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Effects of two different anesthetic protocols on cardiac flow measured by two dimensional phase contrast MRI

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Abstract

Companion animals are anesthetized or heavily sedated to comply for cardiac MRI and different anesthetic protocols are expected to have variable effects on functional parameters measured. This study compared two anesthetic protocols (Protocol A: Midazolam, fentanyl; Protocol B: Dexmedetomidine) for their effect on quantitative and qualitative analysis of blood flow through the aortic, pulmonic, mitral and tricuspid valves using 2D phase contrast (PC) MRI in dogs. Mean flow per heartbeat through the pulmonary artery (Qp) and aorta (Qs) was compared to right (RVSV) and left (LVSV) ventricular stroke volumes determined using 2D Cine balanced steady-state free precession MRI as a reference standard. Pulmonary to systemic flow ratio (Qp/Qs) was also calculated. Differences in flow and Qp/Qs values generated using 2D PC MRI were not different between the two anesthetic protocols ($P=1$). Mean differences between Qp and right ventricular stroke volume (RVSV) were 3.82 (95% limits of agreement: 3.62, -11.26) ml/beat and 1.9 (-7.86, 11.66) ml/beat for anesthesia protocols A and B, respectively. Mean differences between Qs and left ventricular stroke volume (LVSV) were 1.65 (-5.04, 8.34) ml/beat and 0.03 (-4.65, 4.72) ml/beat for anesthesia protocols A and B, respectively. Mild tricuspid or mitral reflux was seen in 2/10 dogs using 2D PC MRI. No aortic or pulmonic insufficiency was observed. This study provides baseline data for evaluation of cardiac blood flow using 2D PC MRI in dogs. Where as no significant difference of cardiac blood flow was found for the anesthetic protocols used, verification in clinically affected patients is desirable.

Keywords

mitral; tricuspid; aortic; pulmonic; heart; dog

Introduction

Currently the assessment of flow through the mitral, aortic, tricuspid and pulmonic valves is routinely performed clinically by Doppler echocardiography in companion animals^{1–4}. Alternative diagnostic imaging modalities include scintigraphic and selective or non-selective angiograms, however, they provide limited functional and morphological information compared to Doppler echocardiography^{5, 6}.

Cardiac magnetic resonance imaging (MRI) offers an alternative to evaluate cardiac morphology and function using electrocardiographic (ECG) triggered cine imaging. Morphological and functional imaging of the heart is primarily conducted using Cine balanced steady-state free precession (SSFP) sequences while flow imaging with MRI is done using flow-sensitive phase contrast (PC) sequences. These techniques are widely used in human cardiac MRI^{7, 8}, and cardiac MRI has found rapidly increasing interest in veterinary patients at in the recent years^{9, 10, 11, 12–16}, even though the potential role of MRI in veterinary cardiology has been critically discussed¹⁷. In contrast to human patients, veterinary patients need to be anesthetized, or at least heavily sedated to undergo these exams, potentially altering cardiovascular parameters. Even though this poses a potential disadvantage to a standard echocardiogram that can be performed on the awake canine patient, MRI exams allow for more opportunities for combined functional and anatomical imaging that may be especially valuable in patients with congenital heart disease. Dogs are often used as experimental models in human medicine^{18–20} but the companion animal patient may currently be underutilized as translational model for congenital as well as acquired cardiac disease.

Since different anesthetic/analgesic agents vary in their cardiovascular effects, we studied two separate, clinically applicable anesthetic protocols using either fentanyl/midazolam or dexmedetomidine as adjuncts. Fentanyl is a commonly used μ -opioid receptor agonist in dogs^{21, 22} with a rapid onset of action and short duration²³. In awake animals, fentanyl produces minimal cardiac depression²⁴, whereas it is associated with bradycardia in isoflurane-anesthetized dogs²⁵. Similarly, midazolam has little effect on the cardiopulmonary system at clinically relevant doses^{26, 27}. In contrast, dexmedetomidine, an α -2 adrenergic receptor agonist, may be associated with bradycardia which is desirable for image quality but may cause profound cardiovascular depression, even at low doses^{28–30}.

