Endothelial Dysfunction and Blood Pressure Variability in Selected Inbred Mouse Strains

Michael J. Ryan, Sean P. Didion, Deborah R. Davis, Frank M. Faraci, Curt D. Sigmund

Abstract—The genetic regulation of blood pressure (BP) and endothelial function is likely to be polygenic. Because there is considerable variability in basal BP among inbred mouse strains, the purpose of this study was to determine whether a similar variability in vascular function exists among 7 “normotensive” strains. We tested the hypothesis that compared with mice with higher BPs, mice with lower BPs would have greater aortic endothelial responses to acetylcholine (ACh). Mean BP ranged from 117 to 145 mm Hg among the 7 strains. The responses of aortic rings to ACh, sodium nitroprusside, and papaverine were assessed after submaximal precontraction with prostaglandin F2\alpha. The aortas from all strains relaxed in a concentration-dependent manner to sodium nitroprusside and papaverine, but responses to ACh were markedly impaired in the aortas, but not carotid arteries, from 129P3/J and 129X1/SvJ mice. Aortas from the other strains relaxed normally to ACh. Furthermore, the endothelium-dependent dilators ADP and A23187 caused similar relaxation in 129P3/J, 129X1/SvJ, and C57BL/6J mice. Although the data do not support the initial hypothesis, the impaired aortic response to ACh in the 129 strains is a novel finding and illustrates the potential impact that genetic background can have on vascular responsiveness. (Arterioscler Thromb Vasc Biol. 2002;22:42-48.)

Key Words: aorta ■ blood pressure ■ endothelium ■ inbred mice

The regulation of arterial blood pressure is extremely complex and is governed by environmental and genetic factors. Because numerous genes and genetic interactions regulate blood pressure, it is difficult to truly decipher the role of any 1 gene in the control of arterial pressure. More recently, however, our ability to understand and answer complex questions related to blood pressure regulation has been aided by the advent of transgenic and gene-targeting technology, along with a continued improvement in our ability to perform physiological experiments in the mouse. Several mouse models of vascular disease and hypertension have been developed through gene-targeted deletions of endothelial NO synthase, apoE, bradykinin receptors, and atrial natriuretic peptide genes, to name a few.1–6 Transgenic mouse models of hypertension have also been developed through gene-targeted deletions of renin and human angiotensinogen genes.7,8 Although these mouse models have proven useful to better understand some of the underlying mechanisms of hypertension and vascular disease, it is important to be aware that the genetic background of the mice used to generate these models may influence the observed phenotype. As an example, Schlager and Weibust,9 using the tail-cuff method, observed a wide range of blood pressure among 15 different inbred mouse strains. These data are particularly relevant for transgenic models of hypertension, given that the models often have a mixed genetic background consisting of genes from 129X1/Sv and C57BL/6J mice. To date, there is limited evidence for variation in vascular function among different mouse strains, although 1 study reported that responses of cerebral arterioles to the classic endothelium-dependent vasodilator, acetylcholine (ACh), was attenuated in C57BL/6 mice compared with SV-129 (now termed 129X1/Sv) mice.10 Vascular function, or the ability for blood vessels to contract and relax in response to a variety of vasoactive substances, is an important determinant of blood pressure. Prolonged increases in pressure are often associated with impaired endothelium-dependent relaxation, which may contribute to increased risk for atherosclerotic disease and other cardiovascular events. However, it is unclear whether the blood pressure variability that exists among inbred mouse strains is associated with a similar variation in vascular function. Therefore, in the present study, we tested the hypothesis that the blood pressure of 7 inbred strains of mice, considered to be normotensive, is inversely related to endothelial function.

Methods

Animals

Seven strains of inbred mice (male) were obtained from Jackson Laboratories (Bar Harbor, Me): A/J, BALB/cJ, C57BL/6J, C3HeB/
By guest on August 30, 2017

concentration–response curves to ACh, ADP, calcium ionophore
mean level of precontraction for each strain is listed in Table 1.

