

Geriatric Cardiology in Dogs - Part 1: Classification and Treatment of Heart Failure in Geriatrics

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Abstract

The purpose of this article is to give current information on the effect of aging on heart, classification of heart failure (HF) in geriatric dogs and therapeutic advances and challenges. The aging process results in a host of physiological and biological changes that lead to progressive HF. Nearly any cardiovascular disease (CVD) can lead to HF. HF in geriatric dogs is broadly classified into: Diastolic heart failure is defined as HF with preserved ejection fraction (HF/PEF), systolic heart failure is also known as HF with low ejection fraction (HF/low-EF). Importantly, HF/PEF accounts for approximately 50% of all HF patients and its prevalence is higher in the elderly. In humans, mortality and morbidity benefits for HF/low-EF have been reported with angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs), β -blockers and aldosterone antagonists, and the hydralazine–nitrate combination in patients intolerant to ACE inhibitors or nitrates. Therapies for symptom control and morbidity benefit include diuretics and digoxin. The most common and suggested therapy for dogs with HF by ACVIM panelists is furosemide, ACE-I and pimobendan. Pharmacological therapy is limited for HF/PEF as the results of small trials have been inconclusive. To date, clinical trials in HF/PEF patients have not shown mortality benefit so that management is focused on symptom relief and treatment of the underlying cause.

Keywords: Geriatric Cardiology, Classification, Treatment, Heart Failure, Dog

Köpeklerde Geriatrik Kardiyoloji - Bölüm 1: Geriatriklerde Kalp Yetmezliğinin Klasifikasyonu ve Tedavisi

Özet

Bu derlemede yaşlanmanın kalp üzerine etkileri, geriatrik köpeklerde kalp yetmezliğinin (HF) klasifikasyonu ve terapötik yaklaşımları konularında güncel bilgiler vermek amaçlanmıştır. Yaşlanma progressif HF'ne yol açan fizyolojik ve biyolojik değişikliklere yol açar. Hemen hemen tüm kardiyovasküler hastalıklar (CVDs) HF'ne yol açabilir. Geriatrik köpeklerde, HF başlıca; diyastolik kalp yetmezliği, HF ile korunmuş ejeksiyon fraksiyonu (HF/PEF) olarak, sistolik kalp yetmezliği, HF ile düşük ejeksiyon fraksiyonu (HF/düşük-EF) olarak sınıflandırılır. Tüm HF hastalarının ortalama %50'sini HF/PEF oluşturur ve geriatriklerde prevalansı daha yüksektir. Geriatrik insanlarda HF/düşük EF için tedavi başlıca ACE inhibitörleri veya ARBs, β -blokörler, aldosterone antagonistleri ve ACE inhibitörleri veya nitrat intoleransı olan hastalara hydralazine–nitrat kombinasyonunu kapsar. Semptomların kontrolü ve morbidite faydası için diüretikler ve digoxin kullanılır. Kalp yetmezliği olan köpeklerde ACVIM panelislerince tavsiye edilen tedaviyi furosemide, ACE-I, ve pimobendan oluşturmaktadır. HF/PEF olan hastalardaki klinik çalışma verileri mortalite faydası olmadığını göstermiştir. Tedavi semptomların iyileştirilmesi ve primer nedenin tedavisine yönelik yapılır.

Anahtar sözcükler: Geriatrik kardiyoloji, Klasifikasyon, Tedavi, Kalp yetmezliği, Köpek

INTRODUCTION

Why geriatric cardiology is important?
Is the term geriatric cardiology redundant?

Technically, geriatric cardiology refers to cardiovascular care of dogs 9 years of age or older (giant breed >7.5

years) ^[1]. It is the practice of cardiovascular (CV) medicine that is adapted to the needs of older dogs. To some degree, all cardiologists know this, recognize this, and in varying capacities, practice this.

Not surprisingly, a recent survey in Near East University, Veterinary Hospital found that almost 50% of patients who



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visited Hospital over the last year would be considered geriatric on the basis of age alone.

But, is there reason to believe that cardiovascular management of these older dogs differs from that of younger cardiovascular patients?

A clue comes from the mission statement of the geriatric cardiology member section of the American College of Cardiology (ACC), which states that the practice of geriatric cardiology should consider “*all matters related to cardiovascular care-giving in relation to aging*”^[2].

In older dogs, multiple medical problems (hypertension, diabetes, hyperlipidemia, frailty, cognitive dysfunction (CD) lead to polypharmacy. Compounding these burdens is that older patients have not only considerable clinical needs, but psychological and social needs too ^[3-5].

In humans, polypharmacy, defined as the concurrent use of 5 or more medications, occurs in up to 40% of older patients. Absorption, bioavailability, and volume of distribution of pharmacologic agents change dramatically with age, significantly increasing the risk of drug interactions, particularly in patients with polypharmacy ^[6]. Importantly, the risk of adverse drug effects is about 50% in patients on 4 chronic medications and approaches 100% in those taking more than 7. Moreover, almost one-half of hospitalizations related to adverse drug events are attributable to cardiovascular medications (particularly diuretics, warfarin, beta-blockers, and angiotensin-converting enzyme inhibitors) ^[7]. The challenge is to prioritize treatments, minimize dangerous interactions, and optimize quality of life ^[3].

Recommendations require thoughtful individualization, based on integrating patient-centered priorities with respect to each patient’s aging experience. This article focuses on the effect of ageing on heart, classification of HF in geriatric dogs and therapeutic advances and challenges.

EFFECTS OF AGING ON THE CARDIOVASCULAR SYSTEM

An accurate biomarker of aging is lacking. Pathophysiologic hallmarks of cardiovascular aging are summarized in *Table 1* ^[8-10].

THE IMPORTANT CARDIOVASCULAR DISEASES IN GERIATRIC DOGS

Most dogs born with congenital heart disease died when they were young and did not reach old age or had the defect corrected surgically (eg, patent ductus arteriosus), and the defect is thus of no concern in old age.