The aim of this study was to establish normal values for 2D PC MRI flow quantification through the tricuspid (TV), mitral (MV), pulmonic (PV) and aortic (AV) valves and compare the effects of these two distinct anesthesia protocols on flow measurements through these areas.

Material and Methods

The University of Wisconsin's Institutional Animal Care and Use Committee approved all procedures. Ten purpose bred healthy beagle dogs with a mean age of 10.4 (range 7–20) months and mean body weight of 10.7 (range 8.9–12.7) kg were used in this study. All dogs underwent standard auscultation and echocardiography while conscious without any

sedation by a board certified cardiologist to evaluate for normalcy prior to MRI. Dogs were examined using MRI on two different days (2–14 days apart), using a different anesthetic regimen on each day.

Anesthesia

Venous access was secured in all dogs with a 20G catheter in both the right and left cephalic veins; the right was used for contrast administration, the left for anesthetic drug and maintenance fluid administration. Two anesthetic protocols were used: Protocol A: fentanyl (West-ward, Eatontown, NJ 07724, USA) 2–5µg/kg intravenous (IV) bolus for premedication followed by 10–20µg/kg/hr and midazolam (Hospira, Inc., Lake Forest, IL 60045, USA) 0.1–0.2mg/kg bolus followed by 0.1–0.2mg/kg/hr continuous rate infusion (CRI). Protocol B: dexmedetomidine (Dexdomitor®, Pfizer Animal Health, New York, New York, 10017, USA) 1–2µg/kg bolus for premedication and 1–2µg/kg/hr CRI. The dogs also received intravenous crystalloid Lactated Ringer's Solution (5–10 ml/kg/hr; Abbott Laboratories, North Chicago, IL 60064, USA) through the left cephalic catheter. Anesthesia was induced in all dogs using a propofol bolus to effect (2–6 mg/kg) for each of the two imaging events. The animals were orally intubated, placed in dorsal recumbency in a custom made trough for positioning and maintained on isoflurane (1–2%) and 100% oxygen using volume-controlled mechanical ventilation to achieve an end-tidal CO₂ level between 35–40mmHg (SAV 2550 Small Animal Ventilator, Smiths Medical, Dublin, OH, 43017, USA).

Standard anesthetic monitoring included pulse-oximetry to monitor heart rate, rhythm and hemoglobin saturation; blood pressure (mean, systolic and diastolic) was monitored with a Cardell® Veterinary Monitor (Model 9401, CAS Medical Systems, Branford, CT, 06405, USA) and the electrocardiographic signal was collected through the MRI unit with the leads placed on the previously clipped chest of the dogs. The vaporizer setting was adjusted to ensure absence of withdrawal, palpebral reflexes with minimal jaw tone.

Magnetic resonance imaging

The MRI exams were performed using a 3 Tesla unit (Discovery MR750, GE Healthcare, Waukesha, WI, USA) using a 32-channel upper torso coil. Short breathhold was applied during the image acquisitions. Standard three plane localizers and 4 plane cardiac gated cine steady-state free precession (SSFP; transverse plane, approximate three chamber, approximate four chamber, short axis plane) acquisitions were performed. Vectorcardiographic (VCG) gating was used to trigger the timing of image acquisition to the cardiac cycle³¹. 2D PC acquisitions (TR 5.3–6ms, TE 3–3.5ms, 30 degree flip angle, 256×256 matrix, FOV 180–230×140–186, pFOV 0.7–0.8, VPS 4, ETL 1, NEX 1, BW 62.5, slice thickness 5–6mm) were performed for the aortic, pulmonic and mitral/tricuspid valves after administration of 2ml gadobenate dimeglumine (Multihance, Bracco Diagnostics Inc., Princeton, Nj, USA; 529mg gadobenate dimeglumine/ml) followed by 10ml saline flush using an automated injector to increase signal to noise ratio for the 2D PC acquisitions. The peak velocity encoding value (Venc) was set at 200cm/s for the aortic, at 150cm/s for the pulmonic, and 80cm/s for the tricuspid and mitral valves, respectively. The image plane was placed approximately 1–2cm above the sinotubular junction for the aorta, for the main pulmonary artery between the pulmonary valve and bifurcation of the main pulmonary

artery and for the atrioventricular valves through the atrioventricular groove at end diastole. All exams were performed with breath holding during image acquisition. Images were reconstructed with 20 time frames per cardiac cycle.

