Influence of genetic background on ex vivo and in vivo cardiac function in several commonly used inbred mouse strains

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Though not as widely used, other inbred strains have found niches in biomedical research due to ease of genetic manipulation or differing propensities for developing specific pathologies. For instance, FVB/N mice are commonly used in conventional transgenesis (51), and 129 substrains have been used almost exclusively for the isolation of embryonic stem (ES) cells used for gene targeting (41, 56). Alternatively, other inbred strains have found use as disease models due to naturally occurring mutations in genes linked to human disease (5, 22, 38, 43). Even in the absence of engineered or known naturally occurring mutations, different inbred mouse strains can vary drastically in their susceptibility to clinically relevant diseases. Previous reports have taken advantage of this naturally occurring variation in susceptibility to a particular disease to identify quantitative trait loci (QTL) that modify disease pathogenesis (2, 6, 13, 48, 49).

Cardiovascular disease is the single leading cause of death in the United States, affecting ~1 in 3 Americans and causing >800,000 deaths in 2006 (27). To effectively investigate the pathological processes associated with cardiovascular disease and devise new therapeutic strategies, the cardiovascular field has embraced genetically modified inbred mouse strains as tools to help understand the fundamental physiological processes governing function in the normal and diseased heart. A survey of the Jackson Labs website shows that they maintain >225 genetically modified mouse lines used for cardiovascular research derived from inbred mouse strains. C57BL/6 is the most common genetic background (Fig. 1A). However, mutations are also maintained on other common inbred backgrounds as well. The majority of these mice were created using ES cells derived from a substrain of the 129 inbred strain, then often backcrossed and maintained on a C57BL/6 or mixed C57BL/6 × 129 background (Fig. 1B).

Several studies have reported strain-dependent differences in cardiovascular function between inbred mouse strains by various in vitro and in vivo methods (4, 7, 23, 37, 40, 47). The majority of these strain-dependent differences in cardiac physiology have been carried out on a small subset of inbred strains in the absence of disease-related injury/stress. Previous reports have also demonstrated the potent effects of genetic background on modifying the cardiac phenotype of genetically modified mice (20, 21, 50). For instance, two distinct transgenic lines expressing hypertrophic cardiomyopathy-linked mutant tropomyosin E180G showed drastically different phenotypes, one displaying relatively mild diastolic dysfunction (29) and the other developing overt hypertrophic cardiomyopathy and heart failure (36). Excluding possible differences in animal care and housing, the main difference between these transgenic mice is their genetic background; one mouse was created on the FVB/N background, the other on the C57BL/6 background. Although the precise mechanism underlying this
Identification of strain-dependent quantitative hemodynamic traits may form the foundation of future studies aimed at understanding the marked physiological divergence reported for naturally varying cardiac function. Collectively, this study highlights the genetic divergence between strains. Secondly, the fixed genetic background of inbred mouse strains serves as a potential substrate for the identification of reproducible quantitative traits that differ between inbred strains. Eight common inbred mouse strains were used, six of which are listed on Jackson Laboratory’s list of the most popular inbred mouse strains (http://jaxmice.jax.org/findmice/popular.html). The techniques used to measure cardiac function for this study are the Langendorff perfused isolated heart preparation and in vivo cardiac hemodynamic function as measured by catheter-based conductance micromanometry. The Langendorff preparation is a well-established technique for assessing function of a heart performing isovolumic contractions at a controlled end diastolic pressure (26, 45). In vivo hemodynamic analysis provides pressure and volume measurements of hearts in the intact animal where physiological loading and autonomic innervation remain intact (33). Additionally, we studied strain-dependent differences in cardiac function following physiologically relevant stress. Specifically, isolated hearts were subjected to global ischemia and reperfusion. Mice instrumented for in vivo hemodynamic measurements were subjected to β-adrenergic blockade and an acute hypoxic challenge. Strain-dependent differences in cardiac function were found both at baseline and following physiologically relevant stress. Collectively, this study highlights strain-dependent differences between inbred mice that provide insight into the marked physiological divergence reported for cardiac transgenic mice generated on differing backgrounds. The identification of strain-dependent quantitative hemodynamic traits may form the foundation of future studies aimed at identifying QTL that modify cardiac function.

