Differences in clinical characteristics of heart failure patients with and without atrial fibrillation

Razmandeh, Asadullah

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

ASADULLAH RAZMANDEH

DIFFERENCES IN CLINICAL CHARACTERISTICS OF HEART FAILURE PATIENTS WITH AND WITHOUT ATRIAL FIBRILLATION

Diploma thesis

Academic Year:
2018/2019

Mentor:
Assist. Prof. Josko Bozic, MD, PhD

Split, June 2019

Table of Contents

ACKNOWLEDGMENTS

First and foremost, I would like to thank God the most Merciful for giving me the strength, knowledge and opportunity to undertake and complete my MD degree and this research project.

I would like to express my immense gratitude to my family for their on-going help, support and prayers.

I have great pleasure in acknowledging my gratitude and indebtedness to my principle supervisor Dr. Joško Božić for his support and contributions to this research project.

Finally, I would like to convey my appreciations to all my friends, who have, in their own ways, supported me on my way to success and assisting me in whatever manner feasible.

1. INTRODUCTION

1.1. Definition of the heart failure

Heart failure (HF) is a heterogeneous clinical syndrome that results from any structural or functional cardiac impairment. By definition, healthy heart achieves normal ejection fraction with normal values of ventricular pressure and volumes. Therefore, heart failure represents a complex entity in which cardiac function is impaired in any of the aforementioned domains (1).

When accounting for the parameters of the cardiac function, HF can be classified to dominantly systolic or dominantly diastolic cardiac dysfunction. Primary pathophysiologic mechanism which initiates HF is the most important determinant in the development of progressive cardiac dysfunction (2).

Clinically, individuals with HF can be stratified based on the contractile function of the left ventricular (LV) myocardium: HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF) or HF with preserved ejection fraction (HFpEF). According to the European society of cardiology (ESC), American college of cardiology (ACC) and American heart association (AHA) guidelines, HFrEF is defined as an ejection fraction ≤40%, whereas HFpEF is defined as an ejection fraction ≥50%. Patients with ejection fraction (EF) ranging from 41% to 49% are classified as HFmrEF (3-5). Each type of HF comprises different underlying causes, co-morbidities and response to medications. Importantly, patients with systolic dysfunction usually represent HFrEF group, while patients with the early phases of the HFpEF have characteristics of diastolic dysfunction. However, patients with long-term diastolic dysfunction eventually develop reduced ejection fraction. Patients with HFmrEF usually have mild systolic dysfunction, but with characteristics of diastolic dysfunction as well (5).

Furthermore, important clinical feature of the HF is duration. Specifically, it can be described as acute, sub-acute, chronic or chronic with acute decompensation. Patients with acute HF have relatively sudden onset of symptoms, while chronic HF patients have long-term, progressive and well-known clinical picture (4,5).

Moreover, HF can also be described based on the primary chamber involvement (left, right, biventricular). Nevertheless, left sided HF usually leads to right sided HF and finally to global HF. The progression of clinical picture in these patients can usually anticipate the aforementioned shift (6).

Finally, HF is a clinical syndrome and is often accompanied with expressed clinical picture (7). However, HF may occur in the absence of these signs and symptoms, especially in the early phases of the HFpEF and patients treated with diuretic therapy. Nevertheless, typical signs and symptoms are usually necessary for the diagnosis and include dyspnea, fatigue,

peripheral or pulmonary edema, displacement of the apex beat and the gallop rhythm upon auscultation (8-10).

1.2. Epidemiology of heart failure

HF is a widespread global issue. Ischemic cardiomyopathy is the most common cause of HF in the industrialized countries. In the developing world Chagas disease and valvular cardiomyopathy is more common with hypertension and diabetes type-2 also becoming more prominent. In sub-Saharan African countries human immunodeficiency virus (HIV) associated cardiomyopathy is often the cause of high mortality from HF (10,11). Data regarding HF in developing countries are limited compare to western societies. Generally, HF patients in these countries tend to be younger and causes are largely non-ischemic. Due to high prevalence of infectious diseases, such as tuberculosis, and pollution, isolated right heart failure is more common (10, 12, 13).

According to AHA, HF affects an estimated 6.5 million Americans aged 20 years and older. HF is continuing to increase due to better survival from MI and aging population. AHA estimates that more than 8 million Americans above the age of 18 years will suffer from HF by 2030 (12). In America, HF is particularly on the rise amongst black and Hispanic men but at the same time mortality has decreased in the last 20 years. HF incidence is similar in men and women but HF mortality is lower in women despite more pronounced symptoms in women. HF total economic cost is projected to reach almost 70 billion dollars by 2030 (10, 13).

1.3. Etiology of heart failure

The etiology of HF varies greatly and includes numerous potential pathophysiologic mechanisms. Nevertheless, factors which increase pressure afterload of the cardiac chambers initiate diastolic dysfunction. Moreover, systolic dysfunction is induced by conditions which increase volume preload of the heart (14) (Table 1).

Table 1. Causes of the cardiac dysfunction

Systolic dysfunction	Diastolic dysfunction
Ischemic heart disease	Ischemic heart disease
Toxic damage	Hypertrophic cardiomyopathy
Infectious heart disease	Arterial hypertension
Dilatative cardiomyopathy	Aortic stenosis
Aortic regurgitation	Aortic coarctation
Mitral regurgitation	Pulmonary hypertension
Anemia	Left sided HF
Hyperthyroidism	Pulmonary stenosis
Liver cirrhosis	Chronic kidney disease
Beriberi disease	Tesaurismosis
Chronic kidney disease	

Moreover, from a clinical viewpoint, the causes of HF could be further differentiated to internal or external, acquired or inherited and cardiovascular or non-cardiovascular (4,7). Moreover, HF is often categorized as ischemic and non-ischemic cardiomyopathy (6,7). Ischemic heart disease is, in fact, the most common cause of HF in the developed countries (15).

Moreover, as noted, patients with hyperdynamic states are prone to the development of HF, specifically systolic cardiac dysfunction. In fact, they represent special group of patients which is often called high-output HF. Additional causes of this type of HF are systemic arteriovenous fistulas, Paget disease of bone, Albright syndrome (fibrous dysplasia), multiple myeloma and pregnancy (16).

Irrespectively of the primary cause, HF is a progressive disease since increased hemodynamic burden or a reduction in oxygen delivery to the myocardium results in further myocardial dysfunction and insufficiency (6,7). The notion that HF is a progressive syndrome is supported by the Framingham Heart study. Specifically, it showed that antecedent systolic or diastolic LV dysfunction is associated with increased risk and incidence of HF. Moreover, Halley et al. reported that moderate or severe diastolic dysfunction is an independent predictor of mortality in HF patients, in their analysis of more than 36,000 patients undergoing echocardiography in the outpatient setting (9).

Importantly, although the prevalence of underlying causes of HF depends on gender, age, ethnicity, comorbidities, and external factors, the majority of cases are preventable (17). However, risk factors must be corrected. Excessive intake of salt is a substantial and independent risk factor for HF development according to ESC (1,18).

Finally, the most important cause of acute HF is the acute coronary syndrome, especially if accompanied with new-onset mitral regurgitation. However, other underlying factors could lead to acute HF like acute aortic regurgitation (with or without aortic dissection); myocardial infarction (MI); myocarditis; arrhythmias and sepsis (6-8).

1.4. Pathophysiology of HF

The pathophysiology of the HF is very complex but its understanding is crucial for all clinicians as it is an imperative for optimal treatment. However, it is often neglected (5,7,9). The healthy heart has strong compensatory possibilities which are manifested as hypertrophic response to increased ventricular loading. Specifically, the need for the increased systolic pressures in the ventricles leads to concentric hypertrophy of the heart. Similarly, the need for the increased diastolic volumes of the ventricles initiates excentric hypertrophy of the cardiac muscles with the following changes in the cardiac cycle (19). Eventually, conditions which increase pressure afterload of the cardiac chambers initiate diastolic dysfunction, while factors which increase volume preload of the heart lead to systolic dysfunction (Table 2) (1-3).

Table 2. Pathophysiology of cardiac dysfunction (in the early stages)

Systolic dysfunction	Diastolic dysfunction
EF reduced	EF normal
LVEDV increased	LVEDV normal
LVEDP normal to increased	LVEDP increased
LVESV increased	LVESV normal
SV reduced to normal	SV normal

Abbreviations: EF – ejection fraction; LVEDV – left ventricular end-diastolic volume; LVEDP – left ventricular end-diastolic pressure; LVESV – left ventricular end-systolic volume; SV – stroke volume.

1.4.1. Pressure and volume overload

According to Frank-Starling mechanism an increased ventricular preload is followed by augment in contractility, and excessive pressure and volume causes a plateau, which leads to reduction in contraction force. This increased preload helps to sustain cardiac performance (5-7).

Hemodynamics aberration leads to heart remodeling, and the vicious cycle of hemodynamic abnormalities continues. The type of HF determines the primary and compensatory changes in geometry and performance that ensues (19).

Ventricular dilatation and end diastolic pressure increase occur as a result of volume overload conditions such as valvular regurgitation and leads to reduced systolic function. Both pressure and volume overload occurs in primary myopathy or myocardial infarction as contractility gets affected. Ventricular dilatation and hypertrophy occurs when reduction in systolic function leads to increase in ventricular end-diastolic pressure (Figure 1). Result of these pathologic remodeling is reduced cardiac output - leading to edema and dyspnea (7).

