Exercising Restraint in Measuring Blood Pressure in Conscious Mice

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A rat’s tail is a slender appendage on which the weight of so much research in hypertension hangs, yet blood pressure measurements recorded from it are usually taken for granted, often abused, but seldom discussed,” observed Buang in an earlier commentary.1 The same methodology has now been adapted to mice. Restraining the animals is a serious problem. A 7-day training period is recommended to accustom the animals to the restrainers.2–4 Nevertheless, heart rates recorded while mice are in a restrainer are higher than those in the resting state.8 Furthermore, blood pressures also appear to be higher, even though coaxing the animals into restrainers becomes easier day-to-day.5 A blood pressure–elevating effect of restrainers has been observed in the rat.6 Telemetric blood pressure and heart rate solves this problem.6

We made telemetric measurements of blood pressure and heart rate on four 129Sv/J mice outfitted with telemetry as described earlier.7 The purpose of our observations was to test the notion that “conditioning” might lessen the effects of restraint on blood pressure and heart rate. After an initial 120-minute control period, the mice were placed for 30 minutes in a 25-mm wide, 110-mm long lucite restrainer. Thereafter blood pressure and heart rate were recorded for an additional 120 minutes. We made daily recordings, 10 recordings for each mouse during 2 weeks. To judge the influence of restraint, we used the heart rate (HR) and the mean arterial pressure (MAP). In mice, tail-cuff pressure correlates well with MAP, according to earlier reports.2,3 Data (mean±SEM) were analyzed with the one-way ANOVA and t tests with the Bonferroni correction. The experimental protocol was approved by the local council on animal care, whose standards correspond to those of the American Physiological Society.

Figure 1 shows HR and systolic (SBP) and diastolic blood pressures (DBP) from a representative mouse during the first restraint and the tenth restraint. The responses do not appear different. At the first restraint, SBP increased to 148 mm Hg, DBP to 113 mm Hg, and HR to 754 beats/min. In the second week, at the tenth restraint, the responses to the restrainer were similar. Figure 2 shows that MAP measured under control conditions for 4 mice was stable throughout the 2-week recording period and averaged 102±8 mm Hg in the first week and 100±7 mm Hg in the second week. The corresponding basal HR values were 522±11 beats/min in the first week and 483±9 beats/min in the second week. No “conditioning” was observed for either MAP or HR when comparing the sessions of the first week with the sessions of the second week (P=NS). Two hours after restraint, blood pressure and heart rate returned to basal levels in the mice.

We conclude that blood pressure and heart rate increases are similar during restraining, independent of “conditioning” over 10 days. The data were convincing to the point that 4 mice were sufficient to illustrate the problem, so we did not study more. The results indicate that both blood pressure and heart rate are increased by restraining, even in animals trained and “accustomed” to the restrainer and are in accordance with results reported earlier for rats.8 We believe the observations are important because tail cuff measurements may lead to erroneous results.

Our observations show that changes in blood pressure measured by tail-cuff reflect not only the basal level of the blood pressure, but also treatment influences and the reactivity of the mouse to restraint. Because mice are more stress-sensitive than rats and because stress-sensitivity may differ between strains, subtle differences in blood pressure may be missed. This state of affairs could result in the failure to identify genes important to blood pressure regulation. Thus, tail-cuff blood pressure values should only be used in experimental situations in which large blood pressure changes ≥15–20 mm Hg are expected or to discriminate between “normotensive” and “hypertensive” mice. L-NAME–treated mice showed an increase of blood pressure and heart rate under restraint. These increases were also observed under conditions without L-NAME as shown in Figure 3. Tail cuff may also be useful when blood pressure levels between groups must be compared repeatedly over long time periods, and telemetric blood pressure measurements cannot be done. Finally, all tail-cuff measurements should periodically be verified in small groups of mice by blood pressure measurements with indwelling catheters.

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**Figure 1.** Representative tracing from a mouse (HR indicates heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure) undergoing restraint (30 minutes) on day 1 and restraint after 10 sessions, 2 weeks later. The responses were dramatic and were no different in kind.

**Figure 2.** Mean data from 4 mice. C1 and C2 are 2 control-hours before restraint. Restraint was conducted for 30 minutes. PC1 and PC2 are post-controls. There was no evidence of “conditioning” despite 10 sessions of training ($P=NS$). *Control period versus restraint; #restraint versus PC2 (60–120 minutes after restraint).
Figure 3. Mean arterial pressure and heart rate in a representative mouse under free-moving conditions (open bars) and under 30 minutes of restraining (hatched bars) are shown. D1 and D2 are the first and second days of L-NAME treatment (5 mg L-NAME/10 mL tap water); D8 and D9 show a interruption of L-NAME treatment for 2 days; D13 and D14 show the MAP and HR reactions 1 week later when L-NAME treatment was resumed. L-NAME increased the blood pressure. Blood pressure and heart rate increased after placement of the mouse in a restrainer, irrespective of L-NAME treatment. The data underscore that the restrainer reaction is independent of a blood pressure-elevating intervention.

References

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