Mice were
saturated with 95% O\textsubscript{2} and 5% CO\textsubscript{2}. Vascular rings were dissected
premaximally precontracted (51% to 110) in Krebs buffer (in mmol/L: pH 7.4, NaCl 118.3, KCl 4.7,
CaCl\textsubscript{2} 2.5, MgSO\textsubscript{4} 1.2, KH\textsubscript{2}PO\textsubscript{4} 1.2, NaHCO\textsubscript{3}, and glucose 11)

Systolic Blood Pressure Measurements

Blood Pressure Measurements

The tail-cuff method (Visitech Systems BP-2000) was used to
measure systolic pressure and heart rate in conscious restrained mice,
as we have previously described.\textsuperscript{11} Thirty cycles of measurements were made for a
period of 10 days, with the mean of the last 5 days of recordings used for the final
determination of systolic blood pressure. In addition to tail-cuff recordings, indwelling carotid
catheters in conscious, freely moving mice were used to record blood pressure as described previously in our laboratory.\textsuperscript{12} Mice were placed under ketamine (120 mg/kg IP) and acetazolamide maleate (12 mg/kg IP) anesthesia. The right carotid artery was dissected from fat and connective tissue so that a sterile heparinized saline (50 U/mL)–filled catheter could be inserted. Catheters were tunneled subcutaneously to the back of the neck between the scapulae, exteriorized, and sutured in place. Catheters were flushed daily with heparinized saline (500 U/mL). Mean arterial pressure and heart rate were recorded 48 hours after surgery for at least 2 days.

Vascular Ring Preparation

Mice were euthanized with pentobarbital (100 mg/kg IP). Subsequently, the thoracic aorta and carotid arteries were removed and placed in Krebs buffer (in mmol/L: pH 7.4, NaCl 118.3, KCl 4.7, CaCl\textsubscript{2} 2.5, MgSO\textsubscript{4} 1.2, KH\textsubscript{2}PO\textsubscript{4} 1.2, NaHCO\textsubscript{3}, and glucose 11) saturated with 95% O\textsubscript{2} and 5% CO\textsubscript{2}. Vascular rings were dissected free of loose connective and adipose tissue and cut into segments of equal length (4 aortic segments and 2 carotid segments per side). The segments were suspended in a 20 mL Krebs organ bath maintained at 37°C and connected to a force transducer for measurement of isometric tension (contraction and relaxation). Resting tension was adjusted stepwise to reach a final resting tension of 0.5 g (aorta) and 0.25 g (carotid). Our laboratory has used these methods previously.\textsuperscript{13–15}

Protocols

Vessels were allowed to equilibrate for 45 minutes. The aortic and carotid vessel segments were submaximally precontracted (51% to 68% of maximum) with prostaglandin F\textsubscript{2\alpha} (PGF\textsubscript{2\alpha}, 10 \mu mol/L) and the thromboxane A\textsubscript{2} mimetic U46619 (60 mmol/L), respectively. The mean level of precontraction for each strain is listed in Table 1. When the vessels reached a stable precontracted tension, concentration–response curves to ACh, ADP, calcium ionophore (A23187), sodium nitroprusside (SNP), and papaverine (PAP, 0.01 to 10.0 \mu mol/L) were generated. Studies using pharmacological approaches and gene-targeted mice have shown that relaxation of the aorta and carotid arteries to ACh is mediated by endothelial NO synthase.\textsuperscript{16,17} At the end of each experiment, dose-response curves to increasing concentrations of PGF\textsubscript{2\alpha} (aorta) and U46619 (carotid) were generated to determine the maximal contractile responses.

Statistical Analysis

ANOVA with repeated measures was used to test for statistically significant differences among the concentration–response curves from different mice. One-way ANOVA was used to measure for statistical differences among the blood pressure, aortic precontraction, and heart weight–to–body weight ratio data. Statistical significance was accepted at a level of \( P<0.05 \).

Results

Blood Pressure

Tail-cuff measurements were performed in restrained mice to measure systolic blood pressure and heart rate. The results demonstrate that there is a large variability in basal blood pressure among different strains, and they also support what has been previously shown by Schlager and Weibust\textsuperscript{5} (Table 2). For example, systolic pressure ranged from 114±2 mm Hg in C57BL/6J mice to 138±3 mm Hg in SWR/J mice. Despite the observation that SWR/J mice have the highest blood pressure, statistically, it is not higher than that of either 129P3/J or 129X1/SvJ mice. Although many investigators have used the tail cuff to measure systolic pressure, this method has some limitations. For example, the tail-cuff method typically underestimates blood pressure and requires increasing the mouse body temperature to increase blood flow to the tail. Therefore, we also measured arterial pressure directly through the use of indwelling carotid catheters in conscious, freely moving, tethered mice. The results obtained by this method generally agree with the tail-cuff data, with SWR/J, 129P3/J, and 129X1/SvJ mice having the highest pressures (Table 2). Statistically, the 129P3/J blood pressures were higher than those of all the other strains except SWR/J, and SWR/J pressures were higher than those of all others except 129P3/J and 129X1/SvJ mice. It is interesting to note the divergent blood pressure in the 2 closely related substrains of 129 mice. From these blood pressure recordings, one might expect the SWR/J and 129P3/J strains to have attenuated endothelial function compared with that of strains with statistically lower pressure.

