Phenotypic screening for heart rate variability in the mouse

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Gehrmann, Josef, Peter E. Hammer, Colin T. Maguire, Hiroko Wakimoto, John K. Triedman, and Charles I. Berul. Phenotypic screening for heart rate variability in the mouse. Am J Physiol Heart Circ Physiol 279:H733–H740, 2000.—We developed a technology for heart rate (HR) variability (HRV) analysis in the mouse for characterization of HR dynamics, modulated by vagal and sympathetic activity. The mouse is the principal animal model for studying biological processes. Mouse strains are now available harboring gene mutations providing fundamental insights into molecular mechanisms underlying cardiovascular diseases. Future progress depends on enhanced understanding of these fundamental mechanisms and the implementation of methods for the functional analysis of mouse cardiovascular physiology. By telemetric techniques, standard time and frequency-domain measures of HRV were computed with and without autonomic blockade, and baroreflex sensitivity testing was performed. HR modulation in the high-frequency component is predominantly mediated by the parasympathetic nervous system, whereas the low-frequency component is under the influence of both the parasympathetic and sympathetic systems. The presented technology and protocol allow for assessment of autonomic regulation of the murine HR. Phenotypic screening for HR regulation in mice will further enhance the value of the mouse as a model of heritable electrophysiological human disease.

Heart rate variability (HRV) and baroreflex sensitivity have been widely used to reflect autonomic activity in the heart (7, 8, 12). In humans, decreased HRV is an independent predictor of increased morbidity and mortality with various forms of heart disease including myocardial infarction (6, 21), coronary artery disease (32), congestive heart failure (9), chronic mitral regurgitation (35), and congenital heart disease (15). Recent progress in murine molecular genetics with gene targeting (35), and congenital heart disease (15). Recent progress in murine molecular genetics with gene targeting and/or transgenesis technology has made possible defined and predictable genetic modifications underlying cardiovascular function, which have created the need for methods to study cardiovascular physiology in genetically altered mice. There have been few basic reports of HRV analysis in smaller mammals such as rats and mice (10, 17, 22). The techniques used have varied, and normal ranges have not clearly been established for the mouse. Recent studies involving genetically altered mouse models relevant to the focus of this report include mice overexpressing atrial β1-adrenoreceptors (25), transgenic mice with cardiac specific Gₛₐ overexpression (37), GIRK4 knockout mice (39), mice with a disruption of the neuronal nitric oxide synthase (nNOS) gene (20) and others. These and future mouse models are of importance for evaluating the effects of specific gene mutations on cardiovascular phenotypes and basic electrophysiological mechanisms, but so far no uniform technique exists for phenotypic characterization of heart rate (HR) control by use of currently recommended standard analysis techniques (36). In this report, we present a technique and protocol developed in our laboratory for cardiovascular phenotyping of HR regulation in mice. The systematic validation of this screening protocol and establishment of normative HRV data can serve as a basis for future studies assessing the role of autonomic nervous system fluctuations in genetically altered mouse strains.

METHODS

Study Animals

Twenty-four inbred male mice from the same genetic background (C57BL/6J) were studied. The mean age was 12 wk; the average weight was 27 ± 3 g. Mice were housed in cages at 24°C in a facility with 12:12-h light-dark cycles, in full compliance with the Public Health Service animal welfare policy and the American Association for the Accreditation of Laboratory Animal Care. An animal research protocol was approved by the Harvard Medical School and Children’s Hospital Animal Care and Use Committee.

Animal Preparation and Surgery

For ambulatory long-term electrocardiogram (ECG) analysis in the conscious state, analogous to Holter monitoring in humans, telemetry devices (model TA10-F20; DataSciences International, St. Paul, MN) were implanted with the use of a sterile technique. Mice were anesthetized with intraperito-

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neal ketamine hydrochloride and pentobarbital (0.033 mg/g each), and a midline incision was made on the back along the spine. An implantable 3.5-g wireless radiofrequency transmitter was inserted into a subcutaneous tissue pocket, and the leads were directed caudally. The cathodal lead was looped forward to an area overlying the scapula and anchored in place with a permanent suture. Another incision was made near the heart apex, through which a trochar with a sleeve was tunneled subcutaneously to the transmitter implant site. The trochar was removed, and the anodal lead was brought through the sleeve to rest near the heart apex. After removal of the sleeve, skin incisions were sutured. A warming light was used to maintain body temperature between 34 and 37°C.