**Materials and Methods**

**Mouse strains.** All mouse strains analyzed in this study were acquired from Jackson labs. Mouse strains and stock numbers were as follows: C57BL/6J (000664), FVB/NJ (001800), DBA/2J (000671), BALB/cJ (000651), C3H/HeJ (000659), 129X1/SvJ (000691), C57BL/10SnJ (000660), and 129S1/SvImJ (002448). Male mice ages 4–6 mo were used in this study. The procedures used in this study are in agreement with the guidelines of the University of Minnesota and approved by the University of Minnesota Committee on the Use and Care of Animals.

**Isolated heart model and ischemia/reperfusion.** Ex vivo measurements of left ventricular function were carried out as previously described (10). Mice were injected with 300 units sodium heparin and anesthetized with pentobarbital sodium. The heart and lungs were then removed following thoracotomy and placed immediately in ice-cold Hanks’ buffered salt solution without calcium and magnesium. The lungs and thymus were trimmed away to expose the aorta, which was then cannulated. Hearts were then perfused at a constant pressure of 80 mmHg with modified Krebs-Henseleit buffer (118 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO4, 1.2 mM KH2PO4, 10 mM glucose, 25 mM NaHCO3, 2.5 mM CaCl2, 0.5 mM EDTA) warmed to 37°C and brought to pH = 7.4 by bubbling with 95% O2, 5% CO2. Hearts were paced at 7 Hz, and changes in left ventricular pressure were monitored by insertion of a water-filled balloon with an in-line pressure transducer into the left ventricle. Within the left ventricle, the balloon was inflated to an end diastolic pressure of 3–8 mmHg. Following 10–15 min of stabilization time, hearts were subjected to global no-flow ischemia for 20 min. Hearts were not paced during ischemia. Hearts were then reperfused for 60 min, and pacing was reinitiated at 8 min following the end of ischemia. Data were collected at a sampling rate of 400 Hz and analyzed using Chart 6 software (ADInstruments).

**In vivo conductance micromanometry.** Measurements of real-time in vivo cardiovascular hemodynamics were obtained using conductance micromanometry as previously described (34, 35, 53, 54). Mice were anesthetized and ventilated via a tracheal cannulation and ventilated via a pressure controlled ventilator with 2% isoflurane at a peak inspiratory pressure of 15 cm H2O and a respiratory rate of 60 breaths/min. With aid of a dissecting microscope, the heart was exposed via a thoracotomy. A 1.4 French Millar pressure-volume catheter (PVR-1045; Millar Instruments, Houston, TX) was then placed into the left ventricular chamber via an apical stab. Left ventricular pressure and volume measurements were collected at a sampling rate of 1 kHz. Data were analyzed with Ponemah software, P3 Plus (DSI International, St. Paul, MN). Transient inferior vena cava (IVC) occlusions were performed to obtain the end systolic and end diastolic pressure-volume relationships. IVC occlusions were performed at baseline and at the end of the esmolol infusion. After baseline hemodynamics (ventilated with isoflurane and O2) were obtained, mice received a continuous infusion of esmolol (188 μg·kg−1·min−1) for 5 min to block all adrenergic responsiveness. After esmolol infusion, mice were infused with dobutamine (42 μg·kg−1·min−1) to enable recovery of baseline function (Supplemental Table S1). After dobutamine infusion cardiac function was allowed to return to baseline levels. Mice were then exposed to an acute...
hypoxic challenge (7% O₂ balanced in nitrogen) and monitored until cardiac pump failure. End-point cardiac decompensation was defined as the point when peak left ventricular systolic pressure (LVSP) dropped <60 mmHg. At this point mice were recovered with 100% O₂ to obtain instrument calibration.