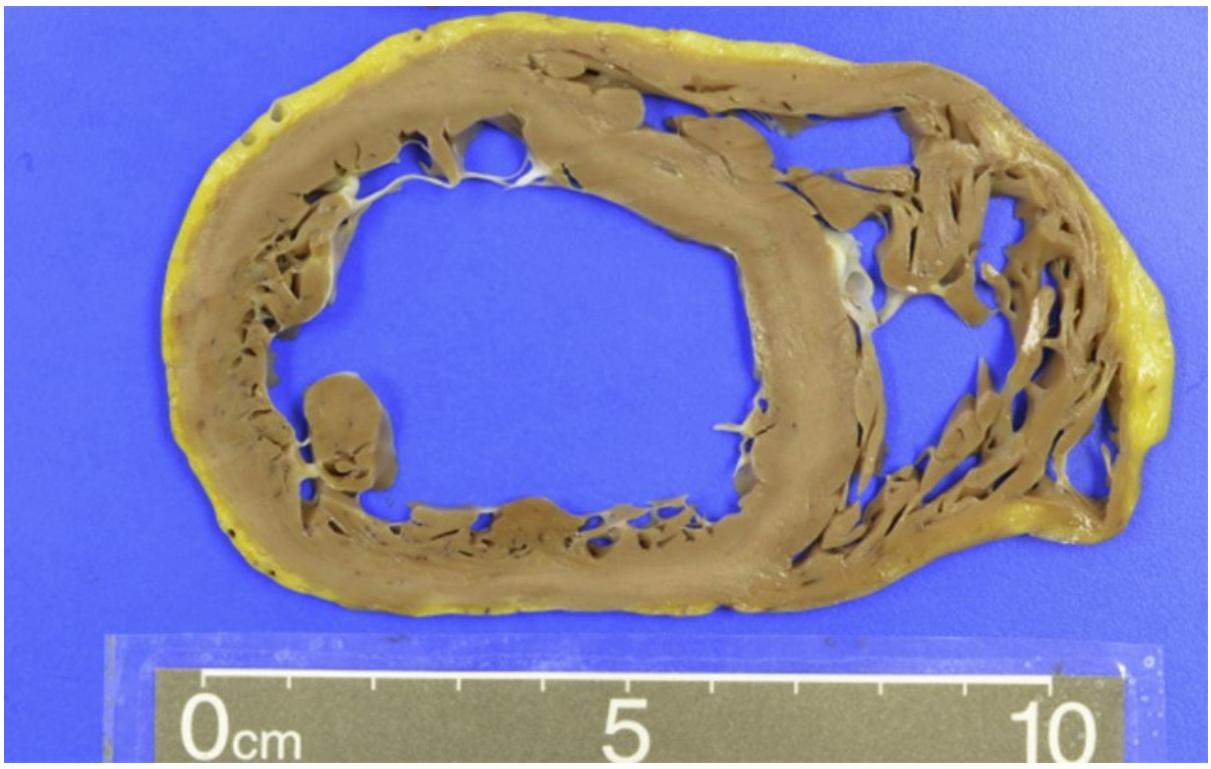

Figure 1. Biventricular dilatation

Taken from: Johnson F. Pathophysiology and Etiology of Heart Failure. Cardiol Clin. 2014;32(1):9-19.

On the other hand, pressure overload conditions such as hypertension and stenotic valves, are the classic examples. This in turn leads to ventricular hypertrophy, stiffening of myocardium, and restricted stroke volume (4,7).

1.4.2. Neurohormonal dysregulation

Acute cardiac dysfunction following myocardial injury leads to activation of a cascade of hemodynamic and neurohormonal derangements that provoke activation of baroreceptor mediated sympathetic nervous system. (20) Activation of sympathetic system elevates heart rate (HR), blood pressure (BP), and causes vasoconstriction which leads to pathologic activation of Renin Angiotensin Aldosterone System (RAAS) (7).

Overproduction of angiotensin II (AT-II) hormone stimulates the adrenal glands to increase catecholamine production, and in turn juxtaglomerular apparatus is stimulated to release renin. Renin causes increase in vascular tone and elevates pressure overload on an already susceptible heart to hemodynamic injury. AT-II also stimulates aldosterone secretion from adrenal glands which leads to reduction in renal excretion of water and sodium, and increased preload, edema, and dyspnea (21). Simultaneously with the increase in vasoconstrictor substances from the RAAS and the adrenergic system, there is decline in counter-regulatory effects of endogenous vasodilators, including nitric oxide (NO), atrial natriuretic peptide (ANP), and B-type natriuretic peptide (BNP), prostaglandins (PGs), and bradykinin (BK) relatively declines (7,10).

Furthermore, myocardial energy expenditure is increased by local production of cardiac AT-II (which decreases lusitropy, increases inotropy and mediates myocardial cellular hypertrophy). AT-II is known to also cause increased myocardial apoptosis, fibrosis and change in cardiac architecture in HF (5,7).

1.4.3. Ischemic injury

Severe myocardial ischemia eventually leads to cardiomyocyte injury, infarction and replacement of damaged tissue by fibrotic tissue. This initiates the vitious circle in which permanent injury and remodelling occurs leading to increased myocardial strain and intracardiac pressure (5,7).

Moreover, sufficient perfusion in the level of subendocardial and transmyocardial blood flow is required for normal systolic function. However, hypoperfusion is particularly insidious

to subendocardial myocardial blood flow, as shown in animal models. Constant hypoperfusion without acute injury in myocardium tissues potentiates their poor contractility. This is potentially reversible and most commonly occur in subendocardium (22). This mechanism can have potentially benefitial cardioprotective effects since heart can temporarily adapt by metabolic modulation on the cellular level (hibernating myocardium). Clinically, it is highly important to discriminate between ischemic fibrosis and hibernating myocardium. As the latter responds to revascularization by showing improvement in LV systolic function, exercise tolerance and increased survival compare to medical therapy alone (5, 7, 9). Therefore, ischemic heart disease eventually leads to both systolic and diastolic HF (23).

1.4.4. Ultrastructural abnormalities

Cardiac remodelling is determined by changes in cellular structure, number and activity of tissues, and changes in the extracellular matrix. Histopathologic findings in cardiomyopathy include myocyte hypertrophy, increased ventricular mass and fibrosis. Other changes consistently present are increase in sarcomere number and rate of apoptosis. Neurohormonal and cytokine signaling with volume and pressure overload combine to create a complex pro-hypertrophic environment (24,25).

In HF, myocardial volume is increased and characterized by larger myocytes and shorter life cycle. Therefore, this unfavorable environment is transmitted to the progenitor cells responsible for replacing lost myocytes. As the underlying pathology processes worsens and myocardial failure is increased, progenitor cells become progressively less effective. This remodeling process leads to early adaptive mechanisms, such as augmentation of SV (Frank-Starling mechanism) and decreased wall stress (Laplace law). Maladaptive mechanisms such as increased myocardial oxygen demand, myocardial ischemia, impaired contractility, and arrhythmogenesis ensues the remodeling process (7,10,11).

1.4.5. Genetic Mutations in HF

Genetic mutations have important role in cardiac diseases. Heart disease due to genetic aberrations can be classified as structural disease caused by abnormal development (congenital heart disease), muscular dystrophies, mutations of contractile and structural proteins, and mutations of ion channels (26). World Health Organization (WHO) recognizes four different phenotypes of cardiomyopathy: hypertrophic (HCM), restrictive (RCM), dilated (DCM), and

arrhythmogenic right ventricular cardiomyopathy (ARVC). ARVC can also affect the LV (arrhythmogenic cardiomyopathy). A new widely recognized phenotype is left ventricular noncompaction (LVNC) (5,7).

1.5. Diagnostics of heart failure

Clinical picture is of high importance in the setting of HF. There are several diagnostic criteria and models in HF patients regarding clinical signs and symptoms. The Framingham criteria for the diagnosis of HF consist of simultaneous presence of either two major criteria or one major and two minor criteria (10,14) (Table 3).

Table 3. The Framingham criteria for the diagnosis of the HF

Major criteria	Minor criteria
Paroxysmal nocturnal dyspnea	Nocturnal cough
Weight loss of 4.5 kg in 5 days in response to treatment	Dyspnea on ordinary exertion
Neck vein distention	A decrease in vital capacity by 1/3
Rales	Pleural effusion
Acute pulmonary edema	Tachycardia (120 bpm)
Hepatojugular reflux	Hepatomegaly
S3 gallop	Bilateral ankle edema
Central venous pressure greater than 16 cm water	
Circulation time of 25 seconds or longer	
Radiographic cardiomegaly	
Pulmonary edema, visceral congestion, or cardiomegaly at autopsy	

N.B. Minor criteria are accepted only if they are not associated with another medical conditions.

Nevertheless, other procedures must be conducted in order to establish proper diagnosis and further therapeutic strategy. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) recommends measuring Brain natriuretic peptide (BNP) in those suspected of HF (27-30). Moreover, if the laboratory test is positive it should be followed by

an echocardiography. ESC proposed a diagnostic protocol using a combination of clinical picture, electrocardiographic (ECG) features, laboratory analysis and thoracic radiogram (28-31) (Table 4).