Study Protocol

Experiments were initiated 4–6 days after recovery from surgical instrumentation. All recordings were performed in the conscious state between 9:00 AM and 3:00 PM in a constant environment.

Protocol 1: baseline HR dynamics and autonomic blockade. After a 15-min control period for HR stabilization, the baseline ECG was recorded for 30–60 min. To study the frequency-specific contributions of the principal cardiovascular control systems, they were selectively blocked by means of specific pharmacological agents: atropine (0.5 mg/kg ip) for parasympathetic blockade, propranolol (1 mg/kg ip) for sympathetic blockade, and atropine (0.5 mg/kg ip) plus propranolol (1 mg/kg ip) for combined autonomic blockade. After a 5-to 10-min equilibration phase after drug administration to allow for HR stabilization, ECG recordings were repeated in the same fashion as in the baseline state. The pharmacological experiments were performed on different days to prevent interference among drugs. The dosages of atropine, propranolol, and phenylephrine were similar to those used in mice by other groups (20, 37), although the completeness of autonomic blockade was not tested with agonist challenge. It was determined in pilot studies that changes in HR occurred within 5 min of intraperitoneal drug injection, after which a steady-state HR was observed.

Protocol 2: baroreflex sensitivity testing. To test for a baroreflex-mediated cardioinhibitory response, mice underwent pressure challenge with phenylephrine hydrochloride (3 mg/kg ip, Neo-Synephrine; Winthrop Laboratories) after β-adrenergic blockade with propranolol (1 mg/kg ip). The pressor challenge was performed after β-adrenergic blockade so that any observed change in HR mean or variability would be due to activation of the inhibitory limb of the baroreflex and not the result of sympathetic withdrawal. After β-adrenergic blockade, phenylephrine was administered, and the ambulatory ECG recording was repeated 1 min later, when visually apparent stable HR conditions were present. Blood pressure was not monitored during the experiments.

Data Acquisition and Analysis

ECG signals were recorded with the use of a telemetry receiver (DataSciences International) and an analog-to-digital conversion data acquisition system (MacLab System, AD Instruments, Milford, MA). The analog signal from the receiver was digitized with 12-bit precision at a sampling rate of 2 kHz. ECG interval (P-R, QRS, Q-T) measurements and calculations (QTc) were performed independently by two experienced investigators in standard fashion. The Q-T intervals were rate corrected with the use of the formula proposed by Mitchell et al. (26) for use in mice. All digital signal processing was performed with the use of customized software written in the MATLAB (The Math Works, Natick, MA) programming language. A 120-s segment of the digitized ECG signal was digitally band-pass filtered (4–140 Hz), and the event was detected with the use of a threshold-lockout algorithm. For standardization, only stable segments of sinus rhythm were used for analysis. A graphic interface of the analysis program allowed visual reviewing and manual editing of erroneously detected events and aberrant ECG complexes, such as premature ventricular beats, electrical noise, or other errant ECG signals, and their adjacent R-R intervals were excluded from analysis. The sequence of interevent times was linearly interpolated to a 20-Hz time series of beat intervals. HRV was quantified with the use of standard time- and frequency-domain techniques on the basis of recent recommendations (36), and parameters are listed in Table 1. Adjacent 120-s signal epochs recorded during a given set of test conditions exhibit very similar HRV metrics, obviating the need for joint time-frequency methods such as the Wigner-Ville distribution, commonly applied to nonstationary signals (25).

Time-Domain Measures

In the time domain, the mean R-R interval (RR mean), median R-R interval (RRmedian), standard deviation of all normal R-R intervals (SDNN), standard deviation of averages of normal R-R intervals (SDANN), and the square root of mean of squared differences between adjacent normal R-R intervals (RMSSD) were calculated directly from the sequence of interevent times. The mean HR (HRmean) was calculated as the mean of the sequence of the reciprocals of the interevent times. Furthermore, as HR changes per se occurring after administration of atropine and propranolol may affect HRV, an additional parameter was calculated: the coefficient of variance (CV), defined as the standard deviation of R-R intervals/RR mean.