The aging process results in a host of physiological and

biological changes that lead to progressive HF (*Table 1*). Nearly any cardiovascular disease (CVD) can lead to HF. Common CVDs causing HF in geriatric dogs are given in *Table 2* ^[1,4,5,11,12].

HEART FAILURE

Heart failure (HF) is a major healthcare burden in dogs and a particularly important problem in the elderly dogs. This is the most common disorder in small animals’ cardio-respiratory clinics, commonly the end-stage in a CVD continuum (*Fig. 1*). It is characterized with progressive decrease in cardiac output and ventricular filling ^[5,13].

Definition of HF: Definitions of HF in dogs and humans is based on a clinical syndrome that emphasizes symptoms and signs ^[5,11]. Briefly, the HF syndrome consists of a triad of;

Typical symptoms; exercise intolerance, weakness, weight loss, chronic cough, peripheral edema, orthopnea, syncope, inappetence.

Typical signs; tachyarrhythmia, tachypnea, pulmonary rales, ascites, pleural effusion, raised jugular venous pressure, hepatomegaly.

Objective evidence of structural and functional abnormality; cardiomegaly, cardiac murmurs, abnormal echocardiogram or raised atrial natriuretic peptide marker level.

Pathophysiology: Most HF patients have myocardial dysfunction. Common causes include muscle damage or loss from mitral regurgitation, hypertensive (pulmonary/systemic) cardiomyopathy, atherosclerosis, diabetic cardiomyopathy, increased vascular resistance and afterload from hypertension, and increased heart rate from tachyarrhythmias such as atrial fibrillation ^[4,5,11,14].

Early cardiocirculatory, hemodynamic and cardio-renal HF models emphasized decreased pump function, cardiac output and renal blood flow, and increased peripheral vasoconstriction and provided the rationale for using diuretics, inotropes and vasodilators ^[15].

Subsequently, the neurohumoral model emphasized the development and progression of asymptomatic to symptomatic HF. In this construct, injury leads to activation of the adrenergic nervous system (ANS), the renin-angiotensin-aldosterone system (RAAS) and cytokine systems that preserve LV function in the short term, and to secondary damage with maladaptive LV remodeling and worsening HF in the long term. After that, LV remodeling is severe and impaired healing can further aggravate remodeling in the elderly ^[15,16].

Whereas activation of the ANS decreases during the progression of HF resulting in decreased norepinephrine (owing to an exhaustion phenomenon) and reuptake, RAAS activation persists. The neurohumoral model provided

Table 1. Pathophysiological changes and pathophysiologic hallmarks during aging

*dysregulation of repair mechanisms: decreased endothelial nitric oxide production and increased endothelial apoptosis, superoxide production and advanced glycation end product
*fibrotic cardiac remodeling: diastolic and systolic dysfunction
*remodeling of the vascular wall: arterial stiffening
*increased collagen, decreased elastin and calcification: atrial fibrillation, bradyarrhythmias
*increase in fibrinogen, coagulation factors, platelet activity, plasminogen activator inhibitor-1, prothrombotic cytokines: atherosclerosis
*enhanced adherence of mononuclear cells to the endothelial surface, promoting an inflammatory microvascular environment: thromboembolism
*abnormal adrenergic responses: blunted β 1-adrenergic myocardial contractility and β 2-adrenergic vasodilatation
*limited ATP production: less contraction or relaxation in response to stress

Table 2. The most common diseases causing HF in geriatric dogs

*mitral regurgitation; valvular diseases, DCM
*hypertensive (pulmonary/systemic) cardiomyopathy
*atherosclerosis
*diabetic cardiomyopathy (hyperlipidemia, Type 2 diabetes)

aldosterone secretion and catecholamine release, whereas AT_2 activation leads to vasodilation, the inhibition of cell growth, natriuresis and bradykinin release. The ratio of AT_1 to AT_2 receptors decreases in HF. Sustained expression of angiotensin II leads to cardiac and renal fibrosis (partly through increased aldosterone), cardiac hypertrophy, and maladaptive cardiac and vascular remodeling. Aldosterone

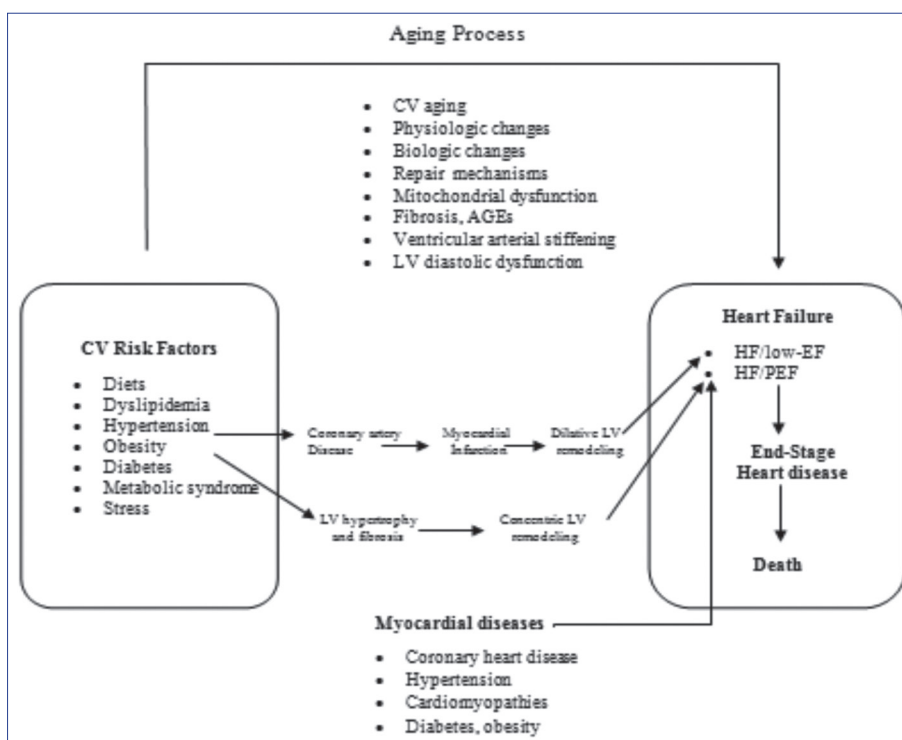


Fig 1. Heart failure, aging and the cardiovascular disease continuum. Heart failure can be considered as a progressive disorder in a disease continuum occurring in parallel with aging and leading to disability and ultimate death. AGE: Advanced glycation end product; CV: Cardiovascular; EF: Ejection fraction; HF: Heart failure; LV: Left ventricular; PEF: Preserved ejection fraction

rationale for using ACE inhibitors, ARBs, aldosterone antagonists and β -blockers in HF [15].