Table 4. Diagnostic table for the HF by the ESC

Assessment	Diagnosis of heart failure	
	Supports if present	**Opposes if normal or absent**
Compatible symptoms	++	++
Compatible signs	++	+
Cardiac dysfunction on echocardiography	+++	+++
Response of symptoms or signs to therapy	+++	++
Electrocardiogram		
Normal		++
Abnormal	++	+
Dysrhythmia	+++	+
Laboratory parameters		
Elevated BNP/NT-proBNP	+++	+
Low/normal BNP/NT-proBNP	+	+++
Low blood sodium	+	+
Kidney dysfunction	+	+
Mild elevations of troponin	+	+
Chest X-ray		
Pulmonary congestion	+++	+
Reduced exercise capacity	+++	++
Abnormal pulmonary function tests	+	+
Abnormal hemodynamics at rest	+++	++

+ = some importance; ++ = intermediate importance; +++ = great importance.

Moreover, after the establishment of proper diagnosis, it is essential to classify and establish the stage of the disease. There are several validated staging and classification systems. The AHA/ACC staging system is defines HF as followed (31):

- Stage A: High risk of heart failure but no structural heart disease or symptoms of heart failure
- Stage B: Structural heart disease but no symptoms of heart failure
- Stage C: Structural heart disease and symptoms of heart failure
- Stage D: Refractory heart failure requiring specialized interventions

Moreover, the New York Heart Association (NYHA) classification system categorizes HF on a scale of I to IV based on patient's physical limitations (4,32):

- Class I: No limitation of physical activity
- Class II: Slight limitation of physical activity
- Class III: Marked limitation of physical activity
- Class IV: Symptoms occur even at rest; discomfort with any physical activity

1.6. Atrial Fibrillation

1.6.1. Definition and classification

Atrial fibrillation (AF) is an supraventricular arrhythmia characterized by expeditious and irregular beating of atria. Therefore, it is usually known as an irregularly irregular arrhythmia among health care professionals (1-3,33). Importantly, it is the most common cardiac arrhythmia and its prevalence is rising with age. Moreover, AF is strongly associated with an elevated risk of HF and stroke. Nevertheless, AF is often asymptomatic which increases the risk of undertreatment and cryptogenic strokes. Still, some patients may present with fainting, palpitations, shortness of breath (SOB), and chest pain (1,2). Finally, AF is defined and classified by the duration of episodes of arrhythmia (Table 5) (34).

Table 5. Different types of AF and their specific definitions

Classification of Atrial Fibrillation	
AF Type	**Duration**
Paroxysmal AF	AF that terminates spontaneously or with intervention within 7 days of onset. Episodes may recur with variable frequency
Persistent AF	Continuous AF that is sustained >7 days
Long-standing persistent AF	Continuous AF >12 months in duration.
Permanent AF	The term "permanent AF" is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm
Nonvalvular AF	AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

Taken from: ACC/AHA Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64:2246–80.

1.6.2. Epidemiology of atrial fibrillation

AF is the most common sustained arrhythmia in clinical settings. It is estimated that globally around 35 million people have AF, excluding those with clinically silent disease (35). The epidemiology of AF is not well established in developing countries but it is believed to be twice as common in the developed countries. In the United States alone around 12 million people are expected to have AF in the next 10 years (10, 13).

Age is an imperative risk factor in AF and the risk doubles with each decades of life. The incidence of AF per 1000 persons is around 1.9 to 3.1 in those younger than 65 years and increase to 31.4 to 38 in men and women above 85 years, respectively, according to Framingham study (36). Paradoxically, whites appear to have higher incidence of AF, compare to other races, despite black people having more risk factors. Men have higher incidence of AF but women tend to have more severe symptoms and more likely to have stroke (37). Furthermore, women were 2.5 fold more likely to die from aggravated cardiovascular diseases due to AF according to Copenhagen City Heart Study (10,13,38).

1.6.3. Pathophysiology of atrial fibrillation

The pathophysiology of AF is complex and not fully understood. However, structural changes of the atria are often present. Structural changes occur as a result of proliferation and differentiation of fibroblasts into myofibroblasts in the interstitium and leading to atrial fibrosis. However, other changes such as accumulation of glycogen and collagen fiber deposition are also usually presen (39,40).

Nevertheless, irrespectively of the cause, an impairment of atrial electrophysiology is required. Specifically, structural changes of the atria definitely lead to its electrophysiological alterations. Generally, three forms of remodeling of the atria is described during AF progression (electrical, contractile and structural). Electrical remodeling occurs due to increased atrial rate and decreased conduction velocity (38-41). Electrical dissociation occurs as a result between muscle bundles and local conduction. Shortening of atrial myocytes refractory periods happen involving inward calcium (Ca^{2+}) and potassium (K^{+}) currents. Loss of gap junctions (structural remodeling) and/or changes in local physiology of atrial myocytes impairs contractility. Impaired Ca^{2+} handling causes contractile remodeling and atrial mechanical dysfunction may occur that may be transient or progress to irreversible dysfunction (1-5,15,42).

The overall results are electrophysiologic changes in the orientations of myocyte fibers in the pulmonary veins which is believed to be the most common site of AF origin. Pulmonary veins have complex fiber architecture and unique electric properties (pacemaker cells, transitional cells, and Purkinje cells) which promote re-entry and ectopic activity to initiate AF. Aforementioned perpetuates or initiates AF episodes (43). The combination of these changes at cellular, structural and electrical level provides remodeling that promote and initiate self-perpetuation of this arrhythmia (5, 7, 15).

Abnormal Ca^{2+} handling is primarily attributed to the molecular basis for triggers in pulmonary veins. Spontaneous myocyte depolarization (early or delayed afterdepolarization) occur when diastolic leak of Ca^{2+} from the sarcoplasmic reticulum initiates an inward moving sodium (Na^{+}) current via Na^{+}/Ca^{2+} exchanger (44). Hyperphosphorylation of protein kinase A, calmodulin kinase II, and the ryanodine receptor type 2 (RYR2), is important contributors to sarcoplasmic reticulum Ca^{2+} overload and diastolic membrane instability. Decremental conduction and repolarization heterogeneity within the pulmonary veins enable localized re-entry and may foster a focal initiator for AF (5,7,15).

1.6.3.1. Functional reentry - leading circular model

Functional models enable understanding for reentry in the absence of anatomic obstacle. Reentry tends to fallow the smallest circuit and the tissue at the vortex remain unexcitable. The unidirectional propagating wave results in constant centripetal activation of the center of the circuit and remains refractory (45). Leading circle model allows an impulse to trigger circus movement in one direction, with the impulse simultaneously spreading outwards and activates the adjacent myocardium. Myocytes fiber orientation controls the impulse propagation in the cardiac tissue. Cell to cell communication is, primarily, gap junction dependent, which is unequally distributed. The longitudinal axis has greater number of gap junctions compare to transverse axis and is responsible for more rapid conduction in this direction. Anisotropic reentry occurs because of this unequal distribution and may account for arrhythmias (16-18).

1.6.3.2 The multiple wavelet hypothesis

This theory suggests that self-perpetuating "daughter wavelets" results from fractionation of wave fronts propagating through the atria. The refractory period, conduction velocity, and mass of atrial tissue determines the number of wavelets (44-46).

The number of wavelets grow by increase in atrial mass and shortened atrial refractory period and thus promote sustained AF. Intra-atrial conduction delay has also been shown to predict recurrence of AF. Moreover, the mechanisms that is responsible for sustaining AF may evolve over time as the atria structurally and electrically remodel and AF progresses from paroxysmal, to persistent and then permanent forms (3, 5, 16-18).

1.7. Heart failure and atrial fibrillation - a dangerous interaction

HF and AF are new epidemics in the area of cardiovascular diseases. They are commonly occurring together and frequently complicate each other. Almost two-thirds of subjects with AF develop HF, and one-third of people with preexisting HF develops AF. Therefore, AF is both a risk factor for and consequence of HF, irrespectively of the type of HF (Figure 2). However, research have shown higher prevalence of AF in HFpEF than in people with HFrEF. Moreover, AF and HFpEF are more common in older, overweight population (15, 18, 29).

This coexistence leads to poor cardiovascular outcomes and the preexisting AF is associated with a greater risk for all-cause mortality and hospitalization for stroke. Both HF and AF continue to increase in prevalence as the risk factors underlying each condition become more common (particularly aging and cardiovascular diseases), with hospitalizations doubling for each diagnosis since 1984. AF and HF are responsible for substantial morbidity, mortality, and health care costs. Stroke and cognitive decline are prominent in both conditions. In patients with AF, deaths caused by HF (30%) exceeded deaths caused by stroke (8%) (15, 18).

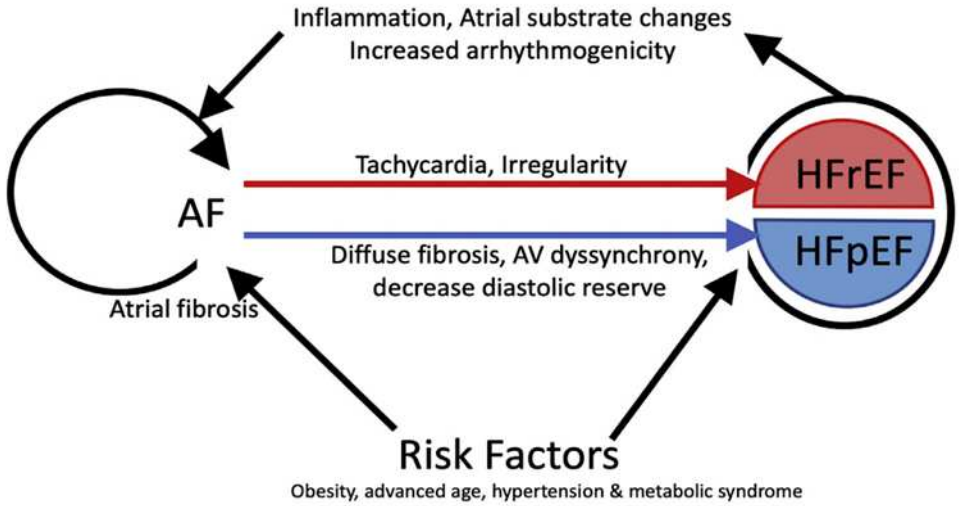

Figure 2. Interaction of AF and HF

Taken from: Dries D, Exner D, Gersh B, Domanski M, Waclawiw M, Stevenson L. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. J Am Coll Cardiol. 1998;32(3):695-703.

