Why the heart is like an orchestra and the uterus is like a soccer crowd

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The human uterus has no pacemaker or motor innervation, yet develops rhythmic, powerful contractions that increase intrauterine pressure to dilate the cervix and force the fetus through the pelvis. To achieve the synchronous contractions required for labor, the muscle cells of the uterus act as independent oscillators that become increasingly coupled by gap junctions toward the end of pregnancy. The oscillations are facilitated by changes in resting membrane potential that occur as pregnancy progresses. Reductions of potassium channels in the myocyte membranes in late pregnancy prolong myocyte action potentials, further facilitating transmission of signals and recruitment of neighboring myocytes. Late in pregnancy prostaglandin production increases leading to increased myocyte excitability. Also late in pregnancy myocyte actin polymerizes allowing actin-myosin interactions that generate force, following myocyte depolarization, calcium entry, and activation of myosin kinase. Labor occurs as a consequence of the combination of increased myocyte to myocyte connectivity, increased depolarizations that last longer, and activated intracellular contractile machinery. During labor the synchronous contractions of muscle cells raise intrauterine pressure to dilate the cervix in a process distinct from peristalsis. The synchronous contractions occur in a progressively larger region of the uterine wall. As the size of the region increases with increasing connectivity, the contraction of that larger area leads to an increase in intrauterine pressure. The resulting increased wall tension causes myocyte depolarization in other parts of the uterus, generating widespread synchronous activity and increased force as more linked regions are recruited into the contraction. The emergent behavior of the uterus has parallels in the behavior of crowds at soccer matches that sing together without a conductor. This contrasts with the behavior of the heart where sequential contractions are regulated by a pacemaker in a similar way to the actions of a conductor and an orchestra.

Key words: emergent behavior, mechanotransduction, pregnancy, uterine synchronization

The heart and the laboring uterus use different mechanisms to coordinate contractions.

This is a discussion of synchrony and coupled oscillatory behavior in the context of the physiology of the laboring uterus and the heart.

One of the great marvels of life is the degree of order that is created as life captures energy and transforms it into physiological structure and function against the forces of entropy (second law of thermodynamics[1]). Life in many ways is a battle against entropy that is inevitably lost for each individual. For human beings, this battle occurs continuously to preserve the function of each tissue. The battle is most heated in the organs that require the most energy: the brain, heart, and laboring uterus. Each uses energy to produce highly organized behavior.

During pregnancy the mother's body diverts a large amount of blood flow to the uterus. This increased blood flow carries energy that is used to create order in the developing fetus. Blood flow and energy are also required to create the regular powerful contractions required for human labor. Intriguingly, the human uterus displays a low level of order for the majority of pregnancy in that contractions are minimal, and activity at any one time, at different places in the uterus, is very similar. This picture changes at the time of labor in a dramatic way with an increase in contractility, energy consumption, and order, as the activity at different times is different, either relaxed or contracting.[2-4] This is quite different from the behavior of the heart. The heart and the uterus have evolved rather different ways of regulating order and contractile behavior. The heart is like an orchestra, playing continuously under the direction of a conductor. The uterus is like a soccer crowd, inactive most of the time but getting together for a song, producing a climax, and then dispersing to remain quiet until the next game.

Effective cardiac function requires the ability to rapidly change cardiac output to meet the varying needs of the corpus. When Olympic champion sprinter Usain Bolt leaves the blocks, his heart rate climbs from perhaps 50 beats per minute to well over 220, with a matching increase in cardiac output. The cardiac output of the ventricles is improved by the preceding contraction of the atria that primes the ventricular pump, increasing the ventricular volume and the efficiency of the contraction. The frequency of contractions is determined by

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a specialized group of pacemaker cells, called the sinoatrial node, within the atria.[5] The pacemaker cells receive input from systemic hormonal signals and from specific neuronal connections. The sinoatrial node generates a pacemaking signal that travels through the atria and causes atrial contraction (Figure 1). Importantly, this signal is delayed at the atrioventricular node; this delay is critical in optimal function of the heart as it allows the ventricles to relax and fill with blood before initiating ventricular contraction. Thus the heart requires a highly orchestrated contraction sequence to work optimally.