While most angiotensin II, the major effector molecule of the RAAS, is formed via the ACE-dependent pathway, angiotensin II can also be produced through renin- and ACE-independent pathways. Angiotensin II acts through the angiotensin II type 1 (AT_1) and angiotensin II type 2 (AT_2) receptors. The predominant subtype is AT_1 in the vasculature and AT_2 in the myocardium, with localization of AT_1 in nerves and AT_2 in fibroblasts and the interstitium. AT_1 activation leads to vasoconstriction, cell growth,

also leads to the inhibition of norepinephrine re-uptake and worsening HF [4,5,15,17].

Classification of HF: The new ACVIM (American College of Veterinary Internal Medicine) classification of cardiac disease that was adapted from the American College of Cardiology and uses an A-through-D categorization scheme (stage A with risk of HF but no structural changes or symptoms; stage B with structural changes but no signs or symptoms; stage C with structural changes and prior or current symptoms; stage D with severe refractory HF requiring specialized interventions [5,18,19].

Currently, HF in geriatric dogs is considered to be the result of structural and functional cardiac disorders that impair ventricular filling and ejection, and is broadly classified into:

Diastolic heart failure (DHF), HF with preserved ejection fraction (HF/PEF).

Systolic heart failure (SHF), HF with low ejection fraction (HF/low-EF).

Importantly, HF/PEF accounts for approximately 50% of all HF patients and its prevalence is higher in the elderly [20,21].

Treatment of HF: Although HF is primarily a disorder of the elderly, there is a lack of evidence-based data from randomized clinical trials (RCTs) of HF, specifically in elderly patients and geriatric dogs. More often drugs have to be chosen based on pathophysiological logic. Dose adjustments are necessary so as not to cause harm [4,5].

Therapies for HF/low-EF: In humans, mortality and morbidity benefits have been reported with angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs), β -blockers and aldosterone antagonists, and the hydralazine–nitrate combination in patients intolerant to ACE inhibitors or nitrates. Therapies for symptom control and morbidity benefit include diuretics and digoxin [7,18].

The most common and suggested therapy for dogs with HF by ACVIM panelists is furosemide, ACE-I, pimobendan. For the following drugs, no consensus has been reached but many cardiologists use spironolactone for its diuretic, potassium-sparing and presumably anti-fibrotic properties, digoxin for rate control, beta adrenergic blockers in cases of atrial fibrillation to control the ventricular rate, or ventricular arrhythmias. Other drugs that can be utilized and are used by some veterinarians are amlodipine (up to 0.1 mg/kg q12 h, needs to be titrated and monitor blood pressure), hydrochlorothiazide (2-4 mg/kg q12 h) and torsemide (0.2 mg/kg q12-24 h) instead of furosemide. These last three drugs are usually reserved for refractory heart failure cases [18,22].

Class D1 and D2 dogs have clinical signs of congestive and or/low output heart failure. Usually they need pleural or abdominal centesis, oxygen, nursing care. Other drugs can be added, such as cough suppressants, bronchodilators, sildenafil, but no consensus has been reached on them [18,22].

- **ACE Inhibitors:** ACE-Is are the first choice in HF pharmacotherapy. They are recommended in patients with HF/low-EF (i.e., EF <40%) regardless of the presence of HF symptoms based on the RCTs [23-26].

A review of 34 RCTs was published and showed decreased mortality and hospitalization. The benefit was primarily related to fewer deaths from progressive HF and was found with enalapril, captopril, ramipril, quinapril and lisinopril, suggesting a class effect [27]. However, ACE-I did not meet consensus by the group at C1 stage of the disease. ACE-I

(dose depends of the drug used) (Enalapril 0.5 mg/kg, 1-2x/d p.o.; Benazepril 0.25-0.5 mg/kg, 1-2x/d p.o.) can be given Class C2 and D dogs [5,18,22].

Although every attempt should be made to use target doses shown to produce mortality benefit in RCTs, it is advisable in elderly patients to start at a low dose and uptitrate to the tolerated dose. Similar precautions are needed in elderly HF patients [4,11]. Over 75% of patients still do not receive the optimal dose of ACE inhibitors. In elderly patients who cannot tolerate the target dose, a lower dose of an ACE inhibitor is still beneficial but a β -blocker should be introduced [11].

- **Angiotensin Receptor Blockers:** Most RCTs for ARBs used ACE inhibitors as comparator and patients received other background therapy such as β -blockers and/or diuretics. In the Valsartan Heart Failure Trial (Val-HeFT), overall mortality was similar in valsartan and placebo groups but combined morbidity and mortality was lower with valsartan [4,28].

In contrast to Val-HeFT, the candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Added trial with candesartan on top of an ACE inhibitor and background therapy showed a reduction in the primary end point (hospitalization or death) [29]. In the CHARM- Alternative trial, use of candesartan in ACE inhibitor-intolerant patients reduced morbidity and mortality [30]. However, 7.7% of the patients developed angioedema.

Similar precautions as with ACE inhibitors should be observed with ARBs [11]. It is reasonable to add a β -blocker before the target dose of an ARB is reached in stable patients.

- **Pimobendan:** Pimobendan does increase contractility without increasing myocardial oxygen consumption. In addition, pimobendan exerts a peripheral vasodilatory effect by phosphodiesterase III inhibition, which may not only be important in the systemic but also in the pulmonary circulation. Furthermore, the vasodilation affects arteries as well as veins, therefore it is expected to reduce afterload and preload. Finally, it may have an anticytokine effect. The ACVIM panelists suggest also using pimobendan at 0.1-0.3 mg/kg q 12 h in dogs with HF [18,22]. It can be combined with many drugs, e.g. furosemide, ACE inhibitors, betablockers, digoxin and amlodipine [5].