The Framingham Heart study has shown that the development of HF in AF patients was associated with three times higher risk of mortality in both gender. However, in HF patients, the AF development was associated with a 60% relative increase in mortality in male and a 170% relative increase in mortality in female (15, 18).

Three main pathophysiologic processes are involved in AF potentiating the development and progression of HFpEF: loss of atrial systole and irregularity, tachycardia and diffuse fibrosis. Coordinated atrial contraction contributes about 20% of the CO in sinus rhythm. Impaired atrioventricular synchrony hinders diastolic filling, which in turn worsens diastolic function and leads to increased left-sided pressure and HF symptoms. AF causes

irregularity in ventricular contraction and increased left atrial (LA) pressure (47). In AF, LV relaxation time is reduced, because of shortened R-R intervals and LA emptying is decreased. Contribution of LA systole to LV filling with aging is particularly imperative mechanism in the AF and HFpEF in the aging population. Sustained tachycardia impairs diastolic function and fast ventricular rate reduces diastolic filling time thereby decreasing CO. Moreover, AF is associated with diffuse interstitial fibrosis which is thought to be due to sympathetic and neurohormonal activation that leads to increased inflammation and diffuse fibrosis. AF induced fibrosis is believed to be via increased collagen synthesis by myofibroblasts and reduced degradation through profibrotic signaling (soluble ST2 and tissue inhibitor of metalloproteinases-1) (5,7,15,18).

Moreover, HF leads to AF through multiple postulated mechanisms. Left ventricular failure is believed to cause electrical, structural, and ionic atrial remodeling, which can facilitate development of AF. HF causes proinflammatory state and upregulation of the sympathetic system, RAAS, endothelin, and inflammatory cytokines as well as diffuse fibrosis and structural remodeling (48). Moreover, BNP has also been shown to be involved in pulmonary vein arrhythmogenesis by alteration in Ca^{2+} handling and favors the development of AF (49). Other pathways such as cyclic GMP activation, Na^{+}/K^{+}-ATPase inhibition and phosphodiesterase 3 inhibition may participate in the BNP modulation of PV and thus atrial tachyarrhythmogenesis in HF. BNP levels are increased in HF patients and therefore supports the notion of HF begetting AF (5,7,15,18,50).

Moreover, the increase in LV filling pressure is transferred to the LA in failing heart. Chronic LA stretch causes activation of stretch-activated channels, anisotropy, increased dispersion of refractoriness and therefore increased vulnerability to AF (51). Prolonged atrial refractoriness, conduction time, P-wave duration, and an increase in fractionated electrograms are demonstrated in atrial electroanatomic properties in HFrEF compared with control subjects (20,21,52).

Finally, HF causes significant changes in ion channels function. Ca^{2+} overload, action potential prolongation and loss of atrial T-tubules with increased sarcoplasmic reticulum Ca^{2+} content also occur (53). Increased atrial pressure leads to increased diastolic calcium leak, and through elevated BNP and increased sarcoplasmic Ca^{2+} content increases after depolarization that commence from pulmonary veins which is well known to triggering AF (13,15,20,22).

2. AIMS AND OBJECTIVES

The goal of this study is to determine the differences in clinical characteristics and selected parameters of the HF patients with and without atrial fibrillation.

Hypotheses of this study are:

1. There is a significant difference in clinical characteristics between heart failure patients with atrial fibrillation and without atrial fibrillation
2. Prevalence of comorbidities is higher among heart failure patients with atrial fibrillation
3. NYHA class is higher among heart failure patients with atrial fibrillation
4. Hospitalization rate is higher among heart failure patients with atrial fibrillation

3. PATIENTS AND METHODS

3.1. Ethical considerations

The study protocol was approved by the Ethics Committee of the University Hospital of Split (approval no. 2181-147-01/06/M.S.-17-2) and University of Split School of Medicine Ethics Committee. All medical procedures were undertaken as in accordance with the Declaration of Helsinki and its latest revision in 2013.

3.2. Patients

This was a cross-sectional study, conducted between January 2018 and February 2019, that included a total of 90 consecutive patients that presented with signs and symptoms of heart failure at the emergency department and were hospitalized at Department of Cardiology of the University Hospital of Split. Patients were enrolled in a 1:1 ratio in terms of sex, had to be NYHA functional class II-IV and have a definitive diagnosis of heart failure based on the ESC guidelines for the diagnosis and treatment of acute heart failure (14). Exclusion criteria included patients below legal age (<18 years), adults younger than 35 years of age and adults older than 90 years of age, patients with documented or newly-established severe valvular or pericardial disease, infiltrative or hypertrophic cardiomyopathy, *cor pulmonale*, primary pulmonary disease, diabetes mellitus type I, primary renal or hepatic disease, active malignant and/or infectious disease, systemic autoimmune disease, hemorrhagic diathesis or significant coagulopathy, systemic immunological and/or immunosuppressive disorder and/or positive recent history of immunosuppressive/cancer chemotherapeutic drug use, positive history of acute coronary syndrome or stroke within 3 months prior to study enrollment, positive history of excessive alcohol, drug, narcotics or sedative consumption, and significantly debilitating psychiatric or neurologic condition.

3.3. Procedures

All patients were evaluated within the first 24 hours of admission and this evaluation consisted of physical examination, medical history interview (via checklist), current medication use, antecubital venous blood sampling, transthoracic echocardiography and a standard 12-lead ECG recording. Atrial fibrillation was documented by series of ECG tracings that were consistent with atrial fibrillation rhythm and/or medical documentation attesting that a patient has AF. Laboratory analyses were carried out at the Department of Medical Laboratory diagnostics and processed according to good laboratory practice. All blood samples were

analyzed in the same certified institutional biochemical laboratory by using standard laboratory procedures.

3.4. Statistical analysis

Data were analyzed by using SPSS Statistics for Windows® (version 25.0, IBM, Armonk, NY, USA). Data were presented as mean ± standard deviation (SD) or median (interquartile range) based on the variable distribution normality or number (N) with percentage (%) within the particular category of interest. Normality of distribution for continuous variables was assessed with the Kolmogorov-Smirnov test. For differences between groups, an independent samples t-test was used for continuous variables with normal distribution. Chi-squared (χ^2) test was used to determine differences between groups in terms of categorical variables.

4. RESULTS

Baseline characteristics of the patients on admission

There was no significant difference in anthropometric and clinical parameters among studied groups on admission, except in age (72.7±9.1 in FA group vs. 67.3±11.0 in non-FA group, *P*=0.012), systolic blood pressure values (131.2±21.9 in FA group vs. 143.5±32.5 in non-FA group, *P*=0.035) and heart rate (103.0±32.0 in FA group vs. 84.0±26.0 in non-FA group, *P*=0.003) (Table 6).

Table 6. Anthropometric and clinical parameters of patients on admission

Variables	HFwAF (n=50)	HFw/oAF (n=40)	*P**
Age (years)	72.7±9.1	67.3±11.0	0.012
BMI (kg/m^2)	30.6±4.0	29.8±4.5	0.372
Waist-hip ratio (WHR)	0.99±0.1	0.97±0.1	0.425
SBP (mmHg)	131.2±21.9	143.5±32.5	0.035
DBP (mmHg)	78.6±10.4	82.6±14.7	0.135
Heart rate (bpm)	103.0±32.0	84.0±26.0	0.003
LVEF (%)	43.3±16.0	43.6±16.0	0.947
NYHA functional class	3.1±0.5	2.9±0.7	0.100
CKD category	2.6±0.9	2.6±1.1	1.000
Number of HF-related hospitalization in the last year	0.66±0.9	0.58±0.98	0.669

Data are presented as mean ± standard deviation
*t-test for independent samples
BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; LVEF – left ventricle ejection fraction; NYHA – New York Heart Association, CKD – chronic kidney disease; HF – heart failure.

Baseline laboratory findings of the patients on admission

There was no statistical difference in baseline laboratory findings between groups, except for activated partial thromboplastin time (30±8 in FA group vs. 25±3 in non-FA group, *P*=0.001), prothrombin time-international normalized ratio (1.7±1.0 in FA group vs. 1.1±0.3 in non-FA group, *P*=0.001) and albumin values (37±4.0 in FA group vs. 39±4.0 in non-FA group, *P*=0.043) (Table 7).

