Review

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Jonathan Mochel * and Jessica Ward

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Review

Treatment of Canine Myxomatous Mitral Valve Disease: Current and Future Approaches

Jonathan P. Mochel [1,2,*] and Jessica L. Ward [3]

[1] Precision One Health Initiative, The University of Georgia, 30602 Athens, GA (USA)
[2] Department of Pathology, The University of Georgia College of Veterinary Medicine, 30602 Athens, GA (USA)
[3] Veterinary Clinical Sciences, Iowa State University, 50011-1250 Ames, IA (USA)
* Correspondence: jpmochel@uga.edu

Abstract: Myxomatous mitral valve disease (MMVD) is a leading cause of cardiac morbidity and mortality in dogs, requiring targeted intervention at various stages of disease progression. MMVD is characterized by thickening of the mitral valve leaflets, leading to mitral regurgitation and cardiac remodeling. This progressive disease impairs valve function, causing volume overload in the left atrium and ventricle, which can eventually lead to congestive heart failure. MMVD involves complex mechanisms, including genetic predisposition, neurohormonal activation, and mechanical stress on the valve. Thickened valve leaflets fail to seal properly during systole, resulting in mitral regurgitation and increased left atrial pressure. This triggers compensatory mechanisms like activation of the renin-angiotensin-aldosterone system (RAAS), contributing to further cardiac remodeling. Chronic RAAS activation results in fluid retention, vasoconstriction, and fibrosis, all of which can worsen heart failure. This mini-review provides an overview of current therapeutic strategies for the management of MMVD and discusses preliminary findings from our consortium regarding the preclinical and clinical efficacy of the sodium-glucose co-transporter type-2 (SGLT-2) inhibitor, dapagliflozin, in dogs.

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Narrative

Brief Overview of the Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) is a critical target in myxomatous mitral valve disease (MMVD) therapy due to its role in pathological cardiac remodeling and disease progression (Brilla et al., 1995; Wilke et al., 1996; Mochel et al., 2013; Keene et al., 2019; Borgarelli et al., 2020). The RAAS consists of several interconnected components that regulate cardiovascular homeostasis. The cascade is initiated by the release of renin from the juxtaglomerular cells of the kidneys, which catalyzes the conversion of angiotensinogen (produced by the liver) into angiotensin I. Angiotensin I is subsequently converted to angiotensin II by the angiotensin-converting enzyme (ACE), primarily in the lungs.

Angiotensin II serves as the principal effector of the RAAS, mediating numerous processes that contribute to cardiovascular pathology (van de Wal et al., 2006; Mochel and Danhof, 2015). This octapeptide functions by inducing potent vasoconstriction, stimulating aldosterone secretion from the adrenal cortex, and promoting sodium and water retention, which in turn elevate blood pressure and contribute to cardiac remodeling. Beyond its hemodynamic effects, angiotensin II also induces myocardial fibrosis and hypertrophy, which leads to progressive cardiac damage and exacerbates disease progression (Broqvist et al., 1989; Swedberg et al., 1990; Aronson and Burger, 2003).

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Recent studies have elucidated alternative RAAS pathways, notably the ACE2/angiotensin-(1-7)/Mas receptor axis, which exerts counter-regulatory effects against the classical angiotensin II/AT1 receptor pathway (Zhuo et al., 2013). The interplay between these pathways is key in modulating the overall impact of RAAS activation on cardiovascular physiology. Activation of ACE2 results in the production of angiotensin-(1-7), a peptide with vasodilatory, antifibrotic, and anti-inflammatory effects, which effectively mitigates the pathophysiological effects of angiotensin II (Ichihara et al., 2004; Esteban et al., 2009).

Chronic activation of the classical RAAS pathway in MMVD leads to sustained vasoconstriction, increased afterload, and excessive myocardial stress, ultimately resulting in adverse cardiac remodeling. Understanding the biological intricacies of the RAAS, including both classical and alternative pathways, is therefore critical for developing effective therapeutic strategies aimed at mitigating the progression of MMVD (McDonagh et al., 2021).