β -blockers. The majority of RCTs added a β -blocker to background therapy that included ACE inhibitors. The addition of a β -blocker to an ACE inhibitor and a diuretic is recommended in clinically stable stage C patients with or without symptoms [11]. Compelling evidence of mortality benefits exists for bisoprolol, sustained-release metoprolol succinate and carvedilol. A meta-analysis of five RCTs with more than 12.000 patients, of whom 4617 (36.3%) were elderly, showed mortality benefits with those three

β -blockers [4,31,32]. β -blockers are therefore recommended in elderly patients with HF/low-EF.

In dogs with HF, β -blockers can be used in cases of atrial fibrillation to control the ventricular rate, or ventricular arrhythmias [18].

Mitochondria in hearts of aged patients seem to be unable to produce increased amounts of ATP to fuel contraction or relaxation in response to stress. The β -adrenergic blocking agents may improve exercise capacity dramatically, in human.

Which of these issues is applicable to the aging pet is unknown [8].

Initiation with the lowest tolerated dose and gradual escalation reduce the risk of hypotension and bradycardia. When hypotension and bradycardia are accompanied by evidence of hypoperfusion (i.e., cold extremities, or worsening of renal or hepatic function), the dose should be decreased or the drug withdrawn (Carvedilol, 0.05-0.4 mg/kg, 1-2x/d p.o.; Atenolol, 0.2-1.5 mg/kg, 1-2x/d p.o.) [4,5].

- *Diuretics*: Patients with a history or symptoms of HF and evidence of fluid retention should be treated with sodium restriction and diuretics such as loop diuretics (furosemide, torsemide and bumetanide), thiazides (metolazone and hydrochlorothiazide) or aldosterone antagonists (spironolactone and eplerenone). Loop diuretics increase sodium excretion (by 25% of filtered load) and free-water clearance unless renal function is severely impaired (creatinine clearance <10 mL/L). Thiazides increase fractional sodium excretion (by 5-10% of filtered load) and decrease free-water clearance unless renal function is moderately impaired (creatinine clearance <30 mL/L) [4,5,33-35].

The ACVIM panel suggested for C1 dogs, furosemide 1-4 mg/kg IV, IM or SC as bolus or 1 mg/kg, constant rate infusion (CRI), the latest being reserved for dogs not responding to a bolus injection. In some cases higher doses of furosemide such as 4-8 mg/kg can be given in severe pulmonary edema cases; the dose depends on the kidney status of the animal, the amount of water taken and age. Monitoring respiratory rate, ECG, urine output and drinking is essential [5,18,33].

Furosemide (1-2 mg/kg q12 h to 4-6 mg/kg q 8 h orally) can be given to Class C2 and D1, D2 dogs with careful monitoring of renal parameters; mild azotemia is unavoidable and well tolerated. Diuresis can be increased by higher dosage or increased frequency of application, also in refractory cases furosemide can be given by SQ injection by the owner instead of a tablet. In these cases, additional diuretics are added like hydrochlorothiazide (1-2 mg q 12-24 h), spironolactone (0.5-2 mg/kg q 24 h) or torsemide (0.1 \times dose of furosemide) [5,18,33].

Hydrochlorothiazide (2-4 mg/kg q 12 h) and torsemide

(0.2 mg/kg q 12-24 h) instead of furosemide can be used in C2 dogs [5,18,33].

Patients on diuretics should be closely monitored. The dose should be individualized, especially in the elderly who are susceptible to orthostatic hypotension and renal dysfunction from over-diuresis. Too low a dose can lead to fluid retention, which in turn can blunt the response to ACE inhibitors and decrease tolerance of β -blockers. Too high a dose can lead hypovolemia, increased susceptibility to hypotension from ACE inhibitors, ARBs and/or other vasodilators, and renal insufficiency from ACE inhibitors or ARBs [4].

In the elderly, it is prudent to initiate therapy with a low dose and titrate upward based on the diuretic response and weight loss. Hypokalemia and hypomagnesemia should be promptly treated to prevent arrhythmias, especially if digoxin is being used. When a loop diuretic is used, an ACE inhibitor or ARB alone, or in combination with an aldosterone antagonist, may reduce the risk of electrolyte depletion [5,18,33].

- *Aldosterone Antagonists*: An important aspect of the RAAS is the AT₁ receptor-mediated activation of aldosterone, which promotes sodium retention, loss of magnesium and potassium, sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, vascular damage and impaired arterial compliance. The rationale for using aldosterone antagonists is that angiotensin II stimulates the release of aldosterone, thereby activating the mineralocorticoid receptor, and the activation of this receptor persists despite the use of ACE inhibitors, ARBs and β -blockers [5,36,37].

While aldosterone antagonists are typically used for their mortality benefits, long-term studies of other diuretics on morbidity and mortality in HF are lacking [36,37]. In dogs with HF, spironolactone is used for its diuretic, potassium-sparing and presumably anti-fibrotic properties [5,18,33].

Based on evidence from two RCTs [34], the addition of an aldosterone antagonist is considered reasonable in patients with moderate-to-severe HF and reduced EF, provided renal function (serum creatinine \leq 2.5 mg/dL in men and \leq 2.0 mg/dL in women) and serum potassium \leq 5.0 mEq/L) can be carefully monitored [11].

The Randomized Aldactone Evaluation Study for Congestive Heart Failure (RALES), which assessed spironolactone on top of background therapy with ACE inhibitors, β -blockers, diuretics and digoxin in patients with moderate-to-severe HF (EF <35%), was prematurely terminated owing to an early finding of a 30% reduction in all-cause mortality but also reduced morbidity and hospitalization [34].

