The Effects of Cardiac Dyssynchrony in Dogs

Summary of Doctor Thesis

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In human medicine, numbers of large clinical trials has shown that the prolonged QRS duration is associated with survival times in heart failure patients. Wide QRS duration indicate ventricular myocardial electrical activation delay (i.e. electrical dyssynchrony). As the electrical dyssynchrony could cause dyscoordinate and inefficient stroke of left ventricular, the wide QRS duration would lead malignant prognosis. This theory has been supported by the marked effects of cardiac resynchronization therapy, which correct only electrical activation timing by pacing device. However, it was reported that the criteria for approving cardiac resynchronization therapy based on QRS duration could cause failure of treatment in 40-50 percent of patients. Therefore, not only electrical dyssynchrony but also mechanical dyssynchrony, which is the delay of myocardial contraction, would be more sensitive criteria for cardiac resynchronization therapy. A large number of indices using echocardiography, cardiac computed tomography, or cardiac magnetic resonance images have been developed for detecting mechanical dyssynchrony.

In veterinary medicine, it was reported that the QRS duration was associated with survival time in dogs with dilated cardiomyopathy, and there is a case report which described left ventricular dysfunction observed in 2 dogs with left bundle branch block (LBBB). As the electrical conduction system of dogs is similar to humans, the impairment of cardiac function by dyssynchrony could also be occurred in dogs with wide QRS duration. However, it has not been sufficiently studied how affected cardiac function by cardiac dyssynchrony and what factor would influence the effects of dyssynchrony. In dogs having higher heart rate, echocardiography would be suitable for detecting mechanical dyssynchrony, as echocardiographic study is non-invasive and have higher time resolution. However, it has not been sufficiently studied whether the echocardiographic indices is useful for identifying mechanical dyssynchrony in dogs.

This study was designed to assess 1) measurements of echocardiographic dyssynchrony indices in normal beagles, 2) the ability of dyssynchrony indices to identifying dyssynchrony in a canine model of left bundle branch block, 3) changes of cardiac function and dyssynchrony indices and effects of exercise in a canine model of left bundle branch block, 4) body size effects of the deterioration of cardiac function in a canine model of left bundle branch block.

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1. Assessment of Dyssynchrony Indices in Normal Beagles (Chapter II)

The electrical conduction time of myocardium is defined by conduction velocity and conduction distance. The reference rage of dyssynchrony indices in each breed should be determined, as body size of dog is varied widely. With regard to echocardiographic dyssynchrony indices, there is only one report which described reference range from dogs of widely variety breeds. Therefore, the dyssynchrony indices using M-mode and two-dimensional speckle-tracking echocardiography (2D-STE) were measured in 53 healthy beagles, and the possibility, repeatability, and reference rage of dyssynchrony indices were assessed. As the septal to posterior wall motion delay (SPWMD) measured as the time difference from the time point of interventricular septal peak inward motion to the time point of left ventricular posterior wall peak inward motion using M mode echocardiography had shown high repeatability and relatively narrow reference rage, the SPWMD would be simplified index for identifying dyssynchrony. With regard to the dyssynchrony indices used 2D-STE, maximal difference of time to peak radial strain for 6 segments (MaxD-TpSR), standard deviation of time to peak strain for 6 segments (6SD-TpSR), and percentage of the frame-to-frame changes which differ from the averaged strain change in systolic phase (DysSR) had shown narrow reference range similar to humans. These dyssynchrony indices would be useful to detect mechanical dyssynchrony

2. *Assessment of the ability of the dyssynchrony indices to identifying mechanical dyssynchrony in a canine model of left bundle branch block (Chapter III)*

There are several number of reports described dyssynchrony indices in dogs, but there was only one report described dyssynchrony indices in dogs with dyssynchrony, which studied the standard deviations of radial and circumferential strain for 6 segments in a canine model of dyssynchrony induced by atrioventricular node ablation and right ventricular pacing. There is no report which compared ability of dyssynchrony indices to identify mechanical dyssynchrony. Therefore, the ability of the dyssynchrony indices from M-mode and 2D-STE, included in difference between first inward peak of interventricular and left ventricular posterior wall (first SPEMD), SPWMD, MaxD-TpSR, 6SD-TpSR, and DysSR, to detect dyssynchrony were assessed in a canine model of left bundle branch block (LBBB) induced by radio frequently ablation. To assess the ability of dyssynchrony indices, receiver operator characteristic analysis was performed using ten beagles undergone left bundle branch ablation as positive control. The optimal cut-off value, sensitivity and specificity were SPWMD 42.7 ms (sensitivity 1.000, specificity 0.400), first SPWMD 143.3 ms (sensitivity 1.000, specificity 1.000), DysSR 7.32 % (sensitivity 1.000, specificity 0.900), MaxD-TpSR 13.5 ms (sensitivity 0.900, specificity 0.600), and 6SD-TpSR 4.21 ms (sensitivity 1.000, specificity 0.500). Although SPWMD would be difficult to use for identifying mechanical dyssynchrony independently, first SPWMD and indices from radial strain using 2D-STE (especially DysSR) were useful to detect mechanical dyssynchrony in a canine model of LBBB.

