

TRANSFORMING HEART HEALTH:

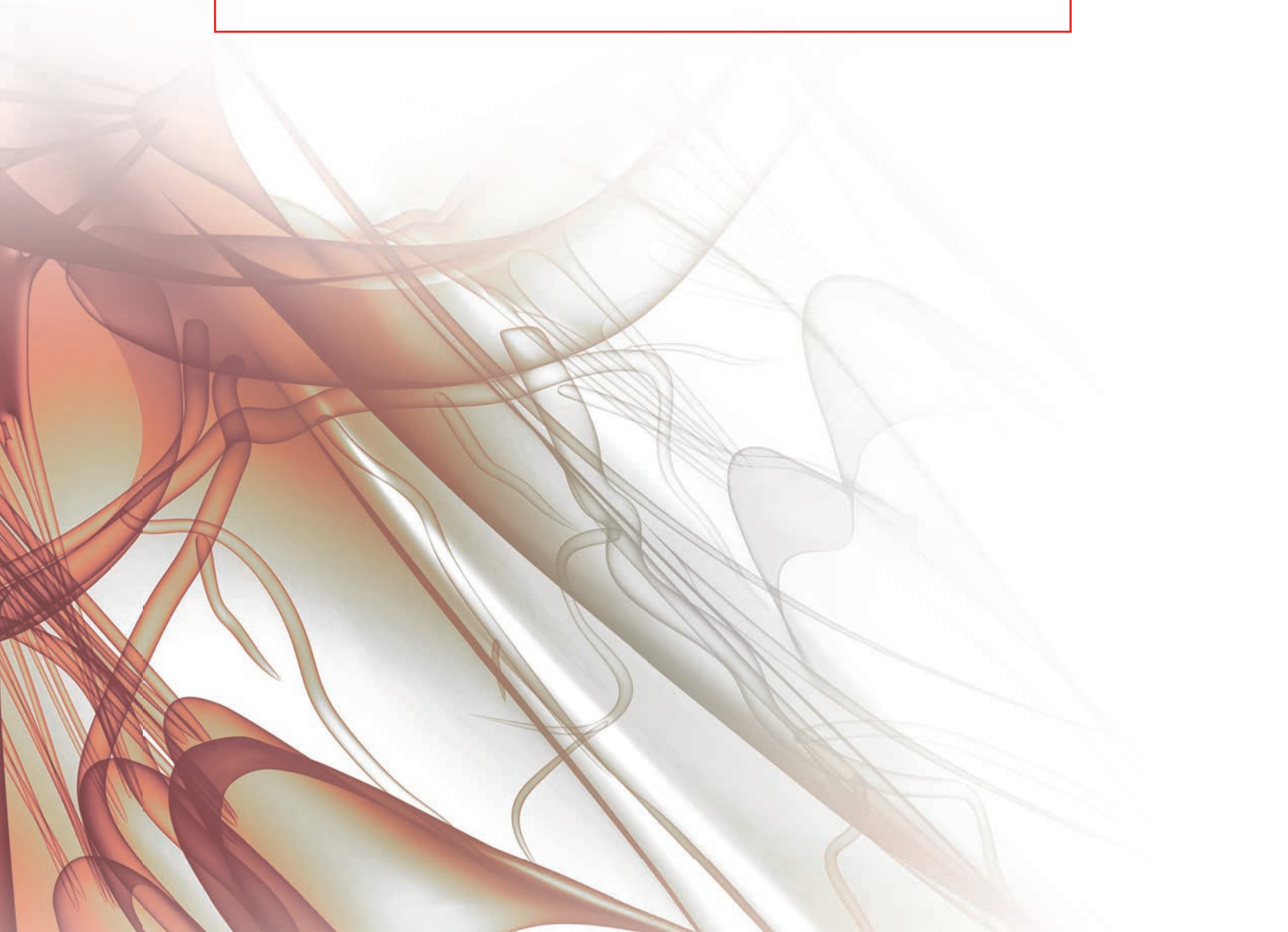
A Novel Dietary Intervention For Dogs With
Early Stage Myxomatous Mitral Valve Disease



Heart disease is one of the most common disorders of dogs, affecting one in ten canine patients seen in primary care practice.¹ The most common cause of acquired canine heart disease is myxomatous mitral valve disease (MMVD).

In this cardiac condition, the mitral valve progressively degenerates, leading to an enlarged left atrium and ventricle, a less efficient heart, and the risk of congestive heart failure.

Although the majority of dogs with MMVD are not—and never will be—in heart failure, about 30% develop advanced heart disease.²⁻⁴ The progression to heart failure carries a much poorer prognosis and diminishes a dog's quality of life. An intervention that could effectively slow the progression of MMVD when dogs are in the early stage stages of heart disease could help these dogs live better, longer lives.



CONTENTS

2

Healthy hearts need a continuous energy supply

2

The failing heart: an energy crisis

3

Insights from studies using omics technologies

4

Myxomatous mitral valve disease (MMVD)

4

Understanding MMVD

6

Progression of MMVD

8

Nutritional breakthrough studies for dogs with early stage MMVD

8

Identification of specific nutrients with cardiac protection benefits

9

Dietary study shows feeding a Cardiac Protection Blend (CPB) slows progression in dogs with early stage MMVD

11

Metabolomics: connects clinical benefits of the CPB nutrients with cellular-level changes

HEALTHY HEARTS NEED A CONTINUOUS ENERGY SUPPLY

A dog's heart may beat up to a billion times during their life.⁵ Keeping the heart pumping under constantly changing conditions—at rest, while running, in sickness and in health—requires a continuous supply of energy, in the form of adenosine triphosphate (ATP).

The heart cannot store energy for future use. If ATP production suddenly stopped, the heart could only contract for about 12 more beats.⁶

To meet these high-energy demands, every cardiomyocyte contains thousands of mitochondria, the cellular factories for energy production.^{7,8}

The healthy adult mammalian heart typically derives up to 90% of ATP from the oxidation of long-chain fatty acids.^{6,9}

However, mitochondria have the metabolic flexibility to use different energy substrates to meet ATP demands depending on cardiac workload, availability of the energy sources, or the nutritional state of the animal.

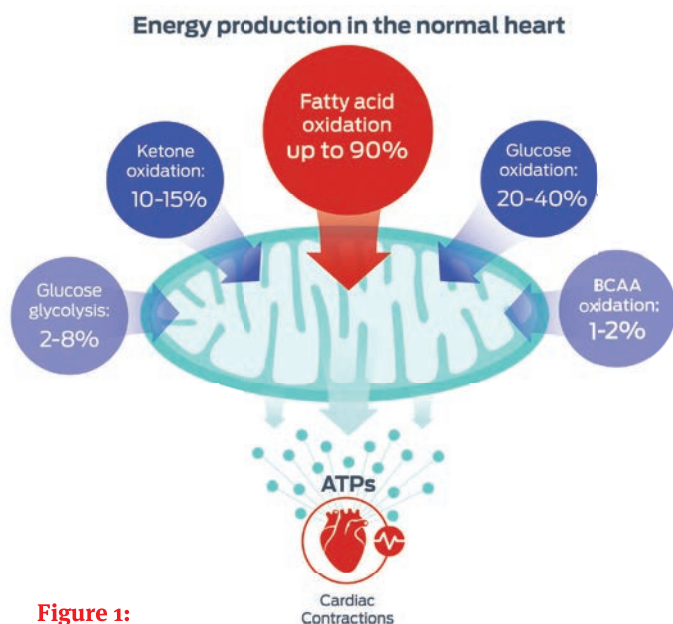


Figure 1:

Long-chain fatty acids are the primary energy substrate in the healthy mammalian adult. The remaining energy comes from the oxidation or glycolysis of glucose, and other energy sources.^{6,9,10}

The failing heart: an energy crisis

Heart disease refers to cardiac pathology—regardless of whether it affects the heart muscle, valves, or metabolism. However, heart failure refers to clinical signs—such as fluid accumulation in the lungs or abdomen—that occur when the heart is unable to compensate for changes associated with the heart disease.

Heart disease does not always lead to heart failure. The prognosis depends on the disease, its rate of progression, and the dog's overall health.¹ For example, in one retrospective study of more than 500 dogs, 70% of dogs with mitral valve disease did not progress to heart failure. However, about 30% progressed to a worse stage of heart disease over several years: 18% of dogs with MMVD developed symptomatic heart failure within one year and about 11% of asymptomatic dogs died from heart failure within 5 years.²

In failing hearts, compromised energy metabolism is a critical factor.^{6,10,11} A brief look at how the heart meets its energy needs reveals how nutrition could play a pivotal role in managing heart disease.

