaluated whether a similar phenomenon occurs in aortic smooth muscle. Under normal conditions (i.e. calcium containing solutions), segments of aortic smooth muscle are usually electrically and mechanically quiescent (Fig-

ure 1) [6]. During incubation in calcium-free solutions containing EGTA, a fast, rhythmic electrical event was produced (Figure 1). Based on the ability of aortic smooth muscle to generate these fast rhythmic electrical events, we posed the question: Might the smooth muscle wall of large arteries also possess the machinery to contract rhythmically *in vivo*?

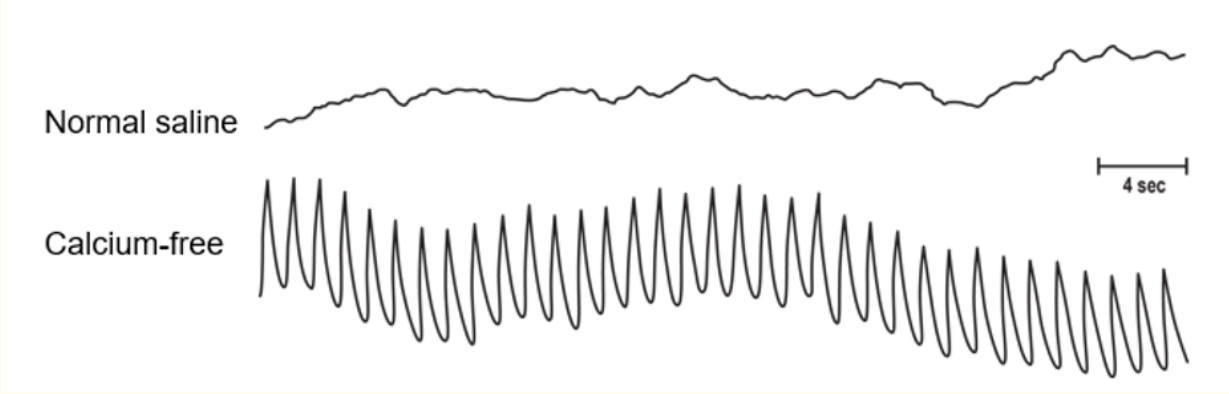

Figure 1: *Incubation of aortic segments from rabbits in normal saline are electrically quiescent (upper trace). In calcium-free solution, a fast rhythmic electrical event is produced (lower trace) [from reference 6].*

Identification of pulse synchronized contractions (PSCs)

Initial studies were done in anesthetized rabbits and dogs [7,8]. Blood flow from segments of rabbit aorta and dog coronary, femoral, and carotid arteries was either bypassed or occluded. In the segments without pulsatile blood flow, either a tension transducer was attached to the smooth muscle wall of the muscle segments or a small slit was made in the vessels and a balloon-tipped catheter attached to a pressure transducer inserted. If the vessel wall produced a contraction, then there would be a tension change recorded with the transducer or a pressure change associated with the balloon-tipped catheter.

With either configuration, in all the vessels studied, contractions occurred in a 1:1 correspondence with the pulse wave [7-9]. Originally it appeared that the phasing of the contractile events was a vessel relaxation occurring with the upstroke of the pulse wave [7]. With technique refinement, evidence emerged that the upstroke of the contraction occurred during the upstroke of the pulse wave (Figure 2) [8]. Subsequently, the identical observations were noted in cat pulmonary arteries and rat aorta [10,11].

Mechanism of generation of PSCs

Considering the absence of spontaneous contractile activity in *in vitro* segments of large conduit arteries, it was deemed likely that the *in vivo* PSCs were of neurogenic versus myogenic origin. Several lines of investigation were performed to test whether this was correct. While recording PSCs in anesthetized animals, application of the neurotoxin tetrodotoxin (TTX) to the segment from which recordings were being made, or proximal to it, blockade of PSCs occurred (Figure 3) [7,8,11]. As TTX does not modulate smooth muscle myogenic activity, this strongly supports a neurogenic activation of PSCs. In addition, the alpha-adrenergic neural blocker phentolamine also reduced PSCs [7,11].