Image evaluation

Image evaluation was conducted by a board certified veterinary radiologist (RD) under direction of a human radiologist specialized in cardiovascular imaging (CJF). The 20 exams were randomized and the reviewer was unaware of the anesthetic protocol used per study. Semi-automated software (ReportCARD™ 4.4.6, GE Healthcare, Waukesha, WI, USA) was used for image analysis and regions of interest were manually drawn outlining the vascular lumen over the respective vessel/valve region throughout the acquired volume and the blood flow was calculated in ml/beat (Figure 1, 2). The RV and LV were segmented during end-diastole (ED) and end-systole (ES) on the cine images to calculate RV and LV stroke volumes (ED-ES), as a standard of reference for Qp and Qs, respectively. The pulmonary to systemic flow ratio (Qp/Qs) was quantified. Additionally the studies were inspected qualitatively for possible reflux at the valves. Using the short axis SSFP acquisitions regions of interest were semi-automatically drawn along the endocardial border of the left ventricle from the apex to the level of the annulus (slices with greater than 25% of annulus in the imaging plane marked the basal border of the ventricle included in the evaluation); and the volumes were automatically calculated.

Statistical analysis

Statistical analysis was performed by one of the coauthors (AMR), a PhD statistician with 4 years experience in cardiovascular imaging research. Analysis of the data was performed using R, an open source software³²; summary statistics were generated for the anesthetic and flow parameters (quartiles, mean, standard deviation (SD), minimum and maximum); mean $\pm$ 1 SD are reported. Baseline comparison between the anesthetic protocols was established using a Friedman rank sum test; significance was set as $P = 0.05$. To compare the flow values generated using the 2D PC acquisitions as well as the volumetric parameters generated using the SSFP acquisitions between the two anesthetic protocols as well as the generated Qp/Qs; the Wilcoxon signed rank test was applied. Significance was also set at $P = 0.05$ and the P-values were then adjusted with Holm-Bonferroni step-down procedure³³.

To assess for any difference between the flow values and the volumetric measurements of the left and right ventricular stroke volumes (LVSV, RVSV) within each anesthetic protocol a Bland-Altman analysis³⁴ was used and the bias, lower and upper levels of agreement are reported.

RESULTS

No significant cardiac abnormalities were detected on auscultation and echocardiogram in any of the dogs. A trivial amount of mitral regurgitation was present in 1/10 dogs and trace tricuspid insufficiency was seen in 1/10 dogs while awake using echocardiography. Using SSFP MRI acquisitions a small amount of mitral and tricuspid reflux was seen during one exam using protocol A and one exam using protocol B (total of 2/10 dogs; Figure 3). In one

of these dogs, trivial tricuspid reflux was also noted on the echocardiogram. The dog that had trivial mitral reflux present on echocardiogram did not show evidence thereof on either of the 2D PC studies. No pulmonary or aortic insufficiency was observed.

Both anesthetic protocols provided adequate anesthesia for all dogs and no complications were encountered in any of the animals. The mean heart rate with protocol A and B was 76 ± 10 bpm and 82 ± 18 bpm respectively during the time of 2D PC acquisition ($P = 1$). The diastolic (Protocol A 36 ± 5 mmHg; Protocol B 51 ± 11 mmHg) and mean arterial (Protocol A 59 ± 7 mmHg, Protocol B 76 ± 8 mmHg) pressures were significantly higher ($P=0.003$ and $P=0.012$) using protocol B. Although the systolic arterial pressure was not statistically different between groups, it tended to be higher using protocol B ($P=0.052$; 87 mmHg Protocol A vs 101 mmHg Protocol B). There was no further significant difference between the groups in the remaining analyzed vital parameters (heart rate: $P=1.0$ and end-tidal CO_2 : $P=0.075$).