The 129P3/J strain, which had one of the highest blood pressures by both methods, had a higher heart weight–to–body weight ratio than did all the other strains. The C3HeB/

<table>
<thead>
<tr>
<th>Strain</th>
<th>Precontraction (10 \mu mol/L PGF\textsubscript{2\alpha})</th>
<th>Maximum Relaxation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/J</td>
<td>0.78±0.04*</td>
<td>79±5</td>
</tr>
<tr>
<td>BALB/cJ</td>
<td>0.65±0.03</td>
<td>82±4</td>
</tr>
<tr>
<td>129P3/J</td>
<td>1.03±0.04†</td>
<td>5±2</td>
</tr>
<tr>
<td>129X1/SvJ</td>
<td>0.87±0.06‡</td>
<td>7±5</td>
</tr>
<tr>
<td>C3HeB/FeJ</td>
<td>0.72±0.02</td>
<td>80±2</td>
</tr>
<tr>
<td>C57BL/6J</td>
<td>0.57±0.03</td>
<td>72±5</td>
</tr>
<tr>
<td>SWR/J</td>
<td>0.57±0.03</td>
<td>67±6</td>
</tr>
</tbody>
</table>

Values are mean±SE.

\* \( P<0.05 \) vs C57BL/6J and SWR/J; † \( P<0.05 \) vs all other strains except 129X1/SvJ; and ‡ \( P<0.05 \) vs C57BL/6J, SWR/J, and BALB/cJ (measured by 1-way ANOVA).
endothelium-dependent relaxation is markedly greater than that observed in C57BL/6J mice. These data suggest that endothelium-dependent relaxation is impaired in the 129P3/J and 129X1/SvJ strains compared with responses in the A/J strain, which had a significantly greater response to ACh compared with that of the 129P3/J strain, which had an equivalent pressure.

**Vascular Function**

To test whether the variability in basal blood pressure corresponds with a similar variability in vessel function, precontracted aortic rings from each strain were treated with various vasodilators. Once a stable contractile plateau was attained, the vessels were treated with various vasodilators. For mean BP values, see Table 1. Concentration-response curves for each strain to ACh were generated (Figure 1).

ACh produces relaxation of the aorta and carotid by activation of endothelial NO synthase, release of NO, and, ultimately, smooth muscle relaxation. \(^4,16\) Responses of the aorta to ACh were markedly impaired in the 129P3/J and 129X1/SvJ strains compared with all other strains studied (Figure 1). With the exception of the A/J strain, which had a significantly greater response to ACh compared with that of the 129P3/J strain at lower doses, aortas from all other strains had similar responses to ACh. Two different investigators (M.J.R. and S.P.D.) independently confirmed the endothelial dysfunction observed in the 129X1/SvJ strain. The marked impairment observed in the 129P3/J and 129X1/SvJ strains was surprising. Therefore, to begin to dissect a possible mechanism, we tested 2 other endothelium-dependent agonists, ADP (receptor-mediated) and A23187 (non–receptor-mediated), in the aortas of 129P3/J, 129X1/SvJ, and C57BL/6J mice (Figure 2). The aortic responses from all 3 strains were not significantly different from each other.

In addition to ACh responses in the aorta, we examined responses of the carotid arteries in C57BL/6J, 129P3/J, and 129X1/SvJ mice to determine whether the impairment to

**Figure 1.** Relaxation of the aorta in response to ACh. Responses to ACh in 129P3/J and its substrain 129X1/SvJ are impaired at all concentrations compared with responses in the other inbred strains. Additionally, the response in A/J mice is greater than that observed in C57BL/6J mice. These data suggest that endothelium-dependent relaxation is markedly impaired in 129P3/J and 129X1/SvJ mice. Values are mean ± SE. *Significantly different (P < 0.05) from C57BL/6J. †Significantly different (P < 0.05) from all other strains except 129X1/SvJ. #Significantly different (P < 0.05) from all other strains except 129P3/J.