Table 7. Laboratory values of patients included in the study

Variables	HFwAF (n=50)	HFw/oAF (n=40)	*P**
Potassium (mmol/L)	4.1±0.5	4.2±0.5	0.331
Sodium (mmol/L)	138±4	139±3	0.314
Calcium (mmol/L)	2.3±0.1	2.3±0.2	0.779
Magnesium (mmol/L)	0.8±0.1	0.8±0.1	0.704
D-dimer (mg/L)	1.7±1.5	1.6±1.3	0.877
APTT (s)	30±8	25±3	0.001
PT-INR	1.7±1.0	1.1±0.3	0.001
HbA1c (%)	6.7±1.4	6.5±1.1	0.453
CRP (mg/L)	17±22	17±24	0.901
Albumin (g/L)	37±4.0	39±4.0	0.043
Total cholesterol (mmol/L)	4.4±1.3	4.4 ±1.3	0.913
HDL-cholesterol (mmol/L)	1.0±0.3	1.2±1.4	0.114
LDL-cholesterol (mmol/L)	2.7±1.1	2.7±1.1	0.908
Triglycerides (mmol/L)	1.5±0.7	1.5±0.6	0.949
Urea (mmol/L)	10±5	11±7	0.427
Creatinine (μmol/L)	110±44	127±74	0.202
Uric acid (μmol/L)	540±170	529±161	0.355

Hemoglobin (g/L)	135±18	131±21	0.229
NT-proBNP (pg/mg)	5723±5522	8892±14457	0.164
hs-cTroponin I (ng/L)	85±181	50±114	0.304

Data are presented as mean ± standard deviation
*t-test for independent samples
APTT – activated partial thromboplastin time; PT-INR – prothrombin time- international normalized ratio; HbA1c – hemoglobin A1c; CRP – C-reactive protein; NT-proBNP – N-terminal pro Brain Natriuremic Peptide; hs – high sensitivity

Prevalence of AF according to gender, etiology and smoking status

There was no statistically significant difference in AF prevalence according to gender between studied groups (*P*=0.962) (Figure 3).

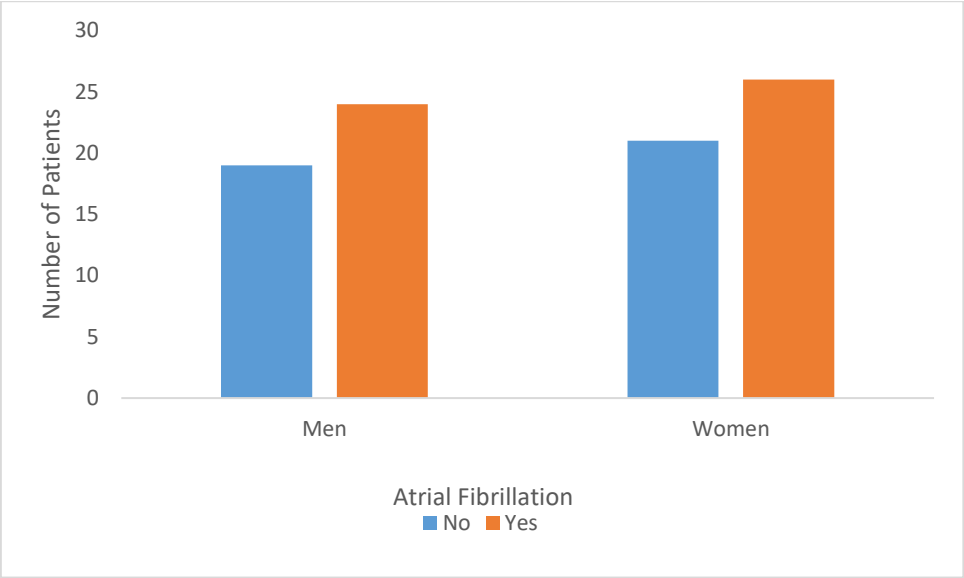

Figure 3. Prevalence of AF according to gender (*P*=0.962)

There was no statistically significant difference in AF prevalence according to the presence of ischemic cause between studied groups (*P*=0.671) (Figure 4).

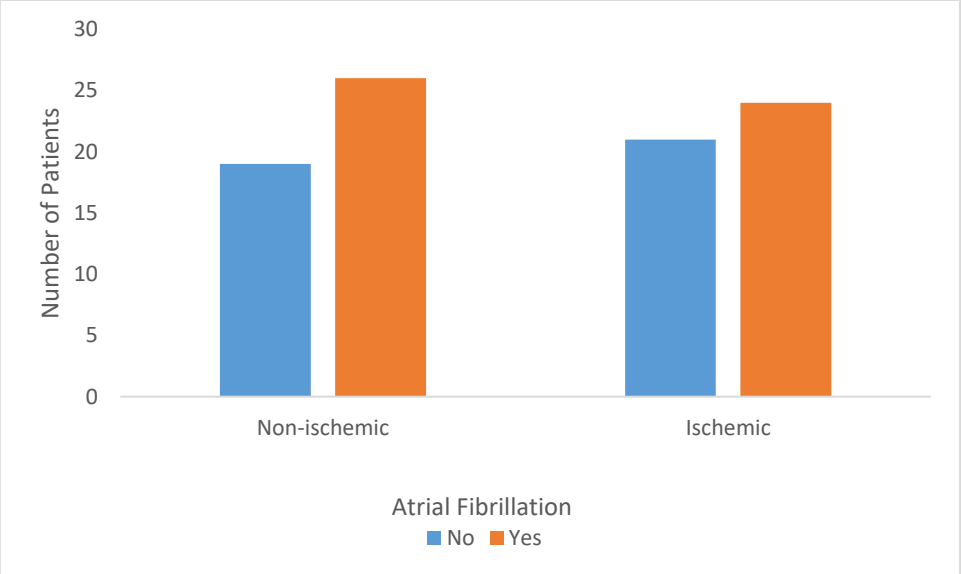

Figure 4. Prevalence of AF with reference to ischemic or non-ischemic etiology of HF (*P*=0.671)

There was statistically significant difference in AF prevalence according to smoking status between studied groups (*P*=0.035) (Figure 5).

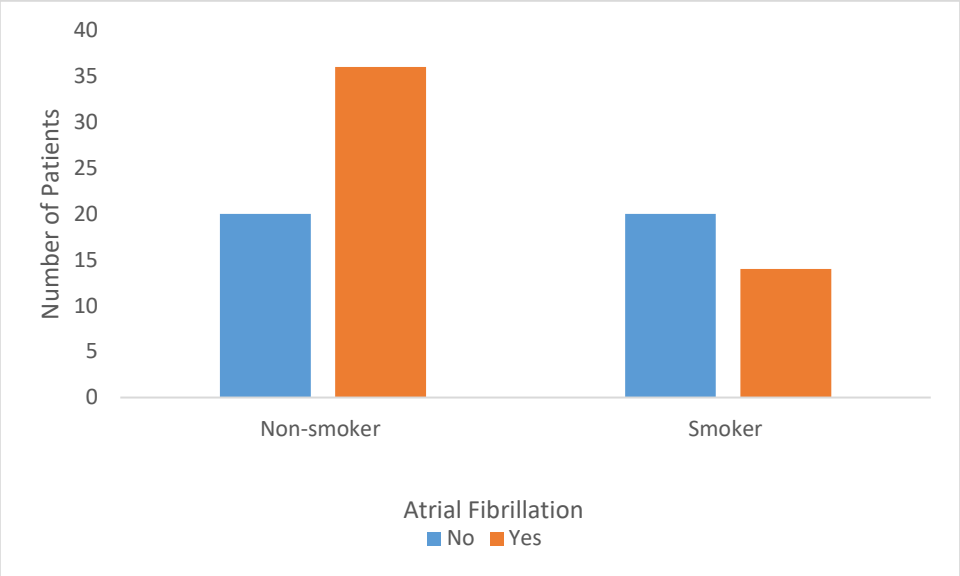

Figure 5. Prevalence of AF according to smoking status (*P*=0.035)

Comparison of medication use between studied groups

Patients with HF and AF use more beta blocker (49, 98.0% vs. 32, 80.0%, *P*=0.009), digoxin (16, 32.0% vs 2, 5.0%, *P*=0.001) and anticoagulants (42, 84.0% vs. 3, 7.5%, *P*<0.001), as well as less acetylsalicylic acid (27, 67.5% vs. 8, 16.0%, *P*<0.001), while there was no statistical difference in other medications (Table 6).

Table 8. Comparison of medication use between group with and without AF

Medications	HFwAF (n=50)	HFw/oAF (n=40)	*P**
ACEI or ARB	39 (78.0%)	28 (70.0%)	0.516
Beta Blocker	49 (98.0%)	32 (80.0%)	0.009
Statins	14 (28.0%)	19 (47.5%)	0.052
MRA	24 (48.0%)	18 (45.0%)	0.792
Digoxin	16 (32.0%)	2 (5.0%)	0.001
Angiotensin receptor neprilysin inhibitor	13 (26.0%)	10 (25.0%)	0.870
Aspirin	8 (16.0%)	27 (67.5%)	<0.001
CCB	5 (10.0%)	8 (20.0%)	0.164
Diuretics (Loop, thiazides and thiazide-like)	46 (92.0%)	36 (90.0%)	0.772
Anticoagulants	42 (84.0%)	3 (7.5%)	<0.001

*Chi-squared test. Data are presented as number of patients and percentage.
ACEI – angiotensin-converting-enzyme inhibitors; ARB – angiotensin II receptor blockers; MRA – mineralocorticoid receptor antagonists; CCB – calcium channel blockers

Comparison of comorbidities between studied groups

Among HF patients, group with AF had significantly higher prevalence of anemia (16, 40.0% vs. 10, 20.0%, *P*=0.038) in comparison to group with AF, while there was no difference in the prevalence of other comorbidities (Table 7).