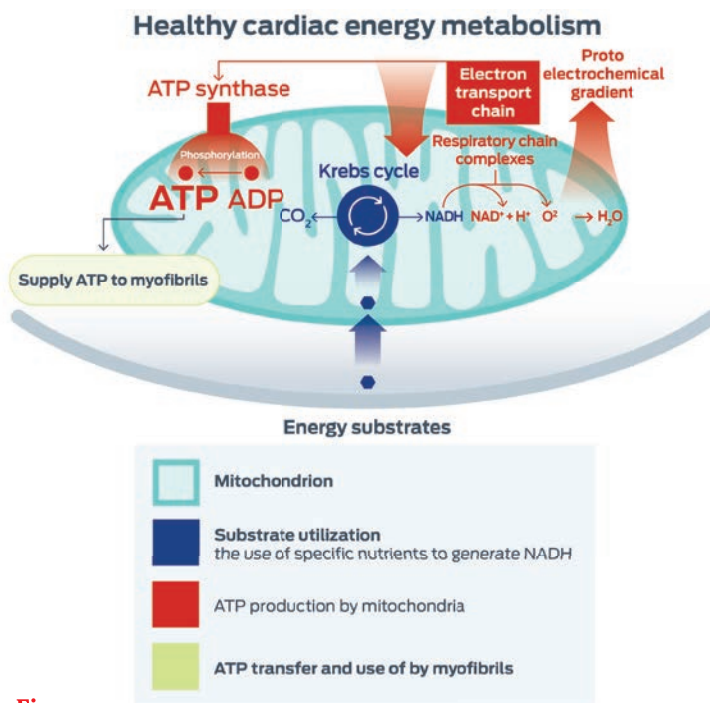


Figure 2:

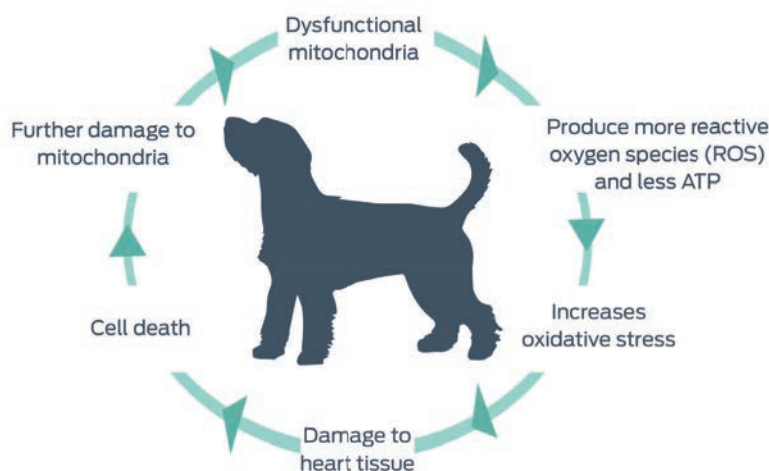
Mitochondria convert the chemical energy stored in fatty acids, glucose and other substrates, into ATP that fuels the heart's contractions. Failure to produce an adequate amount of energy leads to mechanical failure of the heart. [Adapted from Neubauer 2007]

In general, cardiac energy metabolism has three components¹⁰:

- the use of specific substrates to generate energy
- ATP production by mitochondrial oxidative phosphorylation
- transfer of ATP within the heart muscle cells (myofibrils)

Studies in animals and people show changes can occur in any—or all—of the three components of cardiac energy metabolism: substrate utilization, oxidative phosphorylation, or ATP metabolism.¹²

If adverse health conditions cause mitochondria to become dysfunctional, then ATP production becomes less efficient. With less energy to fuel muscle contraction, the heart becomes less effective.



Dysfunctional mitochondria also produce more reactive oxygen species (ROS), which increases oxidative stress and leads to cell damage. This can lead to a cycle of progressively inefficient energy production.^{9,10,12-15}

Insights from studies using omics technologies

Studies in both people and animals have shown that gene expression and metabolite profiles associated with energy metabolism differ significantly between healthy hearts and diseased hearts.¹⁶⁻²⁰

Purina scientists applied metabolomics and transcriptomic technologies to better understand the molecular-level changes that occur in dogs with early stage MMVD.¹⁸

Among the key changes identified in this multi-omics study, the scientists found:

- 54 serum metabolites were significantly different between healthy and MMVD dogs
- More than 1,000 gene transcripts in mitral valve and left ventricular tissue were differentially expressed

These changes represented altered pathways associated with:

- energy metabolism and bioenergetics
- oxidative stress
- inflammatory mediators
- extracellular matrix homeostasis

Additionally, gene expression and metabolite levels for glucose metabolism and anaerobic glycolysis were increased, indicating that in dogs with MMVD, their hearts were using less efficient ATP production pathways that are not typically used by a healthy heart.

Similar to findings in studies of human heart failure,^{6,9,10} these changes suggest that cardiac metabolism in dogs with MMVD shifts away from using long-chain fatty acids as a primary substrate for energy. The process of energy production becomes less efficient overall.

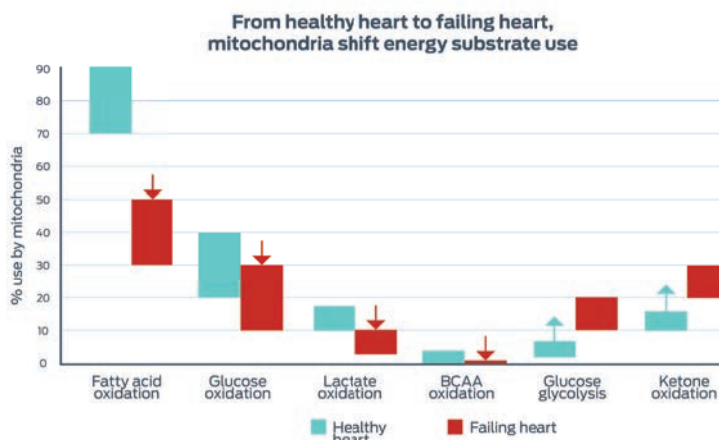


Figure 3:

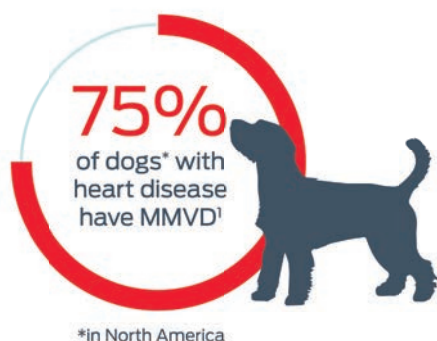
This graph depicts the shift in energy sources used by mitochondria in the failing heart.

These altered bioenergetics offer insights into possibilities for nutritional interventions. Research suggests that nutrients providing alternative energy sources, and addressing other metabolic changes found in MMVD, could transform the management of cardiac health.

MYXOMATOUS MITRAL VALVE DISEASE (MMVD)

Understanding MMVD

Myxomatous mitral valve disease is the most common canine heart disease, accounting for approximately 75% of acquired heart disease in dogs.^{1,21-23} The highest incidence occurs in older, small- to medium-sized dogs weighing less than 20 kilograms.^{1,24}



Small dog breeds such as Miniature Poodles, Dachshunds, Yorkshire Terriers and Whippets are predisposed to MMVD, and nearly 100% of Cavalier King Charles Spaniels develop this cardiac condition.^{25,26} A few large breed dogs, such as German Shepherds and Doberman Pinschers, may also have this valve disease.²

The mitral valve maintains a one-way blood flow from the left atrium to the left ventricle. With myxomatous degeneration, nodules form along the edges of the normally thin and translucent valve. As MMVD progresses, the valve tissue thickens and no longer forms a tight seal when the heart contracts. This “leaky” seal allows blood to regurgitate into the left atrium.

With time, the degenerating valve and increasing mitral regurgitation lead to left atrial enlargement, compensatory left ventricular remodeling and heart failure. About 30% of dogs with MMVD also have tricuspid valve insufficiency.²⁷

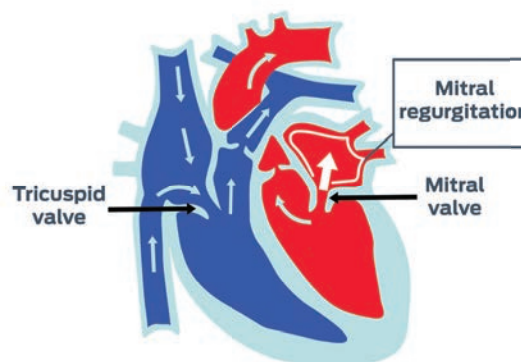


Figure 4:

With MMVD, the mitral valve progressively thickens and becomes less effective at maintaining the one-way flow of blood from the left atrium to the left ventricle. This mitral regurgitation leads to remodeling of the heart and, eventually, the risk of heart failure.

At the molecular level, a key step in the development of MMVD is the transformation of specific cells in the extracellular matrix of the valve. Studies show that valvular interstitial cells (VICs) change into active myofibroblasts, disrupting the flexible structure (and function) of the valve.²⁸ The mechanism behind these changes is not yet known, but serotonin (5-hydroxytryptamine or 5HT) appears to have an important role in the pathogenesis of the disease. Better understanding how serotonin helps trigger VIC activation may lead to improved MMVD management in the future.^{29,30}

The list of synonymous terms for MMVD reflect the array of changes that occur in this disease.^{2,27}

- Mitral valve disease (MVD)
- Degenerative mitral valve disease (DMVD)
- Chronic mitral valve insufficiency (CMVI)
- Atrioventricular valve disease (AVD)
- Chronic valvular disease (CVD)
- Atrioventricular valvular insufficiency (AVVI)
- Endocardiosis
- Chronic valvular endocarditis
- Valve fibrosis
- Muroid degeneration

The diagnosis of subclinical MMVD is based on auscultation and signalment. In most dogs the heart disease will be discovered when a left apical systolic murmur is auscultated during a routine exam.^{1,31} Further diagnostics may include thoracic radiography to obtain a baseline vertebral heart score (VHS), assess heart size, and evaluate any pulmonary changes.

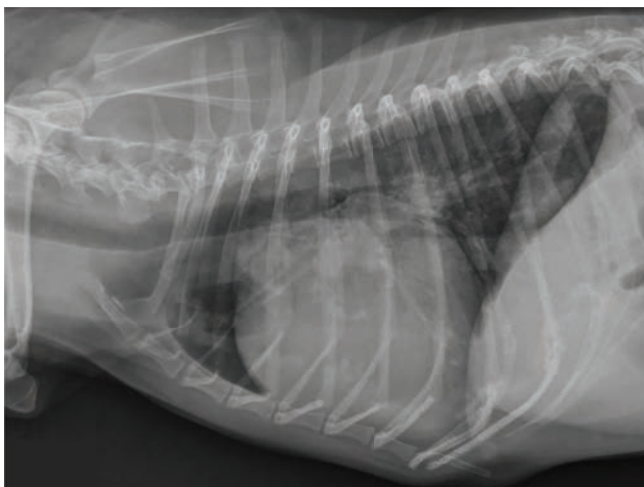


Figure 5:

Right lateral thoracic radiograph of a dog in ACVIM stage B2 MMVD
Image courtesy of: Rebecca Stepien, DVM, MS, DACVIM (Cardiology)
University of Wisconsin, USA

Although recent studies show that radiographs can confirm a diagnosis of MMVD³², the echocardiogram is

still considered the gold standard for evaluating cardiac structure and function.