- *Digoxin*: The addition of digoxin is recommended if HF symptoms persist despite optimal treatment with an ACE inhibitor, β -blocker and/or a diuretic [11]. The Randomized

Assessment of Digoxin on Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) study reported worsening after the withdrawal of digoxin in HF patients who were in sinus rhythm and stable on a regimen of digoxin, diuretics and ACE inhibitors [38].

In dogs with HF, digoxin (0.22 mg/m²) can be used for rate control [18]. Since digoxin has a narrow therapeutic index and is excreted by the kidneys and the elderly are at risk of renal dysfunction and/or lean body mass loss, a low initial dose of 0.125 mg daily or every other day should be used in patients aged over 70 years [11]. While the serum digoxin level does not seem to correlate with clinical benefits, a serum digoxin level over 1 ng/mL is associated with increased mortality, in humans [39]. A level less than 1.2 ng/mL might therefore be safer for dogs [5].

- **Vasodilators:** Based on three RCTs, the addition of a combination of isosorbide dinitrate and hydralazine is considered reasonable if the symptoms persist despite ACE inhibitor and β -blocker therapy, or if patients are intolerant to ACE inhibitors or ARBs [11]. Val-HeFT I reported that the addition of isosorbide dinitrate and hydralazine can be favourable in male patients with mild-to-severe HF (EF <45%) receiving digoxin and diuretics (Isosorbide dinitrate ½-1 hub, rubben on hairless skin; Hydralazine 0.5-3 mg/kg orally q 12 h for dogs) [4,40].

Amlodipine (0.15-0.25 mg/kg SID, needs to be titrated and monitor blood pressure) can be used in C2 and D1 dogs, especially in cases with high blood pressure because of renal failure [5,18].

Medical Therapy of HF/PEF: Heart failure/PEF increases with age, is very common in the elderly [21]. It considers HF/PEF as a triad of [41]: (1) signs and symptoms of HF, (2) normal or mildly abnormal LV systolic function (LV EF >50% or LV end-diastolic volume index <97 mL/m²), and (3) evidence of LV diastolic dysfunction (echocardiographic/Doppler E/E' >15, E' < 8 cm/sn or elevated NTproBNP concentration >450 pmol/L with abnormal echocardiographic/ Doppler parameters) [5,42].

In contrast to HF/low-EF, patients with HF/PEF are more likely to be elderly, and hypertensive, and less likely to have previous therapy with ACE inhibitors and ARBs [43].

Mortality is similar to that with HF/low-EF. While survival over time has improved for HF/low-EF, it has remained unchanged for HF/PEF. Major causes of HF/PEF in the elderly include LV hypertrophy, hypertrophic cardiomyopathy, aortic stenosis with normal EF, ischemic heart disease, restrictive cardiomyopathy with idiopathic causes or infiltrative cardiomyopathy [44]. In humans, it is believed that systolic dysfunction is a consequence of diastolic dysfunction because of decreased preload [4].

The nonpharmacological strategy is similar to that for patients with HF/low-EF (i.e., daily monitoring of weight,

attention to diet and lifestyle, and close medical follow-up) together with aggressive control of hypertension, tachycardia and other precipitating causes of decompensation. Emerging evidence suggests that exercise training improves outcome (i.e., improves quality of life, increases longevity and decreases symptoms) [4].

Pharmacological therapy is limited as the results of small trials have been inconclusive. To date, clinical trials in HF/PEF patients have not shown mortality benefit so that management is focused on symptom relief and treatment of the underlying cause. Beyond, the established beneficial effects of ACE inhibitors in patients with hypertension that may be due, at least in part, to attenuation of cardiac fibrosis or other anti-fibrotic strategies (such as AGE breakers) may exert beneficial actions in high-risk elderly patients with diastolic heart failure [9]. In the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial, the ACE inhibitor perindopril in patients aged over 70 years (mean: 76 years of age) and HF-PEF did not reduce the primary end point but the event rates were lower than anticipated [26]. However, there was a trend towards reduced HF hospitalization at 1 year.

In the CHARM-Preserved trial in patients with mild-to-moderate HF and LV EF more than 40%, the ARB candesartan on top of standard therapy had no mortality benefit; 22% of patients in the candesartan group and 24% in the placebo group reached the primary end point (cardiovascular death or HF hospitalization) [45].

In the irbesartan in Patients with Heart Failure and Preserved Ejection Fraction Study (I-PRESERVE), the ARB irbesartan in 4128 patients aged 60 years or over (mean: 72 years of age) showed no benefit [46].

In a substudy of the Digitalis Investigation Group (DIG) trial, digoxin did not change the primary end point of HF hospitalization or cardiovascular mortality [47].

In summary, specific medical therapy for HF/PEF is lacking. Current recommendations for the treatment of HF/PEF include [4,11]: (a) control of systolic and diastolic hypertension, (b) control of ventricular rate in patients with atrial fibrillation, (c) control of pulmonary congestion and peripheral edema with diuretics, (d) treatment of coronary artery disease and demonstrable myocardial ischemia with coronary revascularization, (e) restoration and maintenance of sinus rhythm in patients with atrial fibrillation, (f) use of digoxin in selected patients.

Other HF Treatments

- **Supraventricular Arrhythmias:** Both patients with HF/PEF and HF/low-EF develop atrial fibrillation and other supraventricular arrhythmias [48]. Deleterious effects of supraventricular tachyarrhythmias are due to: (1) loss of atrial contribution to ventricular filling, (2) increased myocardial oxygen demands and decreased perfusion, (3)

impaired contraction and relaxation, (4) stasis of blood in the atria leading to thrombus formation and embolism, (5) the development of cardiomyopathy from sustained tachycardia^[11].

Atrial fibrillation is the most common treatable supra-ventricular or atrial arrhythmia. It leads to decreased exercise capacity and aggravates long-term prognosis. Atrial fibrillation begets atrial fibrillation, which begets HF. It is also more common in the elderly^[49].

Two important aspects of therapy in HF patients are rate and/or rhythm control and prevention of thrombo-embolism. The goal is to decrease the ventricular rate to less than 80-90 bpm at rest and to less than 110-130 bpm with moderate exercise^[11].