Pacemaker for PSCs

As noted above, the frequency of PSCs occurs at an identical rate as the pulse wave or heartbeat. Several lines of evidence suggest the pacemaker for PSCs is in the right atrium, similar to that of the heart. As shown in figure 4, when the right atrial region was paced to a

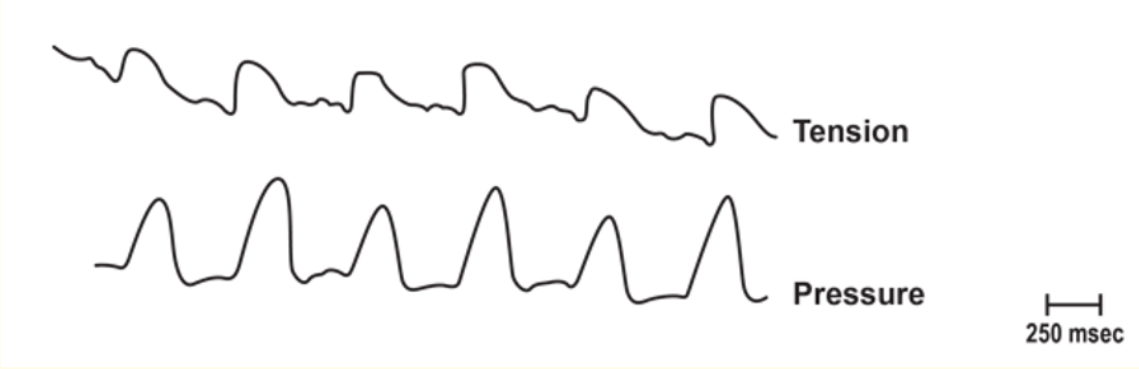

Figure 2: *Rhythmic tension changes (pulse synchronized contractions [PSCs]) were recorded with a 1:1 correspondence to the pulse wave from this anesthetized rabbit [from reference 8].*

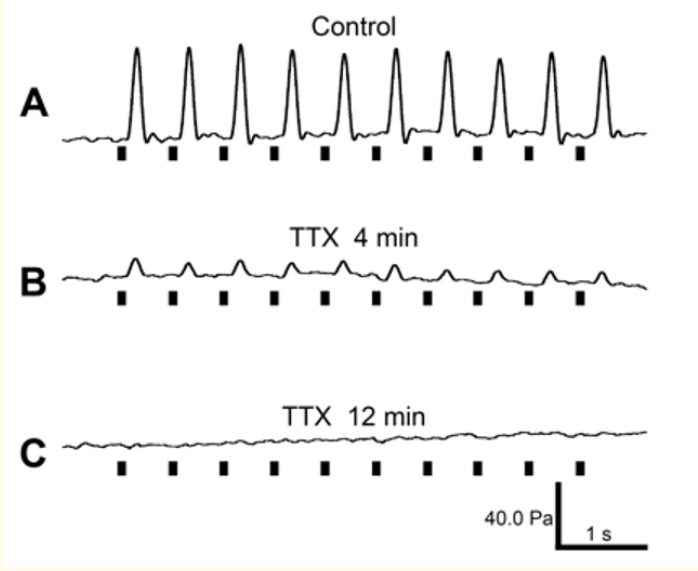

Figure 3: *Electrical stimulation of the rat aorta in vivo produced contractions similar to PSCs. These contractions were eliminated by the neural blocker tetrodotoxin (TTX). Black bars represent timing of stimulation [from reference 11].*

frequency greater than the spontaneous rate, PSCs followed this rate even if heart block occurred, such that large-amplitude ventricular contractions developed at a slower rate than the stimulation rate (Figure 4) [8].

PSCs were still observed if animals were bled; thus, they do not represent an artifact produced by movement of the bypassed segment by the pulse wave at the border of the bypass. Excision of the left atrium did not alter PSC activity. However, excision of the right atrium