Statistics. All results are expressed as means ± SE. Significance was established as P < 0.05. All multivariable assays were assessed using a one-way analysis of variance with Dunnett’s post hoc test comparing all groups to C57BL/6J. Survival after the in vivo acute hypoxic challenge was assessed by the Fisher exact test.

RESULTS

Baseline ex vivo cardiac function. To quantify strain-specific differences in ex vivo cardiac function, hearts from eight inbred mouse strains were isolated and perfused retrograde through the aorta. To simplify data analysis, all inbred strains were compared with the C57BL/6J strain. In general, baseline ex vivo whole heart function of the inbred strains tested was similar to C57BL/6J (Table 1). One notable exception was FVB/NJ, which showed significantly higher left ventricular developed pressure (LVDP) than C57BL/6J (Table 1, P < 0.05). Additionally, FVB/NJ mice showed significantly higher coronary flow rates than C57BL/6J mice at baseline (Supplemental Table S2, P < 0.05). There were no significant differences between C57BL/6J and other inbred strains as measured by the maximum derivative of left ventricular pressure, another measure of systolic function (Table 1). There were no significant differences in diastolic function at baseline between C57BL/6J and other inbred strains as measured by the minimum derivative of left ventricular pressure and the rate constant tau (Table 1). A previous report showed that BALB/c mice have highly variable contractile function in the isolated working heart preparation associated interanimal variability in α-skeletal actin expression (19). However, in our hands the variance of LVDP for BALB/cJ mice was statistically similar to all other strains by Bartlett’s analysis of variance (data not shown).

Effects of ischemia and reperfusion on ex vivo cardiac function. To study strain-dependent differences in the response to a physiologically relevant stress, isolated hearts were subjected to 20 min of global ischemia followed by 60 min of reperfusion (Figs. 2, 3). During reperfusion, three strains showed reduced cardiac function compared with C57BL/6J: 129X1/SvJ, 129S1/SvImJ, and C57BL/10SnJ. Each of these strains showed reduced systolic function during early (20 min) reperfusion compared with C57BL/6J as shown by reduced LVDP and % recovery of baseline LVDP (Figs. 2 and 3A, P < 0.05). Additionally, these strains showed reduced diastolic function compared with C57BL/6J as shown by increased left ventricular end-diastolic pressure (LVEDP) (Figs. 2 and 3A, P < 0.05). During late (60 min) reperfusion, 129S1/SvImJ showed reduced systolic function compared with C57BL/6J as shown by reduced LVDP and recovery of baseline LVDP (Figs. 2 and 3B, P < 0.05). 129X1/SvJ showed reduced diastolic function compared with C57BL/6J during late reperfusion as shown by increased LVEDP (Figs. 2 and 3B, P < 0.05). Additionally, the duration of sustained ventricular tachycardia (VTach) during reperfusion was also recorded as a measure of ischemic injury (17). C57BL/6J rarely entered into VTach during reperfusion. However, 129X1/SvJ and C57BL/10SnJ entered into VTach for >20 min during reperfusion (Fig. 3C, P < 0.05 compared with C57BL/6J). Because VTach generally occurs early in reperfusion, this finding suggests that depressed systolic function of 129X1/SvJ and C57BL/10SnJ during early reperfusion is caused by increased heart rate. This is supported by the finding that systolic function of 129X1/SvJ and C57BL/10SnJ was similar to C57BL/6J once VTach had resolved during late reperfusion. 129S1/SvImJ rarely entered into VTach, suggesting that reduced systolic function in these mice was due to reduced contractility following ischemic injury. In addition to 129X1/SvJ, C57BL/10SnJ, and 129S1/SvImJ, several other strains showed more subtle differences in cardiac function compared with C57BL/6J during ex vivo ischemia and reperfusion. These data can be found in Supplemental Fig. S1.