Current Treatment Strategy for Preclinical MMVD

In the advanced preclinical stage of the disease (**stage B2**), the therapeutic objective of MMVD management is to delay the onset of congestive heart failure (CHF). The calcium sensitizer and phosphodiesterase-III inhibitor pimobendan enhances myocardial contractility without increasing myocardial oxygen consumption, and also acts as a balanced vasodilator reducing both preload and afterload. The EPIC study showed that treatment with pimobendan led to an approximate 15-month delay in the progression to CHF compared to placebo (Boswood et al., 2016), and this drug is included in current ACVIM Consensus Guidelines as recommended standard of care for stage B2 MMVD (Keene et al., 2019).

Two studies have investigated the use of the ACE inhibitor enalapril in dogs with advanced preclinical MMVD, with discordant results. The VETPROOF study demonstrated that prescription of enalapril improved CHF-free survival and all-cause mortality compared to placebo (Atkins et al., 2007), whereas the SVEP showed no benefit of enalapril compared to placebo in prolonging time to CHF (Kvart et al., 2022). Reasons for this discrepancy may include differences in dog demographics, disease severity, and dose of enalapril, among others (Atkins and Häggström, 2012). Of note, the SVEP trial involved only Cavalier King Charles spaniels, a breed with high frequency of a polymorphism in the gene for ACE that might decrease impact of ACE inhibition (Meurs et al., 2018).

The DELAY study also reported negative results for the effect of combination therapy with spironolactone and benazepril in stage B2 MMVD on delaying onset of HF in dogs with preclinical MMVD (Borgarelli et al., 2020). These results might suggest that early RAAS blockade does not significantly delay the onset of CHF in dogs with advanced preclinical MMVD. However, this combination therapy induced beneficial effects on cardiac remodeling and these results could be of clinical relevance. Importantly, the DELAY trial (as with SVEP) employed relatively low doses of ACE inhibitor, which might have affected results. Based on available evidence, the ACVIM Consensus Panel was split with respect to recommendation for ACEi in stage B2 MMVD, with five of ten panelists recommending ACEi prescription at this stage (Keene et al., 2019). The findings of these clinical trials suggest that targeting RAAS at this early stage may not provide the anticipated therapeutic benefit, emphasizing the complexity of disease-modifying strategies in MMVD.

Treatment of Congestive Heart Failure in Dogs with MMVD

Upon progression to CHF (**stage C**), a quadruple therapy regimen involving pimobendan, diuretics, ACE inhibitors, and spironolactone is currently recommended by the American College of Veterinary Internal Medicine (Keene et al., 2019).

Diuretics. Diuretics, especially loop diuretics such as furosemide and torsemide, are the mainstay therapy for management of canine CHF to mitigate pulmonary edema. By promoting diuresis, loop diuretics effectively reduce preload and alleviate venous congestion, resulting in marked improvements in clinical signs such as coughing, dyspnea, and exercise intolerance (Keene et al., 2019). The primary therapeutic objective of any diuretic therapy is to achieve optimal fluid balance while minimizing the risks of dehydration and electrolyte disturbances (Giorgi et al., 2022).

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Careful monitoring of fluid status and serum electrolyte levels is essential to ensure effective management and prevent complications related to over-diuresis or electrolyte depletion.

Pimobendan. Pimobendan exerts both positive inotropic and vasodilatory effects. By sensitizing cardiac troponin C to calcium, pimobendan enhances myocardial contractility without increasing myocardial oxygen demand. The QUEST trial demonstrated that pimobendan significantly improves survival outcomes in dogs with MMVD and CHF (Häggström et al., 2008).