**Figure 2.** Relaxation of the aorta in response to ADP and A23187. Increasing concentrations of ADP (A) and A23187 (B) were used with aortas from C57BL/6J, 129P3/J, and 129X1/SvJ mice. No significant differences were detected among the responses.
ACETYLCHELINE (-Log M)

Figure 3. Relaxation of the aorta and carotid in response to ACh. Representative effects of ACh in aortas (left) and carotid arteries (right) from 3 different mouse strains (C57BL/6J, 129P3/J, and 129X1/SvJ) are shown. ACh responses were markedly impaired in the aorta but not in the carotid arteries from 129P3/J and 129X1/SvJ mice, suggesting that the impaired endothelial function may not be present throughout the entire vasculature. Carotid arteries were precontracted with the thromboxane analogue U46619 (60 nM/L).

ACh seen in the aorta was present in other blood vessels (Figure 3). Surprisingly, relaxation of the carotid artery to ACh was similar (and not impaired) in the 3 strains tested. There was no significant difference in the response to 10^{-5} mol/L ACh in carotid arteries among C57BL/6J (86±3%, n=4), 129P3/J (71±24%, n=3), and 129X1/SvJ (69±5%, n=3) strains, measured by 1-way ANOVA. These data suggest that the impaired ACh responses were specific for the aorta.

Despite the evidence suggesting that the aortic dysfunction in the 129P3/J and 129X1/SvJ strains is confined to the aorta and more specifically to ACh, the possibility that the underlying smooth muscle may respond differently to dilators among the different strains still exists. Therefore, concentration-response curves to an endothelium-independent NO donor, SNP, were generated for each strain. The aortas from all strains relaxed in a concentration-dependent manner and to the same maximal level in response to SNP (Figure 4A). Relaxation of aortas in the 129P3/J strain was significantly impaired at the lower concentrations (0.1 to 0.1 μmol/L) of SNP compared with aortic relaxation in all other strains. In addition to SNP, an endothelium- and NO-independent vasodilator, PAP, was used in each strain. The aortas from all strains relaxed in a concentration-dependent manner and to the same maximal level in response to PAP (Figure 4B). PAP, from the benzylisoquinoline family of drugs, reportedly acts through the inhibition of calcium channels in smooth muscle to promote relaxation. PAP produced similar maximal vasorelaxation in all strains (by >95%). However, the aortic response to PAP was modestly impaired in the 129P3/J mice compared with BALB/cJ, C3HeB/FeJ, C57BL/6J, and SWR/J mice (at concentrations of 10^{-7} to 3×10^{-6} mol/L). Moreover, the PAP response was significantly attenuated in aortas from 129X1/SvJ mice compared with aortas from SWR/J mice at lower concentrations (0.1 to 1.0 μmol/L). Although there are some differences among strains with respect to either the SNP or PAP responses, it is clear that both agonists cause a dose-dependent relaxation of the aorta in each strain and result in similar maximal responses, suggesting that vascular muscle is intact and functioning. Importantly, the modest impairment that was observed in the 129P3/J and 129X1/SvJ strains in response to SNP or PAP was much less than that observed in these strains with ACh. However, it cannot be ruled out from the present data that this impairment to SNP or PAP may influence the ability of aortas from 129P3/J and 129X1/SvJ mice to relax to ACh.

Figure 4. Relaxation of the aorta in response to endothelium-independent dilators. A, The aortic response to SNP was attenuated at lower concentrations (0.01 to 0.1 μmol/L) in the 129P3/J mouse strain. However, at higher concentrations, there was no statistical difference among any strain. Values are mean±SE. *129P3/J is significantly different (P<0.05) from all other strains. B, All mouse strains relaxed similarly to a maximal concentration of PAP. However, vasorelaxation at submaximal concentrations of PAP in 129P3/J mice was shifted significantly to the right. Values are mean±SE. †Significantly different (P<0.05) from BALB/cJ, C3HeB/FeJ, C57BL/6J, and SWR/J mice. ‡Significantly different (P<0.05) impaired 129X1/SvJ response compared with SWR/J response.

Contractile responses were measured by stimulating the aorta of each mouse with increasing concentrations of PGF_{2α} (10 to 300 μmol/L). Responses of the aorta to a submaximal concentration of PGF_{2α} are shown in Figure 5 for each mouse strain. Maximal contraction of the aorta with U46619 (0.43 μmol/L) was also determined (data not shown). On average, 129P3/J, 129X1/SvJ, and A/J aortas contracted in response to both agents to a greater extent than did the BALB/cJ, C57BL/6J, and SWR/J aortas.