![Table 1. Definitions of time- and frequency-domain measures of HRV](http://ajpheart.physiology.org/)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Frequency Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time domain measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRmean, ms</td>
<td>Mean of all R-R intervals</td>
<td></td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>SD of all normal R-R intervals</td>
<td></td>
</tr>
<tr>
<td>SDANN, ms</td>
<td>SD of averages of normal R-R</td>
<td></td>
</tr>
<tr>
<td>CV, %</td>
<td>SDNN/RRmean × 100</td>
<td></td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>Square root of mean of sum of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>squares of differences between</td>
<td></td>
</tr>
<tr>
<td></td>
<td>adjacent normal R-R intervals</td>
<td></td>
</tr>
<tr>
<td><strong>Frequency domain measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP, ms/seg</td>
<td>Variance of normal R-R</td>
<td>≤4 Hz</td>
</tr>
<tr>
<td></td>
<td>intervals over temporal segment</td>
<td></td>
</tr>
<tr>
<td>LF, ms/seg</td>
<td>Power in LF range</td>
<td>0.4–1.5 Hz</td>
</tr>
<tr>
<td>LF norm, nu</td>
<td>LF power in normalized units</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[LF/TP – VLF] × 100</td>
<td></td>
</tr>
<tr>
<td>HF, ms/seg</td>
<td>Power in HF range</td>
<td>1.5–4 Hz</td>
</tr>
<tr>
<td>HF norm, nu</td>
<td>HF power in normalized units</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[HF/TP – VLF] × 100</td>
<td></td>
</tr>
<tr>
<td>LF/HF</td>
<td>Ratio of LF to HF (ms/m^2)</td>
<td></td>
</tr>
</tbody>
</table>

HRV, heart rate variability; SD, standard deviation; CV, coefficient of variance; TP, total power; LF, low frequency; HF, high frequency; VLF, very low frequency; nu, normalized units.
Effects of autonomic blockade on time-domain measures of HRV

Table 3. Effects of autonomic blockade on time-domain measures of HRV

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>CV, %</th>
<th>SDNN</th>
<th>SDANN</th>
<th>RMSSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n = 24)</td>
<td>83 ± 4</td>
<td>3.9 ± 1.2</td>
<td>3.3 ± 1.0</td>
<td>1.3 ± 0.7</td>
<td>6.1 ± 1.4</td>
</tr>
<tr>
<td>Atropine (n = 10)</td>
<td>86 ± 5(NS)</td>
<td>1.5 ± 0.5†</td>
<td>1.3 ± 0.5‡</td>
<td>0.65 ± 0.25*</td>
<td>1.2 ± 0.2‡</td>
</tr>
<tr>
<td>Propranolol (n = 10)</td>
<td>120 ± 9§</td>
<td>7.6 ± 1.9‡</td>
<td>8.6 ± 2.3†</td>
<td>4.1 ± 2.0*</td>
<td>9.1 ± 3.0‡</td>
</tr>
<tr>
<td>Combined (n = 10)</td>
<td>109 ± 11‡</td>
<td>1.8 ± 0.7*</td>
<td>1.5 ± 0.8*</td>
<td>0.75 ± 0.36*</td>
<td>2.7 ± 1.8*</td>
</tr>
</tbody>
</table>

All values are means ± SD, with intervals measured in ms unless otherwise indicated. *P < 0.05 and †P < 0.01 vs. baseline.
which reflexively increases parasympathetic activity, was followed by an increase in mean R-R interval (140.6 ± 12 ms, \( P < 0.001 \)) and an increase in indexes of HRV: SDNN (110.3 ± 6.4 ms, \( P < 0.001 \)), SDANN (12.6 ± 2 ms, \( P < 0.05 \)), RMSSD (130.7 ± 12 ms, \( P < 0.001 \)), total power (12149 ± 844 ms\(^2\), \( P < 0.001 \)), LF (1601 ± 279 ms\(^2\), \( P < 0.05 \)), and HF (1324 ± 126 ms\(^2\), \( P < 0.01 \)).