ACE Inhibitors. Angiotensin-converting enzyme (ACE) inhibitors are recommended by the ACVIM Consensus Guidelines for treatment of CHF associated with MMVD (Keene et al., 2019). This therapeutic class blocks the conversion of angiotensin I to angiotensin II, thereby reducing vasoconstriction, aldosterone secretion, and sodium retention (King et al., 1995; Atkins et al., 2007; Mochel et al., 2013; Mochel et al., 2015). The efficacy of ACE inhibitors in canine CHF has been well-documented through various clinical trials, such as LIVE (1998), COVE (1995), IMPROVE (1995), and BENCH (1999) (Ettinger et al., 1998; Kvart et al., 2002; Atkins et al., 2007), which demonstrated improvements in survival and quality of life for dogs with CHF.

Spironolactone. Spironolactone, a mineralocorticoid receptor antagonist (MRA), mitigates the effects of aldosterone, thereby promoting natriuresis and reducing cardiac fibrosis (Pitt et al., 2008). The anti-aldosterone properties of spironolactone are particularly important in managing canine MMVD, as aldosterone breakthrough has been demonstrated in dogs with MMVD treated with ACE inhibitors (Ames et al., 2017). The BESST trial demonstrated that adding spironolactone to a standard treatment regimen significantly reduced morbidity and mortality in dogs with CHF, highlighting its importance in a comprehensive therapeutic management approach (Coffman et al., 2021). A preclinical pharmacology study by Masters et al. (2024) demonstrated that spironolactone increases serum aldosterone concentrations in healthy dogs and influences other biomarkers in both the classical and alternative RAAS pathways.

Optimizing the Dose of ACE Inhibitors in CHF Management

The optimal dosing regimen for ACE inhibitors in dogs with CHF remains a critical area of investigation. Recent studies have highlighted the potential benefits of tailoring ACE inhibitor dosing for improved therapeutic efficacy and maximizing long-term clinical outcomes. A retrospective study involving dogs with cardiac disease, including myxomatous mitral valve disease (MMVD), demonstrated that twice-daily (q12h) dosing of ACE inhibitors significantly improved survival outcomes compared to once-daily (q24h) dosing, suggesting that increased dosing frequency may be essential for optimizing cardioprotection (Ward et al., 2021). This finding is particularly relevant in cases where the progression of heart disease is rapid, and more frequent dosing may help stabilize cardiac function more effectively.

Further insights were provided by a prospective study in healthy dogs, which assessed different benazepril doses and their effects on the renin-angiotensin-aldosterone system (RAAS) (Sotillo et al., 2023). This study indicated that higher doses of benazepril led to a greater reduction in angiotensin II levels and a more pronounced increase in protective RAAS components, such as angiotensin-(1-7). These findings underscore the importance of dose optimization to achieve maximal RAAS modulation. Importantly, achieving an optimal balance between RAAS suppression and the upregulation of beneficial pathways can contribute to minimizing adverse effects while enhancing the cardioprotective properties of ACE inhibitors.

To further refine dosing strategies, a quantitative-systems pharmacology (QSP) model was employed to predict the dose-response effects of benazepril (Schneider et al., 2023). The mathematical model demonstrated that twice-daily dosing provided more consistent RAAS suppression compared to once-daily dosing, emphasizing the importance of maintaining steady therapeutic levels of ACE inhibition. This approach not only highlights the advantages of higher dosing frequency but also provides a robust basis for future clinical trials to validate these predictions in dogs with CHF. The QSP model allowed for detailed simulations, showing how variations in dose and frequency could impact biomarkers response. This modeling approach also underscores the utility of leveraging

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advanced technologies in veterinary medicine to improve treatment precision and predict patient-specific responses.

The implications of these findings are significant for clinical practice. Higher dosing frequencies and dose optimization of ACE inhibitors could potentially improve the clinical outcomes for dogs with CHF, particularly by enhancing the inhibition of deleterious RAAS activity while supporting beneficial alternative RAAS pathways.

Emerging Therapies for Canine CHF: A Focus on Sodium-glucose Cotransporter-2 Inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, such as empagliflozin, dapagliflozin, velagliflozin and bexagliflozin, represent a promising class of pharmacologic agents for heart failure management (Cowie and Fisher, 2020). Initially developed for glycemic control in human patients with diabetes, these agents have demonstrated significant cardioprotective and renoprotective effects that extend beyond their glucose-lowering capabilities (McMurray et al., 2019).

