Anesthetic concerns for the cardiac examination of the great apes  
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When considering echocardiographic examination of cardiac function in the great apes, the main goal is to correctly identify and diagnose animals with cardiac disease, ante mortem. A secondary goal, if cardiac disease is diagnosed and treated, is to be able to assess the effects of any therapeutic interventions. Because the heart disease that has been described in the great apes is characterized by myocardial and systolic dysfunction, the use of drugs that artifactually result in decreased systolic function (e.g., ejection fraction) may result in the incorrect diagnosis of heart disease, and the possibility of instituting unnecessary therapeutics.

A relevant concern regarding echocardiography in the great apes is the fact that most (if not all) animals must be anesthetized for a complete exam (although progress is being made towards awake echocardiography in some species). General anesthesia is necessary for the safety of the echocardiographer as well. Thus, a complete echocardiographic exam in a great ape requires general anesthesia, and the examining veterinarian must take the drug effects on the cardiovascular system into consideration. The optimal anesthetic drugs thus have minimal effects on the cardiovascular system (especially for those animals that may have preexisting heart disease), and should allow clear delineation between diseased and healthy hearts. In addition, qualities such as reversibility, speed of induction, and ease of administration should be considered.

Anesthetics that have been used for immobilization of the great apes include ketamine, with or without adjunct tranquilizer (such as midazolam or other benzodiazepine); telazol, a proprietary mixture of tiletamine and zolazepam; and medetomidine, in combination with either telazol or ketamine.\textsuperscript{1,2} All of these protocols generally provide safe and effective immobilization, and can allow maintenance of anesthesia via endotracheal intubation and inhalant anesthetics or a total or partial intravenous anesthesia.

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In normal animals, the dissociative agents (ketamine, tiletamine) generally result in a mild increase in heart rate, which increases cardiac output. This is generally due to an increase in sympathetic tone. Based on echocardiographic studies in cats and rats, cardiac fractional shortening is maintained following ketamine and telazol. Anesthesia with ketamine alone did not affect the appearance of the electrocardiogram in squirrel monkeys, and the echocardiographic ejection fraction obtained in awake monkeys (74.5±9%) was greater than that obtained from squirrel monkeys anesthetized with a combination of ketamine (30 mg/kg) and xylazine (6 mg/kg) (58%), which was likely a result of the xylazine (ejection fraction is similar, but not synonymous with the fractional shortening, although both are indicators of left heart function). In cynomologous monkeys, a comparison of echocardiographic parameters obtained under anesthesia with ketamine (10 mg/kg) or telazol (4 mg/kg, with atropine), showed no difference between the two drugs with regards to systolic cardiac function, with a fractional shortening of 39 ± 8% and 40 ± 8%, respectively.

The expected cardiovascular effects of alpha-2 agonists (xylazine, detomidine, medetomidine, dexmedetomidine) are generally referable to the strong increase in systemic vascular resistance (SVR) caused by interaction of the drug with the alpha receptors on the peripheral vasculature. The intense vasoconstriction results in a reflex bradycardia (which can be profound, and which may also result in the appearance of ventricular ectopy). A secondary effect of the increased SVR is an increased afterload in the cardiovascular system, which provides a pressure gradient for the left ventricle (LV) to pump against. decreases in LV blood flow results in decreased cardiac output (due to both decreased stroke volume and decreased heart rate). As the peripheral vasoconstrictive effects of the drugs wane (usually after 30-60 minutes, this effect is dose dependent), the central effects (primarily decreased sympathetic output) become more pronounced, and animals may develop hypotension.