Digoxin is more effective in slowing atrioventricular

(AV) conduction at rest than during exercise. β -blockers are more effective than digoxin during exercise. The combination of digoxin and β -blockers may be more effective for rate control. When β -blockers fail to control HF or are contraindicated, amiodarone (10 mg/kg orally q 12 h for 7-14 days or 10-15 mg/kg orally q 24 h for 7-14 days, than 5-7.5 mg/kg orally q 24 h for dogs) can be used. If pharmacotherapy fails to control heart rate, AV-node ablation is indicated. R-wave synchronized cardioversion is recommended when rapid rate is unresponsive to therapy for patients with ischemia, hypotension angina or HF^[48].

Anticoagulation should be maintained in all patients with atrial fibrillation regardless of whether sinus rhythm is restored owing to the high recurrence rate with associated embolic risk^[5].

- *Ventricular Arrhythmias, Sudden Death:* Both patients with HF/PEF and HF/low-EF can develop ventricular arrhythmias and sudden death. Sudden death can result from two main causes: (1) arrhythmias, usually ventricular tachyarrhythmias such as non-sustained or sustained ventricular tachycardia (VT) but less often bradycardia and pulseless supraventricular rhythms, especially in stage D HF, (2) ischemia with ACS and acute MI, electrolyte imbalance and vascular events, including pulmonary and systemic embolism^[11].

In addition, HF/low-EF patients with dilative LV remodeling are prone to develop VT (non-sustained or sustained) and sudden death besides non-sudden death from pump failure^[11].

Definitive therapy for myocardial ischemia or other reversible factors can prevent the recurrence of tachyarrhythmia such as polymorphic VT, non-sustained VT and ventricular fibrillation. Medical therapies that decrease disease progression such as Lidocain (2 mg/kg i.v. over 1-2 min (repeat in 2 mg/kg boluses up to 8 mg/kg in 10 min) or 0.8

mg/kg/min i.v. infusion (up to 8 mg/kg)), β -blockers^[32,50] and aldosterone antagonists^[36,37] can decrease sudden deaths in HF/low-EF patients.

In addition, the negative inotropic effects of antiarrhythmic drugs is a concern as they may aggravate HF and augment the risk of serious arrhythmias in HF/low-EF patients^[5].

Importantly, in humans, implantable cardioverter-defibrillator (ICD) devices that terminate sustained arrhythmias can further decrease sudden death in that group. ICDs are therefore recommended for all patients with life-threatening tachyarrhythmias and otherwise good prognosis^[11].

Patients with stage D HF/low-EF often (in 33%) have a QRS duration of more than 0.12 s and LV dyssynchrony or delayed activation of the LV free wall. Ventricular dyssynchrony is associated with increased mortality in HF patients. Previously known as biventricular pacing, cardiac resynchronization therapy (CRT) re-coordinates ventricular beating by the insertion of atrial-synchronized biventricular pacing catheters, thereby eliminating dyssynchrony^[51]. CRT can also reduce secondary mitral regurgitation.

Other Considerations: Hospitalized stage C/D HF patients are at increased risk for thromboembolic complications and should receive prophylactic anticoagulation with intravenous unfractionated heparin (Heparin sodium: 300-500 IU/kg i.v. (loading dose), then 100-300 IU/kg s.c. q 6-8 h) or low- molecular-weight heparin (Dalteparin: 100-150 IU/kg s.c. q8h) unless contraindicated. Warfarin is a reasonable in HF patients with antecedent embolic events or with paroxysmal or persistent atrial fibrillation^[52].

Surgical Management of Refractory End-Stage HF (Stage D): Ventricular assist devices (VADs), cardiac transplantation, total artificial hearts, myocardial vascularization with coronary artery bypass grafting (CABG) and mitral valve repair or replacement are beneficial in stage D patients with demonstrable myocardial viability, in human^[4,51].

Dogs with severe mitral regurgitation have poor prognosis even with all the pharmacological options that currently exist^[53]. Recent improvements in cardiopulmonary bypass techniques have enabled its use in small breed dogs. In the case of prosthetic valves, matching the size of the valve and conquering thrombosis is essential for long-term prognosis. Recently, successful techniques for mitral valve repair with annuloplasty and chordal replacement have been utilized, which enables long-term survival for severe myxomatous mitral valve disease patients. Costs and availability are the major drawbacks of this option^[54-57].

CONCLUSION

The aging process results in a host of physiological and

biological changes that lead to progressive HF. Nearly any CVD can lead to HF. HF in geriatric dogs is considered to be the result of structural and functional cardiac disorders that impair ventricular filling and ejection, and is broadly classified into: Diastolic heart failure is defined as HF with preserved ejection fraction (HF/PEF), systolic heart failure is also known as HF with low ejection fraction (HF/low-EF). Importantly, HF/PEF accounts for approximately 50% of all HF patients and its prevalence is higher in the elderly.

In humans, mortality and morbidity benefits for HF/low-EF have been reported with angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs), β -blockers and aldosterone antagonists, and the hydralazine-nitrate combination in patients intolerant to ACE inhibitors or nitrates. Therapies for symptom control and morbidity benefit include diuretics and digoxin. The most common and suggested therapy for dogs with HF by ACVIM panelists is furosemide, ACE-I, pimobendan. Pharmacological therapy is limited as the results of small trials have been inconclusive. To date, clinical trials in HF/PEF patients have not shown mortality benefit so that management is focused on symptom relief and treatment of the underlying cause.