According to consensus guidelines of the American College of Veterinary Internal Medicine (ACVIM), dogs with MMVD are classified into one of four stages based on clinical findings and echocardiographic evaluation. This staging scheme was developed, and updated, by a panel of veterinary cardiologists to link the severity of morphologic heart changes and clinical signs with appropriate treatments for each stage.^{1,24}

ACVIM CLASSIFICATION SCHEME FOR MMVD

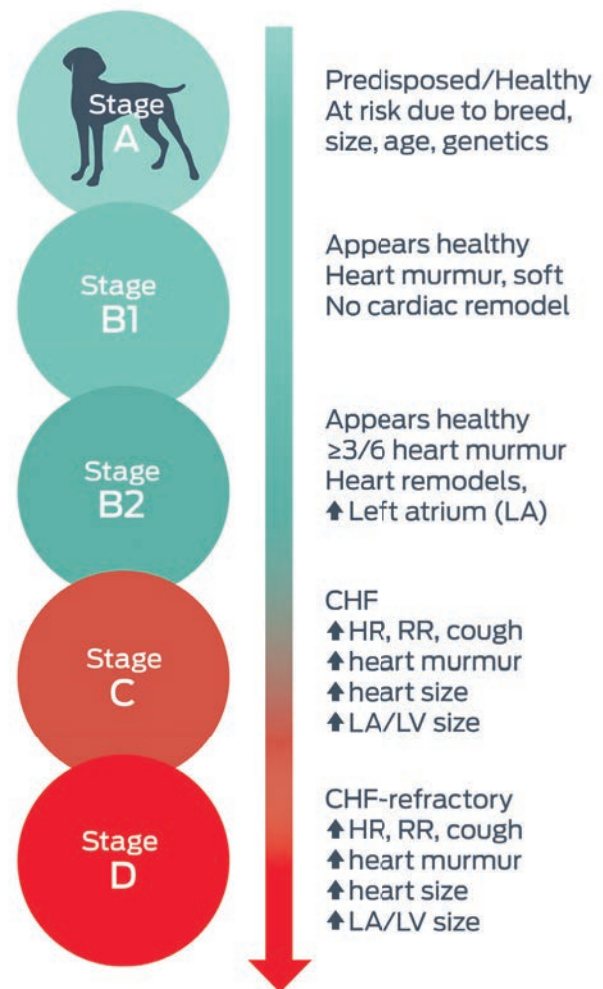


Figure 6:

The ACVIM consensus guidelines for staging dogs with MMVD were adapted from functional classification systems for heart disease in people and dogs, including systems developed by the New York Heart Association (NYHA) and the International Small Animal Cardiac Health Council (ISACHC).

Compared to early stage dogs with MMVD, those with signs of congestive heart failure (CHF) have a much shorter survival time.³²⁻³⁷

Heart failure is the third most common cause of death in dogs.³⁸

Once dogs experience clinical heart failure, the goals are to manage clinical signs, delay further progression and maintain quality of life. Most dogs receive some combination of medical therapy with diuretics, angiotensin-converting enzyme (ACE) inhibitors, aldosterone receptor blockers, and/or positive inotropes.^{1,24,39}

Dietary management recommendations for dogs with MMVD currently target later stages of disease, after heart failure occurs, and are focused on controlling clinical signs.

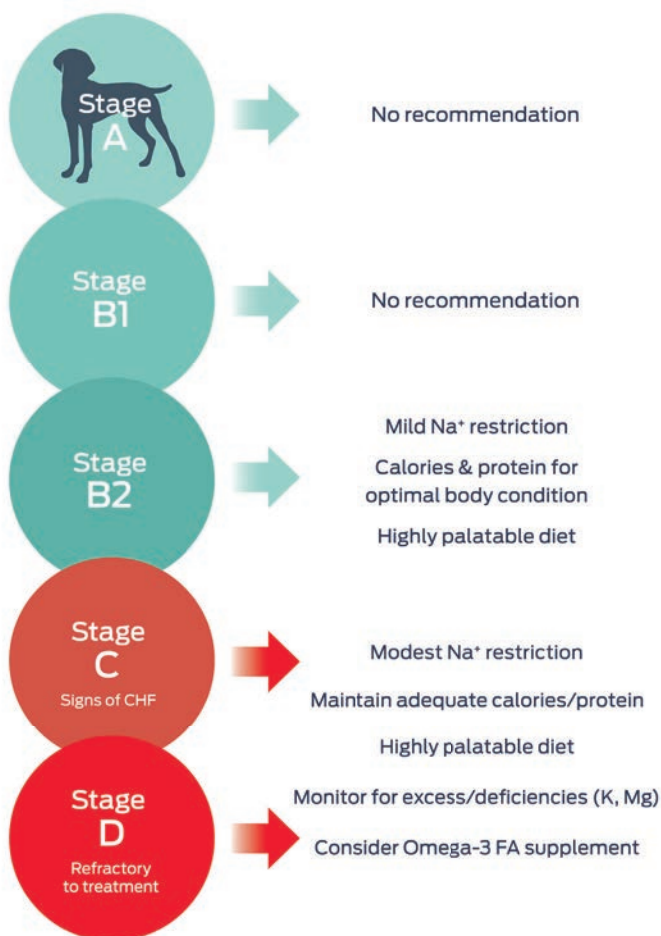


Figure 7:

This diagram highlights the current ACVIM recommendations for the nutritional management of dogs with MMVD.¹

These recommendations include:

- maintaining protein and calorie intake
- monitoring potassium levels due to losses from diuretic medications
- moderately restricting sodium intake to mitigate fluid accumulation

Although studies in people have linked high salt intake with high blood pressure and, in turn, negative impacts on heart health, studies have not shown that sodium has a role in causing heart disease in dogs. Excessive restriction of sodium should be avoided as it stimulates aldosterone activation, which can have adverse effects.⁴⁰ Moderate sodium restriction, however, can help manage symptoms of fluid overload in heart failure. (Reduced cardiac output in heart failure stimulates the renin-angiotensin system and leads to increased fluid retention.)⁴¹⁻⁴⁴

Diet palatability is also an important nutritional factor. Cardiac cachexia is common in dogs with CHF, and is associated with significantly shorter survival times.⁴⁵⁻⁴⁷ Omega-3 fatty acids are also recommended to help reduce inflammation, which may be important in cachexia.^{45,48-51}

All of these recommendations are aimed at reducing the workload of the failing heart and managing clinical signs.

Progression of MMVD

The rate of progression from one stage of MMVD to the next is variable and hard to predict. However, the prognosis is more favorable for dogs in early stage stages of MMVD, without signs of congestive heart failure (CHF).^{1,34,52}

Numerous studies describe potential biomarkers for predicting the progression of MMVD. Identifying prognostic factors that are easily obtainable by testing a blood sample could aid veterinary practitioners when managing dogs with MMVD, and help inform dog owners of the likely outcome for their pet.⁵³

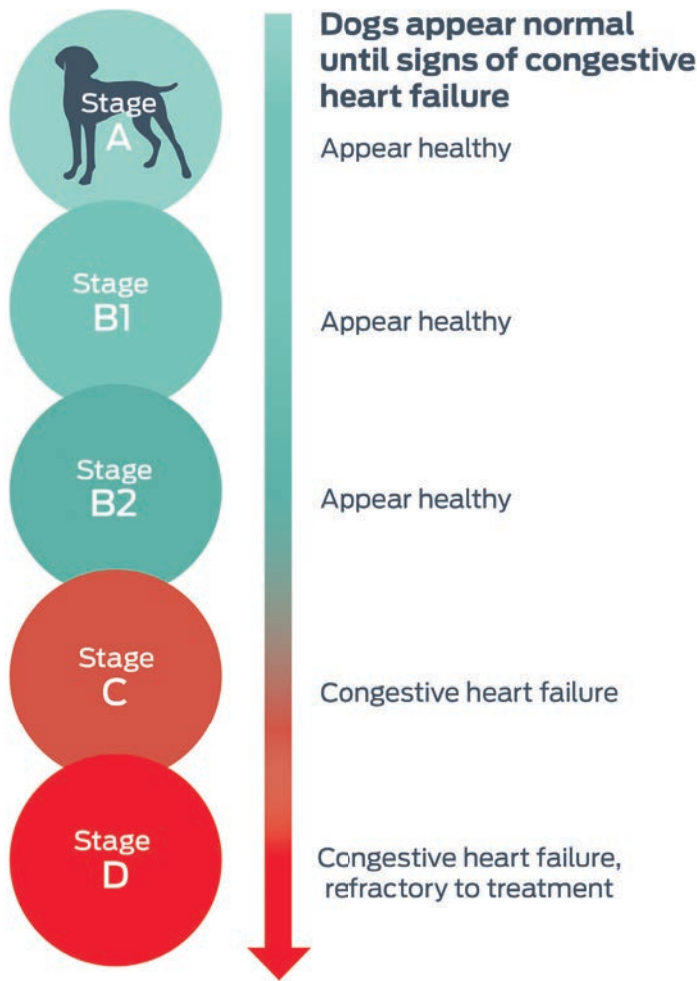


Figure 8:

Based on the ACVIM classification scheme for dogs with MMVD, dogs show no clinical signs until they experience congestive heart failure.

Two biomarkers with some demonstrated value for MMVD dogs are: N-terminal pro b-type natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI).