Recent studies, including those utilizing a Western diet-induced model of obesity-independent metabolic syndrome, have shown that SGLT-2 inhibitors not only lower blood glucose but also exert favorable effects on systemic metabolism, inflammation, and oxidative stress (Cowie and Fisher, 2020; Packer, 2020; Mochel and Ward, 2024). Specifically, these agents reduce markers of oxidative stress, shift metabolic processes toward ketone body production, and enhance autophagy, thereby contributing to improved cardiovascular and renal outcomes (Lopaschuk and Verma, 2020). Notably, these beneficial effects are observed irrespective of diabetic status, underscoring the utility of SGLT-2 inhibitors in patients with concurrent cardiovascular and renal diseases (Griffin et al., 2020; Inzucchi et al., 2020). Moreover, SGLT-2 inhibitors lower intraglomerular pressure, thereby mitigating further renal damage and slowing the progression of chronic kidney disease (Bailey et al., 2022).

Clinical and preclinical evidence indicates that SGLT-2 inhibitors can reduce heart failure hospitalizations, improve renal function, and confer survival benefits (Zannad et al., 2020), positioning them as a valuable addition to the therapeutic repertoire for MMVD, especially in companion animals with concurrent renal dysfunction. Emerging data from animal models, such as those involving Western diet-induced obesity-independent metabolic syndrome, support the hypothesis that SGLT-2 inhibitors may have pleiotropic effects extending beyond glycemic control. These pleiotropic effects include enhanced mitochondrial efficiency, reduced systemic inflammation, and improved endothelial function, all of which are critical in managing MMVD and its complications.

In a recent preclinical study from our consortium (Mochel et al., 2024), 18 dogs were randomized into three treatment groups: control (**CTRL**, N=6), low-dose dapagliflozin (**LD**, 0.3 mg/kg, N=6), and high-dose dapagliflozin (**HD**, 1.0 mg/kg, N=6). Dapagliflozin was administered orally once daily for three weeks. Blood samples were collected after the first dose (***DOS1***) and at steady state (***DOS21***). Urinary catheterization was performed to determine the total urine volume and glucose excreted over a 24-hour period. Results indicated that dapagliflozin increased insulin levels after ***DOS1*** compared to the control group (LD $P = 0.026$; HD $P = 0.061$), and significantly decreased fasting blood glucose levels at ***DOS21*** (LD $P = 0.005$; HD $P = 0.018$), though blood glucose remained within reference range. Additionally, 24-hour urine volume and glucose excretion significantly increased in the dapagliflozin-treated groups compared to the control (LD $P = 0.008$; HD $P = 0.047$). No significant differences were observed between the effects of the two doses of dapagliflozin. In conclusion, the study demonstrated that treatment with dapagliflozin significantly impacted glucose homeostasis, resulting in reduced circulating glucose levels, increased insulin levels, and enhanced urinary glucose excretion. These findings support the potential of SGLT-2 inhibitors like dapagliflozin in managing metabolic syndrome that might complicate MMVD.

Pharmacological data from this preclinical study were later supported by a pilot open-label clinical study conducted by our consortium, which evaluated the efficacy and safety of the SGLT-2 inhibitor, dapagliflozin, in dogs with naturally occurring heart disease, including MMVD and dilated cardiomyopathy (DCM). Observed effects included increased urine glucose and decreased urine potassium and sodium. These findings were partially presented at the 2024 American College of

Veterinary Internal Medicine (ACVIM) Forum in Minneapolis (Mochel and Ward, 2024) and will soon be submitted for publication.

To conclude, by modulating key metabolic and inflammatory pathways, SGLT-2 inhibitors show promise as a transformative therapy for heart failure in dogs, especially in those with coexisting renal and metabolic comorbidities. The use of SGLT-2 inhibitors in managing CHF in veterinary cardiology could fundamentally improve current treatment paradigms, offering a novel mechanism of action that addresses both cardiovascular and renal pathophysiology in a more integrated approach.

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