Letter to the Editor: When what you see might not be what you get: prudent considerations of anesthetics for murine echocardiography

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TO THE EDITOR: we read with great interest the recently published article by Pachon et al. (5) in the American Journal of Physiology-Heart and Circulatory Physiology. In their well-designed experiments, the authors compared four popular anesthetic regimens (ketamine-xylazine, ketamine alone, avertin, and isoflurane) used in mice during echocardiographic measurement, with conscious state as a reference. They elegantly demonstrated that the anesthetic with the least effect on left ventricular (LV) function and heart rate was ketamine alone at a dose of 150 mg/kg. Although isoflurane is the most commonly used anesthetic in mouse echocardiography (shown by the authors in Table 1), surprisingly, it was second to last among the four anesthetics in maintaining normal LV function and heart rate. They thus clearly concluded that ketamine is the best anesthetic, as opposed to isoflurane.

Although that referenced study was well performed, we believe that the findings allow for alternative interpretations. Currently, all known anesthetics have effects on the sympathetic and parasympathetic nervous systems, vascular tone, and contractile properties of the myocardium (8). In other words, the autonomic nervous system could play an important role in LV function and heart rate during ketamine-induced anesthesia. Indeed, several lines of evidence have indicated that ketamine induces agitation, muscle hypertonicity and spasm, hyperexcitability, hypertension, and tachycardia, which can be regarded as side effects of sympathomimetic stimulation by ketamine (6). Other studies have also suggested that ketamine produces more remarkable negative effects than isoflurane both on LV systolic function and as a whole. For instance, awakening times are shorter in mice exposed to isoflurane versus ketamine, as referenced by us and others (3, 9). We have also reported that no significant differences were found in LV systolic function or heart rate between mice exposed to 1% isoflurane and those exposed to 2.5% isoflurane (11), whereas Xu et al. (10) demonstrated that when accompanying equivalent doses of xylazine, 100 mg/kg ketamine resulted in a lower heart rate than did 50 mg/kg ketamine, suggesting that ketamine was more inclined to interfere with cardiovascular homeostasis. In summation, mild reductions in LV function and heart rate in ketamine-administered mice might not result from the minimal depressant effect caused by the anesthetic; on the contrary, they may be a result of significant activation of the autonomic nervous system.

The selection of an optimal anesthetic agent must also be placed in the context of the operation being performed, the individual animal and the operator. Several of the criteria that are applied to mouse surgery can also serve as good standards for mouse echocardiography, including the following: 1) ease of handling, 2) a low-stress induction and recovery, 3) minimal impact on physiological parameters, 4) the ability to adjust the level of anesthesia or to prolong it if necessary, and 5) rapid recovery from the anesthesia (1). Notably, in many cases, diastolic function is required in addition to LV systolic function, which would be difficult to calculate with merged E waves and A waves due to the relatively high heart rate that occurs as a result of intraperitoneal anesthesia (7). Moreover, in the more recently developed echo techniques for systolic function measurement, such as speckle tracking-based strain imaging, inhalatory anesthesia is more preferable than intraperitoneal anesthesia because of its stability during observations (2, 9).

We agree with the authors that the values of LV systolic function and heart rate derived from ketamine are closer to those obtained during a conscious state, which is helpful to explain the higher LV ejection fractioning that was observed in our earlier studies using intraperitoneal anesthetics (4). However, whether ketamine has fewer depressant effects or causes marked activation of the autonomic nervous system is debatable. Further research into autonomic imbalance is warranted to provide a rational basis for solving this conundrum. Moreover, a complete set of variables that influences the selection and optimization of anesthetic regimens for mouse echocardiography should be taken into account, not merely the virtual values of LV systolic function and heart rate.

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