Study on right ventricular morphology and function evaluated by right heart catheterization and echocardiography in dogs

Summary of Doctoral Thesis

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With recent academic and technological advances in veterinary medicine, many veterinarians have increased opportunities to diagnose pulmonary hypertension (PH), a life-threatening disease that induces right ventricular (RV) pressure overload. Therefore, the evaluation of the right heart system has received increased attention. Currently, echocardiography is the most common modality to evaluate the right heart system. However, echocardiographic indices for RV morphology and function have been reported to be influenced by changes in loading conditions, which might complicate the interpretation of right heart pathophysiology. Furthermore, few studies have compared RV morphological and functional indices obtained by echocardiography and right heart catheterization in dogs, although right heart catheterization is a gold standard for evaluating RV function.

Therefore, in order to investigate the influence of various loading conditions on echocardiographic indices for RV morphology and function, our studies aimed to evaluate RV morphology and function using right heart catheterization and echocardiography in dogs under changes in the following loading conditions: increase in pulmonary arterial pressure (*i.e.*, RV afterload) in Chapter 2, myocardial contractility and venous return in Chapter 3, and respiration and heart rate in Chapter 4. Additionally, in Chapters 5 and 6, we investigated the RV morphology and function in dogs with myxomatous mitral valve disease (MMVD), the most common cardiac disease and the most common cause of PH in dogs. Furthermore, we evaluated the clinical utility of tricuspid annular plane systolic excursion (TAPSE) normalized by RV size indicators and pulmonary vascular resistance estimated by echocardiography in dogs with MMVD.

Chapter 2. Influence of increase in right ventricular pressure overload due to microsphere embolization on right ventricular morphology and function in dogs.

Naturally, the right heart has significantly lower pressure than the left heart, and is critically affected by pulmonary artery pressure (pressure load). In this study, we investigated the changes in various echocardiographic RV indices associated with the increase in pulmonary arterial pressure in dogs experimentally induced chronic embolic PH.

Seven healthy beagles were used in this study. In non-sedated dogs, pulmonary arterial pressure (PAP) was increased by embolization of 150–300 μm microsphere into the peripheral pulmonary artery through a multipurpose catheter set at main pulmonary arterial pressure. When systolic PAP (sPAP) reached 30, 40, and 50 mmHg, all dogs underwent echocardiography including two-dimensional speckle tracking echocardiography (2D-STE). Additionally, When the sPAP was maintained at 50 mmHg or more for 4 weeks without injection of microspheres, the time point was defined as "chronic" and echocardiography was performed.

In this study, 2D-STE-derived RV longitudinal strain (RV-SL) was decreased at sPAP 30 mmHg compared with baseline, and was gradually increased at sPAP 40 and 50 mmHg compared with sPAP 30 mmHg. Additionally, RV-SL and RV longitudinal strain rate (RV-SrL) was decreased at chronic phase compared with sPAP 50 mmHg, although dogs in chronic phase also had sPAP 50 mmHg or more.

The changes in 2D-STE-derived RV-SL and RV-SrL with increasing sPAP could reflect RV adaptive remodeling to RV pressure overload in the acute phase and nonadaptive remodeling to chronic and excessive pressure overload. Therefore, 2D-STE indices could detect the RV compensative mechanism against PH pathophysiology.

Chapter 3. Influence of changes in right ventricular contractility and volume overload on right ventricular morphology and function in healthy dogs: clinical utility of real-time three-dimensional echocardiography.

Right heart is responsible for pulmonary circulation, which receives venous blood return from the entire body and circulates it to the lungs. Therefore, the right heart would be critically influenced by venous return. In this study, we investigated the influence of changes in RV contractility and venous return on RV morphology and function evaluated by RV pressure-volume loops and echocardiography in dogs.

Ten healthy anesthetized beagles were used in this study. Each dog underwent RV pressure-volume loops measurement and two- and three-dimensional echocardiography (2DE and 3DE, respectively) when 10 minutes after continuous administration of 5 and 10 μg/kg/min dobutamine, 15 and 30 minutes after infusion of

lactated Ringer's solution at a rate of 150 mL/kg/hour, and 15 and 30 minutes after administration of 4.0 mg/kg furosemide.

In this study, 3DE-derived RV volume, ejection fraction, and stroke volume could detect the changes in the RV pressure-volume loops with altered RV contractility and volume loading conditions. Additionally, a ratio of stroke volume to end-systolic RV volume obtained by 3DE was significantly associated with a ratio of end-systolic elastance to effective arterial elastance (Ees/Ea), an indicator of RV–pulmonary arterial coupling. Whereas, the strongest association with end-systolic elastance (Ees), an indicator of load-independent RV myocardial contractility, was observed in the 2D-STE indices.

These results indicate that 3DE could detect the changes in RV morphology that could not be detected by 2DE. Additionally, 3DE might be useful for estimating RV-pulmonary arterial coupling. Whereas, 2D-STE had superior usefulness in the evaluation of intrinsic RV myocardial contractility.

Chapter 4. Influence of respiration and changes in heart rate on right ventricular morphology and function in healthy dogs.