Additionally, to demonstrate the stability and reproducibility of these findings, Supplemental Fig. S2 shows the results of an initial study carried out with cohorts of FVB/NJ, C3H/HeJ, and BALB/cJ mice. As above, isolated hearts from these mice were subjected to ex vivo ischemia and reperfusion. The findings of this initial study were comparable with those of the main study, supporting the reproducibility of our findings.

In vivo baseline hemodynamic function. To study differences in real-time in vivo hemodynamic function between inbred strains, mice were instrumented with a 1.4 French Millar conductance micromanometer catheter. This methodology allows for precise, real-time assessment of cardiac function by simultaneous measurement of left ventricular pressure and volume (33). There were significant differences in systolic and diastolic function between C57BL/6J and other strains at baseline, with C57BL/6J generally displaying higher cardiac function than the other strains tested (Fig. 4, Supplemental Table S3). In measures of systolic function, C57BL/6J mice showed increased LVSP compared with FVB/NJ, DBA/2J, BALB/cJ, and C3H/HeJ mice, as well as increased maximal dP/dt com-

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Baseline functional data for isolated hearts of inbred mouse strains. Systolic function indicated by left ventricular end-systolic pressure (LVESP), left ventricular developed pressure (LVDP), and the maximum derivative of left ventricular pressure (−dP/dt), diastolic function indicated by left ventricular end-diastolic pressure (LVEDP), minimum derivative of left ventricular pressure (−dP/dt), and the rate constant tau. All values expressed as means ± SE. *P < 0.05 compared with C57BL/6J mice; n = 5–8 for each group.
pared with BALB/cJ mice (Fig. 4, $P < 0.05$). C3H/HeJ mice showed a greater ejection fraction (EF) than C57BL/6J. However, this may have been a manifestation of smaller cardiac dimensions in C3H/HeJ mice as they showed reduced heart weight and maximum volume compared with C57BL/6J mice (Supplemental Table S4, Fig. 4; $P < 0.05$). C57BL/6J mice also displayed greater diastolic function compared with other inbred strains, as shown by a more negative minimum $dP/dt$ compared with DBA/2J and BALB/cJ (Fig. 4, $P < 0.05$).