NT-proBNP is a marker of myocardial wall stress secondary to volume or pressure overload. This naturetic peptide has been shown to help differentiate CHF from primary respiratory diseases.⁵⁴⁻⁵⁷ Studies show that NT-proBNP may also have prognostic value in early stage MMVD.^{53,58,59}

Cardiac troponins are released into the bloodstream after injury to heart muscle cells. They are sensitive and specific markers of cardiac injury from any underlying cause. Studies show that plasma levels of cTnI are abnormally increased in dogs with moderate and severe MMVD, and cTnI concentration is negatively associated with prognosis. However, this marker is most strongly associated with all-cause mortality, not cardiac-specific causes.^{53,60-64}

Many factors are associated with the progression of MMVD, including: age, gender, intensity of heart murmur, degree of valve prolapse, severity of valve lesions, the degree of mitral valve regurgitation, degree of left atrial enlargement, severity of eccentric hypertrophy, and rupture of chordae tendinae.^{3,21,25,34,57,65}

Of these factors, the degree of left atrial enlargement (LAE) appears to be the most consistent indicator of progression.

^{39,66,67}

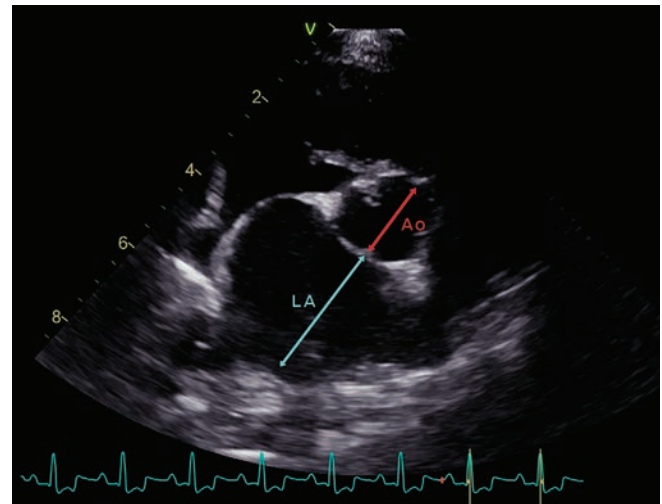


Figure 9:

Echocardiographic measurement of left atrial diameter (LA) and aortic root (Ao) Image courtesy of: Rebecca L. Stepien, DVM, MS, ACVIM (Cardiology) University of Wisconsin, USA

LAE is evaluated by the ratio of left atrial diameter to aortic root diameter (LA/Ao), as measured by echocardiography.

Once progression occurs, a dog's lifespan and quality of life diminish. The goal, therefore, is to slow or prevent progression of MMVD.

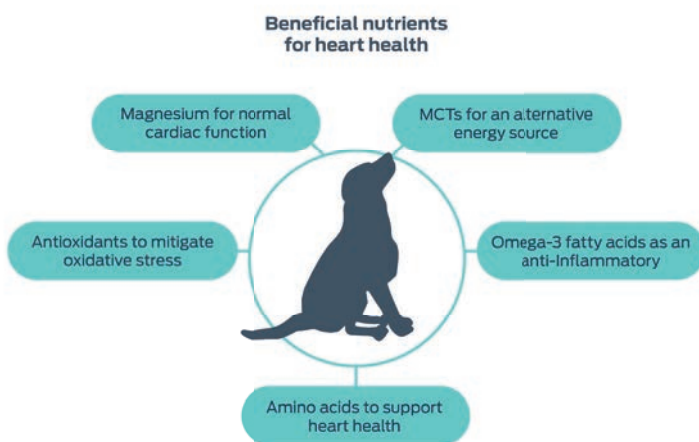
Owners rate quality of life better than quantity for dogs in heart failure.⁶⁸

NUTRITIONAL BREAKTHROUGH STUDIES FOR DOGS WITH EARLY STAGE MMVD

While studies have shown the beneficial roles for many nutrients in heart health, nutrition is often overlooked in the management of heart disease. With the goal of slowing disease progression in dogs with early stage MMVD—before dogs show signs of CFH—Purina scientists developed a blend of nutrients that could address key metabolic changes they previously identified in dogs with MMVD.

Identification of specific nutrients with cardiac protection benefits

Based on insights from previous omics research, Purina scientists formulated a **cardiac protection blend (CPB) of nutrients that includes medium-chain triglycerides (MCTs) as an alternative energy source, omega-3s to help reduce inflammation, Vitamin E and other antioxidants, together with key amino acids and minerals important for cardiac health and function.**



Long-chain fatty acids are the primary substrate used by healthy cardiac mitochondria to generate energy. In heart disease, energy metabolism becomes less efficient—particularly regarding long-chain fatty acids.^{9,10,69}



MCTs are readily hydrolyzed to medium-chain fatty acids (MCFAs), which provide a more available substrate for cellular energy.

With a shorter carbon chain, MCFAs provide a more available source of energy because they do not require membrane transporters for uptake into cells and mitochondria.^{70,71} In contrast, long-chain fatty acids need carnitine cofactors for transport into the mitochondria.⁷²

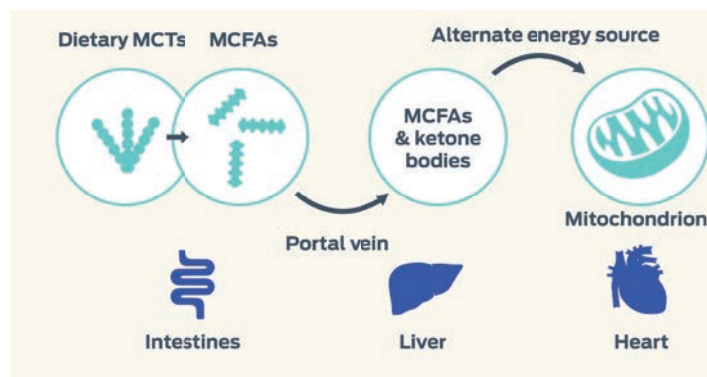


Figure 10:

Dietary medium-chain triglycerides (MCTs) can provide an alternative energy source for cardiac mitochondria. MCTs are metabolized into MCFAs, which do not need transporters to enter mitochondria for ATP production.

Studies also show that MCTs reduce mitochondrial and cytoplasmic ROS, and can have a favorable impact on cardiac disease progression.^{70,73,74}



The long-chain **omega-3 fatty acids, especially eicosapentaenoic acid (EPA), have demonstrated numerous cardiac benefits.** Studies show that omega-3s from fish oil help reduce inflammatory mediators and oxidative stress, stabilize cardiac arrhythmias in dogs, reduce blood pressure, and reduce cardiac remodeling.^{49, 75-80}

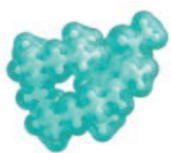
Taurine is the most abundant amino acid in heart tissue. While it is not an essential nutrient for dogs, studies have shown that taurine has a key role in maintaining heart muscle contractility and homeostasis.⁸¹⁻⁸³ Research has also linked deficiencies to the development of heart disease.⁸¹

Low taurine levels have been associated with decreases in the sensitivity of cardiac muscle to calcium and the loss of myofibrils.⁸³⁻⁸⁵ While the exact mechanism for taurine

deficient cardiomyopathy is still not known, taurine-responsive heart disease has been reported in breeds including: the American Cocker Spaniel, Golden Retrievers, Doberman Pinschers, and Newfoundlands.⁸¹

Lysine and methionine are amino acid precursors for the biosynthesis of carnitine, a peptide which helps transport LCFAs acids into the mitochondria.^{86, 87}

Vitamin E is a well-established antioxidant, has anti-inflammatory properties, and can also influence gene expression in ways that help prevent heart disease.^{86,88,89}



As an antioxidant, Vitamin E scavenges free radicals by either preventing their formation or removing them before they can cause damage.

While free radicals are a consequence of normal cell metabolism, if these ROS are not adequately cleared then oxidative stress occurs. Increasing oxidative stress leads to cell membrane damage, DNA damage and protein denaturation.

One recent study showed that superoxide dismutase activity, a common free radical scavenger, gradually decreased in dogs with advanced stages of mitral valve disease.⁹⁴

Magnesium is a mineral proven to play multiple roles in maintaining healthy heart function. In heart cells, it complexes with ATP to deliver this molecular energy



outside the mitochondria. Among its roles, magnesium provides antiarrhythmic action and acts as an antioxidant. In people, inadequate levels of magnesium correlate with heart failure and increased risk for cardiovascular disorders.⁹⁵⁻⁹⁸

Dietary study shows feeding a Cardiac Protection Blend (CPB) slows progression in dogs with early stage MMVD

A six-month, placebo-controlled, dietary intervention study demonstrated the efficacy of a CPB of nutrients in slowing disease progression and helping improve heart function in dogs with early stage (stage B1 or B2) MMVD.⁹⁹

This blinded, randomized feeding trial enrolled 19 dogs in stage B1 or B2 heart disease. The dogs were divided into two groups randomized by age, sex, breed, body weight, and murmur grade, then fed a complete and balanced diet that was either a control diet (CON) or the CPB-supplemented diet. Any dogs on cardiac medications prior to enrollment were maintained on the same medications throughout the study. All dogs were evaluated with echocardiography at three time points: baseline, three months and six months.

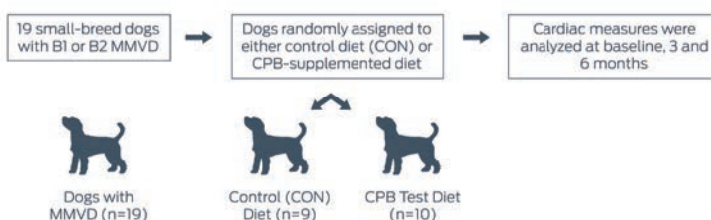


Figure 11:

Antioxidants can reduce the impact of reactive oxygen species (ROS) and prevent damage to cell proteins, cell membranes or DNA.

Studies show that antioxidants may be even more important in heart disease because levels of ROS increase under conditions of mitochondrial dysfunction—a key feature of heart failure.⁹⁰⁻⁹³

Although MMVD is a variably progressive heart disease, within six months the study results showed that disease progression in dogs with MMVD was slowed in dogs supplemented with the CPB.

