Characteristics and biomarkers in patients with heart failure to indicate necessity of ventilatory support

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CHARACTERISTICS AND BIOMARKERS IN PATIENTS WITH HEART FAILURE TO INDICATE NECESSITY OF VENTILATORY SUPPORT

DIPLOMA THESIS

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1. INTRODUCTION

1.1 Definition of heart failure

Due to its increasing prevalence and high mortality rate, heart failure (HF) is an important disease to consider. As per definition according to the American College of Cardiology, HF is a complex clinical syndrome that results in an abnormal heart function regarding ventricular filling, ejection of blood, as well being caused by any structural abnormality leading up to these impairments (1). Furthermore, it is characterized by a series of symptoms (i.e., orthopnoea and dyspnoea) as well as signs (i.e., pulmonary congestion). Some of the main pathogenic pathways resulting in HF include ischemic related dysfunctions, ventricular remodelling, genetic mutations, accelerated apoptosis and increased hemodynamic overload (2).

Heart failure is divided into: HFpEF (heart failure with preserved ejection fraction) with an ejection fraction (EF) $\geq$ 50%, HFmrEF (heart failure with mid-range ejection fraction) with EF between 40% and 49% and HFrEF (heart failure with reduced ejection fraction) with EF $\leq$ 40%. Along the above-mentioned criteria's for diagnosing a particular HF, elevated levels of natriuretic peptides and at least one of the following: A relevant structural heart disease (left ventricular hypertrophy - LVH and/or left atrial enlargement - LEA) or diastolic dysfunction; must be found to be present in HFpEF and HFmrEF for its correct diagnosis (3). Moreover, HF is categorized as acute, subacute, chronic, or chronic with acute decompensation (4). The New York Heart Association (NYHA) is used to identify HF based on intensity of symptoms and the amount of exertion expected to induce symptoms (5).

1.2 Epidemiology

HF is an issue ubiquitous on a global scale. Its prevalence has been estimated to be approximately 1-2 % in developed countries and its tendency is seen to increase with age. It has been estimated that >10% of people over the age of 70 years have some problems related to HF (6). The fact that the life expectancy is increasing, and this prolonged life expectancy is seen in all developed countries, along with better treatments and medical support for different heart related disease such as myocardial infarction (MI), arrythmias and valvular diseases; the overall prevalence of HF is on the rise (7). As a general note, men are usually more impacted than females. Several epidemiological studies have shown that HFpEF patients are more likely to be women, elderly, obese and of a higher New York Heart Association (NYHA) class along with

cardiovascular comorbidities (i.e., diabetes, atrial fibrillation, and hypertension) as well as non-cardiovascular comorbidities (such as anaemia, chronic renal disease and chronic pulmonary disease). Furthermore, patients with HFpEF with comorbidities such as atrial fibrillation and hypertension show a lower rate of MI while coronary artery disease (CAD) is the main determinant of HFrEF (8,9).

Important to note is that there are geographic variations seen in relations to prevalence, morbidity, and mortality depending on the different aetiologies and clinical characteristics observed in patients with HF (10). A plethora of laboratory parameters, clinical indications and scoring systems have been used in the aid of prognosis and outcomes of HF patients with preserved as well as reduced systolic function; the S_2PLiT-UG score is an example of such a score. This scoring system is based on independent predictors of 1-year all-cause mortality following discharge after an acute heart failure (AHF) event. It divides patients into categories of three: low, intermediate, and high. Which are used to facilitate the risk stratification and therapeutic decision-making (11).

1.3 Etiology

As per effect, any condition that affects the structure and/or function of the heart can cause heart failure. An important consideration is to reflect over the different causes that can cause HF and the detection of these causes is of great importance. The division of the different etiology of HF can be divided into three categories of causes, these are: predisposing, determining and precipitation (12).

Predisposing causes, better known as risk factors, are identified in the general population that is without any symptoms of HF. These risk factors generate alterations in the normal physiology of the heart and include structural alterations, congenital or acquired, as well as disorders involving the peripheral vessels and/or cardiac valves which also de facto bring about alterations of the normal physiology of the heart. Coronary artery disease (CAD) is directly responsible for over 50% of HF cases in the United States seen mainly in men (13) with less prevalent factors being dilated cardiomyopathy and congenital cardiac abnormalities (10, 14). Hypertension being a major contributor to HF, arterial hypertension (AHT) has been found to have an indirect influence on the progressive deterioration of the ventricular function, most seen in

women and black individuals with HF (15). Over time AHT may lead to left ventricular hypertrophy which is also a risk factor for HF. This finds support in the Framingham study, which states the risk for HF is doubled in the population that have mild AHT and a four-fold increase in risk is seen in those with arterial pressures of 160/95 mmHg. Worth of note is that the risk for HF in diabetic women is five times higher compared to non-diabetic women, but also higher than in diabetic men (16).