Respiration changes the venous return through the fluctuation in intrathoracic pressure. Additionally, an increase in heart rate (HR) has two aspects: one is a decrease in venous return due to the shortening of relaxation time, and the other is an increase in myocardial contractility through force-frequency relation. In this study, we investigated the influence of respiration and changes in HR on RV morphology and function evaluated by RV pressure-volume loops and echocardiography in dogs.

Eight healthy anesthetized beagles were used in this study. Each dog underwent RV pressure-volume loops measurement and echocardiography for when inspiratory phase (*i.e.*, positive pressure ventilation), expiratory phase, and each right atrial pacing rates: baseline, 120, 140, 160, and 180 bpm.

In this study, conventional RV functional variables including TAPSE and 2D-STE-derived RV-SL were significantly decreased during the inspiratory phase and with an increase in HR. However, Ees showed no significant change with respiration and was

increased with increased HR. Similar tendencies were observed between Ees and 2D-STE-derived RV-SrL. In the multiple regression analyses, RV-SrL obtained from the whole right ventricle showed a significant association with Ees, and RV-SrL obtained from the RV free wall showed a significant association with Ees/Ea.

Our results suggested that conventional RV functional variables would be critically influenced by changes in intrathoracic pressure and venous return associated with respiration and HR. Whereas, 2D-STE-derived RV-SrL might be useful for estimating Ees and Ees/Ea non-invasively.

Chapter 5. Echocardiographic assessment of right ventricular morphology and function in dogs with myxomatous mitral valve disease: clinical utility of tricuspid annular plane systolic excursion normalized by right ventricular size indicators.

As we found in Chapters 2 to 4, 2D-STE was expected to be useful as non-invasive indices reflecting RV myocardial contractility and RV–pulmonary arterial coupling. On the other hand, conventional RV functional indices, including TAPSE, might overestimate or underestimate RV function depending on changes in loading conditions, suggesting that loading conditions should be taken into account when evaluating RV function using conventional RV functional indices. In this study, we investigated detailed RV myocardial function using 2D-STE in dogs with MMVD, the most common cardiac disease and the most common cause of PH in dogs. Additionally, we evaluated the clinical utility of TAPSE normalized by RV size indicators in dogs with MMVD.

Client-owned 20 healthy dogs and 71 dogs with MMVD were prospectively enrolled in this study. Dogs with MMVD were classified into one of four PH severity groups: non-, mild, moderate, and severe PH. Each dog underwent echocardiography including 2D-STE. The TAPSE was normalized by RV size indicators (*e.x.*, RV internal dimension, RV area, and RV wall thickness).

The RV-SL, systolic and early-diastolic RV-SrL showed higher in the moderate PH groups and lower in the severe PH group. Additionally, TAPSE normalized by RV size indicators showed the same tendency as RV-SL and had a significant correlation with RV-SL.

Our results of 2D-STE suggested that the right ventricle was adapted to mild to moderate PH pathophysiology by activating RV systolic and diastolic function. However, both RV systolic and diastolic function would be impaired in the severe PH, reflecting maladaptation of the right ventricle. Additionally, TAPSE normalized by RV size indicators, especially TAPSE normalized by end-diastolic RV internal dimension, was able to detect the RV systolic dysfunction in severe PH pathophysiology, which could not be detected by non-normalized TAPSE.

Chapter 6. Clinical utility of pulmonary vascular resistance estimated by echocardiography in dogs with myxomatous mitral valve disease.

Pulmonary hypertension secondary to left heart disease is called post-capillary PH. Increased pulmonary vascular resistance (PVR) contributes to the pathophysiological progression of post-capillary PH (*i.e.*, progression to combined post- and pre-capillary PH [Cpc-PH]) and is associated with poor prognosis in patients with post-capillary PH. In this study, we evaluated the clinical utility of PVR estimated by echocardiography (PVRecho), which has been reported to be useful in human medicine, in dogs with MMVD.

Client-owned 54 dogs with MMVD and detectable tricuspid regurgitation (TR) were enrolled in this study. Dogs were classified into one of three PH probability groups: low, intermediate, and high probability of PH. The PVRecho was calculated using TR velocity and velocity–time integral of the pulmonary artery flow.

In this study, PVRecho was a significantly higher value with the increase in PH probability. Additionally, increased PVRecho was significantly associated with the presence of right-sided heart failure.

Our results suggested that PVRecho might be an additional useful tool to detect the increased PVR (*i.e.*, progression to Cpc-PH). Additionally, since PVRecho was calculated using TR velocity and velocity–time integral of the pulmonary artery flow, PVRecho might also reflect the RV performance, reflecting the balance of RV afterload and RV systolic function. Consequently, PVRecho would be useful for the diagnosis and stratification of PH in dogs with MMVD.

Overall, this study revealed that changes in loading conditions associated with venous return, respiration, and heart rate might cause some dissociations between right heart catheterization variables and conventional echocardiographic variables for RV morphology and function. On the other hand, novel modalities, such as 2D-STE and three-dimensional echocardiography, could be useful tools to detect RV myocardial contractility (Ees) and RV–pulmonary arterial coupling (Ees/Ea) non-invasively. Additionally, two newly proposed indicators, TAPSE normalized by RV size indicators and PVRecho, might be additional tools for evaluating detailed RV function in dogs.