Dietary study results

MMVD progression from ACVIM stage B1 to B2

During the 6-month study, none of the dogs fed the CPB showed progression of MMVD heart disease. However, more than one-third of dogs on the control diet progressed from stage B1 to B2.

These were statistically significant results, $P < 0.001$.

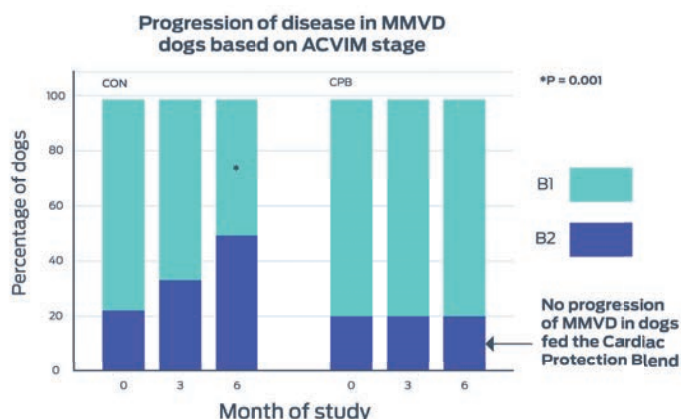


Figure 12:

During the 6-month dietary intervention study, more than one-third of CON dogs progressed from ACVIM stage B1 to Stage B2. None of the CPB-fed dogs progressed. (* $P < 0.001$)

Left atrial size

The most reliable independent indicator for MMVD progression is left atrial enlargement, measured by the ratio of left atrial diameter to aortic root (LA/Ao) with echocardiography.^{66,100}

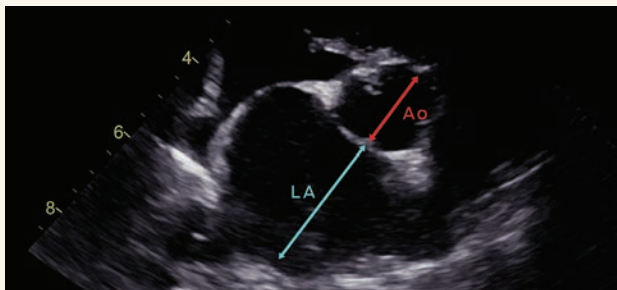


Figure 13:

Echocardiographic measurement of left atrium (LA) and aortic root (Ao) in a dog with stage B2 MMVD. Image courtesy of: Rebecca L. Stepien, DVM, MS, ACVIM (Cardiology) University of Wisconsin, USA

Study results showed that the CON-fed dogs had significant left atrial enlargement with an average 10% increase in LAD and LA/Ao ratio.

In contrast, left atrial size in CPB-fed dogs showed about a 3% average decrease. These results were significant, $P < 0.05$.

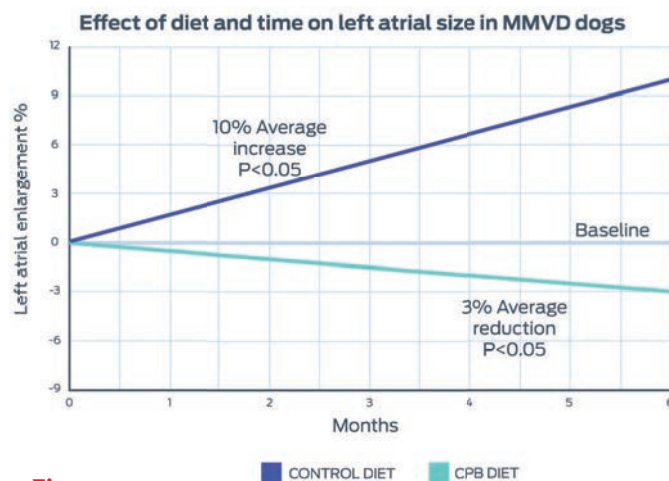


Figure 14:

Graph of changes in atrial size for CON-fed dogs vs. CPB-fed dogs during the 6-month dietary intervention study.

These significant changes in left atrial size started as early as 3 months in the dietary study.

Mitral regurgitation

The severity of the mitral regurgitation (MR), based on echocardiographic exam, is also a key indicator of MMVD progression.

In this study, 30% of CPB-fed dogs had less severe MR, and only 10% worsened. However, CON-fed dogs showed no improvement, and 25% worsened.

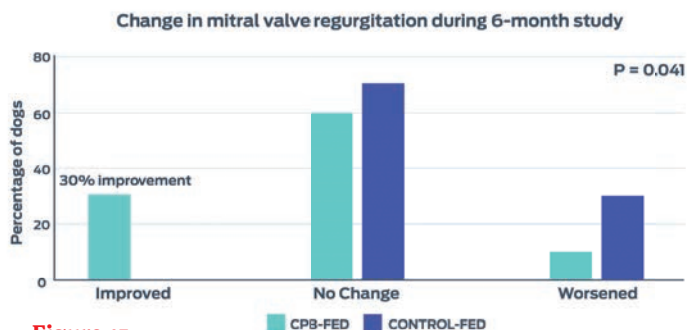


Figure 15:

This graph depicts changes in the severity of mitral regurgitation for CON-fed dogs vs. CPB-fed dogs during the 6-month dietary intervention study.

These results were significant: $P = 0.041$

Metabolomics: connects clinical benefits of the CPB nutrients with cellular-level changes

In follow-up research, Purina scientists analyzed serum metabolites of dogs in the dietary study.¹⁰¹

Among more than 100 differential metabolites, the results showed that clinical benefits demonstrated during the dietary study were also associated with positive changes at the metabolic level:

- improved fatty acid use and bioenergetics
- reduced markers of inflammation
- reduced oxidative stress

Significant metabolite changes in CPB group	Impact on heart health
↑ 2.7-fold increase in alpha-aminobutyrate	Modulates glutathione balance; glutathione protects against oxidative stress, especially in the heart.
↑ 2-fold increase in arginine and citrulline	These amino acids are precursors for nitric oxide biosynthesis. Nitric oxide acts mainly against oxidative stress and helps optimize cardiac pump function.
↑ 3-fold increase in caprate	This is a 10-carbon, medium-chain fatty acid (MCFA). MCFAs from MCTs are sources of energy that get directly into mitochondria. They do not need special transporters or pathways that use carnitine.
↑ 2.5-fold increase in deoxycarnitine	An amino acid that is the immediate precursor of carnitine biosynthesis. Carnitine's prime function is to shuttle long-chain FAs to the mitochondria for energy production.
↑ ceramides and sphingomyelins with very long-chain fatty acids	Research in humans has shown decreased risk of heart failure when ceramides and sphingomyelins were increased with VLCFAs.
↓ margarate and methylpalmitate	These FAs correlated with changes in left atrial diameter—a key measure of MMVD progression. Dogs with lower margarate and methylpalmitate showed less expansion of left atrial diameter, so less progression of MMVD.
↓ greater decrease in ratios of omega-6 to omega-3 fatty acids	Inflammation plays an important role in cardiovascular disease. Omega-3 FAs such as eicosapentaenoic acid have key anti-inflammatory/anti-aggregatory effects while omega-6 FAs, such as arachidonic acid, are generally pro-inflammatory.
↓ Acylcarnitines: oleoylcarnitine, adipoylcarnitine, and margaroylcarnitine	Suggests an improvement in cardiac fat utilization.

This sequence of studies demonstrates that dietary intervention with a blend of specific nutrients formulated to address key metabolic changes identified in dogs with MMVD was able to improve key cardiac measures and slow the progression of subclinical heart disease. Importantly, the combined effects of these nutrients achieved the documented efficacy.

Balanced nutrition has always played a key role in maintaining heart health. Now, a novel nutritional approach offers clinical benefits for dogs with early stage MMVD. Studies demonstrate that the synergistic effects of a unique blend of nutrients can help improve cardiac function and slow progression in dogs with early stage myxomatous mitral valve disease.