Alterations of the regulating factors controlling the heart rate, hemodynamic load, and ventricular function fall under the determining causes of HF (12). Right ventricular free wall longitudinal strain (RV FWS) Is an echocardiographic method used to calculate systolic activity of the right ventricle and its mechanics. The right ventricle has complex morphology due to its noncylindrical form and demonstrates different hemodynamic qualities compared to LV. As known, the right ventricle (RV) consists mainly of oblique and longitudinal myofibers and a shared interventricular septum with the LV, thus the RV FWS corresponds primarily to right ventricle mechanical function and is therefore a strong predictor for cardiovascular and all-cause mortality among patients with HFrEF and pulmonary arterial hypertension, independent of LV systolic function (17). Idiopathic dilated cardiomyopathy affects both sexes and is characterized by a prominent LV systolic dysfunction. Depicted by an alteration in cardiac compliance with rapid early diastolic filling, restrictive cardiomyopathy falls under this etiological category of HF. Genetic disorders presenting themselves as hypertrophic cardiomyopathy often lack any apparent cause and are characterized by hypertrophy of the LV (18,19). The precipitating factors are typified by the fact that they lead to decompensation in a stable patient that has or has not been previously diagnosed with HF but has an underlying structural cardiac abnormality. Furthermore, these factors are divided into cardiac and extracardiac causes (20). Arrythmias and acute myocardial infarction (AMI) fall under the cardiac causes whereas pulmonary embolism (PE), physical or psychological stress, infections of the respiratory tract, anemia and toxic habits along with drugs that cause sodium retention fall under the extracardiac causes (12, 21).Moreover, the most common reason for symptomatic HF in the United States is CAD. As one or both ventricles become spherical and demonstrate atrioventricular valve incompetence leading to annular dilation over time the resulting matter is a combined systolic and diastolic HF, with a systolic dysfunction predominating in most patients (22). Other major reasons for developing HF are myocardial infarction, rheumatic heart disease, chronic obstructive pulmonary disease (COPD) and hypertension (HT) (23). MI being

caused by an occlusion in one or more of the coronary arteries due to different precipitating causes where one of the most common causes is common atherosclerotic plaque rupture. The risk factors for MI include obesity, smoking and diabetes. COPD is a progressive and chronic disease of the respiratory system; the greatest risk factor for COPD is smoking. HT specific etiology is mostly diffuse and often unknown, although in a small percentage of cases an underlining etiology can be found, for instance: renal artery stenosis. Less frequent causes include cardiomyopathies which have infectious, metabolic cardiomyopathies and toxic origins (24).

Regardless the causes of HF, the disease is a progressive disease that is worsened by increased hemodynamic burden and/or a reduction in the oxygen delivery to a heart that haves an increasingly higher demand of oxygen and a majority of the underlying causes of HF is gender, age, ethnicity and comorbidity dependent (25)

1.4 Pathophysiology

The pathophysiology of HF is an extremely complex topic, and it is a topic that is under continuous investigation, but the main concept is that a certain event causes the heart to lose its optimal capability to pump blood. The event can cause a systolic dysfunction namely that is loses its ideal capacity of pumping blood towards the aorta. The event can in other cases presents itself as a diastolic dysfunction in which the heart in incapable to accommodate enough blood into its chambers, this would eventually with time transform into a systolic dysfunction as the disease would progress (26). So, in its essence, the disease is a damaged state of the hearts systolic function which is followed by a state of low cardiac output (CO), in other words, cardiac failure (27).

Stroke volume is the amount of blood ejected from the heart with every heartbeat. This value is affected by three main variables, namely: preload, afterload, and contractility of the heart. Preload being defined by the total myocardial stretch at the end of diastole, afterload being defined by the resistance the ventricles must overcome to eject the blood, and contractility is the ionotropic state of the heart. A maintenance and optimization of these variables is needed for the heart to function properly and effectively. A disparity to any of these hemodynamical variables would effectively lead to symptoms associated with HF (22, 28).

1.4.1 Ventricular dysfunction

There are two categories regarding this topic: systolic and diastolic dysfunction. Systolic dysfunction entails impaired ventricular contraction and ejection, while impaired relaxation and ventricular filling falls under diastolic dysfunctions. Systolic dysfunction maybe due to impaired cardiac contractile function, left heart structural abnormalities, ischemic disease, infarction, uncontrolled HT or incompetence of the valves, to name a few. Whereas diastolic dysfunction results from increase blood volumes in the ventricles that may cause increase in both end-diastolic and end-systolic volumes. This would lead to an increase in left ventricle end-diastolic pressure (LVEDP) causing an elevated pulmonary venous pressure and in effect mean that a diastolic dysfunction would be clinically manifested as pulmonary congestion. Like that note is that a common cause of right ventricular failure is left ventricular failure (30, 31).

