how masks the nuclear localization signal ensuring that mPer1 is retained in the cytoplasm (see the figure) (*11*). But in the absence of casein kinase Iε, mPer1 moves to the nucleus where it represses transcription of *per* genes (*11*). In another recent study, Keesler *et al.* (*12*) link phosphorylation of human PER to a decrease in its stability. The results so resemble those obtained with DBT in *Drosophila*—where binding of TIM periodically shields PER from phosphorylation, retention in the cytoplasm, and degradation (*9, 10*)—that we might expect casein kinase Iε to play a central role in timekeeping everywhere in the animal world (see the figure).

The most recent common ancestor of insects and mammals is thought to have lived more than 550 million years ago, and, not surprisingly, differences have been recognized in the unfolding clockworks of mammals and flies. In mammals, CRYs are transcriptional regulators of the clock but may not be the key players in photoreception that they are in the fly (*1, 3, 13–15*). The TIM and CLOCK proteins appear to be involved in mammalian and fly clocks, yet circadian cycling of the expression of both genes may be limited to *Drosophila*. Although TIM and PER heterodimerize in *Drosophila*, and CRY and PER associate in mammals, only direct interactions between TIM and CRY may be conserved among all animals (*1, 3, 13*). Yet easily overshadowing the differences is a compelling conservation of each of the known clock genes. With the cloning of *tau* the supply of mammalian clock mutants has been exhausted for the moment, but there is little doubt that many of the critical elements of animal clocks have been identified. A rudimentary clockworks, now known to us, is surely marking time throughout the animal kingdom.

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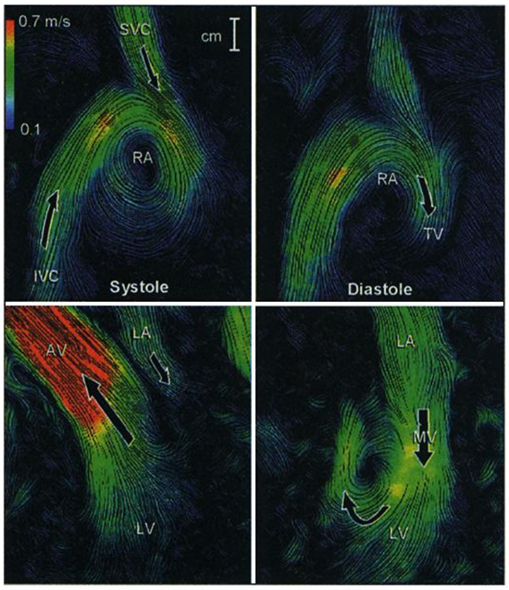
NOTA BENE: PHYSIOLOGY

Contortions of the Heart

The mammalian heart is an odd-looking organ, with four different-sized muscular chambers (two atria on top and two ventricles beneath) and a spectacular array of curving blood vessels that loop around each other in a contorted plumbing system. In a recent report, Kilner *et al.* (*1*) reveal that blood does not flow in a smooth, continuous stream but rather adopts asymmetric swirling patterns as it moves through the chambers of the heart. These whirlpools of blood may seem to be the antithesis of a well-heeled plumbing system, but the investigators argue that they are in fact beneficial, aiding the heart as its contractions increase during exercise.

The heartbeat has two principal phases: systole (contraction) and diastole (relaxation). In systole, the muscular walls of the ventricles contract, squeezing blood from the left ventricle into the aorta and from the right ventricle into the pulmonary artery. Meanwhile, the atrial walls relax and blood flows from the pulmonary veins into the left atrium and from the superior and inferior caval veins into the right atrium. In diastole, the walls of the ventricles relax (those of the atria contract), the tricuspid and mitral valves open, and blood flows from the right atrium into the right ventricle and from the left atrium into the left ventricle.

With the help of a noninvasive imaging technique, magnetic resonance phase-velocity mapping, Kilner *et al.* investigated changes in blood flow during the diastole and systole of successive heartbeats in healthy human volunteers at rest. They found that blood flow was asymmetric and that the streaming patterns that developed during diastole and systole were characteristic for each chamber. For example, as the ventricles contract, blood streaming into the expanding right atrium (RA) from the superior and inferior caval veins (SVC; IVC) does not collide but rather adopts a forward rotating, swirling motion that redirects flow toward the tricuspid valve (TV) (see figure, top left). The ventricles then relax and the blood moves leftward out of its clockwise rotation (away from the viewer) and through the tricuspid valve (top right). As the left ventricle (LV) contracts, blood is ejected into the aorta (bottom left) through the aortic valve (AV); then, as the left ventricle relaxes, blood streams into it from the left atrium through the mitral valve (MV), setting up a whirlpool below the valves' flexible leaflets (bottom right).



But why has the mammalian heart evolved such a sophisticated pattern of blood flow? Earlier work by Kilner's group using echocardiography to look at heart blood flow in exercising volunteers yields a possible answer. As the heart rate speeds up to at least double its normal rate during vigorous exercise, the contractions of the ventricles and atria alternate rapidly. The authors propose that asymmetries in blood flow conserve energy (by minimizing energy-consuming collisions between opposing streams of blood) and help to redirect blood movement, enabling its smooth passage to the next destination. They propose that, with exertion, the whirlpools of ventricular blood are hurtled in a slingshot motion along the sinuous curves of the blood vessels, minimizing disruption to the flow. Indirect evidence that the contorted curves of the vertebrate heart may be associated with dynamic efficiency comes from studying invertebrates such as the snail (not known for its virtuosity on the race track), which has a simple, linear two-chambered heart (with not a curve in sight). The researchers hope to test their hypothesis with a more advanced magnetic resonance system that should provide the rapid imaging necessary to follow the dynamics of heart blood flow in exercising volunteers.

—ORLA SMITH

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