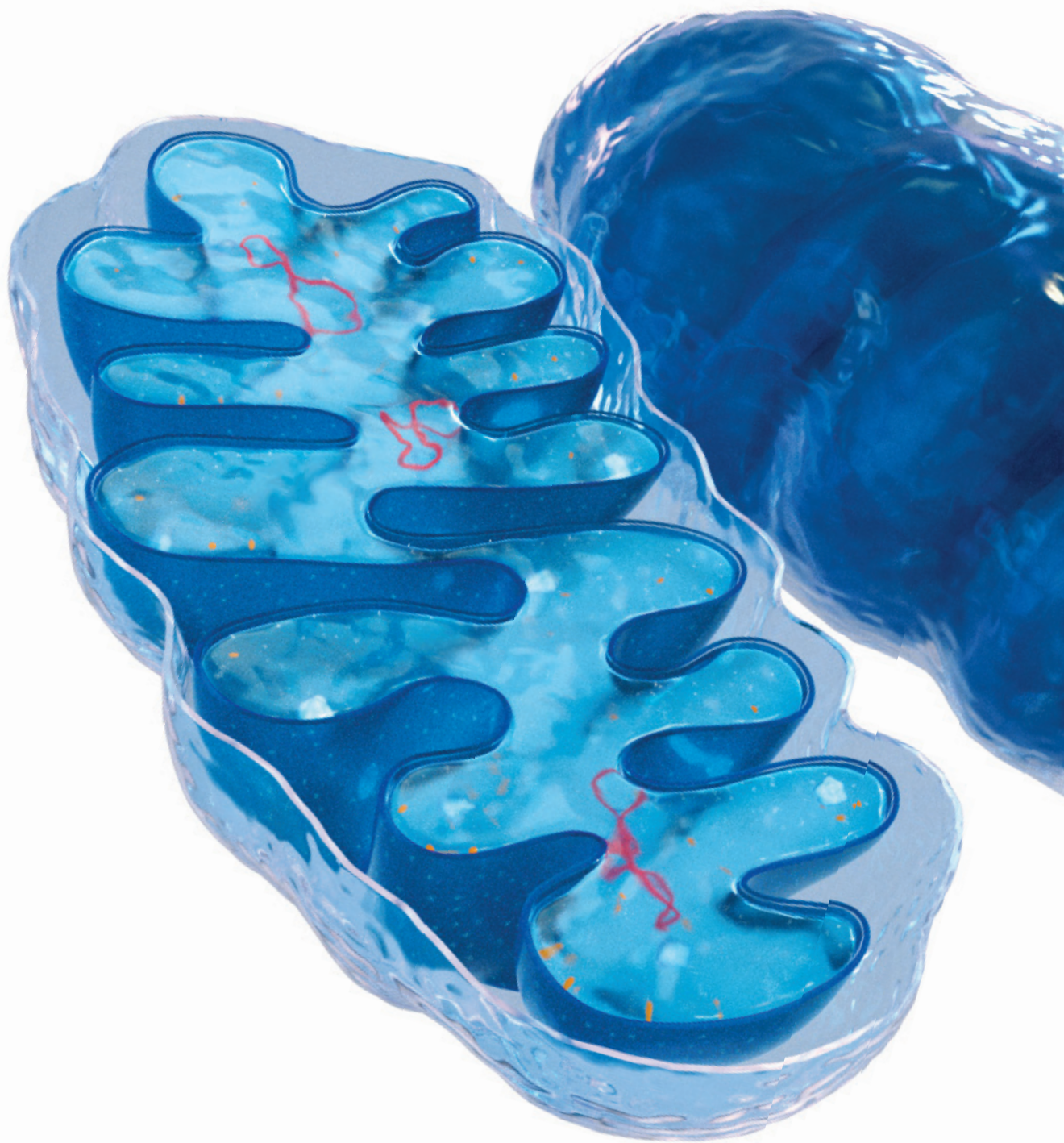
REFERENCES

1. Keene, B. W., Atkins, C. E., Bonagura, J. D., Fox, P. R., Häggström, J., Fuentes, V. L., Oyama, M. A., Rush, J. E., Stepien, R., & Uechi, M. (2019). ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. *Journal of Veterinary Internal Medicine*, 33(3), 1127-1140.
2. Borgarelli, M., & Buchanan, J. W. (2012). Historical review, epidemiology and natural history of degenerative mitral valve disease. *Journal of Veterinary Cardiology*, 14(1), 93-101.
3. Boswood, A., Gordon, S. G., Häggström, J., Wess, G., Stepien, R. L., Oyama, M. A., ... Watson, P. (2018). Longitudinal analysis of quality of life, clinical, radiographic, echocardiographic, and laboratory variables in dogs with early stage myxomatous mitral valve disease receiving pimobendan or placebo: the EPIC Study. *Journal of Veterinary Internal Medicine*, 32(1), 72-85.
4. Reynolds, C. A., Brown, D. C., Rush, J. E., Fox, P. R., Nguyenba, T. P., Lehmkuhl, L. B., Gordon, S. G., Kellihan, H. B., Stepien, R. L., Lefbom, B. K., Meier, C. K., & Oyama, M. A. (2012). Prediction of first onset of congestive heart failure in dogs with degenerative mitral valve disease: the PREDICT cohort study. *Journal of Veterinary Cardiology: the official journal of the European Society of Veterinary Cardiology*, 14(1), 193-202.
5. Haskins, S., Pascoe, P. J., Ilkiw, J. E., Fudge, J., Hopper, K., & Aldrich, J. (2005). Reference cardiopulmonary values in normal dogs. *Comparative Medicine*, 55(2), 156-161.
6. Lopaschuk, G. (2017). Metabolic Modulators in Heart Disease: Past, Present, and Future. *Canadian Journal of Cardiology*, 33, 838-849.
7. Fernández-Vizarra, E., Enríquez, J. A., Pérez-Martos, A., Montoya, J., & Fernández-Silva, P. (2011). Tissue-specific differences in mitochondrial activity and biogenesis. *Mitochondrion*, 11(1), 207-213.
8. Veltri, K. L., Espiritu, M., & Singh, G. (1990). Distinct genomic copy number in mitochondria of different mammalian organs. *Journal of Cell Physiology*, 143(1), 160-164.
9. Doenst, T., Nguyen, T. D., & Abel, E. D. (2013). Cardiac metabolism in heart failure: implications beyond ATP production. *Circulation Research*, 113(6), 709-724.
10. Neubauer, S. (2007). The failing heart—an engine out of fuel. *The New England Journal of Medicine*, 356(11), 1140-1151.
11. Taegtmeier, H. (2004). Cardiac metabolism as a target for the treatment of heart failure. *Circulation*, 110(8), 894-896.
12. Stanley, W. C., Recchia, F. A., & Lopaschuk, G. D. (2005). Myocardial substrate metabolism in the normal and failing heart. *Physiological Reviews*, 85, 1093-1129.
13. Kiyuna, L. A., Albuquerque, R., Chen, C. H., Mochly-Rosen, D., & Ferreira, J. (2018). Targeting mitochondrial dysfunction and oxidative stress in heart failure: Challenges and opportunities. *Free Radical Biology & Medicine*, 129, 155-168.
14. Martín-Fernández, B., & Gredilla, R. (2016). Mitochondria and oxidative stress in heart aging. *Age (Dordrecht, Netherlands)*, 38(4), 225-238.
15. Pashkow, F. J. (2011). Oxidative Stress and Inflammation in Heart Disease: Do Antioxidants Have a Role in Treatment and/or Prevention? *International Journal of Inflammation*, 2011, 514623.
16. Janus, I., Kandefer-Gola, M., Ciaputa, R., Noszczyk-Nowak, A., Paslawska, U., Tursi, M., & Nowak, M. (2017). Cardiomyocyte marker expression in dogs with left atrial enlargement due to dilated cardiomyopathy or myxomatous mitral valve disease. *Folia Histochemica et Cytobiologica*, 55(2), 52-61.
17. Jiang, L., Wang, J., Li, R., Fang, Z. M., Zhu, X. H., Yi, X., Lan, H., Wei, X., & Jiang, D. S. (2019). Disturbed energy and amino acid metabolism with their diagnostic potential in mitral valve disease revealed by untargeted plasma metabolic profiling. *Metabolomics*, 15(4), 57.
18. Li, Q., Freeman, L. M., Rush, J. E., Huggins, G. S., Kennedy, A. D., Labuda, J. A., Laflamme, D. P., & Hannah, S. S. (2015). Veterinary Medicine and Multi-Omics Research for Future Nutrition Targets: Metabolomics and Transcriptomics of the Common Degenerative Mitral Valve Disease in Dogs. *OMICS*, 19(8), 461-470.
19. Lanfear, D. E., Gibbs, J. J., Li, J., She, R., Petucci, C., Culver, J. A., ... Gardell, S. J. (2017). Targeted Metabolomic Profiling of Plasma and Survival in Heart Failure Patients. *Journal of the American College of Cardiology, Heart failure*, 5(11), 823-832.
20. Oyama, M. A., & Chittur, S. V. (2006). Genomic expression patterns of mitral valve tissues from dogs with degenerative mitral valve disease. *American Journal of Veterinary Research*, 67(8), 1307-1318.
21. Buchanan, J. W. (1977). Chronic valvular disease (endocardiosis) in dogs. *Advances in Veterinary Science*, 21, 57-106.
22. Detweiler, D. K., & Patterson, D. F. (1965). The prevalence and types of cardiovascular disease in dogs. *Annals of the New York Academies of Science*, 127, 481-516.
23. Häggström, J., Kvart, C., & Pedersen, H. D. (2005). Acquired valvular disease. In: Ettinger, S. J., Feldman, E. C., eds. *Textbook of Veterinary Internal Medicine*, 6th ed. St Louis: Elsevier: 1022-1039.
24. Atkins, C., Bonagura, J., Ettinger, S., Fox, P., Gordon, S., Häggström, J., ... Stepien, R. (2009). Guidelines for the diagnosis and treatment of canine chronic valvular heart disease. *Journal of Veterinary Internal Medicine*, 23, 1142-1150.
25. Häggström, J., Hansson, K., Kvart, C., & Swenson, L. (1992). Chronic valvular disease in the cavalier King Charles spaniel in Sweden. *Veterinary Record*, 131(24), 549-553.
26. Parker, H. G., & Kilroy-Glynn, P. (2012). Myxomatous mitral valve disease in dogs: does size matter? *Journal of Veterinary Cardiology: the official journal of the European Society of Veterinary Cardiology*, 14(1), 19-29.
27. Fox, P. R. (2012). Pathology of myxomatous mitral valve disease in the dog. *Journal of veterinary cardiology: the official journal of the European Society of Veterinary Cardiology*, 14(1), 103-126.
28. Oyama, M. A., Elliott, C., Loughran, K. A., Kossar, A. P., Castillero, E., Levy, R. J., & Ferrari, G. (2020). Comparative pathology of human and canine myxomatous mitral valve degeneration: 5HT and TGF- β mechanisms. *Cardiovascular Pathology*, 46, 107196.
29. Ayme-Dietrich, E., Lawson, R., Da-Silva, S., Mazzucotelli, J. P., & Monassier, L. (2019). Serotonin contribution to cardiac valve degeneration: new insights for novel therapies? *Pharmacological Research*, 140, 33-42.
30. Driesbaugh, K. H., Branchetti, E., Grau, J. B., Keeney, S. J., Glass, K., Oyama, M. A., Rioux, N., Ayoub, S., ... Ferrari, G. (2018). Serotonin receptor 2B signaling with interstitial cell activation and leaflet remodeling in degenerative mitral regurgitation. *Journal of Molecular and Cellular Cardiology*, 115, 94-103.
31. Côté, E., Edwards, N. J., Ettinger, S. J., Fuentes, V. L., MacDonald, K. A., Scansen, B. A., Sisson, D. D., & Abbott, J. A. (2015). Management of incidentally detected heart murmurs in dogs and cats. *Journal of Veterinary Cardiology*, 17(4), 245-261.

