EDITORIAL

Does Tail-Cuff Plethysmography Provide a Reliable Estimate of Central Blood Pressure in Mice?

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Radiotelemetric recording is widely recognized as the best method for establishing a blood pressure phenotype, or evaluating interventions that affect blood pressure, in mice.[1] However, the necessary hardware and software is costly, and successful surgical implantation of the transmitters requires some skill. Furthermore, the transmitter-catheter system is too large for use in mice below a certain weight range and generally requires ligation of a major artery (carotid) supplying the brain with blood.[2] Although prolonged surgical recovery from radiotelemetry transmitter implantation surgery is possible and desirable before starting blood pressure measurements, there also is some concern about the impact on blood pressure of the surgery itself and the requirement for a relatively large foreign body to be resident in the abdominal cavity or under the skin.[3]

For these reasons, there are situations in which many investigators choose to use the more traditional method of tail-cuff plethysmography to either establish the blood pressure phenotype of a strain of mice or to assess the effects on blood pressure of an experimental intervention. However, just as with plethysmographic methods used in humans, highly contrasting findings have been reported on the reproducibility and accuracy of tail-cuff blood pressure measurements in mice. In this issue of *JAHA*, Brain et al[4] review much of the earlier work on the topic and report on their own careful and thorough studies using the now gold-standard technique of radiotelemetry to evaluate the accuracy of the tail-cuff method in mice. In addition, they sought to identify the technical factors most likely to affect the accuracy of tail-cuff measurements.

Included among the potentially relevant technical factors investigated were: several distinct methods for handling the mice before blood pressure measurement; stress responses associated with restraint or with cuff inflation; previous heating of the animals (necessary to maximize blood flow to the tail); and even the sex of the investigator doing the measurements, given that this was shown by others to potentially influence tail-cuff blood pressure values in mice.[5] Finally, because some users of the technique report that more reproducible measurements can be obtained when mice are "trained" on the procedure,[6] the authors explored the possibility that, through repetition, mice could be habituated to the technique with the goal of attenuating any stress-related effects on blood pressure during measurement.

The results related to technical factors that might influence blood pressure values obtained using the tail-cuff method were interesting and, to a degree, unexpected. First, even the mere entry of the investigator into the room where measurements were performed, and moving the cages in which the mice were housed, was sufficient to slightly increase telemetrically determined arterial pressure and heart rate. Less surprisingly, handling the mice was associated with large and significant increases in these hemodynamic variables; similar increments were observed regardless of which of the 3 handling techniques was used. These effects were all rather short-lived. On the other hand, restraint of the mouse and inflation of the cuff on the tail caused large and sustained increments in blood pressure and heart rate. Moderate heating to induce dilation of the tail artery did not change either variable. Similar results were obtained regardless of the sex of the investigator performing the measurements. Finally, in agreement with most other published reports, the authors found that changes in blood pressure and heart rate induced by restraint stress and tail-cuff inflation did not diminish in magnitude, even after many repeated trials.

How did blood pressure values determined from tail-cuff measures compare with simultaneously obtained values using radiotelemetry? The data showed that tail-cuff readings were, on average, 39.3±16.1 and 31.4±19.4 mm Hg (mean±SD)

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lower than telemetric measurements for systolic and diastolic blood pressure, respectively. Furthermore, and importantly, there was wide animal-to-animal variation in the degree to which tail-cuff measures underestimated "true" (ie, telemetric) blood pressure. The authors discuss possible reasons for this disparity, including the yet untested idea that blood pressure in the dilated tail artery might, in fact, be substantially lower that blood pressure in the "central" arterial system (in the animals studied here, the tip of the radiotelemetry pressure catheter was in the aortic arch). This is not an implausible idea given the small size of the murine vasculature and the fact that systolic and mean arterial pressures measured using a central catheter were reported to correlated well with telemetric measurements.[6] Whatever the explanation, it is evident that blood pressure derived from the tail-cuff technique is not an accurate (nor very reproducible) estimate of actual central blood pressure in mice.

Nevertheless, "resting" blood pressures obtained nonsimultaneously by radiotelemetry and tail cuff were found to correlate reasonably well (r=0.51 for systolic blood pressure and 0.47 for diastolic blood pressure). It seems likely that this was largely a fortuitous result of the fact that the tail-cuff technique underestimates central arterial pressure by almost exactly the same amount that restraint stress increases central arterial pressure (ie, $\approx$35 mm Hg). Finally, tail-cuff measurements revealed a similar rise in blood pressure during chronic angiotensin II infusion (a common experimental model of hypertension) as did radiotelemetry. It is important to remember, though, that the tail-cuff measurements could reflect an actual effect of angiotensin II on central blood pressure (the desired variable) or merely an effect of angiotensin II on the blood pressure response to acute restraint stress. Differentiating these 2 possibilities would require telemetric measurements, as has been shown previously with other models of hypertension.[7]

Overall, this careful and thoughtful study strongly suggests important caveats to the routine use of tail-cuff blood pressure recording in mice, especially if small interindividual differences in blood pressure are a critical aspect of the experimental design, for example, when it is desirable to correlate blood pressure in individual animals with other quantitative measures from that animal. It is unlikely, however, to be the last word on the subject. For example, some strains of mice may be found that exhibit only minor hemodynamic responses to restraint stress. New technical approaches to tail-cuff plethysmography may be developed that are less stressful to mice. Or, it may be possible to use current tail-cuff systems, but reduce stress responses, by applying light anesthesia or other drug treatments before blood pressure measurement.[8] The widespread use of genetically modified mice to investigate the biology of blood pressure regulation, and the costs and other limitations for radiotelemetry in this species, certainly warrant continuing efforts to develop reliable and inexpensive noninvasive methods to determine blood pressure in this species.

Disclosures

None.

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