Periodic heart rate decelerations in premature infants

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A normal healthy heart beats at a variable rate with extraordinarily complex fluctuations across a wide range of time scales. Reduced complexity of heart rate has both clinical and dynamical significance - it may provide warning of impending illness, or clues about the dynamics of the heart's pacemaking system.

In work published in the April issue of *Experimental Biology and Medicine*, simple and interesting heart rate dynamics in premature human infants is reported - reversible transitions to large-amplitude periodic oscillations - and the appearance and disappearance of these periodic oscillations is described by a simple mathematical model, called a Hopf bifurcation. The work was carried out by Abigail Flower, as part of her PhD thesis in biophysics, working together with Randall Moorman and Douglas Lake at the University of Virginia, and John Delos, at the College of William and Mary.

Dr. Moorman explained the background of this research. "Two periodic cycles of heart rate have been known for over a century. One is respiratory sinus arrhythmia, the coupling of heart rate to breathing (our heart rate increases when we inhale and decreases when we exhale). Another cycle of heart rate is correlated with a cycle of blood pressure called Mayer waves. Abby's work is quite different".

Dr. Flower examines a different and previously uncharacterized heart rate cycle involving large decelerations of heart rates of infants in neonatal intensive care units (NICU's). A deceleration is a decrease in heart rate followed by a return to the base rate. She devised a heart rate deceleration detector using a pattern-matching algorithm inspired by wavelet theory, and applied it to a large clinical database. She found that large decelerations are common, and similar in shape among infants; they are usually isolated, but they sometimes appear in clusters. In rare cases a deceleration appears every fifteen seconds for epochs as long as two days. These long periodic sequences of decelerations occur spontaneously - they were not induced by controlled means - so they must be a normal or pathological mode of regular dynamics in the human cardiac pacemaking system near the time of birth.

This phenomenon is interesting from both clinical and dynamical perspectives. Periodic decelerations are dynamically interesting because they show that the control system of the heart rate can go into a previously uncharacterized oscillatory mode. Presently there is no physiological explanation for this phenomenon. Dr. Flower developed a mathematical theory, based upon Hopf bifurcation theory, which describes the abrupt beginnings and endings of clusters of periodic decelerations. A Hopf bifurcation is the most general theory describing how a system can change from stable to oscillatory. Such bifurcations occur for example in laser systems, oscillatory chemical reactions, predator-prey dynamics, and in the Hodgkin-Huxley model of the firing of nerve cells.

Dr. Moorman said "These observations and computations therefore provide a new point of contact with mathematical models of the heart rate control system. The group is presently investigating models of the control loops connecting heart rate with respiration and blood pressure to see whether the available models show such behavior."

Heart rate decelerations, whether periodic or not, are clinically interesting because clusters of decelerations in neonates are statistically correlated with impending sepsis, a severe bacterial infection of the bloodstream. Clusters of decelerations may begin to appear as many as 24 hours before any clinical signs of illness, so deceleration detection can provide early warning of bacterial infection in this vulnerable population.

"One of the pleasures of this kind of work is its interdisciplinary nature" said Dr. Delos. "As an undergraduate, Abby did a senior project with me in physics, studying the hydrogen atom. Then a few years ago she emailed me and asked if I would like to participate in this project, working with her and Randall, a cardiologist, and Doug, a statistician. Since then I've been like a kid in a candy store, absorbing all the knowledge I could, and working intensely - maybe I should say playing intensely - trying to make sense of the data. People have been using electronic methods to monitor the heart for over a century. Now Abby has developed new, continuous, noninvasive, purely electronic methods to monitor infants for infectious disease. It is a delightful result."

Related methods of clinical monitoring, using noninvasive electronic observations and advanced mathematical tools to monitor for infectious disease, are now in use in more than 1000 NICU beds, and a large randomized clinical trial is underway to test the effect on infants' outcomes.

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said "In this outstanding interdisciplinary study Dr. Flowers has reported interesting heart rate dynamics in premature human infants. This research team from the University of Virginia and the College of William and Mary has elegantly described reversible transitions to large-amplitude periodic oscillations by a mathematical model based upon Hopf bifurcation theory."

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