Echocardiographic examinations of animals that have received alpha-2 agonists are notable for the presence of an enlarged LV (due to impaired LV outflow and slow heart rate). Significant increases in LV pressure may also result in the

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appearance/induction of mitral valve regurgitation, which may or may not be present when not under the influence of the drugs. The increased LV pressure may result in left atrial enlargement, and the appearance of systolic dysfunction. These effects do not seem to be dose dependent.⁹ In humans administered 1.4 mcg/kg of medetomidine IV, cardiac output decreased by 23%,¹⁰ and another study found a 41% maximum decrease in cardiac index following administration of 2 mcg/kg IV dexmedetomidine to humans.¹¹ These results are similar to those seen in gorillas who were initially anesthetized using ketamine (5-7 mg/kg) and medetomidine (50-70 mcg/kg) IM and subsequently anesthetized with sevoflurane, followed by reversal with atipamezole. In these gorillas, some of whom were receiving ACE inhibiting drugs, the fractional shortening as calculated by echocardiography increased from 43.3±4.5 to 61.4 ± 4% following atipamezole therapy (with continued sevoflurane anesthesia).² Similar effects on fractional shortening have been noted in dogs (a drop of 10% to 21±5%)¹², cats (a drop of 20% to 27 ± 7%),¹³ and wolves.¹⁴ A fractional shortening in humans and dogs with normal cardiac function is expected to be above 25%, with minor variability, so some of these values could be consistent with systolic dysfunction, which may be an indicator of cardiomyopathy.

Inhalant anesthetics also have depressant effects on cardiac function; in dogs, isoflurane resulted in decreases in fractional shortening and ejection fraction,¹⁵ and sevoflurane does the same in humans and dogs.¹⁶ The use of other medications for induction and maintenance of anesthesia lowers the amount of inhalant anesthetic that is necessary for general anesthesia, and the cardiodepressant effects are generally dose related.

In animals with cardiac disease, the effects of different anesthetics on cardiac function are not well characterized. Due to overall increases in sympathetic tone, ketamine may predispose animals to cardiac arrhythmias, and tachycardia may result as well, but a dissociative protocol may be safest with compromised animals.¹⁴ Pagel et al. evaluated single doses of dexmedetomidine (from 1.25 – 5 mcg/kg) in dogs with pacing-induced cardiomyopathy.¹⁷ In this study, while dexmedetomidine resulted in decreases in heart rate, aortic flow and stroke volume,
these changes were not significantly different from the echocardiographic parameters following dexmedetomidine documented in the dogs before the induction of cardiomyopathy. The similarities of this experimentally-induced disease to the naturally-occurring cardiomyopathy in the great apes is unclear. In great apes that are receiving drugs that affect heart rate or systemic blood pressure, the effects of alpha-2 agonists may be magnified. In particular, the combination of dexmedetomidine and a beta-blocking agent has been associated with hypotension in humans, although another study that administered low doses of dexmedetomidine did not document specific adverse effects in patients receiving medications for hypertension. In animals with hypertrophic cardiomyopathies with LV outflow tract obstruction (e.g. cats), the use of medetomidine is associated with a slowing of the heart rate which may actually improve LV outflow due to a decreased obstruction to flow. In clinical usage, there is not a difference between medetomidine or dexmedetomidine, other than dosage. The systemic sympatholysis that results from use of alpha-2 agonist drugs may be beneficial in patients with diseases associated with high circulating catecholamines.

Although there is not sufficient data to provide a clear contraindication on the use of alpha-2 agonists for anesthesia of great apes that will undergo cardiac examination or in those who may have cardiac disease, the risk/benefit ratio of a protocol using a dissociative agent with or without tranquilizer may be superior to a protocol using alpha-2 agonist medications. Whilst the alpha-2 agonists are useful adjuncts to anesthesia and provide sedation, anxiolysis, and analgesia, the effects on cardiac function may result in incorrect echocardiographic diagnoses of heart disease in some animals, and may put animals with preexisting heart disease at increased risk of anesthetic-related death. The latter argues against the practice of induction of anesthesia with an alpha-2 agonist that is subsequently reversed, as the vasoconstriction is most intense at the onset of anesthesia, and the later effects are primarily hypotension and bradycardia, which may be magnified by other anesthetic drugs (eg. inhalant anesthetics) and by atipamezole (through its actions as an alpha receptor antagonist.)

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References:


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Additional references:


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