Table 9. Comparison of comorbidities between groups with and without AF

Comorbidities/interventions	HFwAF (n=50)	HFw/oAF (n=40)	*P**
PAD	10 (20.0%)	9 (22.5%)	0.773
PCI and/or CABG	16 (32.0%)	16 (40.0%)	0.431
COPD/Asthma	14 (28.0%)	7 (17.5%)	0.242
Diabetes Mellitus	20 (40.0%)	17 (42.5%)	0.811
Obesity (BMI ≥30)	23 (46.0%)	15 (37.5%)	0.246
Anemia	10 (20.0%)	16 (40.0%)	0.038
LBBB	20 (40.0%)	15 (37.5%)	0.809
Pacemaker/ICD/CRT	6 (12.0%)	7 (17.5%)	0.461
Renal dysfuntion	24 (48.0%)	22 (55.0%)	0.509
Hyperuricemia	42 (84.0%)	35 (87.5%)	0.786

PAD – I ; PCI – percutaneous coronary intervention ; CABG – I ; COPD – I ; BMI – body mass index; LBBB – ; ICD – I ; CRT – I

Comparison of echocardiographic parameters between studied groups

There was no statistical difference in echocardiographic parameters between studied groups (Table 8).

Table 10. Comparison of echocardiography parameters between group with and without AF

Echocardiography Parameters	HFwAF (n=50)	HFw/oAF (n=40)	*P**
LVEDd (mm)	56.5 ± 10.6	59.5 ± 7.4	0.130
LVESd (mm)	41.4 ± 12.3	44.0 ± 11.8	0.323
IVSd (mm)	11.1 ± 2.0	11.4 ± 2.4	0.560
LVPWd (mm)	11.1 ± 1.8	10.7 ± 2.1	0.327
LV mass (g)	264.1 ± 106.1	285.9 ± 79.3	0.286

Data are presented as mean ± standard deviation
*t-test for independent samples
LVEDd – I ; LVESd – I ; IVSd – I ; LVPWd – I ; LV – left ventricle

5. DISCUSSION

It has been well-established that HF an AF are closely linked cardiac conditions with rising prevalence, shared risk factors and common disease mechanisms. However, studies which interrogate differences in HF patients regarding concomitant AF are lacking. Therefore, our study aimed to highlight possible clinical differences in specific subgroups of HF which could have enormous clinical significance. Only when accounting for the patient-reported outcomes, patients with HF and AF can have uncomfortable symptoms with severe reduction in quality of life and longevity with increased economical burdens (4).

One of the important factors which guide clinical therapy in HF patients is NYHA stage. In fact, in a prospective study with heart failure without AF, the onset of AF was shown to be correlated with highly significant worsening of the NYHA stage (54). Moreover, Mercer et al., also reported AF prevalence with HF to be NYHA class dependent; ranging from 10% prevalence in NYHA class I to 50% prevalence with NYHA class IV (28). Importantly, we did not show any significant difference in NYHA functional class between our subgroups regarding AF. Aforementioned studies included a group of 344 and 791 respectively, so it could be that insufficient number of subjects in our study did not enable small differences to manifest. Nevertheless, further studies with strong sample size are necessary.

Moreover, BNP can be used to guide therapy in HF patients, as it is widely used diagnostic and prognostic marker in HF (10). However, BNP elevated plasma levels are also seen in lone AF even in the absence of heart disease (26). Therefore, the importance of BNP levels in HF patients with AF is not fully understood. One of the reasons for that is the presence of multiple other comorbidities which predispose cardiac patients to increased BNP levels (27). Importantly, subjects from our study did not differentiate in CKD stage, LVEF and BMI status which could all affect BNP levels (55). Nevertheless, we did not reveal any differences in NT-proBNP levels between subgroups of patients regarding AF. However, studies have shown that BNP can predict incidence of AF more than other risk factors. Following cardioversion BNP levels correlate with the risk for AF recurrence and is a predictor for new AF during hospitalization in patients with acute ischemic stroke, reinforcing the pathophysiological association between the two closely related conditions (27). However, the data on importance of cumulative disease (AF plus HF) on BNP is both difficult to interpret and lacking. Therefore, other studies with strong control of possible covariates are necessary in order to establish true importance of NT-proBNP in patients with HF and AF.

Moreover, low albumin level have been described as an independent negative prognostic factor for many cardiovascular diseases, stroke and AF (56). Our data have shown lower levels of albumin in HF patients with AF. This could indicate a poorer clinical outcome

in these patients, considering the physiological importance of albumin as an anti-inflammatory, antioxidant, anticoagulant and antiplatelet aggregation activity, as well as its colloid osmotic effect (23). However, cross-sectional design of our study prevents from establishment of any longitudinal correlation. Therefore, prospective studies are necessary.

Furthermore, the prevalence of AF is strongly correlated with advancing age as shown in the numerous studies (30,36). Therefore, our finding of a significant older age in subgroup of patients with HF and AF was anticipated. However, different age is the confounding variable in our study which could affect some of the results. Future studies with strong control for the age covariate are necessary.

HF and AF are interconnected in many ways and the efficacy of conventional HF drugs in primary prevention of AF is an additional evidence to this. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and mineralocorticoid receptor antagonists all have shown to reduce AF incidence in HF (3,25). Therefore, our findings of high prevalence of usage of aforementioned medications among HF patients with and without AF are encouraging.

Moreover, key strategies when treating patients with HF and AF include thromboembolism to prevent stroke, control of HR to prevent further ventricular damage andremodeling and restore SR for patients who would most benefit (44). Current guidelines recommend two antiarrhythmic agents for rhythm control in patients with HF and AF, namely amiodarone and dofetilide (44). On the other hand, several medications are available for rate control in AF patients. Our data showed that 91% of patients were on β-blockers and 98% of those who had AF were taking β-blockers. This indicates that rate control in AF patients is mostly managed by β-blockers by the general clinicians (52).

Furthermore, as patients with AF are at increased risk of thromboembolism and 85.6% of our patients were on some form of anticoagulation. The risk of stroke is increased, by five times in non-valvular AF, and 20 times in the setting of mitral stenosis. Risks of recurrent strokes and more severe disability and mortality is also elevated. Therefore, clinicians are required to fully understand CHA2DS2-VASc and HAS-BLED scoring system to reduce both risks of thromboembolism and hemorrhage (1, 46,48).

APTT and PT-INR were longer in HF patients with AF, which is expected due to anticoagulation use in these patients. Still, mean PT-INR among AF subgroup was not in the desired safe range. The reason for that could be the increasing use of direct oral anticoagulant medications which don’t correlate perfectly with PT-INR values. Newer anticoagulants such as dabigatran, apixaban and rivaroxaban are used in nonvalvular AF and slowly has replaced

Warfarin due to lesser need for frequent monitoring (41,42,45,51). However, further studies about patient adherence are necessary in order to prevent additional stroke events.

Moreover, current guidelines suggest that acetylsalicylic acid alone is not sufficient for thromboembolism prevention in AF and anticoagulant therapy is needed. In fact, if used concomitantly with anticoagulant therapy it significantly increases the risk for bleeding (51). Among subgroup of patients with AF acetylsalicylic acid was used in only minority of patients. It would be worth questioning the presence of some other indication for acetylsalicylic acid use in these patients. Nevertheless, the findings are encouraging as we can presume that most patients are safely advised about their therapy.

Furthermore, equal number of patients had ischemic and non-ischemic HF in our study. In both ischemic and non-ischemic groups, the number of patients with AF were only slightly higher. The association of AF with ischemic and non-ischemic HF varies with HFpEF and HFrEF. Mercer et al., reported an increased risk of death with AF associated with HFrEF of ischemic pathogenesis (28). The increased death is believed to be due to more rapid progression of HF with ischemic pathogenesis. Moreover, in a large retrospective study, Dries et al. analyzed 6517 patients with LVEF <35% and reported AF to be an independent predictor for all-cause mortality. AF patients had increased mortality compared to those in sinus rhythm (29). Some authors associate this increase in mortality with the data obtained from old pharmacological treatment which is not comparable with new management strategies. Nevertheless, further studies are required to elucidate this association considering the HFrEF pathogenesis with new treatment guidelines.

Similarly, in Digitalis Investigation Group trial, 7788 patients were enrolled, and over 3 years follow-up period, 11% developed supraventricular tachycardia including, but not limited to AF. Risk of total mortality, stroke and hospitalization for worsening congestive heart failure was independently increased as a result of supraventricular tachycardia (30).

Finally, long-term mortality and morbidity associated with AF was also reported in the Valsartan in Acute Myocardial Infarction trial, which enrolled 14,703 subjects with acute myocardial infarction complicated by HF (31). In 2006, in a prospective study of 651 older persons, Aronow and Konzon reported that AF leads to a significantly higher 6-month mortality rate than those with sinus rhythm if they had an abnormal or normal LVEF in HF after prior myocardial infarction (34).

Our study did not provide mortality rate as it was not designed in that manner as well as it was a short-term study. Nevertheless, there were no differences in rate of hospitalizations in one year between different subgroups of patients. Rate of hospitalization is an important

clinical outcome which summarizes multiple factors in HF patients. Therefore, based on our findings it could be stated that AF doesn't influence hospitalization rate in patients with AF in short-term, one-year time. However, further prospective studies are necessary with short- and long-term duration.