32. Stepien, R. L., Rak, M. B., & Blume, L. M. (2020). Use of radiographic measurements to diagnose stage B2 early stage myxomatous mitral valve disease in dogs. *Journal of the American Veterinary Medical Association*, 256(10), 1129-1136.
33. Beaumier, A., Rush, J. E., Yang, V. K., & Freeman, L. M. (2018). Clinical findings and survival time in dogs with advanced heart failure. *Journal of Veterinary Internal Medicine*, 32(3), 944-950.
34. Borgarelli, M., Savarino, P., Crosara, S., Santilli, R. A., Chiavegato, D., Poggi, M., ... Tarducci, A. (2008). Survival characteristics and prognostic variables of dogs with mitral regurgitation attributable to myxomatous valve disease. *Journal of Veterinary Internal Medicine*, 22, 120-128.
35. BENCH study group. The effect of benazepril on survival times and clinical signs of dogs with congestive heart failure: Results of a multicenter, prospective, randomized, double-blinded, placebo controlled, long-term clinical trial. (1999). *Journal of Veterinary Cardiology*, 1, 7-18.
36. Ettinger, S. J., Benitz, A. M., Ericsson, G. F., Cifelli, S., Jernigan, A. D., Longhofer, S. L., Trimboli, W., & Hanson, P. D. (1998). Effects of enalapril maleate on survival of dogs with naturally acquired heart failure. The Long-Term Investigation of Veterinary Enalapril (LIVE) Study Group. *Journal of the American Veterinary Medical Association*, 213(11), 1573-1577.
37. Häggström, J., Boswood, A., O'Grady, M., Jöns, O., Smith, S., Swift, S., ... DiFrancia, R. (2008). Effect of pimobendan or benazepril hydrochloride on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease: the QUEST study. *Journal of Veterinary Internal Medicine*, 22(5), 1124-1135.
38. Lewis, T. W., Wiles, B. M., Llewellyn-Zaidi, A. M., Evans, K. M. & O'Neill, D. G. (2018). Longevity and mortality in Kennel Club registered dog breeds in the UK in 2014. *Canine Genetics and Epidemiology*, 5, 10.
39. Gordon, S. G., Saunders, A. B., & Wesselowski, S. R. (2017). Asymptomatic Canine Degenerative Valve Disease: Current and Future Therapies. *Veterinary Clinics of North America Small Animal Practice*, 47(5), 955-975.
40. Miller, W. L., Borgeson, D. D., Grantham, J. A., Luchner, A., Redfield, M. M., & Burnett, J. C., Jr (2015). Dietary sodium modulation of aldosterone activation and renal function during the progression of experimental heart failure. *European Journal of Heart Failure*, 17(2), 144-150.
41. DiNicolantonio, J. J., Chatterjee, S., & O'Keefe, J. H. (2016). Dietary Salt Restriction in Heart Failure: Where Is the Evidence? *Progress in Cardiovascular Diseases*, 58(4), 401-406.
42. Kong, Y. W., Baqar, S., Jerums, G., & Ekinci, E. I. (2016). Sodium and Its Role in Cardiovascular Disease - The Debate Continues. *Frontiers in Endocrinology*, 7, 164.
43. Pedersen, H. D. (1996). Effects of mild mitral valve insufficiency, sodium intake, and place of blood sampling on the renin-angiotensin system in dogs. *Acta Veterinaria Scandinavica*, 37(1), 109-118.
44. Rush, J. E., Freeman, L. M., Brown, D. J., Brewer, B. P., Ross, J. N., Jr, & Markwell, P. J. (2000). Clinical, echocardiographic, and neurohormonal effects of a sodium-restricted diet in dogs with heart failure. *Journal of Veterinary Internal Medicine*, 14(5), 513-520.
45. Freeman, L. M. (2009). The pathophysiology of cardiac cachexia. *Current Opinion in Supportive and Palliative Care*, 3, 276-281.
46. Freeman, L. M. (2012). Cachexia and sarcopenia: emerging syndromes of importance in dogs and cats. *Journal of Veterinary Internal Medicine*, 26(1), 3-17.
47. Ineson, D. L., Freeman, L. M., & Rush, J. E. (2019). Clinical and laboratory findings and survival time associated with cardiac cachexia in dogs with congestive heart failure. *Journal of Veterinary Internal Medicine*, 33(5), 1902-1908.
48. Dupont, J., Dedeyne, L., Dalle, S., Koppo, K., & Gielen, E. (2019). The role of omega-3 in the prevention and treatment of sarcopenia. *Aging Clinical and Experimental Research*, 31(6), 825-836.
49. Freeman, L. M., Rush, J. E., Kehayias, J. J., Ross, J. N. Jr, Meydani, S. N., Brown, D. J., ... Roubenoff, R. (1998). Nutritional alterations and the effect of fish oil supplementation in dogs with heart failure. *Journal of Veterinary Internal Medicine*, 12(6), 440-448.
50. Gorjao, R., Dos Santos, C., Serdan, T., Diniz, V., Alba-Loureiro, T. C., Cury-Boaventura, M. F., Hatanaka, E., Levada-Pires, A. C., Sato, F. T., Pithon-Curi, T. C., Fernandes, L. C., Curi, R., & Hirabara, S. M. (2019). New insights on the regulation of cancer cachexia by N-3 polyunsaturated fatty acids. *Pharmacology & Therapeutics*, 196, 117-134.
51. Robinson, S. M., Reginster, J. Y., Rizzoli, R., Shaw, S. C., Kanis, J. A., Bautmans, I., ... Cooper, C., & ESCO working group (2018). Does nutrition play a role in the prevention and management of sarcopenia? *Clinical Nutrition (Edinburgh, Scotland)*, 37(4), 1121-1132.
52. Moonarmart, W., Boswood, A., Luis Fuentes, V., Brodbelt, D., Souttar, K., & Elliott, J. (2010). N-terminal pro B-type natriuretic peptide and left ventricular diameter independently predict mortality in dogs with mitral valve disease. *The Journal of Small Animal Practice*, 51(2), 84-96.
53. Mattin, M. J., Brodbelt, D. C., Church, D. B., & Boswood, A. (2019). Factors associated with disease progression in dogs with presumed early stage degenerative mitral valve disease attending primary care veterinary practices in the United Kingdom. *Journal of Veterinary Internal Medicine*, 33(2), 445-454.
54. Boswood, A., Dukes-McEwan, J., Loureiro, J., James, R. A., Martin, M., Stafford-Johnson, M., Smith, P., Little, C., & Attree, S. (2008). The diagnostic accuracy of different natriuretic peptides in the investigation of canine cardiac disease. *The Journal of Small Animal Practice*, 49(1), 26-32.
55. Fine, D. M., DeClue, A. E., & Reinero, C. R. (2008). Evaluation of circulating amino terminal-pro-B-type natriuretic peptide concentration in dogs with respiratory distress attributable to congestive heart failure or primary pulmonary disease. *Journal of the American Veterinary Medical Association*, 232(11), 1674-1679.
56. Oyama, M. A., Fox, P. R., Rush, J. E., Rozanski, E. A., & Lesser, M. (2008). Clinical utility of serum N-terminal pro-B-type natriuretic peptide concentration for identifying cardiac disease in dogs and assessing disease severity. *Journal of the American Veterinary Medical Association*, 232(10), 1496-1503.
57. Tarnow, I., Olsen, L. H., Kvar, C., Hoglund, K., Moesgaard, S. G., Kamstrup, T. S., Pedersen, H. D., & Häggström, J. (2009). Predictive value of natriuretic peptides in dogs with mitral valve disease. *Veterinary Journal (London, England: 1997)*, 180(2), 195-201.
58. Chetboul, V., & Tissier, R. (2012). Echocardiographic assessment of canine degenerative mitral valve disease. *Journal of Veterinary Cardiology*, 14(1), 127-148.