3. *The effects of exercise on deterioration of cardiac function via the cardiac dyssynchrony in a canine model of left bundle branch block (Chapter IV)*

With regard to changes of cardiac function in a canine model of dyssynchrony, one report had shown significant decrease of left ventricular ejection fraction immediately by induction, while the other report had shown no significant change of left ventricular ejection fraction. Therefore, it has not been clear whether the dyssynchrony could induce deterioration of cardiac function independently. Moreover, it was reported that right ventricular high frequent pacing could decrease left ventricular ejection fraction significantly. Therefore, the hypothesis that dyssynchrony with some stress could cause deterioration of cardiac function was studied. Twelve beagles (body weight 10.4 ± 1.0 kg) undergone left bundle branch ablation was divided into 2 groups; non-exercise group ($n = 6$), cage rest during observation period, and exercise group ($n = 6$), added treadmill exercise (13 km/hour, for 15 minutes, once in a day) from 2 week after ablation, and echocardiography and measurements of dyssynchrony indices were performed at before (Pre) and 4 weeks (i.e. 2 weeks after starting exercise stress; Ex2weeks) and 8 weeks (i.e. 6 weeks after starting exercise stress; Ex6weeks) after ablation. In non-exercise group, the left ventricular ejection fraction was not changed significantly (Pre vs. Ex2weeks, $p = 0.188$, Pre vs. Ex6weeks, $p = 0.087$). In exercise group, however, the left ventricular ejection fraction was decreased with time, and significant changes were observed when comparing Pre with Ex2weeks and Pre with Ex6weeks ($p = 0.030$, $p = 0.005$, respectively). In both groups, DysSR measured as an index of mechanical dyssynchrony were increased with time, and significant changes were observed as follow; in non-exercise group, when comparing Pre with Ex2weeks, Pre with Ex6weeks, and Ex2 weeks with Ex6weeks ($p = 0.004$, $p < 0.001$, $p = 0.024$, respectively); in exercise group, when comparing Pre with Ex2weeks and Pre with Ex6weeks ($p = 0.008$, $p < 0.001$, respectively). In both groups, first SPWMD was increased with time, and significant changes were observed when comparing Pre with Ex2weeks and Pre and Ex6weeks ($p < 0.001$, respectively). Dyssynchrony induced by LBBB could not cause left ventricular dysfunction independently during 8 weeks observation period, however, with exercise, it cause significant decrease of left ventricular ejection fraction with time. These findings were not according to a previous study. It might be caused by difference of body size of dogs. In both groups, echocardiographic dyssynchrony indices were increased with time. It would support the theory of "dyssynchrony begets dyssynchrony".

4. *The effects of body size on deterioration of cardiac function via the cardiac dyssynchrony in a canine model of left bundle branch block (Chapter V)*

From the results of Chapter IV, deterioration of cardiac function by dyssynchrony would be associated with body size of animals (i.e. heart size). To assess this hypothesis, six mongrel dogs (body weight 21.5 ± 3.4 kg) larger than beagles undergone left bundle branch ablation were divided into 2 group; non-exercise group (n = 3) and exercise group (n = 3). Echocardiographic study and measurements of dyssynchrony indices were performed before (Pre) and 4 weeks (i.e. 2weeks after starting exercise stress; Ex2weeks) and 8 weeks (i.e. 2 weeks after starting exercise stress; Ex6weeks) after ablation. Different from the results of Chapter IV, the left ventricular ejection fraction was decreased with time and significantly decreased when comparing Pre with Ex6weeks (p = 0.014) in non-exercise group. In both groups, DysSR measured as index of mechanical dyssynchrony were increased with time, and significant increase was observed when comparing Pre with Ex2weeks and Pre with Ex6weeks (p =0.032, p = 0.013, respectively) in exercise group. In both groups, first SPWMD were increased after ablation, and significant increase were observed when comparing Pre with Ex2weeks and Ex6weeks (p < 0.001, respectively). In large breed dog, therefore, dyssynchrony induced by LBBB could cause deterioration of cardiac function without any exercise stress. Deterioration of cardiac function via dyssynchrony would depend on body size. Although the LVEF decrease has not been emphasized by exercise stress, the dyssynchrony was developed earlier in exercise group. In large dogs, dyssynchrony was more severe than beagles. Thus, the effect of exercise might be more significant in this study.

This study confirmed that the ability of dyssynchrony indices from M mode and 2D-STE reported in human medicine were assessed in dogs, cardiac function and dyssynchrony indices changes with time were observed in a canine model of LBBB, and the factor, especially exercise and body size, could influence the effect of dyssynchrony. First SPWMD from M mode and indices from radial strain based on 2D-STE were useful to identify mechanical dyssynchrony in dogs. In these dyssynchrony indices from radial strain, DysSR would have highest reproducibility and ability to detecting mechanical dyssynchrony.

In medium size dogs, such as beagles, or more small size dogs, dyssynchrony from LBBB could not cause significant deterioration of cardiac pump function independently, though dyssynchrony with exercise could cause that. While in large size dogs, dyssynchrony from LBBB could cause left ventricular dysfunction without any exercise stress. In veterinary practice, therefore, the body size of dogs should be considered when assess mechanical dyssynchrony in dogs suspected dyssynchrony, such as dogs with ventricular electrical conduction delay, without evidence of cardiac disease. Assessment of mechanical dyssynchrony would provide beneficial information to estimate the risk of left ventricular dysfunction without primary cardiac disease. Moreover, an exercise could cause deterioration of dyssynchrony and might influence long term survival in large dogs. Even in medium or smaller size dogs suspected electrical activation delay, assessment of dyssynchrony and consideration whether exercise restriction should be imposed would be important.

In veterinary medicine, the prevalence of LBBB is relatively rare. However, the cases of dogs undergone ventricular pacemaker treatment for bradyarrhythmia have been reported frequently, and these patients would show similar electrical conduction behavior to dogs with LBBB. Therefore, evaluating dyssynchrony would be important in dogs undergone pacemaker treatment in practice. Finally, farther investigation intended for clinical cases is expected.