Duration of the three 2D PC acquisitions was 3.14 ± 0.57 minutes. In the first dog, the acquisitions for the tricuspid and aortic valve were repeated to adjust scan parameters. One acquisition over the aortic valve was excluded from the evaluation due to misalignment of the image plane with the anatomy as no measurement could be generated.

The results for the flow values through the four areas of interest are summarized in Table 1 and Figure 4. Differences in flow measurements between anesthesia protocols were not significant ($P=1$).

Bland-Altman analysis showed small differences between 2D PC and SSFP sequences, with slightly greater variability using protocol B (Table 2).

Discussion

In this study the use of 2D PC MRI was for successfully applied in normal dogs for evaluation of right and left ventricular as well as valvular function. This, and the comparison of two applicable anesthetic protocols for use with this specific modality have not been previously documented in the veterinary literature to the authors knowledge and will help to further guide utilization of this imaging technique in veterinary cardiac patients. Whereas standard echocardiography includes Doppler evaluation of the flow pattern and velocity over the aortic, pulmonic, tricuspid and mitral valves in addition to morphological and functional evaluation of the cardiac structures¹⁻⁴, cardiac MRI examination may provide further insights into congenital or acquired conditions in companion animal patients who may also serve as a translational research model because of its greater contrast and 3D capabilities¹⁷.

Veterinary patients undergoing cardiac MRI have to be anesthetized, or at least heavily sedated, to stay in position for these exams. Compared to sedation, general anesthesia allows for breath holding and was therefore chosen in our study to enable optimal image quality. Currently, there are no standardized anesthesia protocols for cardiac MRI, which is significant because of their potential hemodynamic effects. Therefore, the aim of this study was to evaluate two different protocols on cardiac MRI flow quantification. Both protocols used an injectable drug for premedication and as continuous rate infusion during

maintenance to reduce the minimal alveolar concentration (MAC) of inhalant needed. Protocol A combined midazolam and fentanyl: Midazolam acts as a GABAA receptor agonist³⁵ and has little effect on the cardiopulmonary system at clinical doses, but causes decreased cardiac output when used at very high doses^{26, 27}; Fentanyl is an μ -opioid receptor agonist and is commonly used in dogs for analgesia, using a bolus followed by a constant rate infusion due to the rapid onset and short duration of this drugs action^{21–23}. Fentanyl produces minimal changes in cardiac index in awake animals²⁴, but bradycardia has been reported in isoflurane-anesthetized dogs²⁵. Together, these agents reduced the inhalant level required while minimizing cardiac depression.

Protocol B utilized dexmedetomidine, a α -2 adrenergic receptor agonist, that causes sedation and analgesia; constant rate infusions even at low doses are also associated with bradycardia and profound cardiovascular depression^{28,29,30, 36, 37}. It may have been speculated that the heart rate with protocol B would be lower compared to protocol A, but this effect was not seen likely due to the low dosing and combined effect with the inhalant. Even though this protocol provided adequate anesthetic level to complete the image acquisition with no purposeful movement for the healthy dogs used in our study, elevation of diastolic and mean, and borderline elevation of the systolic pressures was noted possibly due to alpha-2 receptor mediated vasoconstriction. Its use may therefore not be recommended in dogs with cardiovascular disease unable to tolerate increases in cardiac afterload.