**In vivo hemodynamic function during $\beta$-adrenergic blockade.** We next investigated strain-dependent differences in the effects of adrenergic signaling on cardiac function. Here, in vivo hemodynamic function was recorded during an acute infusion of the $\beta$-blocker esmolol. This manipulation allows the dissection of the role of adrenergic signaling in maintaining normal cardiovascular performance in different mouse strains. Comparison of the response to esmolol infusion revealed strain dependent variation in cardiac function during $\beta$-blockade (Fig. 5, Supplemental Table S5). In the absence of $\beta$-adrenergic signaling, and similar to baseline in vivo functional measurements, C57BL/6J mice maintained higher levels of cardiac function compared with most, but not all, of the inbred strains tested (Fig. 5B). As described above, there were significant differences in cardiac function between inbred strains at baseline. To account for these differences in baseline function when assessing the effects of $\beta$-adrenergic blockade on cardiac function, the difference between functional parameters at baseline and following 3 min of esmolol infusion was determined (Fig. 5C). Esmolol infusion caused a general depression in cardiac function of all strains tested. However, there were strain-dependent differences in the degree to which $\beta$-blockade depressed cardiac function. In particular, esmolol infusion had a marked effect on the cardiac function of C3H/HeJ mice (Fig. 5C). All C3H/HeJ mice underwent severe cardiac decompensation within 3 min of the start of esmolol infusion as shown by greater reductions in LVSP, EF, and maximum $dP/dt$ compared with C57BL/6J (Fig. 5C, $P < 0.05$). The effects of $\beta$-blockade were also more severe on 129X1/SvJ compared with C57BL/6J as shown by greater reductions in maximum $dP/dt$ and LVSP (Fig. 5C, $P < 0.05$). C57BL/10SnJ showed a greater decrease in EF compared with C57BL/6J followed esmolol infusion as well (Fig. 5C, $P < 0.05$).
In vivo hemodynamic function during an acute hypoxic challenge. To assess the capacity for inbred mouse strains to respond to an acute cardiac stress, mice instrumented with a pressure-volume catheter were exposed to an acute hypoxic challenge by ventilation with 7% oxygen (10). Significant differences in cardiac function and survival were observed between C57BL/6J and other inbred strains during this challenge (Fig. 6). To assess cardiac function during hypoxia, hemodynamic parameters were compared at 6 min, 40 s into the hypoxic challenge at which time C57BL/6J mice underwent cardiac decompensation as defined in MATERIALS AND METHODS. Unlike our findings at baseline and during esmolol infusion, C57BL/6J mice showed relatively poor cardiac function during an acute hypoxic challenge compared with other inbred strains (Fig. 6B and Supplemental Table S6). To account for differences in baseline function when determining the strain-dependent differences in the response to hypoxia, the difference between functional parameters at baseline and following acute hypoxia was determined (Fig. 6C). Unlike the effects of β-blockade, acute hypoxia had much more severe effects on the cardiac function of C57BL/6J mice than most other inbred strains tested. 129X1/SvJ, 129S1/SvImJ, and FVB/NJ maintained contractility to a greater degree compared with C57BL/6J during acute hypoxia as shown by less negative change in LVSP following hypoxia (Fig. 6C, P < 0.05). Additionally, FVB/NJ, BALB/cJ, 129X1/SvJ, and 129S1/SvImJ showed greater maintenance of EF, stroke volume, and maximum dP/dt following hypoxia compared with C57BL/6J (Fig. 6C, P < 0.05). FVB/NJ, DBA/2J, BALB/cJ, C3H/HeJ, 129X1/SvJ, and 129S1/SvImJ showed greater maintenance of stroke work following hypoxia compared with C57BL/6J (Fig. 6C, P < 0.05). Analysis of survival during acute hypoxia also emphasizes the functional deficit of C57BL/6J mice compared with other inbred strains. C57BL/6J mice showed significantly shorter survival during hypoxia compared with DBA/2J, FVB/NJ, C3H/HeJ, BALB/cJ, 129X1/SvJ, and 129S1/SvImJ (Fig. 6C, P < 0.05). C57BL/10SnJ was the only strain that did not perform significantly better than C57BL/6J during acute hypoxia.

DISCUSSION

To our knowledge this is the first detailed comparative analysis of in vivo and ex vivo heart performance between several commonly used inbred strains. In the past decade, there have been tremendous advances in cardiac biology enabled by exquisite cardiac transgenesis and gene targeting studies in mice (1, 12, 14, 15, 18, 32, 52). Cardiac transgenic, knockout,
and other genetically modified mice have been created and backcrossed to a wide array of inbred mouse strains, including those tested in this study. As the number of genetically modified mouse models used in cardiovascular research continues to grow, so to does the need to identify and appreciate the differences in cardiovascular physiology that arise from the genetic diversity within these inbred mouse strains.