REFERENCES

- Haydardedeoğlu AE:** Geriatrik hasta köpeklerde fiziksel, biyokimyasal ve radyolojik bulguların değerlendirilmesi. *Doktora Tezi*, Ankara Üniv. Sağlık Bil. Enst., 2012.
- CardioSource.org:** Geriatric cardiology member section. <http://org/ACC/ACC-Membership/Sections-Segments-Councils/Cardiovascular-Care-for-Older-Adults>. Accessed: August 13, 2014.
- Goldwater DS:** Geriatric cardiology: A fellow's perspective. *J Am Coll Cardiol*, 64, 13, 695-715, 2014. DOI: 10.1016/j.jacc.2014.08.009
- Bell SP, Orr NM, Dodson JA, Rich MW, Wenger NK, Blum K, Harold JG, Tinetti ME, Maurer MS, Forman DE:** What to expect from the evolving field of geriatric cardiology. *J Am Coll Cardiol*, 66 (11): 1288-1299, 2015. DOI: 10.1016/j.jacc.2015.07.048
- Turgut K:** Klinik Kedi ve Köpek Kardiyolojisi. Nobel Tıp Kitabevleri Tic. Ltd. Şti, 2017.
- McLean AJ, Le Couteur DG:** Aging biology and geriatric clinical pharmacology. *Pharmacol Rev*, 56, 163-184, 2004. DOI: 10.1124/pr.56.2.4
- Bonow RO, Mann DL, Zipes DP, Libby P:** Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th edn., Philadelphia, Elsevier Health Sci, 2011.
- Hamlin RL:** Geriatric heart diseases in dogs. *Vet Clin North Am: Small Anim Pract*, 35, 597-615, 2005. DOI: 10.1016/j.cvsm.2005.01.003
- Chen W, Frangogiannis NG:** The role of inflammatory and fibrogenic pathways in heart failure associated with aging. *Heart Fail Rev*, (5): 415-422, 2010. DOI: 10.1007/s10741-010-9161-y
- Schwartz JB, Zipes DP:** Cardiovascular disease in the elderly. In, Libby P, Bonow RO, Mann DL, Zipes DP (Eds): Braunwald's Heart Disease. A Textbook of Cardiovascular Medicine. Vol. 2. 1923-1953, Saunders Elsevier, PA, USA, 2008.
- Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW:** 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*, 119,, 1977-2016, 2009. DOI: 10.1161/CIRCULATIONAHA.109.192064
- Güneş V, Uyanık F, Eren M, Kibar M, Aslan Ö, Onmaz AC:** The rapid analyses of cardiac troponins in dogs with dilated cardiomyopathy, distemper or parvoviral infection. *Kafkas Univ Vet Fak Derg*, 6, 921-927, 2014. DOI: 10.9775/kvfd.2014.11403
- Jugdutt BI:** Aging and remodeling during healing of the wounded heart: Current therapies and novel drug targets. *Curr Drug Targets*, 9, 325-344, 2008. DOI: 10.2174/138945008783954934
- Dickstein K1, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K:** ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. *Eur J Heart Fail*, 10, 933-989, 2008. DOI: 10.1016/j.ejheart.2008.08.005
- Mann DL:** Management of heart failure patients with reduced ejection fraction. In, Libby P, Bonow RO, Mann DL, Zipes DP (Eds): Braunwald's Heart Disease. A Textbook of Cardiovascular Medicine. Vol. 1. 611-640, Saunders Elsevier, PA, USA, 2008.
- Bujak M, Kweon HJ, Chatila K:** Aging-related defects are associated with adverse cardiac remodeling in a mouse model of reperfused myocardial infarction. *J Am Coll Cardiol*, 51, 1384-1392, 2008. DOI: 10.1016/j.jacc.2008.01.011
- Jugdutt BI:** Valsartan in the treatment of heart attack survivors. *Vasc Health Risk Manag*, 2, 125-138, 2006.
- Petric AD:** Myxomatous mitral valve disease in dogs - An update and perspectives. *Mac Vet Rev*, 38, 1, 13-20, 2015. DOI: 10.14432/j.macvetrev.2014.11.026
- Atkins C, Bonagura J, Ettinger S, Fox P, Gordon S, Haggstrom J, Hamlin R, Keene B, Luis Fuentes V, Stepien R:** Guidelines for the diagnosis and treatment of canine chronic valvular heart disease. *J Vet Intern Med*, 23, 6, 1142-1150, 2009. DOI: 10.1111/j.1939-1676.2009.0392.x
- McCullough PA, Khandelwal AK, McKinnon JE, Shenkman HJ, Pampati V, Nori D, Sullivan RA, Sandberg KR, Kaatz S:** Outcomes and prognostic factors of systolic as compared with diastolic heart failure in urban America. *Congest Heart Fail*, 11, 6-11, 2005. DOI: 10.1111/j.1527-5299.2005.03731.x
- McDonald K:** Diastolic heart failure in the elderly: Underlying mechanisms and clinical relevance. *Int J Cardiol*, 125, 197-202, 2008. DOI: 10.1016/j.ijcard.2007.10.002
- Atkins, CE, Häggström J:** Pharmacologic management of myxomatous mitral valve disease in dogs. *J Vet Cardiol*, 14 (1): 165-184, 2012. DOI: 10.1016/j.jvc.2012.02.002
- Giles TD, Katz R, Sullivan JM:** Short- and long-acting angiotensin-converting enzyme inhibitors: A randomized trial of lisinopril versus captopril in the treatment of congestive heart failure. *J Am Coll Cardiol*, 13, 1240-1247, 1989.
- The SOLVD Investigators:** Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*, 325, 293-302, 1991. DOI: 10.1056/NEJM199108013250501
- Ryden L, Armstrong PW, Cleland JG:** Efficacy and safety of high-dose lisinopril in chronic heart failure patients at high cardiovascular risk, including those with diabetes mellitus. Results from the ATLAS trial. *Eur Heart J*, 21, 1967-1978, 2000. DOI: 10.1053/eurhj.2000.2311
- Cleland JG, Tendera M, Adamus J:** The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J*, 27, 2338-2345, 2006. DOI: 10.1093/eurheartj/ehl250
- Garg R, Yusuf S:** Overview of randomized trials of angiotensin converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA*, 273, 1450-1456, 1995. DOI: 10.1001/jama.1995.03520420066040
- Cohn JN, Tognoni G:** A randomized trial of angiotensin receptor blocker valsartan in chronic heart failure. *N Engl J Med*, 345, 1667-1675, 2001. DOI: 10.1056/NEJMoa010713
- McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA:** Effects of candesartan in patients with chronic heart failure and reduced left-ventricular