Figure 5. Contraction of the aorta in response to a submaximal concentration of PGF_{2α} (100 μmol/L) is shown. Values are mean±SE. *Significantly different (P<0.05) from BALB/cJ, C3HeB/FeJ, C57BL/6J, and SWR/J mice but not C3HeB/FeJ mice.
Discussion

In the present study, we report that systolic blood pressure and mean arterial blood pressure are variable among 7 different inbred mouse strains measured by the tail-cuff method and indwelling carotid artery catheters, respectively. In addition, aortic responses to ACh were different in A/J, 129P3/J, and 129X1/SvJ strains compared with responses in the other strains tested. For example, A/J mice had a more sensitive response to ACh at submaximal concentrations, whereas the 129P3/J and 129X1/SvJ aortic response to ACh was markedly attenuated at all concentrations. The impaired response to ACh observed in the aortas of the 129 strains was not present in the carotid arteries or after use of additional endothelium-dependent dilators, ADP and A23187. Aortas from all strains relaxed similarly to maximal concentrations of the endothelium-independent agonists, SNP and PAP. Although blood pressure and endothelial function varied among the mouse strains studied, an inverse relationship between blood pressure and endothelial function was not evident. For example, the aortic response to ACh was noticeably different between 129P3/J and SWR/J mice despite having mean blood pressures that were statistically the same.

Genetic Background

As the use of mouse models has become commonplace to address important physiological questions, so too has it become increasingly important to consider the genetic background of these animals when controls are selected and results are interpreted. Indeed, there have been several reports of strain-related differences among a variety of physiological characteristics.

These phenotypic differences can be used in genetic crosses to identify genetic loci that might be important for the regulation of the desired characteristic. For example, differences between mouse strains in their susceptibility to developing gallstones or in their behavioral responses caused by methamphetamine have been used to map quantitative trait loci that contain specific genes likely to influence those specific phenotypes. More important, variability in blood pressure among different mouse strains has been used as a segregating phenotype to map loci that contain genes important for the regulation of pressure in mice.

Understanding the importance of how genetic background mediates different phenotypes among mouse strains has become important for vascular biologists as well. For example, Paigen et al. studied the effect of diet on aortic lesion size in various mouse strains by ranking them for susceptibility for developing atherosclerosis. C57BL/6 mice were reported to be highly susceptible, SWR mice were moderately susceptible, and 129 (129P3J) and BALB/c mice were resistant to atherosclerotic plaque formation. Still, others have shown that activation of proatherogenic genes, such as macrophage colony-stimulating factor or hemeoxygenase, by minimally modified LDL differs between inbred strains. These data provide further evidence of the influence of genetic background in determining physiological or pathophysiological characteristics of an animal.

Given the potential influences of genetic background on a variety of traits, it is evident that one should be aware of strain-related differences when targeted gene deletions in mice are generated, because it is very common for transgenic mice to have a mixed genetic background. For example, DNA is commonly targeted to embryonic stem cells harvested from 129 mice, which are subsequently implanted into blastocysts of C57BL/6 mice. The mice created from this process are often bred with C57BL/6 mice because of their greater reproductive performance. When heterozygotes are bred to generate a knockout, the genetic background becomes a random mix of 129 and C57BL/6 DNA.

Genetic Variations in Blood Pressure

In addition to our present findings, others have reported strain-related differences in blood pressure. For example, Schlager and Weibust have reported a wide variation in systolic blood pressure of many inbred mice by use of the tail-cuff method. To the contrary, Mattson reported that there were no differences in mean arterial pressure among several inbred strains but that SWR/J mice had a significantly higher systolic pressure than did other strains. The latter study used chronically implanted femoral catheters in conscious, freely moving (but tethered) mice; use of the catheters was cited as the difference between the studies. The present experiments used the tail-cuff method and indwelling carotid catheters to measure arterial blood pressure. Consistent with the report of Schlager and Weibust, we observed a wide range of blood pressure by using both methods. The discrepancy between our data and the data of Mattson is unclear, although age-related differences might be a factor. The average age ranged from 8 to 13 weeks in the study of Mattson and from 16 to 22 weeks in the present study.