### DISCUSSION

This report describes the development of a technique for murine HRV analysis and the application to the study of normal C57BL/6J mice. The presented ECG measurements and their response to pharmacological autonomic influences (see Table 2) may serve as a useful standard for future studies. In vivo ECG parameters have been characterized in anesthetized C57BL/6J mice (5), but similar data are not yet available for conscious mice. Indexes of HRV in the time domain and frequency domain were analyzed under physiological baseline conditions and under pharmacological sympathetic, parasympathetic, and total autonomic blockade. This study systematically examined contributions of the time and frequency components of physiological HRV in mice by use of currently recommended standard analysis techniques. We developed software, described the technical requirements to measure HRV in the mouse, designed a protocol for autonomic testing, and presented normative data.

### Table 4. Effects of autonomic blockade and baroreflex modulation on frequency-domain measures of HRV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TP</th>
<th>LF</th>
<th>HF</th>
<th>nLF</th>
<th>nHF</th>
<th>LF/HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>102 ±22</td>
<td>15 ±5</td>
<td>13 ±3</td>
<td>0.51 ±0.1</td>
<td>0.49 ±0.1</td>
<td>1.4 ±0.3</td>
</tr>
<tr>
<td>Atropine</td>
<td>21 ±6†</td>
<td>0.3 ±0.1*</td>
<td>0.8 ±0.1†</td>
<td>0.3 ±0.1*</td>
<td>0.7 ±0.1*</td>
<td>0.5 ±0.1*</td>
</tr>
<tr>
<td>Propranolol</td>
<td>740 ±116‡</td>
<td>169 ±52‡</td>
<td>50 ±11‡</td>
<td>0.73 ±0.1†</td>
<td>0.27 ±0.1†</td>
<td>3.1 ±0.3‡</td>
</tr>
<tr>
<td>Combined</td>
<td>18 ±2.9†</td>
<td>0.8 ±0.3‡</td>
<td>3.8 ±1.4†</td>
<td>0.22 ±0.1†</td>
<td>0.78 ±0.13</td>
<td>0.3 ±0.1†</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>2,889 ±960‡</td>
<td>770 ±331‡</td>
<td>374 ±137†</td>
<td>0.63 ±0.16</td>
<td>0.37 ±0.16</td>
<td>2.2 ±1.3</td>
</tr>
</tbody>
</table>

All values are means ± SD, with intervals measured in ms\(^2\). LF, low-frequency component; HF, high-frequency component; nLF, normalized LF; nHF, normalized HF. *\( P < 0.05 \), †\( P < 0.01 \), and ‡\( P < 0.001 \) vs. baseline control. Phenylephrine group compared with propranolol as control group.
HRV is a Gauge of Autonomic Modulation

This study demonstrates that quantitative characterization of autonomic nervous system modulation of beat-to-beat HR regulation is technically feasible in the conscious mouse. In addition, norms are established for physiological baseline conditions and in response to pharmacological sympathetic and parasympathetic agonists/antagonists on HR, ECG intervals, and HRV parameters. The power spectrum of HRV in the mouse resembled those derived from humans, dogs, and rats. Two major spectral components were observed. Alterations in the LF/HF ratio with pharmacological blockade suggest that the control of HRV over these two spectral regimes is similar in mice to humans and larger animals, with the LF component (0.4–1.5 Hz) regulated by both sympathetic and vagal inputs and the HF component (1.5–4 Hz) predominantly parasympathetically mediated.

Sympathetic Tone Predominates in Mice

A resting mean HR [724 beats/min (bpm)] was demonstrated to be similar (slightly higher) to other groups (650–714 bpm) (11, 39). Baseline HR in normal conscious mice is most likely determined by enhanced sympathetic activity, because after combined sympathetic and parasympathetic blockade, the resultant “intrinsic HR” (19) was significantly reduced. In contrast to other reports (11), but in agreement with Wickman et al. (39) and Mansier et al. (25), an increase in HR in response to β-adrenergic agonists (e.g., isoproterenol and epinephrine) or vagal antagonists (atropine) was not observed in conscious, freely moving mice. The lack of HR increase in conscious mice after parasympathetic blockade or sympathetic stimulation further supports the supposition of predominant sympathetic activity or low vagal tone under physiological conditions.