2D phase contrast techniques exploit the sensitivity of MRI for moving protons to evaluate vessel anatomy for angiography or to measure blood flow velocities³⁸. Velocity encoding techniques subsequently use the changes associated with the MRI signal phase along a magnetic field gradient to determine blood flow velocity. Flow dependent phase changes can be identified when using bipolar velocity encoding gradients in two acquisitions that only differ slightly in the velocity-dependent signal phase^{39–41}. The background is subsequently removed by subtraction of these two phase images which allows for calculation of the velocity images in PC MRI, also called flow-sensitive MRI or MRI velocity mapping. These acquisitions are split over multiple cardiac cycles and are acquired using retrospective EKG-gating and during a breath hold; a series of time resolved (cine) images will be acquired that will represent the pulsatile flow during the cardiac cycle^{39, 41, 42}. For 2D acquisitions, velocity maps of individually placed slices are generated, that will record one directional or ‘through plane’ velocity along the predominant blood flow direction of the investigated anatomical area. For these exams a user defined upper velocity limit is set (V_{enc}), which is defined as the positive or negative maximum velocity that can be recorded without error. Above this set limit aliasing will occur. The setting of V_{enc} adjusts the strength and duration of the applied velocity encoding gradients. Encoding of lower velocities will require larger gradient areas and therefore longer time to echo and repetition (TE, TR) need to be applied^{39, 43}. Utilizing these sequences enables to quantify flow and measure flow velocity as well as valvular dysfunction.

Except for an operator error in image plane alignment from one dog, diagnostic studies were successfully acquired during all anesthetic episodes. In addition, no significant difference was found for the generated flow values between the two anesthetic protocols used in this study. Intermittent and incidental mitral or tricuspid reflux was detected as reverse flow over

the respective valve area in two dogs. As this technique has not been previously reported in companion animal patients, application of these sequences and specific anesthesia protocols in dogs with functional or morphological cardiovascular abnormalities needs to be evaluated and their use verified.

We did perform an internal verification comparing the generated measurements to those acquired using standard morphological cardiac MRI using SSFP acquisitions for volumetric evaluation of the right (RVSV) and left (LVSV) ventricular stroke volume^{10, 18, 44, 45}. The results compared favorably using the Bland-Altman analysis but greater variability between the measurements using protocol B for pulmonary flow quantification. A greater variability of the values was seen using the volumetric estimation of the right ventricular stroke volume (RVSV) that likely caused this difference, however, the origin of this discrepancy is not fully clear and deems further investigation in a larger study population as this may possibly relate to the small study group used.

Our study provides a baseline of Qp/Qs as generated using 2D PC MRI using two different protocols and no significant difference between the protocols was encountered. The Qp/Qs values, 1.08 and 1.13, are within the expected normal range accounting for the fact that aortic flow measurements were acquired above the coronary artery origins. Validation of the utility and efficacy of this technique in companion animal patients with cardiovascular abnormalities is needed. Quantification of the pulmonary to systemic flow ratio (Qp/Qs) has been previously studied in the dog using Doppler echocardiography with good repeatability and reproducibility with moderate variability in normal dogs⁴⁶. The Qp/Qs is routinely used to assess the shunt ratio in humans with known or suspected congenial heart defects. Although the gold standard for measuring Qp/Qs is invasive catheter angiography based on cardiac output measuring using the thermodilution or Fick methods, non-invasively measured pulmonary artery and aorta flow using 2D PC MRI is being used more frequently clinically⁴⁷.

A limitation of our study was the low sample size; therefore, it is possible our interpretation of the used protocols might be equivocal and due to inter-subject variation. Although the flow measurements through the pulmonary and aortic valves were validated using stroke volumes from SSFP acquisitions, no other standard of reference was used. However, SSFP sequences has been previously validated for quantification of stroke volumes and is a reasonable alternative and is considered by many to be the gold standard for ventricular volume quantification⁴⁸.