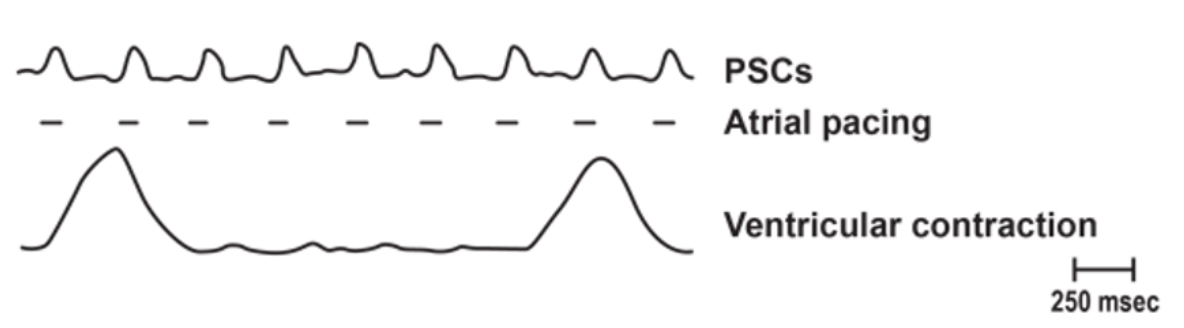

Figure 4: *Shown is an example of right atrial pacing in a bled rabbit. PSCs followed the pacing rate. In this and other animals, heart block developed with corresponding large amplitude ventricular contractions. This experiment supports both the pacemaker for PSCs residing in the right atrium and that PSCs are not secondary to a movement artifact from the heart [from reference 8].*

in bled animals resulted in abolishment of PSCs (Figure 5) [8]. This occurred even if the ventricles were stimulated to ensure ventricular contractions were larger than prior to right atrial excision. Thus, PSCs are not produced as an artifact of ventricular "tug" on the aorta.

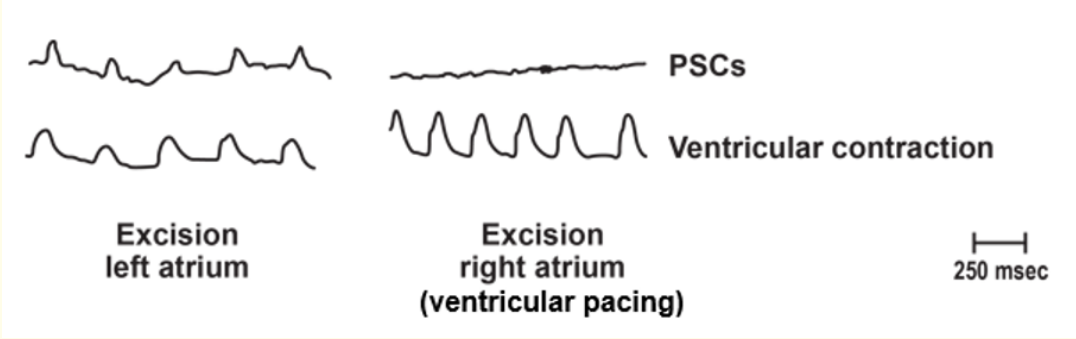

Figure 5: *Following bleeding of rabbits, PSCs continued. In this configuration, ventricular muscle contractions were also recorded and pacing of the ventricles occurred. These studies (a) eliminated the pulse wave as an artifact, as animals were bled; (b) eliminated cardiac contractions as an artifact producing PSCs, as following excision of the right atrium with ventricular contractions paced to supra baseline levels, PSCs were not produced (right trace); and (c) suggested the PSC pacemaker is in the right atrium as excision of the right, but not left, atrium abolished PSCs [from reference 8].*

Studies by Heyman and colleagues

In a series of studies between 1957 and 1961, Heyman and colleagues showed that the Windkessel Hypothesis did not accurately characterize the behavior of the smooth muscle wall of the large conduit arteries [12-14]. Specifically, they observed and concluded:

1. Extra-arterially recorded brachial pulses sometimes precede intra-arterially recorded pulses. This suggested to them that arterial diameter may change in advance of distension from the pulse wave (i.e. a contraction).
2. The difference between extra-arterially and intra-arterially pulse waves was abolished by stellate ganglion block. Simply, these events were neurogenic in origin.
3. Overall, Heyman and colleagues [12-14] concluded that the smooth muscle wall of arteries does not behave according to the principles of passive elasticity, but, by contrast, their studies demonstrated active participation of the arterial wall.

Unfortunately, the scientific community has ignored these important and rigorously conducted studies.

Conclusion

The smooth muscle wall of the large conduit arteries in animals and humans show rhythmic, neurally-activated contractions *in vivo*. It is intriguing that the rising phase of the contractions slightly precedes the rising phase of the pulse wave, as distension of the vessel wall by the upstroke of the pulse wave would lead to an increase in Laplacian forces acting on the vessel wall. Contraction of the vessel wall at this time by the PSC could serve a protective function, serving to decrease the Laplacian forces on the vessel wall. It has been suggested [8,11] that this phasing may serve a protective function in aneurysm formation and dissection. Furthermore, the pacemaker for PSCs resides in the right atrium, potentially allowing for coordination between cardiac and PSC activity. Whether PSCs represent a new target for the development of cardiovascular therapeutics remains an important area for evaluation in the laboratory and clinic.

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