

EDITORIAL

Mining Metabolomics in Mitral Valve Disease

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As the most common naturally acquired cardiovascular disease in dogs, myxomatous mitral valve disease, or MMVD, affects roughly 9% of the canine population,¹ with greater incidence in smaller breeds and geriatric dogs. Initially known as Barlow disease² in humans, it affects an estimated 2% to 3% of the global population, with ≈15% of those individuals requiring valve surgery³; age is a risk factor in developing the disease, as is the case with dogs, and prevalence in humans is expected to increase as the mean age of the population increases.²

See Article by Li et al.

The disease is typified by ballooning of a section of a mitral leaflet and its chordae, thereby causing mitral regurgitation, which may progress to congestive heart failure. MMVD in dogs is most often detected by the presence of a heart murmur, and ancillary examinations confirm the diagnosis as well as offer prognostic insight.⁴ However, there are few known molecular or metabolic diagnostic indicators, although it stands to reason that they would effectively supplement the currently used physical and echocardiographic parameters.⁵

In this issue of the *Journal of the American Heart Association (JAHA)*, Li et al identified numerous biochemical markers in an untargeted metabolomic study that compared and analyzed the profiles of each stage of MMVD in dogs.⁶ The authors generated extensive profiles of 84 client owned dogs, 27 of which were healthy, staff-owned dogs. The 57 remaining subjects were in various stages of MMVD, as defined by the American College of Veterinary Internal Medicine. In addition to the serum metabolomic assay,

echocardiographic studies generated structural information for each subject that indicated the subject's disease severity. Although dogs with severe, systemic diseases or complicating prior conditions were not included in the study, there were no exclusions on the basis of size, age, breed, or sex.

Because the development of congestive heart failure can introduce metabolic changes independent of MMVD, the authors were particularly interested in significant differences between healthy dogs and a pre-clinical stage of MMVD marked by the presence of an mitral regurgitation-induced heart murmur but the absence of clinical signs of congestive heart failure. The authors identified 173 known metabolites with significant differences in concentration between all groups, of which 94 were between the healthy and the pre-clinical stages. The identified metabolites were associated with several key pathways, >30% of which were linked to energy production.

Ketone bodies were increased in all disease stages, an occurrence that previous studies have linked to congestive heart failure progression in humans.⁷ Twenty-two acylcarnitines were positively associated with MMVD severity, as was carnitine concentration, together indicating a disruption in long-chain fatty acid transport and oxidation. Reduced nicotinamide and increased quinolinate concentrations were observed in all disease groups, which the authors suggest could indicate a compromised nicotinamide adenine dinucleotide (NAD⁺) salvage pathway and subsequent activation of de novo NAD⁺ synthesis. Reprogramming of arginine and proline metabolism as well as renal insufficiency were evidenced by changes in numerous uremic toxins, including arginine, 2-oxoarginine, 4-guanidinobutanoate, trimethylamine N-oxide, urea, and uric acid.

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The study by Li and colleagues offers a wealth of potential biomarkers and insight on the intricate balance of the heart-kidney-gut axis.⁶ Their findings, however, cannot be further explored without also acknowledging the limitations of their work. Their control group was made up of dogs that were significantly younger and larger than the other groups, both of which are factors that lower their risk of developing MMVD.^{1,2,4,6,8} It was a sample of convenience, as the authors themselves mention, and in such a preliminary study they certainly cannot be faulted for it. It should not be ignored, however, that such a small sample size, particularly one vulnerable to so many confounding factors, inevitably brings with it the possibility of inaccuracy. The authors did attempt to mitigate this effect with a bootstrap resampling method, and although it was effective in that it greatly increased the accuracy and trustworthiness of their findings, no amount of statistical analysis can completely fix a bad sample or avoid the risk of overfitting. In a similar vein, components, such as diet and breed, were not explored or corrected for as potential confounding effects, even though breed has been suggested to have an effect on MMVD development and progression.⁸ To their credit, the authors readily admit the shortcomings of their work and suggest many future directions that could eliminate these issues.

This study addressed the hypothesis that “serum metabolomics changes reflect adaptations of energy substrates and interruptions of energy metabolic machinery during MMVD progression.” By doing so, the authors provide a platform for future hypotheses to test clinical and mechanistic studies of the metabolites identified and intertissue communication in forms of progressive heart disease. The study was undeniably successful in doing what it set out to do: direct further inquiry. From novel therapeutic targets to potential prognostic and diagnostic factors to insight on the subtle interplay between metabolic pathways in

disease, the authors brought forth a wealth of knowledge that should both fuel and direct considerable future investigation.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Li Q, Freeman LM, Rush JE, Laflamme DP. Expression profiling of circulating microRNAs in canine myxomatous mitral valve disease. *Int J Mol Sci*. 2015;16:14098–14108. DOI: 10.3390/ijms160614098.
2. Markby GR, Summers KM, MacRae VE, Corcoran BM. Comparative transcriptomic profiling and gene expression for myxomatous mitral valve disease in the dog and human. *Vet Sci*. 2017;4:34–10.3390/vetsci4030034.
3. Neto FL, Marques LC, Aiello VD. Myxomatous degeneration of the mitral valve. *Autops Case Rep*. 2018;8:e2018058. DOI: 10.4322/acr.2018.058.
4. Mattin MJ, Boswood A, Church DB, Brodbelt DC. Prognostic factors in dogs with presumed degenerative mitral valve disease attending primary-care veterinary practices in the United Kingdom. *J Vet Intern Med*. 2019;33:432–444. DOI: 10.1111/jvim.15251.
5. Dewey CM, Spittler KM, Ponce JM, Hall DD, Grueter CE. Cardiac-secreted factors as peripheral metabolic regulators and potential disease biomarkers. *J Am Heart Assoc*. 2016;5:e003101. DOI: 10.1161/JAHA.115.003101.
6. Li Q, Larouche-Lebel E, Loughran KA, Huh TP, Suchodolski JS, Oyama MA. Metabolomics analysis reveals deranged energy metabolism and amino acid metabolic reprogramming in dogs with myxomatous mitral valve disease. *J Am Heart Assoc*. 2021;10:e018923. DOI: 10.1161/JAHA.120.018923.
7. Lommi J, Kupari M, Koskinen P, Naveri H, Leinonen H, Pulkki K, Harkonen M. Blood ketone bodies in congestive heart failure. *J Am Coll Cardiol*. 1996;28:665–672. DOI: 10.1016/S0735-1097(96)00214-8.
8. Borgarelli M, Crosara S, Lamb K, Savarino P, La Rosa G, Tarducci A, Haggstrom J. Survival characteristics and prognostic variables of dogs with preclinical chronic degenerative mitral valve disease attributable to myxomatous degeneration. *J Vet Intern Med*. 2012;26:69–75. DOI: 10.1111/j.1939-1676.2011.00860.x.