Our study has several limitations. Firstly, our research was organized in a cross-sectional manner so it was not possible to establish any causal relationship or follow longitudinal cognitive alterations. Moreover, subgroups were not perfectly matched as there were age differences in baseline characteristics. Moreover, our findings were not adjusted for the effect of possible covariates. As well, sample size analysis was not conducted a priori to the research onset and therefore it is not possible to establish true significance of our findings.

In conclusion, the findings of this study provide a further step in elucidating the clinical differences in patients with HF regarding concomitant AF presence.

6. CONCLUSION

1. There is no major difference in clinical characteristics between patients with HF and AF compared to patients with HF and without AF
2. There is no significant difference in NYHA class between patients with HF and AF compared to patients with HF and without AF
3. There is no significant difference in hospitalization rate between patients with HF and AF compared to patients with HF and without AF
4. Patients with HF and without AF have higher prevalence of anemia compared to patients with HF and AF
5. Patients with HF and without AF have higher prevalence of acetylsalicylic acid use compared to patients with HF and AF

7. REFERENCES

1. McCulloch B. Heart Failure and Atrial Fibrillation. Crit Care Nurs Clin North Am. 2015;27(4):427-38.
2. Scheinman M. Atrial Fibrillation and Congestive Heart Failure. Circulation. 1998;98(10):941-2.
3. Ferreira J, Santos M. Heart Failure and Atrial Fibrillation: From Basic Science to Clinical Practice. Int J Mol Sci. 2015;16(2):313-47.
4. DePasquale E, Fonarow G. Impact of Atrial Fibrillation on Outcomes in Heart Failure. Heart Fail Clin. 2013;9(4):437-49.
5. Prabhu S, Voskoboinik A, Kaye D, Kistler P. Atrial Fibrillation and Heart Failure — Cause or Effect?. Heart Lung Circ. 2017;26(9):967-74.
6. Gigli L, Ameri P, Secco G, De Blasi G, Miceli R, Lorenzoni A, et al. Clinical characteristics and prognostic impact of atrial fibrillation in patients with chronic heart failure. World J Cardiol. 2016;8(11):647.
7. Johnson F. Pathophysiology and Etiology of Heart Failure. Cardiol Clin. 2014;32(1):9-19.
8. Ziaeian B, Fonarow G. Epidemiology and etiology of heart failure. Nat Rev Cardiol. 2016;13(6):368-78.
9. Halley C, Houghtaling P, Khalil M, Thomas J, Jaber W. Mortality Rate in Patients With Diastolic Dysfunction and Normal Systolic Function. Arch Intern Med. 2011;171(12):1082-7.
10. Shibazaki K, Kimura K, Fujii S, Sakai K, Iguchi Y. Brain Natriuretic Peptide Levels as a Predictor for New Atrial Fibrillation During Hospitalization in Patients With Acute Ischemic Stroke. Am J Cardiol. 2012;109(9):1303-7.
11. Lip G, Banerjee A, Lagrenade I, Lane D, Taillandier S, Fauchier L. Assessing the Risk of Bleeding in Patients With Atrial Fibrillation. Circ Arrhythm Electrophysiol. 2012;5(5):941-8.
12. Benjamin E, Blaha M, Chiuve S, Cushman M, Das S, Deo R, et al. Heart Disease and Stroke Statistics 2017 Update: A Report From the American Heart Association. Circulation. 2017;135(10):e146-e603.
13. Karnik A, Gopal D, Ko D, Benjamin E, Helm R. Epidemiology of Atrial Fibrillation and Heart Failure. Cardiol Clin. 2019;37(2):119-29.
14. Ponikowski P, Voors A, Anker S, Bueno H, Cleland J, Coats A, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail. 2016;18(8):891-75.

15. Sugumar H, Nanayakkara S, Prabhu S, Voskoboinik A, Kaye D, Ling L et al. Pathophysiology of Atrial Fibrillation and Heart Failure. Cardiol Clin. 2019;37(2):131-8.
16. Miyazawa K, Lip G. Atrial fibrillation. Medicine. 2018;46(10):627-31.
17. Staerk L, Sherer J, Ko D, Benjamin E, Helm R. Atrial Fibrillation. Circ Res. 2017;120(9):1501-17.
18. Yamazaki M, Jalife J. Pathophysiology of atrial fibrillation: From initiation to maintenance. J Arrhythm. 2012;28(3):129-39.
19. Madan N, Itchhaporia D, Albert C, Aggarwal N, Volgman A. Atrial Fibrillation and Heart Failure in Women. Heart Fail Clin. 2019;15(1):55-64.
20. 73. Sanders P, Morton J, Davidson N, Spence S, Vohra J, Sparks P et al. Electrical Remodeling of the Atria in Congestive Heart Failure. Circulation. 2003;108(12):1461-8.
21. Morin D, Bernard M, Madias C, Rogers P, Thihalolipavan S, Estes N. The State of the Art. Mayo Clin Proc. 2016;91(12):1778-810
22. Carlisle M, Fudim M, DeVore A, Piccini J. Heart Failure and Atrial Fibrillation, Like Fire and Fury. JACC Heart Fail. 2019;7(6):447-56.
23. Arques S. Human serum albumin in cardiovascular diseases. Eur J Intern Med. 2018;52:8-12.
24. Efremidis M. Atrial Fibrillation in Heart Failure Patients. Eur Cardiol Rev. 2009;5(1):41.
25. Batul S, Gopinathannair R. Atrial Fibrillation in Heart Failure: a Therapeutic Challenge of Our Times. Korean Circ J. 2017;47(5):644.
26. Hussein A, Saliba W, Martin D, Shadman M, Kanj M, Bhargava M et al. Plasma B-Type Natriuretic Peptide Levels and Recurrent Arrhythmia After Successful Ablation of Lone Atrial Fibrillation. Circulation. 2011;123(19):2077-82.
27. Tang Y, Yang H, Qiu J. Relationship between Brain Natriuretic Peptide and Recurrence of Atrial Fibrillation after Successful Electrical Cardioversion: A Meta-Analysis. Int Med Res. 2011;39(5):1618-24.
28. Mercer B, Koshy A, Drozd M, Walker A, Patel P, Kearney L et al. Ischemic Heart Disease Modifies the Association of Atrial Fibrillation With Mortality in Heart Failure With Reduced Ejection Fraction. J Am Heart Assoc. 2018;7(20).
29. Dries D, Exner D, Gersh B, Domanski M, Waclawiw M, Stevenson L. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in

patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. J Am Coll Cardiol. 1998;32(3):695-703.

30. Mathew J, Hunsberger S, Fleg J, Mc Sherry F, Williford W, Yusuf S. Incidence, Predictive Factors, and Prognostic Significance of Supraventricular Tachyarrhythmias in Congestive Heart Failure. Chest. 2000;118(4):914-22.
31. Køber L, Swedberg K, McMurray J, Pfeffer M, Velazquez E, Diaz R et al. Previously known and newly diagnosed atrial fibrillation: A major risk indicator after a myocardial infarction complicated by heart failure or left ventricular dysfunction. Eur J Heart Fail. 2006;8(6):591-8.
32. 74. Khan M, Jaïs P, Cummings J, Di Biase L, Sanders P, Martin D et al. Pulmonary-Vein Isolation for Atrial Fibrillation in Patients with Heart Failure. N Engl J Med. 2008;359(17):1778-85.
33. Kang S, Kim J, Park J, Oh I, Yoon C, Kim H, et al. Risk of stroke in congestive heart failure with and without atrial fibrillation. Int J Cardiol. 2017;248:182-7.
34. 75. Aronow W, Ahn C, Kronzon I. Prognosis of congestive heart failure after prior myocardial infarction in older persons with atrial fibrillation versus sinus rhythm. Am J Cardiol. 2001;87(2):224-5.
35. Middlekauff H, Stevenson W, Stevenson L. Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. Circulation. 1991;84(1):40-8.
36. Corell P, Gustafsson F, Schou M, Markenvard J, Nielsen T, Hildebrandt P. Prevalence and prognostic significance of atrial fibrillation in outpatients with heart failure due to left ventricular systolic dysfunction. Eur J Heart Fail. 2007;9(3):258-65.
37. Pedersen O, Bagger H, Køber L, Torp-Pedersen C. Impact of congestive heart failure and left ventricular systolic function on the prognostic significance of atrial fibrillation and atrial flutter following acute myocardial infarction. Int J Cardiol. 2005;100(1):65-71.
38. Crijns H. Prognostic value of the presence and development of atrial fibrillation in patients with advanced chronic heart failure. Eur Heart J. 2000;21(15):1238-45.
39. Ahmed A, Perry G. Incident atrial fibrillation and mortality in older adults with heart failure. Eur J Heart Fail. 2005;7(7):1118-21.
40. Van Gelder I, Hagens V, Bosker H, Kingma J, Kamp O, Kingma T et al. A Comparison of Rate Control and Rhythm Control in Patients with Recurrent Persistent Atrial Fibrillation. N Engl J Med. 2002;347(23):1834-40.