59. Serres, F., Pouchelon, J. L., Poujol, L., Lefebvre, H. P., Trumel, C., Daste, T., ... Chetboul, V. (2009). Plasma N-terminal pro-B-type natriuretic peptide concentration helps to predict survival in dogs with symptomatic degenerative mitral valve disease regardless of and in combination with the initial clinical status at admission. *Journal of Veterinary Cardiology*, 11(2), 103-21.
60. Chan, I. P., Wu, S. Y., Chang, C. C., & Chen, W. Y. (2019). Serial measurements of cardiac troponin I in heart failure secondary to canine mitral valve disease. *The Veterinary Record*, 185(11), 343.
61. Hezzell, M. J., Falk, T., Olsen, L. H., Boswood, A., & Elliott, J. (2014). Associations between N-terminal procollagen type III, fibrosis and echocardiographic indices in dogs that died due to myxomatous mitral valve disease. *Journal of Veterinary Cardiology: the official journal of the European Society of Veterinary Cardiology*, 16(4), 257-264.
62. Hori, Y., Iguchi, M., Hirakawa, A., Kamiya, Z., Yamano, S., Ibaragi, T., ... Yuki, M. (2020). Evaluation of atrial natriuretic peptide and cardiac troponin I concentrations for assessment of disease severity in dogs with naturally occurring mitral valve disease. *Journal of the American Veterinary Medical Association*, 256(3), 340-348.
63. Ljungvall, I., & Häggström, J. (2016). Adult-onset valvular heart disease. In: Ettinger, S. J., & Feldman, E. C. *Textbook of Veterinary Internal Medicine: Disease of the Dog and Cat*. Philadelphia: WB Saunders, pp: 1249-1265.
64. Polizopoulou, Z. S., Koutinas, C. K., Dasopoulou, A., Patsikas, M., York, M., Roman, I., ... O'Brien, P. J. (2014). Serial analysis of serum cardiac troponin I changes and correlation with clinical findings in 46 dogs with mitral valve disease. *Veterinary Clinical Pathology*, 43(2), 218-225.
65. Toaldo, B., Romito, G., Guglielmini, C., Diana, A., Pelle, N. G., Contiero, B., & Cipone, M. (2018). Prognostic value of echocardiographic indices of left atrial morphology and function in dogs with myxomatous mitral valve disease. *Journal of Veterinary Internal Medicine*, 32(3), 914-921.
66. Borgarelli, M., & Haggstrom, J. (2010). Canine degenerative myxomatous mitral valve disease: Natural history, clinical presentation and therapy. *Veterinary Clinics of North America Small Animal Practice*, 40, 651-663.
67. Häggström, J., Hoglund, K., & Borgarelli, M. (2009). An update on treatment and prognostic indicators in canine myxomatous mitral valve disease. *Journal of Small Animal Practice*, 50(Suppl 1), 25-33.
68. Oyama, M. A., Rush, J. E., O'Sullivan, M. L., Williams, R. M., Rozanski, E. A., Petrie, J. P., Sleeper, M. M., & Brown, D. C. (2008). Perceptions and priorities of owners of dogs with heart disease regarding quality versus quantity of life for their pets. *Journal of the American Veterinary Medical Association*, 233(1), 104-108.
69. van der Vusse, G. J., van Bilsen, M., & Glatz, J. F. (2000). Cardiac fatty acid uptake and transport in health and disease. *Cardiovascular Research*, 45(2), 279-93.
70. Labarthe, F., Khairallah, M., Bouchard, B., Stanley, W.C., & Des Rosiers, C. (2005). Fatty acid oxidation and its impact on response of spontaneously hypertensive rat hearts to an adrenergic stress: benefits of a medium-chain fatty acid. *American Journal of Physiology-Heart and Circulatory Physiology*, 288(3), H1425-36.
71. Labarthe, F., Gélinas, R., & Des Rosiers, C. (2008). Medium-chain fatty acids as metabolic therapy in cardiac disease. *Cardiovascular Drugs and Therapy*, 22(2), 97-106.
72. Montgomery, M. K., Osborne, B., Brown, S. H., Small, L., Mitchell, T. W., Cooney, G. J., & Turner, N. (2013). Contrasting metabolic effects of medium-versus long-chain fatty acids in skeletal muscle. *Journal of Lipid Research*, 54(12), 3322-3333.
73. Bach, A. C., & Babayan, V. K. (1982). Medium-chain triglycerides: an update. *American Journal of Clinical Nutrition*, 36(5), 950-962.
74. Saifudeen, I., Subhadra, L., Konnottil, R., & Nair, R. R. (2017). Metabolic Modulation by Medium-Chain Triglycerides Reduces Oxidative Stress and Ameliorates CD36-Mediated Cardiac Remodeling in Spontaneously Hypertensive Rat in the Initial and Established Stages of Hypertrophy. *Journal of Cardiac Failure*, 23(3), 240-251.
75. Bauer, J. E. (2006). Metabolic basis for the essential nature of fatty acids and the unique dietary fatty acid requirements of cats. *Journal of the American Veterinary Medical Association*, 229(11), 1729-1732.
76. Billman, G. E., Hallaq, H., & Leaf, A. (1994). Prevention of ischemia-induced ventricular fibrillation by omega 3 fatty acids. *Proceedings of the National Academy of Sciences of the United States of America*, 91(10), 4427-4430.
77. Billman, G. E., Kang, J. X., & Leaf, A. (1999). Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs. *Circulation*, 99(18), 2452-2457.
78. Freeman, L. M. (2010). Beneficial effects of omega-3 fatty acids in cardiovascular disease. *Journal of Small Animal Practice*, 51(9), 462-470.
79. London, B., Albert, C., Anderson, M. E., Giles, W. R., Van Wagoner, D. R., Balk, E., ..., Lathrop, D. A. (2007). Omega-3 fatty acids and cardiac arrhythmias: prior studies and recommendations for future research: a report from the National Heart, Lung, and Blood Institute and Office Of Dietary Supplements Omega-3 Fatty Acids and their Role in Cardiac Arrhythmogenesis Workshop. *Circulation*, 116(10), e320-e335.
80. Smith, C. E., Freeman, L. M., Rush, J. E., Cunningham, S. M., & Biourge, V. (2007). Omega-3 fatty acids in Boxer dogs with arrhythmogenic right ventricular cardiomyopathy. *Journal of Veterinary Internal Medicine*, 21(2), 265-273.
81. Sanderson S. L. (2006). Taurine and carnitine in canine cardiomyopathy. *The Veterinary Clinics of North America; Small Animal Practice*, 36(6), 1325-viii.
82. Schaffer, S., Solodushko, V., & Azuma, J. (2000). Taurine-deficient cardiomyopathy: role of phospholipids, calcium and osmotic stress. *Advances in Experimental Medicine and Biology*, 483, 57-69.
83. Schaffer, S. W., Jong, C. J., Ramila, K. C., & Azuma, J. (2010). Physiological roles of taurine in heart and muscle. *Journal of Biomedical Science*, 17 Suppl 1(Suppl 1), S2.
84. Eley, D. W., Lake, N., & ter Keurs, H. E. D. J. (1994). Taurine depletion and excitation contraction coupling in rat myocardium. *Circulation Research*, 74(6), 11210-11219.
85. Lake, N. (1993). Loss of cardiac myofibrils: mechanism of contractile deficits induced by taurine deficiency. *American Journal of Physiology*, 264, H1323-H1326.
86. Kim, H. K., & Han, S. N. (2019). Vitamin E: Regulatory role on gene and protein expression and metabolomics profiles. *IUBMB life*, 71(4), 442-455.

87. Wang, Z., Liu, Y., Liu, G., Lu, H., & Mao, C. (2018). L-Carnitine and heart disease. *Life Sciences*, 184, 88-97.
88. Han, S. N., Adolffson, O., Lee, C. K., Prolla, T. A., Ordovas, J. & Meydani, S. N. (2004). Vitamin E and Gene Expression in Immune Cells. *Annals of the New York Academy of Sciences*, 1031, 96-101.
89. Saboori, S., Koohdani, F., Nematipour, E., Yousefi Rad, E., Saboor-Yaraghi, A. A., Javanbakht, M. H., Eshraghian, M. R., Ramezani, A., & Djalali, M. (2016). Beneficial effects of omega-3 and vitamin E coadministration on gene expression of SIRT1 and PGC1 α and serum antioxidant enzymes in patients with coronary artery disease. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD*, 26(6), 489-494.
90. Birringer, M., & Lorkowski, S. (2019). Vitamin E: regulatory role of metabolites. *International Union of Biochemistry and Molecular Biology, Life*, 71(4), 479-486.
91. Pryor, W. A. (2000). Vitamin E and heart disease: basic science to clinical intervention trials. *Free Radical Biology & Medicine*, 28(1), 141-164.
92. Sagols, E., & Priymenko, N. (2011). Oxidative stress in dog with heart failure: the role of dietary fatty acids and antioxidants. *Veterinary Medicine International*, 180206.
93. Sozen, E., Demirel, T., & Ozer, N. K. (2019). Vitamin E: regulatory role in the cardiovascular system. *International Union of Biochemistry and Molecular Biology Life*, 71(4), 507-515.
94. Michałek, M., Tabiś, A., Cepiel, A., & Noszczyk-Nowak, A. (2020). Antioxidative enzyme activity and total antioxidant capacity in serum of dogs with degenerative mitral valve disease. *Canadian Journal of Veterinary Research = Revue canadienne de recherche veterinaire*, 84(1), 67-73.
95. Del Gobbo, L. C., Imamura, F., Wu, J. H., de Oliveira Otto, M. C., Chiuve, S. E., & Mozaffarian, D. (2013). Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. *American Journal of Clinical Nutrition*, 98(1), 160-173.
96. Freeman, L. M., Rush, J. E., & Markwell, P. J. (2006). Effects of dietary modification in dogs with early chronic valvular disease. *Journal of Veterinary Internal Medicine*, 20, 1116-1126.
97. Qu, X., Jin, F., Hao, Y., Li, H., Tang, T., Wang, H., Yan, W., & Dai, K. (2013). Magnesium and the risk of cardiovascular events: a meta-analysis of prospective cohort studies. *PLoS One*, 8(3), e57720.
98. Tardy, A. L., Pouteau, E., Marquez, D., Yilmaz, C., & Scholey, A. (2020). Vitamins and Minerals for Energy, Fatigue and Cognition: A Narrative Review of the Biochemical and Clinical Evidence. *Nutrients*, 12(1), E228.
99. Li, Q., Heaney, A., Langenfeld-McCoy, N., Boler, B. V., & Laflamme, D. P. (2019). Dietary intervention reduces left atrial enlargement in dogs with early early stage myxomatous mitral valve disease: a blinded randomized controlled study in 36 dogs. *BMC Veterinary Research*, 15(1), 425.
100. Dickson, D., Caivano, D., Matos, J. N., Summerfield, N., & Rishniw, M. (2017). Two dimensional echocardiographic estimates of left atrial function in healthy dogs and dogs with myxomatous mitral valve disease. *Journal of Veterinary Cardiology*, 19, 469-479.
101. Li, Q., Laflamme, D. P., & Bauer, J. E. (2020). Serum untargeted metabolomic changes in response to dietary intervention on dogs with early stage myxomatous mitral valve disease. *PLoS One*, 15(6), e0234404.



Cross section of mitochondrion



Advancing Science for Pet Health

Learn more at
PurinaInstitute.com

PURINA TRADEMARKS ARE OWNED BY SOCIÉTÉ DES PRODUITS NESTLÉ S.A.
ANY OTHER MARKS ARE PROPERTY OF THEIR RESPECTIVE OWNERS. RG/CRCR