Genetic Differences in Vascular Function

Arterial blood pressure and endothelial function have a strong inverse relationship such that hypertension is often associated with impaired endothelium-dependent relaxation. Although there is a wealth of data describing strain-related differences in the susceptibility to atherosclerosis, there is very little evidence pertaining to possible strain-related differences in endothelial function. To assess whether variability in endothelial function exists among different inbred mouse strains and whether this variability correlates with the variability in blood pressure, the aortic response to ACh was evaluated. The ACh dose-response curves show that most of the strains respond similarly to increasing concentrations of ACh, with 2 notable exceptions. First, the A/J strain, which had one of the lowest blood pressures, had a significantly greater response to ACh than did the C57BL/6J strain (also 129P3/J and 129X1/SvJ strains), particularly at lower concentrations (0.01 to 1.0 μmol/L). Second, the response to ACh in the 129P3/J (and the 129X1/SvJ) strain was markedly attenuated compared with the ACh response in all other strains. Initially, the design of these experiments included only the 129P3/J strain of 129 inbred mice. However, in view of recent evidence that contamination of an unknown genetic background was introduced circa 1978 to the 129 strain, the authors felt it necessary to assess whether the impaired function was specific only to 129P3/J or whether it was present in other 129 substrains. Thus, the 129X1/SvJ strain was selected and found to have the same impaired response as 129P3/J to ACh. Although it is beyond the scope of the present study to...
examine the mechanism of all strain-related differences in endothelial function, it is important to consider different explanations for the divergent ACh response in aortas, particularly aortas from 129P3/J and 129X1/SvJ mice.

The concentration response to ADP and A23187 for the 129P3/J, 129X1/SvJ, and C57BL/6J strains may shed some light on the potential mechanism. The results of the present study demonstrate that the aortas from all 3 of these strains respond similarly to these agonists. These data suggest that the impaired response to ACh may not be the result of global endothelial dysfunction but rather a mechanism more specific to the ACh signaling pathway in the aorta. This is further supported by the lack of impaired ACh response in the carotid arteries of the 129P3/J and 129X1/SvJ strains. However, a more global impairment of aortic function cannot be ruled out given the modest impairment of aortic segments to SNP and PAP for the 129P3/J strain and PAP for the 129X1/SvJ strain.

Finally, contractile responses of the aortas from the various inbred strains were assessed. These data are more difficult to interpret considering the wide variability in responses. Statistically, there were 2 groups. The group with the greatest average response consisted of 129P3/J, 129X1/SvJ, and A/J mice, which had significantly greater responses than the second group, which consisted of C57BL/6J, BALB/cJ, and SWR/J mice. It is interesting to note that the 129P3/J and 129X1/SvJ strain were in the group with the highest average contraction. Not surprisingly then, the average precontraction for each individual experiment was higher for the 129P3/J and 129X1/SvJ strains than for most other strains (Table 1). This led us to consider the possibility that the impaired ACh response observed in the aortas of 129P3/J and 129X1/SvJ mice was an artifact resulting from the different levels of precontraction. However, 2 main factors argue against this. First, even though the aortas of the various strains are precontracted to different absolute tensions, aortas from all strains respond similarly to maximal doses of SNP and PAP. Second, even more telling is the fact that the aortic responses to ADP and A23187 for 129P3/J, 129X1/SvJ, and C57BL/6J strains were not different despite the statistically higher level of precontraction in the 129P3/J and 129X1/SvJ strains.

In conclusion, the present study supports the variability in blood pressure among inbred mice reported by others and demonstrates for the first time that endothelial function varies among different inbred mouse strains. However, we did not observe a correlation between the variability of endothelial function and variability of blood pressure. The striking impairment in ACh-induced relaxation in aortas from the 129 strains makes the findings considerably more intriguing, given that the 129 strains are commonly used in the process of developing gene-targeted transgenic mice. The present findings provide important (and previously unavailable) baseline data regarding vascular function in different inbred strains of mice. One should not assume that the present data are representative of the entire vasculature, given that responses of the aorta and carotid arteries were different in the 129 mice. However, because most studies of vascular function in genetically altered mice used the aorta, these data can be used as a starting point from which to design experiments and to remind investigators using transgenic and gene-targeted models that genetic background can play a crucial role in studies of vascular biology and hypertension.19

nally, it is noteworthy to point out that the drastically different ACh responses in the 129 mouse strains may be used as a segregating phenotype in genetic crosses to ultimately identify genes important for vascular function.

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References


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