41. Ling L, Kistler P, Kalman J, Schilling R, Hunter R. Comorbidity of atrial fibrillation and heart failure. Nat Rev Cardiol. 2015;13(3):131-47.
42. Thihalolipavan S, Morin D. Atrial Fibrillation and Congestive Heart Failure. Heart Fail Clin. 2014;10(2):305-18.
43. Swedberg K, Olsson L, Charlesworth A, Cleland J, Hanrath P, Komajda M et al. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. Eur Heart J. 2005;26(13):1303-8.
44. Papadimitriou L, Hamo C, Butler J. Heart failure guidelines: What's new?. Trends Cardiovasc Med. 2017;27(5):316-23.
45. Snipelisky D, Chaudhry S, Stewart G. The Many Faces of Heart Failure. Card Electrophysiol Clin. 2019;11(1):11-20.
46. aBalsam P, Gawałko M, Peller M, Tymińska A, Ozierański K, Zaleska M et al. Clinical characteristics and thromboembolic risk of atrial fibrillation patients with and without congestive heart failure. Results from the CRATF study. Medicine. 2018;97(45): e13074.
47. Temu T, Lane K, Shen C, Ng'ang'a L, Akwanalo C, Chen P et al. Clinical characteristics and 12-month outcomes of patients with valvular and non-valvular atrial fibrillation in Kenya. PLoS One. 2017;12(9):e0185204.
48. Abdul-Rahim A, Perez A, Fulton R, Jhund P, Latini R, Tognoni G et al. Risk of Stroke in Chronic Heart Failure Patients Without Atrial Fibrillation. Circulation. 2015;131(17):1486-94.
49. Yamashita K, Ranjan R. Imaging for Risk Stratification in Atrial Fibrillation with Heart Failure. Cardiol Clin. 2019;37(2):147-56.
50. Agasthi P, Tseng A, Lee J, Mulpuru S. Atrial Fibrillation Ablation Should Be First-line Therapy in Patients with Heart Failure Reduced Ejection Fraction. Cardiol Clin. 2019;37(2):185-95.
51. El-Harasis M, DeSimone C, Yao X, Noseworthy P. Prediction and Management of Recurrences after Catheter Ablation in Atrial Fibrillation and Heart Failure. Cardiol Clin. 2019;37(2):221-30.
52. Campodonico J, Piepoli M, Clemenza F, Bonomi A, Paolillo S, Salvioni E et al. Dose-dependent efficacy of β-blocker in patients with chronic heart failure and atrial fibrillation. Int J Cardiol. 2018;273:141-6.

53. Waldmann V, Laredo M, Abadir S, Mondésert B, Khairy P. Atrial fibrillation in adults with congenital heart disease. Int J Cardiol. 2019;287:148-54.
54. Pozzoli M, Cioffi G, Traversi E, Pinna GD, Cobelli F, Tavazzi L. Predictors of primary atrial fibrillation and concomitant clinical and hemodynamic changes in patients with chronic heart failure: a prospective study in 344 patients with baseline sinus rhythm. J Am Coll Cardiol. 1998; 32: 197–204.
55. Christenson R, Azzazy H, Duh S, Maynard S, Seliger S, deFilippi C. Impact of Increased Body Mass Index on Accuracy of B-Type Natriuretic Peptide (BNP) and N-Terminal proBNP for Diagnosis of Decompensated Heart Failure and Prediction of All-Cause Mortality. Clin Chem. 2010;56(4):633-41.
56. Arques S, Ambrosi P. Human Serum Albumin in the Clinical Syndrome of Heart Failure. J Card Fail. 2011;17(6):451-8.

8. SUMMARY

Objectives: Heart failure (HF) and atrial fibrillation (AF) are two distinct but related entities and their coexistence create a very dangerous interaction. The aim of this study was to determine the differences in clinical characteristics and selected parameters between HF patients with and without AF.

Patients and Methods: This was a cross-sectional study, that included a total of 90 patients that presented with signs and symptoms of heart failure at the emergency department. Patients were enrolled in a 1:1 ratio in terms of sex, had to be New York Heart Association (NYHA) functional class II-IV. Data were analyzed by using SPSS Statistics for Windows® (version 25.0, IBM, Armonk, NY, USA).

Results: There was no significant difference in anthropometric and clinical parameters among studied groups, except in age (72.7±9.1 in FA group vs. 67.3±11.0 years in non-FA group, P=0.012), systolic blood pressure values (131.2±21.9 in FA group vs. 143.5±32.5 mmHg in non-FA group, P=0.035) and heart rate (103.0±32.0 in FA group vs. 84.0±26.0 in non-FA group, P=0.003). Moreover, there was no statistical difference in baseline laboratory findings between groups, except for activated partial thromboplastin time (30±8 in FA group vs. 25±3 seconds in non-FA group, P=0.001), prothrombin time-international normalized ratio (1.7±1.0 in FA group vs. 1.1±0.3 in non-FA group, P=0.001) and albumin values (37±4.0 in FA group vs. 39±4.0 g/L in non-FA group, P=0.043). Furthermore, patients with HF and AF use more beta blocker (49, 98.0% vs. 32, 80.0%, P=0.009), digoxin (16, 32.0% vs. 2, 5.0%, P=0.001) and anticoagulants (42, 84.0% vs. 3, 7.5%, P<0.001), as well as less acetylsalicylic acid (27, 67.5% vs. 8, 16.0%, P<0.001), while there was no statistical difference in other medications. Among HF patients, group without AF had significantly higher prevalence of anemia (16, 40.0% vs. 10, 20.0%, *P*=0.038) in comparison to group with AF, while there was no difference in the prevalence of other comorbidities. Finally, there was no statistical difference in echocardiographic parameters between studied groups.

Conclusion: There is no major difference in clinical characteristics, NYHA class and hospitalization rate between patients with HF and AF compared to patients with HF and without AF. However, patients with HF and without AF have higher prevalence of anemia and acetylsalicylic acid use compared to patients with HF and AF.

9. CROATIAN SUMMARY

Naslov: Razlike u kliničkim obilježjima bolesnika koji boluju od zatajenja srca s i bez fibrilacije atrija.

Ciljevi: Zatajenje srca (HF) i fibrilacija atrija (AF) dva su različita, ali povezana entiteta i njihova istodobna prisutnost stvara vrlo opasnu interakciju. Cilj ovog istraživanja bio je utvrditi razlike u kliničkim obilježjima i odabranim parametrima između HF bolesnika s AF i bez AF.

Pacijenti i metode: Ovo je presječno istraživanje koje je uključivalo ukupno 90 bolesnika sa simptomima zatajenja srca na hitnoj službi. Pacijenti su bili uključeni u omjeru 1: 1 s obzirom na spol, a morali su pripadati klasi II-IV prema New York Heart udruženju (NYHA). Podaci su analizirani uz pomoć SPSS Statistics for Windows® (verzija 25.0, IBM, Armonk, NY, USA).

Rezultati: Nije bilo značajne razlike u antropometrijskim i kliničkim parametrima među skupinama, osim u dobi (72,7±9,1 u skupini FA naspram 67,3±11,0 godina u ne-FA skupini, P=0,012), vrijednostima sistoličkog krvnog tlaka (131,2±21,9 u FA skupini naspram 143,5±32,5 mmHg u ne-FA skupini, P=0,035) i otkucajima srca (103,0±32,0 u FA skupini naspram 84,0±26,0 u ne-FA skupini, P=0,003). Štoviše, nije bilo statističke razlike u osnovnim laboratorijskim nalazima između skupina, osim za vrijednosti aktiviranog parcijalnog tromboplastinskog vremena (30±8 u FA skupini naspram 25±3 sekundi u ne-FA skupini, P=0,001), protrombinskog vremena - međunarodnog normaliziranog omjera (1,7±1,0 u FA skupini naspram 1,1±0,3 u ne-FA skupini, P=0,001) i albumina (37±4,0 u FA skupini naspram 39±4,0 g/L u ne-FA skupini, P=0,043). Nadalje, bolesnici s HF i AF koriste više beta blokatora (49, 98,0% naspram 32, 80,0%, P=0,009), digoksina (16, 32,0% naspram 2, 5,0%, P=0,001) i antikoagulansa (42, 84,0% naspram 3, 7,5%, P<0,001), kao i manje acetilsalicilne kiseline (27, 67,5% naspram 8, 16,0%, P<0,001), dok nema statističke razlike u drugim lijekovima. Kod HF bolesnika, skupina bez AF imala je značajno veću prevalenciju anemije (16, 40,0% naspram 10, 20,0%, P=0,038) u usporedbi s skupinom s AF, dok nije bilo razlike u učestalosti drugih komorbiditeta. Konačno, nije bilo statističke razlike u ehokardiografskim parametrima između ispitivanih skupina.

Zaključak: Nema velike razlike u kliničkim karakteristikama, NYHA klasi i stopi hospitalizacije između bolesnika s HF i AF u usporedbi s bolesnicima s HF i bez AF. Međutim, bolesnici s HF-om i bez AF imaju veću prevalenciju anemije i uporabe acetilsalicilne kiseline u usporedbi s bolesnicima s HF i AF.

10. CURRICULUM VITAE

Personal Data

Name: Asadullah Razmandeh

Email: asadullah_44@yahoo.com

Address: England, United Kingdom

Education:

MD 2019, Split, Croatia

12 GCSE 2005-2008, England, United Kingdom

4 A-levels 2008-2010, England, United Kingdom

BSc (Hons) 2010-2013, England, United Kingdom

Languages:

English (fluent)

Persian (fluent)

Pashto (fluent)

Urdu and Hindi (intermediate)

Arabic (basic)

Croatian (basic)