One main finding of this study is that genetic divergence between commonly used inbred mouse strains significantly affects cardiac function. All inbred strains showed functional divergence from C57BL/6J to some degree. In ex vivo preparations, most inbred strains were similar to C57BL/6J at baseline, which is in general agreement with previously published findings on baseline ex vivo cardiac function (37). However, following ischemic injury 129X1/SvJ, C57BL/10SnJ, and 129S1/SvImJ showed significantly reduced cardiac function compared with C57BL/6J. C57BL/10SnJ and 129X1/SvJ showed reduced function that was associated with a higher incidence of sustained VTach during the early periods of reperfusion compared with C57BL/6J. This is in agreement with previously published findings that isolated C57BL/6 hearts are relatively resistant to arrhythmia (55). This suggests that C57BL/10SnJ and 129X1/SvJ differ from C57BL/6J in their propensity for arrhythmogenicity, and not in contractility, following ischemic injury. Conversely, 129S1/SvImJ showed reduced cardiac function throughout reperfusion in the absence of VTach, suggesting that ischemic injury compromises contractility of these mice without promoting arrhythmia. In vivo hemodynamic analyses also showed strain-dependent differences in cardiac function between C57BL/6J and other inbred strains. The most striking of these was the effect of esmolol on C3H/HeJ mice. As expected, β-adrenergic blockade reduced cardiac function of all mice to some degree. However, esmolol infusion caused severe cardiac decompensation of C3H/HeJ within 3 min, whereas other inbred strains maintained a reduced, but sustainable, level of cardiac function. Additionally, C57BL/6J mice showed greater susceptibility to hypoxia compared with all inbred strains with the exception of the closely related C57BL/10SnJ. This finding under hypoxic challenge is in contrast to the majority of findings in this study, where C57BL/6J performed as well or better than other inbred strains in cardiac performance tests. A recently published study by Shah and colleagues (42) reports a similar finding when comparing the cardiac function of four inbred strains of mice in vivo by echocardiography and in vitro by recording sarcomere shortening and intracellular calcium handling. Compared with other strains tested.
(BALB/c, C57BL/6 and FVB), 129 mice showed reduced contractility as measured by echocardiography but increased calcium handling and sarcomere shortening in vitro. Collectively, these findings suggest that the mechanism by which cardiac performance is modified by genetic divergence between strains are complex and may be governed by specific genetic loci that respond differentially to regulate cardiac function depending on the conditions being used to assess cardiac function.

**Fig. 5.** In vivo hemodynamic function of inbred mouse strains during β-blockade. A: representative raw PV loops for each strain acquired by conductance micromanometry after 3 min of esmolol infusion (PV loops: vertical scale bar, 50 mmHg; horizontal scale bar, 10 µl). B: absolute values for cardiac function during esmolol infusion. Mean data for each strain for various cardiac hemodynamic parameters derived from real-time PV loop analysis at 3 min following the start of esmolol infusion. C: representative changes in the positive pressure derivative (+dP/dt) during the time course of esmolol infusion showing marked differences in adrenergic tone between strains (top left). Mean data for each strain for various cardiac hemodynamic parameters derived from real-time PV analysis. For all groups n = 7–9. Values are expressed as means ± SE. *P < 0.05 compared with C57BL/6J.
**Fig. 6.** In vivo hemodynamic function of inbred mouse strains during acute hypoxia. A: representative raw PV loops for each strain acquired by conductance micromanometry at 6:40 into the hypoxia challenge (PV loops: vertical scale bar, 50 mmHg; horizontal scale bar, 10 μl). B: absolute values for cardiac function during acute hypoxia. Mean data for each strain for various cardiac hemodynamic parameters derived from real-time PV analysis at 6 min, 40 s following the start of esmolol infusion. C: the mean change in cardiac function from the start of hypoxia to 6:40 into the hypoxic challenge indicating the delta values for given hemodynamic parameters during hypoxia compared with baseline. Mean survival values for each strain during the acute hypoxic challenge showing significant differences between groups compared with C57BL/6J (bottom right). For all groups n = 7–9. Values are expressed as means ± SE. *P < 0.05 compared with C57BL/6J.
Although a priori we predicted cardiac function to be similar between in vivo and ex vivo preparations, it is not surprising that differences were observed given the significant differences between these assays (11, 33). Specifically, the absence of physiological loading conditions and autonomic innervation in the ex vivo Langendorff preparation are possible reasons for these differences. Additionally, these techniques also differ in their methods of anesthesia. Prior to the extraction and perfusion of the heart for ex vivo functional measurements mice are anesthetized with pentobarbital. Pentobarbital is known to depress cardiac function in vivo (39, 44). However, once the heart is isolated and perfused, it is generally believed that the effects of pentobarbital are quickly washed out from the heart (11). This is supported by the lack of ex vivo functional differences between C57BL/6J and DBA/2J hearts, despite previously published findings that DBA mice are highly susceptible to pentobarbital compared with C57BL/6 mice (31). Conversely, during in vivo measurement of cardiac function, mice were constantly anesthetized with isoflurane. Isoflurane has been shown to have strain-dependent cardiodepressive effects in vivo (8, 9, 28, 30, 46). Additionally, isoflurane anesthesia has been shown to be cardioprotective from ischemic injury through mechanisms that are not fully understood but are thought to mimic ischemic preconditioning (25). Collectively, these previously published findings may provide insights to explain the discrepancies in cardiac function between ex vivo and in vivo preparations. Specifically, the cardiodepressive effects of isoflurane may differentially affect each inbred strain, confounding our comparison of their intrinsic cardiac function. Additionally, given that isoflurane has been shown to be cardioprotective during ischemia, it stands to reason that isoflurane may have a similar effect during hypoxia. If so, and if the magnitude of this effect is strain-dependent, then this may be another mechanism to explain the differences between our ex vivo and in vivo findings.

