High Heart Rate in Pregnancy Is Modulated by Augmented Expression of an Ion Channel, HCN-2, in Pacemaker Tissue

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It is established that in healthy human pregnancies, there are changes in cardiovascular status, including a significant (≈15%–20%) increase in resting heart rate. Although the underlying mechanisms are not well understood, it has been suggested that this pregnancy-related elevation in heart rate may be mediated by increased efferent activity of and/or sensitivity to sympathetic stimulation, concurrent with decreased sensitivity of the heart to parasympathetic activity. This sensitivity to sympathetic stimulation, concurrent with decreased may be mediated by increased efferent activity of and/or sen-

sivity to sympathetic stimulation, concurrent with decreased sensitivity of the heart to parasympathetic activity. This increased sympathetic stimulation may be a reflex response to the pregnancy-related decrease in total peripheral resistance and systemic vascular tone, consistent with the need to maintain arterial blood pressure. The elevation in resting heart rate is usually benign, although an increase in the incidence of ventricular arrhythmias may result. At present, both intrinsic (pacemaker activity or automaticity) and extrinsic (eg, adrenergic tone) reflex responses are being considered as proarhythmic factors; however, there is no consensus concerning the underlying ionic mechanisms.

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result of enhanced expression of these channels in the sarco-

lemna. No change in steady-state voltage dependence, that is, the range of membrane potentials for activation, could be detected. The Fiset Groups also identify the particular channel protein, HCN-2, that is responsible for the increase in macroscopic pacemaker current. Any contribution from increased adrenergic tone could be ruled out because all results were obtained by use of a single isolated myocyte preparation. The extensive multidisciplinary experimental design (in vitro heart recordings, single-cell electrophysiology, and molecular analyses) is used to advantage, and the data provide novel insights into a fundamental physiological mechanism: primary pacemaker activity.

Careful inspection of the data in this article gives rise to some interesting possibilities for additional experimental analyses, some of which may yield clinically relevant insights. First, from the Discussion, it is clear that during pregnancy $I_f$ increases in size and its onset kinetics (activation) are somewhat faster. In principle, this observation is important because the diastolic depolarization or pacemaker potential in the mouse sinoatrial node myocyte is of very short duration and the maximum diastolic potential is approximately 60 mV, a membrane potential that is very near the foot of the activation curve for $I_f$. In fact, the observed pregnancy-induced change in channel protein could be expected to express a macroscopic current with faster activation kinetics on the basis of the demonstration that HCN-2, as opposed to HCN-4, is selectively upregulated.

In situations when an important physiological response is generated by a net current change that is very small (in fact, in this case, it is near the resolution of the whole-cell patch-clamp method), it is useful to integrate and illustrate the experimental findings through the use of a mathematical model. This approach has been used to advantage in previous studies of cardiac pacemaker mechanisms in the rabbit and mouse, and these models continue to be improved as new experimental data sets are published. We have adapted the original Bondarenko et al model of the mouse ventricular action potential to simulate the action potential and pacemaker depolarization in mouse sinoatrial node myocyte. In this setting, the approximately 70% to 80% increase in $I_f$, that is reported by El Khoury et al results in an ≈10% to 12% increase in heart rate. When this increase in expression level (size) is combined with the observed ≈20% acceleration in the kinetic current onset, there is an additional, small increase in heart rate (Figure). At this stage of its development, our model is useful when applied for the purpose of illustrating the relative sizes and time courses of a number of so-called pacemaker currents,
but it has limitations. Our emphasis has been on defining the contribution of the deactivation of $I_{K_r}$ HERG; this current change is illustrated in the Figure (B).

It is known that both the activation and deactivation kinetics of $I_{f}$ are complex. Their detailed interpretation and the resulting kinetic descriptors can alter the apparent voltage dependence of activation and the onset time course. In addition, so-called channel mode switching needs to be accounted for, although El Khoury et al found no change in $I_{f}$ voltage dependence in myocytes from pregnant donors.11–13 The contribution of both T- and L-type calcium channels to the pacemaker potential or pacemaker depolarization is an important area that our model in its present form cannot accurately recapitulate.14

It is also known that in the mouse sinoatrial node, primary pacemaker activity (heart rate) is modulated by the expression of Na$^+$ channels. The resulting activation of inward current takes place very late in the diastolic depolarization and enhanced excitability.15 This current is included in our model of pacemaker activity in the adult mouse heart. $I_{Na}$ is changed (reduced) significantly as a result of the depolarization of the maximum diastolic potential caused by the increase in $I_{f}$.

The results of El Khoury et al should also be considered in the context of a different model or conceptual framework for the electrogenic mechanisms that produce pacemaker activity in the mammalian heart. This voltage clock–Ca$^{2+}$ clock hypothesis has been proposed by the Lakatta group,16 and evidence continues to be presented and advanced.17 In this paradigm, the direct and indirect effects of changes in intracellular Ca$^{2+}$ resulting from both transmembrane Ca$^{2+}$ fluxes and Ca$^{2+}$-induced Ca$^{2+}$ release from the sarcoplasmic reticulum, interact and sometimes combine to strongly modulate the net current that is responsible for the pacemaker depolarization. In this scheme, a change in $I_{f}$ would still be important in setting the overall heart rate, in part because the change in its amplitude contributes to the net current balance. We note that early descriptions of $I_{f}$ drew attention to the fact that it can be modulated by changes in intracellular Ca$^{2+}$;18 it is also well known that a Ca$^{2+}$-sensitive isoform of adenyl cyclase is expressed in cardiac pacemaker tissue.19 Any related Ca$^{2+}$-dependent increases in cAMP that targeted $I_{f}$ and in particular HCN-2 could also result in an augmented microscopic $I_{f}$ current. Finally, it may be important to recall that the ion flux that corresponds to $I_{f}$ is mainly Na$^+$ movement into the pacemaker myocyte. In principle, this could result in an increased level of intracellular Na$^+$, and if this change were relatively large, modulation of the Na$^+$/Ca$^{2+}$ exchange current and stimulation of the electrogenic Na$^+$/K pump could result. Integration of the $I_{f}$ records shown in the Figure suggests that only very small changes (>$1\text{mmol/L}$) would be expected, but this result may need to be reconsidered after details on the intracellular volume of distribution for Na$^+$ and Ca$^{2+}$ have been determined on the basis of new experimental work.

In summary, an important new component of the underlying causes for the well-known increase in heart rate resulting from pregnancy in healthy women has been identified.4 The $I_{f}$ current, which is 1 of 4 or 5 important contributors to the small net current change that gives rise to the pacemaker depolarization, is increased in size and its activation time course is accelerated. The physiology, molecular biology, and microanatomy details and principles that interact to contribute to primary cardiac pacemaker activity continue to present important opportunities and challenges for basic and clinician scientists.20

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Disclosures

None.
References


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