Conclusion

This study provides baseline information for the application of 2D PC MRI and comparison to stroke volume measured using the Simpson Method in steady-state free precession (SSFP) cine MRI acquisitions when applying two different applicable anesthetic protocols in dogs. Evaluation of valvular function showed transient mitral and tricuspid dysfunction. Where as no difference between the anesthetic protocols was encountered evaluating cardiac flow in this study, use of protocol A may be preferable in clinically affected patients. Less effects on blood pressure values are expected compared to protocol B. Future use of 2D PC

MRI in evaluation of patients with congenital or acquired cardiac disease remains to be evaluated for the clinical utility of this diagnostic imaging method.

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Figure 1.

Two dimensional phase contrast MRI images showing positive through plane flow (cm/s) displayed in lighter shades of grey (Ao (A), P (B)), negative trough plane flow (cm/s) displayed in darker shades of grey (T, M; C). LV = left ventricle, LA = left atrium, RV = right ventricle

Figure 2.

Time-Velocity curve generated from the through-plane 2D PC MRI sequences ReporCARD® software. Flow (ml/s) is given over the aortic and pulmonic valves in positive values and for the mitral and tricuspid valves in negative values based on the direction of the respective flow through the plane, flow per beat (ml/beat) is calculated automatically by the software and given below the graph.

Figure 3.
Phase difference 2D PC image showing trace mitral (A) and tricuspid (B) reflux (arrows) that was inconsistently seen in two dogs and considered transient and insignificant. T = tricuspid valve region, right ventricular inflow Tract; M = mitral valve region, left ventricular inflow tract; Ao = aorta; P = main pulmonary artery

Figure 4.

Box plots for comparison of the flow measured over the aortic (AV; A), pulmonic (PV; B), mitral (MV; C) and tricuspid (TV; D) valve and the calculated Qp/Qs (E) using anesthetic protocols A (MidFent) and B (Dex). No significant differences were found between protocols. The connected dots represent the individual dogs evaluated.

Table 1

Results of the 2D PC flow analysis over the aortic (Ao), pulmonic (PA), mitral and tricuspid valve comparing the results using two different anesthetic protocols. Pulmonary to systemic flow ratio (Qp/Qs) was calculated. There was no significant difference in flow measured over either valve using 2D PC or volumetric measurement of left and right ventricular output using steady-state free precession (SSFP) cine acquisitions comparing protocol A versus protocol B ($P > 0.05$).

	Protocol A (ml/beat)	Protocol B (ml/beat)	Holm-Bonferroni Adjusted P-values
Ao (Qs)	20.74 ± 3.51	18.01 ± 4.91 *	0.223
PA (Qp)	23.26 ± 3.15	18.31 ± 3.01	0.068
Mitral valve	11.96 ± 4.79	9.14 ± 4.64	0.262
Tricuspid valve	12.21 ± 7.12	7.79 ± 5.31	0.109
Qp/Qs	1.13 ± 1.16	1.08 ± 0.28 *	1

* One acquisition was excluded due to misalignment of the image plane; only 9 dogs are included in the analysis.

Table 2

Bland-Altman Analysis was used to compare the flow values generated over the aortic (Ao) and pulmonic (PA) valves using the 2D PC to the volumetric measurements of left and right ventricular stroke volumes (LVSV, RVSV) generated using steady-state free precession (SSFP) acquisitions. The mean difference (bias), 95% upper and lower level of agreement (ULOA, LLOA) and the percentage difference to the left (LVSV) and right (RVSV) ventricular stroke volume calculated from the steady-state free precession (SSFP) acquisitions (%) are given below.

	LLOA	Bias	ULOA
Protocol A			
Ao (Qs) vs LVSV (ml/beat)	− 5.04 (−26.4%)	1.65 (8.64%)	+ 8.34 (43.66%)
PA (Qp) vs RVSV (ml/beat)	− 3.62 (−18.6%)	3.82 (19.65%)	+ 11.26 (57.94%)
Protocol B			
Ao (Qs) vs LVSV (ml/beat)	− 4.65 (−27.1%)	0.03 (0.2%)	+ 4.72 (27.5%)
PA (Qp) vs RVSV (ml/beat)	− 7.86 (−47.9%)	1.9 (11.6%)	+ 11.66 (71.0%)