Our findings of significant differences in cardiac function between inbred mouse strains are telling of the impact of genetic divergence between strains on cardiovascular physiology. Although strain-dependent differences in physiological function can be challenging when comparing findings of studies in which multiple inbred strains have been used, they can also be taken advantage of to expand our understanding of complex disease processes. Similar to humans, selected cohorts of mice show distinct susceptibility to specific disease processes and these characteristics can be used to inform experimental design. For example, when creating a transgenic mouse that expresses a gene thought to confer resistance to cardiac ischemic injury, it may be beneficial to create or cross this transgenic line to a strain that shows particular susceptibility to cardiac ischemic injury such as 129S1/SvImJ as shown here. Carefully selecting the genetic background of novel genetically engineered mice in this way may maximize the differences between treated and untreated groups when attempting to test a particular therapeutic strategy. Additionally, because disease therapies are designed to treat patients that presumably show increased susceptibility to the disease of interest, it makes sense that research studies be designed in a similar fashion.

Another useful outcome of this study is the identification of quantitative traits that arose from the phenotypic diversity between inbred mouse strains. Future studies could center on tracking and identification of QTL that modify particular cardiac disease-related physiological processes. Previous studies have demonstrated the feasibility of using the genetic homogeneity of inbred mouse strains to isolate and identify physiologically significant QTL (2, 6, 13, 20, 21, 48, 49). In this study, we observed significant functional differences between inbred strains that were evident when subjected to the stresses of ischemia/reperfusion, β-blockade, and acute hypoxia. Because these challenges have direct clinical correlates, we anticipate that future studies focused on identifying the QTL to mechanistically explain observed functional differences between these strains will be of value. For example, a QTL analysis could be designed with C3H/HeJ and C57BL/6J mice to identify loci that cause the marked loss of function in C3H/HeJ mice following esmolol infusion. Such a study may provide new mechanistic and clinically relevant insight into the regulation of cardiac function by β-adrenergic signaling by elucidating alterations in this pathway between these strains. This may be valuable in identifying factors that alter adrenergic signaling in the normal and diseased heart (16, 24). Finally, the finding that under baseline hemodynamic conditions C57BL/6J mice had improved in vivo heart performance compared with other strains, including FVB/N, may help explain earlier reports of marked differences in mutant transgene outcomes between these inbred strains (29, 36).

Collectively, the results of this study emphasize the importance of genetic divergence between inbred mouse strains and the complex manner in which this influences cardiac function. Additionally, we found that differences in cardiac function between inbred strains are modified by both genetic background and the physiological test setting (ex vivo/in vivo) used to assess cardiac function. Finally, in this study we have identified numerous quantitative traits that may serve as the substrate for future studies on genetic modifiers of cardiac function. The demonstration here of reproducible and robust physiological traits, provoked under baseline or pathophysiological challenges, should aid future works attempting to identify new genetic modifiers of heart performance.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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