Frequency Components Represent Distinct Autonomic Inputs

Mean HR is subject to many diverse control mechanisms and is not a reliable marker of autonomic activity and tone. Because the frequency components of the HR spectra are affected by both the sympathetic and parasympathetic nervous systems, HRV analysis allows quantification of the respective contributions. We observed two major spectral components. Diminished modulation of vagal activity after administration of the parasympathetic antagonist atropine was established by a decrease in time- and frequency-domain measures of HRV. In the frequency domain, both the HF and LF components of the HRV spectrum were significantly reduced. Whereas HF power is widely accepted as a marker of cardiac parasympathetic control (2), the underlying control of the LF power has yet to be fully elucidated. In agreement with studies in humans (1, 4, 33, 40) and dogs (16), our data suggest that the LF component of the murine HR power spectrum receives both sympathetic and parasympathetic contributions. The finding that atropine significantly reduced LF power is consistent with a large parasympathetic component to LF power, although it may somewhat reflect the selection of 1.5 Hz as the LF/HF division. This phenomenon is further evident after administration of the β-adrenergic receptor antagonist propranolol. In addition to its pronounced bradycardic effect, all measures of HRV in the time and frequency domain increased significantly, including the LF component. If the LF power has a large sympathetic component, one would predict that β-adrenergic blockade should abolish this sympathetic component. If LF control is necessary to counteract disturbances and maintain blood pressure, then parasympathetic LF HR control could fill in, resulting in no observable change in LF power. On the contrary, unopposed (withdrawal of sympathetic influence) parasympathetic influence led to enhanced HRV in both frequency components. Thus our results are consistent with findings in humans (13, 30, 31) contending that the LF component is not a reliable measure of sympathetic activity. Combined autonomic blockade resulted in marked reductions in all HRV parameters, as expected.

Baroreflex Activation Increases HRV

It is known that moderate physical exercise increases LF components of HRV, whereas maximal physical exercise induces a marked reduction in the LF
component and total power (23, 28, 30). We demonstrated that saturated sympathetic tone or abolition of autonomic tone inhibits the modulation by other physiological control mechanisms. During baroreflex activation, administration of the pressor agent phenylephrine induced a decrease in mean HR and an increase in HRV, representing a typical baroreflex-mediated rise in parasympathetic tone. Although blood pressure was not measured, these findings are consistent with previous research in larger mammals, including humans (14, 29, 34, 38). Spectral analysis of HRV was shown to provide distinct measures of vagal and sympathetic modulation of the heart. HF power represents the vagal control to the heart, modulated by breathing (2, 30, 33), whereas LF power has contributions from both vagal and sympathetic inputs (2, 3, 24, 27). Akselrod et al. (2) assessed beat-to-beat HR control in dogs and showed the same frequency-specific contributions to the HR power spectrum, and later these findings were confirmed in humans (30). Thus various lines of evidence are provided that the mechanism of short-term cardiovascular control in mice, as measured by means of quantitative analysis of HRV, approximates that found in other species.

**HRV in Genetically Modified Mice**

HRV assessment allows for the quantitative dissection of complex cardiac signaling pathways and has been studied recently in genetically engineered mice, including models with enhanced β-adrenergic receptor signaling (25, 37) and deficient ion-channel acetylcholine-modulated potassium current (I_{KACN}) function by disruption of GIRK4 gene (39) and nNOS-deficient (nNOS−/−) mice (20). HRV analysis revealed abnormalities not apparent when probing HR alone and emphasizes the need for a valid tool to study the impact of the autonomic nervous system on HR regulation in the mouse. These studies utilized different nomenclature, data acquisition and analyses, study protocols, and pharmacological regimens, and there is a lack of standardized measurements, making appropriate comparisons between studies difficult. Also, experimental conditions are not uniform, and experiments are performed with the use of different surgical approaches (e.g., transmitter implant in the peritoneal cavity vs. the back). Furthermore, data acquisition was done within different time intervals after recovery from surgical instrumentation. In studies using the abdominal approach, mean HR was strikingly lower (500 bpm) (25) compared with those implanting the transmitter on the back (650 bpm, Ref. 39; 750 bpm, own data). Increase in vagal tone by phase 1 of the Valsalva effect (decreased venous return), with the transmitter located in the abdomen, might be one confounding factor, although during phase 2 there may be hypotension and potentially a reflex sinus tachycardia. Diaphragmatic dysfunction may additionally impair the breathing pattern and hence artificially alter respiration as a basic constituent of neurocardiovascular control.