The behavior of the heart parallels the behavior of an orchestra under the guidance of a conductor. Each musician is capable of independent activity and rhythm, but if each played without knowledge of the others, there would be a low level of order. For the orchestra to function effectively the conductor invests energy to regulate the activity of individual musicians to achieve coherence and synchrony of behavior. Connectivity of individual musicians is provided by visual cues from the conductor and by visual and aural cues from other musicians. The actual output of any given musician is determined by the score and by that individual's ability. The operation of a conductor allows an individual to influence the behavior of a large number of components in a wide range of behaviors, changing tempo, mood, and volume.

The contrast between the heart and the human uterus is quite stark. The heart is equipped with specialized pacemaker and conducting systems while the human uterus has no innervation regulating contractility. Most smooth muscle cell organs or tissues demonstrate spontaneous contractility, especially in response to stretch, such as the bowel or bladder. The reproductive tract of mammals is rather different. A key aspect of the evolution of amniotes, of which primates are an order, is the ability to lay eggs on dry land that are impermeable to water yet permeable to oxygen. These eggs have a tough outer membrane that is formed inside the reproductive tract. To form this specialized egg the conceptus must be retained in the reproductive tract and contractions of the tract must be arrested. Mammals have taken this process further and the conceptus is retained with amniotic membranes within the reproductive tract while additional nutrition for fetal development is provided by the placenta. Throughout this period of fetal development the contractile activity of the reproductive tract must be suppressed, and in particular its response to stretch.

In the human being, contractility of the uterus is suppressed at the beginning of pregnancy to allow implantation. Hormonal signals suppress uterine contractility. The signals come from the maternal ovary that produces progesterone and the developing morula of fetal and trophoblastic cells that secretes chorionic gonadotrophin.[6] The progesterone and the chorionic gonadotrophin together suppress myometrial contractility, providing a "brake" on the uterus. The brake reduces uterine contractility for the vast majority of pregnancy. The brake mechanism includes keeping individual myocytes disconnected from one another. This is achieved by reducing gap junctions between individual myocytes.[7] Gap junctions are connections between individual cells that are formed by the protein connexin 43 (Cx43). These junctions allow the passage of small molecules, such as inositol trisphosphate, and facilitate electrical connection. The formation of Cx43 is inhibited by a transcription factor called zinc finger E-box binding homeobox (ZEB)1, which is stimulated by progesterone.[8] As pregnancy proceeds the production of progesterone gradually increases and the enlarging placenta becomes the major source of progesterone. The suppression of Cx43 expression ensures that even if a myometrial cell depolarizes, the electrical signal does not travel far and no increase in intrauterine pressure occurs.

Depolarization and contraction of uterine myocytes during pregnancy are also suppressed by other mechanisms. Progesterone has antiinflammatory effects and suppresses production of prostaglandins that stimulate myocyte depolarization.[9,10] Hormones produced by the placenta also act to reduce contractile pathways within myometrial cells.[11] Chorionic gonadotrophin acts on the myocytes through 7 transmembrane domain receptors that link to $G_{\alpha s}$ proteins that activate adenylate cyclase to stimulate production of the intracellular messenger cyclic AMP (cAMP). cAMP activates protein kinase A (PKA), which activates phosphatases that reduce myosin light chain kinase phosphorylation, decreasing the myosin-actin cross-bridge cycling that underlies muscle contraction. The cAMP-activated pathways also likely reduce formation of actin fibers that are required for the development of tension.[12,13] Chorionic gonadotrophin is not the only placental hormone that can affect these pathways to promote relaxation. The placenta also produces corticotrophin-releasing hormone (CRH), which increases exponentially through pregnancy[14] and promotes relaxation of myometrial myocytes through cAMP-dependent pathways.[15]

The likelihood of a myometrial cell depolarizing and contracting is related to the electrical potential difference it maintains across its plasma membrane. The membrane potential is created and maintained by an energetically driven process; sodium ions (Na^+)/potassium ions (K^+) adenosine triphosphatase moves K^+ into the cell and Na^+ ions out of the cell against their ionic gradients. K^+ then diffuse out of the cell down the concentration gradient to generate an electrochemical gradient, leaving the inside of the cell relatively negative compared to the outside. Intracellular calcium concentrations rise when a cell expresses an action potential, voltage-activated calcium channels open, and calcium ions (Ca^{2+}) move into the cell through the channels.[9] Rises of intracellular free Ca^{2+} then lead to active contraction through the activation of myosin light chain kinase, effective myosin-actin interaction, and production of tension.[16]

During pregnancy the relatively high K^+ gradient makes it difficult to depolarize the cell and thereby assists in maintaining quiescence.[17] Therefore, multiple pathways interact during pregnancy to prevent the development of uterine contractions and to promote