- systolic function taking angiotensin-converting-enzyme inhibitors: The CHARM-Added Trial. *Lancet*, 362, 767-771, 2003. DOI: 10.1016/S0140-6736(03)14283-3
- 30. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K:** Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: The CHARM-Alternative Trial. *Lancet*, 362, 772-776, 2003. DOI: 10.1016/S0140-6736(03)14284-5
- 31. Dulin BR, Haas SJ, Abraham WT, Krum H:** Do elderly systolic heart failure patients benefit from β -blockers to the same extent as the non-elderly? Meta-analysis of >12.000 patients in large-scale clinical trials. *Am J Cardiol*, 95, 896-898, 2005. DOI: 10.1016/j.amjcard.2004.11.052
- 32. Packer M, Coats AJ, Fowler MB:** Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*, 344, 1651-1658, 2001. DOI: 10.1056/NEJM200105313442201
- 33. Matos JM, Glaus TM:** Medical treatment of canine heart failure. *EJCAP*, 20, 171-176, 2010.
- 34. Pitt B, Zannad F, Remme WJ:** The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*, 341, 709-717, 1999. DOI: 10.1056/NEJM199909023411001
- 35. Zannad F, Alla F, Dousset B, Perez A, Pitt B:** Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: Insights from the randomized aldactone evaluation study (RALES). Rales Investigators. *Circulation*, 102, 2700-2706, 2000. DOI: 10.1161/01.CIR.102.22.2700
- 36. Pitt B, Remme W, Zannad F:** Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*, 348, 1309-1321, 2003. DOI: 10.1056/NEJMoa030207
- 37. Pitt B, White H, Nicolau J:** Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol*, 46, 425-431, 2005. DOI: 10.1016/j.jacc.2005.04.038
- 38. Packer M, Gheorghiade M, Young JB:** Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin converting-enzyme inhibitors. *N Engl J Med*, 329, 1-7, 1993. DOI: 10.1056/NEJM199307013290101
- 39. Rathore SS, Curtis JP, Wang Y:** Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA*, 289, 871-878, 2003. DOI: 10.1001/jama.289.7.871
- 40. Cohn JN, Archibald DG, Ziesche S, Francis JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, Goldman S, Cobb FR, Shah PM, Saunders R, Fletcher RD, Loeb HS, Hughes, VC, Baker B:** Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med*, 314, 1547-1552, 1986. DOI: 10.1056/NEJM198606123142404
- 41. Paulus WJ1, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbély A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL:** How to diagnose diastolic heart failure: A consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J*, 28, 2539-2550, 2007. DOI: 10.1093/eurheartj/ehm037
- 42. Redfield MM:** Heart failure with normal ejection fraction. In, Libby P, Bonow RO, Mann DL, Zipes DP (Eds): Braunwald's Heart Disease. A Textbook of Cardiovascular Medicine. Vol. 1. 641-664, Saunders Elsevier, PA, USA, 2008.
- 43. Masoudi FA, Havranek EP, Smith G:** Gender, age, and heart failure with preserved left ventricular systolic function. *J Am Coll Cardiol*, 41, 217-223, 2003. DOI: 10.1016/S0735-1097(02)02696-7
- 44. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K:** Short-term risk of death after treatment with nesiritide for decompensated heart failure: A pooled analysis of randomized controlled trials. *JAMA*, 293, 1900-1905, 2005. DOI: 10.1001/jama.293.15.1900
- 45. Yusuf S1, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J:** Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: The CHARM-Preserved Trial. *Lancet*, 362, 777-781, 2003. DOI: 10.1016/S0140-6736(03)14285-7
- 46. Massie BM, Carson PE, McMurray JJ:** Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*, 359, 2456-2467, 2008. DOI: 10.1056/NEJMoa0805450
- 47. Ahmed A1, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF Jr, Gheorghiade M:** Effects of digoxin on morbidity and mortality in diastolic heart failure: The ancillary digitalis investigation group trial. *Circulation*, 114, 397-403, 2006. DOI: 10.1161/CIRCULATIONAHA.106.628347
- 48. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL:** ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation): Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*, 114, e257-e354, 2006. DOI: 10.1161/CIRCULATIONAHA.106.177292
- 49. Maisel WH, Stevenson LW:** Atrial fibrillation in heart failure: Epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol*, 91, 2D-8D, 2003. DOI: 10.1016/S0002-9149(02)03373-8
- 50. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vitovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Janosi A, Thorgeirsson G, Dunselman PHJM, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P:** Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure. *JAMA*, 283, 1295-1302, 2000. DOI: 10.1001/jama.283.10.1295
- 51. Jugdutt BI:** Current and novel cardiac support therapies. *Curr Heart Fail Rep*, 6, 19-27, 2009.
- 52. Geerts WH1, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, Ray JG:** Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*, 126 (Suppl. 3): 338S-400S, 2004. DOI: 10.1378/chest.126.3_suppl.338S
- 53. 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*, 26, 69-75, 2012. DOI: 10.1111/j.1939-1676.2011.00860.x
- 54. Kanemoto I1, Taguchi D, Yokoyama S, Mizuno M, Suzuki H, Kanamoto T:** Open heart surgery with deep hypothermia and cardiopulmonary bypass in small and toy dogs. *Vet Surg*, 39, 674-679, 2010. DOI: 10.1111/j.1532-950X.2010.00687.x
- 55. Yamano S, Uechi M, Tanaka K, Hori Y, Ebisawa T, Harada K, Mizukoshi T:** Surgical repair of a complete endocardial cushion defect in a dog. *Vet Surg*, 40, 408-412, 2011. DOI: 10.1111/j.1532-950X.2011.00797.x
- 56. Orton EC, Hackett TB, Mama K, Boon JA:** Technique and outcome of mitral valve replacement in dogs. *J Am Vet Med Assoc*, 226, 1508-1511, 2005. DOI: 10.2460/javma.2005.226.1508
- 57. Uechi M:** Mitral valve repair in dogs. *J Vet Cardiol*, 14, 185-192, 2012. DOI: 10.1016/j.jvc.2012.01.004