Other factors potentially influencing the accuracy and comparability of the measurements include performance of studies at different phases of the circadian rhythm and different pharmacological study protocols. The methodological obstacles potentially impeding appropriate comparison of recently published studies is briefly exemplified. There is considerable uncertainty as to when to pick the correct “study time” in terms of interfering variables such as level of anesthesia, surgery-related stress, or implantation-related factors. Some studies emphasized that initiation of experiments should occur, at the earliest, 1 wk after instrumentation (18), whereas others stated it was safe to begin as early as 12 h after recovery from anesthesia (11); furthermore, others performed their experiments on day 4 (39) or on days 3 to 6 (25, 37) after instrumentation. To assess these potentially confounding variables and test for reproducibility of parameters, we studied HR and heart variability indexes systematically on a daily basis on 6 consecutive days, starting from day 1 after surgery/anesthesia. We found that procedure-related factors obviously do not constitute significant stress for mice 24 h after the procedure, as there was no substantial difference in measures between different days (data not shown).

In addition to providing a description of HRV analysis in mice, this report may help to identify the uncertainty evolving from heterogeneity of current study design, to recognize an area for future research, and to encourage standardization of methods to make HRV analysis a more powerful tool in murine cardiovascular research.

**Study Limitations**

Because we analyzed only on one mouse strain, we did not examine whether significant interstrain variability in these parameters exists. In a small cohort of a different strain (FVB/N) of mice, no significant differences in measures of HRV were apparent (data not shown). In our interpretation of the results of pharmacological blockade, we assumed complete blockade effect of autonomic blockade, although we did not specifically test for the completeness of the blockade. The dosages used are similar to those used by others to achieve complete autonomic blockade, but this was not reconfirmed in the present studies. Scaling of frequency bands by the approximate ratio of mouse-to-human resting HR is not fully justified. Although neural conduction path lengths might be shorter in the mouse by an ~10-fold ratio, membrane kinetics, which probably dominate autonomic response times, may not substantially differ between humans and mice. Although we documented a stable HR, the blood pressure after phenylephrine injection may be nonstationary, potentially affecting the accuracy of HRV baroreflex assessment. Our chronic mouse preparation precluded making invasive blood pressure measurements in the conscious state. It has been shown by others (11) that administration of the α-adrenergic receptor agonist phenylephrine resulted in immediate hypertension...
and simultaneous reflex bradycardia in mice. All of the recordings were obtained during daytime hours, and because mice are nocturnal animals, the most active phase of the circadian cycle was not assessed. During daytime recordings, however, appropriate grooming behaviors and physical activity were documented. Future experiments might employ timed nighttime recordings to delineate circadian differences. Despite the value of genetic manipulation potential, the mouse may not serve as the most relevant model for directly extrapolating to human clinical disease pathophysiology or electrophysiological risk stratification. Species variability in HR and intervals, chamber volumes and mass, potential reentrant circuit substrates, gap junction isoforms and distribution, and ion-channel diversity may limit the power of mouse models of human electrophysiology.

Conclusions and Implications

We demonstrate the feasibility of using quantitative analysis of beat-to-beat fluctuations in murine HR to assess parasympathetic and sympathetic influences on HR modulation. The responses to pharmacological manipulation are quantifiable, reproducible, and qualitatively similar to those in larger mammals including humans. Thus the murine model may be valid for the study of HR regulation in human cardiovascular disease. The application of standardized HRV analysis technique and study protocols to the mouse should allow appropriate comparisons among future studies addressing the role of the autonomic nervous system in HR regulation and extend the phenotypic characterization of the murine heart. For instance, such an approach would allow for systematic assessment of the impact of autonomic modulating activity on disease entities including mouse models of familial cardiomyopathies, the long QT syndromes, and familial atrial fibrillation. The method may also be useful in the investigation of cardiac-signal transduction pathways involving individual receptors, the G-protein ion-channel system, or endothelial and nNOS-mediated pathways. With the availability of well-defined experimental models of sympato-vagal interactions on different substrates and their contributions to alterations in HR dynamics, HRV analysis may be able to define the potential contribution of the autonomic nervous system to electrical stability/instability in the context of an underlying arrhythmogenic substrate.

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