The Frank-Starling mechanism not only clarifies the compensatory actions the heart takes in early stages of HF, but it also explains how several compensatory mechanisms try to support the demands in adequate tissue perfusion by maintaining the mean arterial pressure (MAP) (Figure 1). The figure presents CO as a function of LVEDP, which is directly related to left ventricle end-diastolic volume (LVEDV) or in other words, preload. Of note, these mechanisms are in fact beneficial in an initial state but will worsen the patient's HF in the long-term as it will show tendencies of being a vicious circle (31).

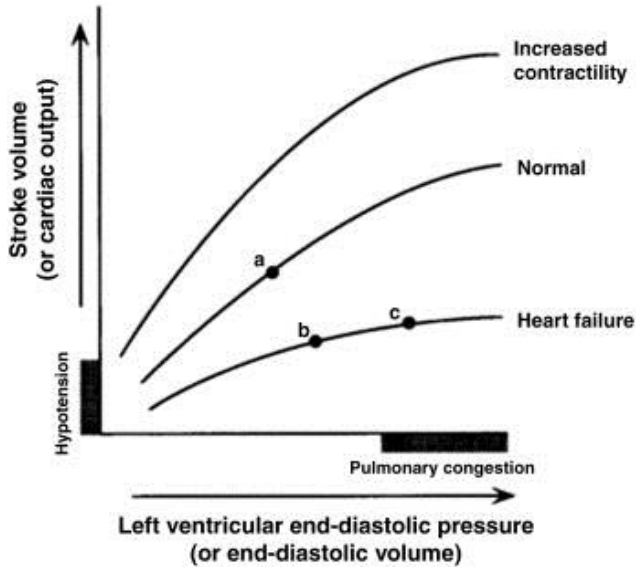


Figure 1. The Frank-Starling mechanism. The figure presents CO (cardiac output) as a function of LVEDP (left ventricle end-diastolic pressure) which is directly related to left ventricle end-diastolic volume (LVEDV) or in other words, preload.

Taken from: Kemp C, Conte J. The pathophysiology of heart failure. Cardiovasc Pathol. 2012;21(5):365-71.

The complexity of HF sheds light on the fact that diastolic and systolic HF are not separate entities. A phenotype of HF is comprised to some extent of diastolic dysfunction and to some extent of systolic dysfunction (Figure 2). It is obvious from this figure that a left ventricular ejection fraction (LVEF) of 45 to 55% would be in the middle of the continuum of disease spectrum (27).

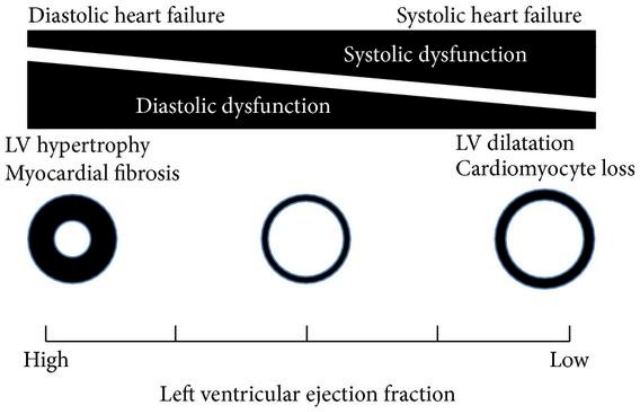


Figure 2. Single syndrome hypothesis of heart failure.

Taken from: Komamura K. Similarities and Differences between the Pathogenesis and Pathophysiology of Diastolic and Systolic Heart Failure. Cardiol Res Pract. 2013;2013:1-6.

1.4.2 Ischemic injury and ventricular remodelling

Ventricular remodelling, ischemic replacement fibrosis and permanent injury are seen after ischemic injuries to the heart such as MI. Left ventricular stress injuries leads to remodelling in untreated patients after a large MI (22). Furthermore, the sub endocardium is susceptible to acute injury caused by hypoperfusion (33). With ventricular remodelling caused by hemodynamic stresses, the shape, size, structure, and function of the heart will take on a more characteristic appearance as those seen in patients with HF. The heart will become more spherical in contrast to its original shape of being elliptical. Overall, the failing heart will try to compensate in size to maintain the demand put on it and maintain the SV and CO. An increase in mass and thickness is seen in the pursuit of increasing its contractility. Changes to the heart can also be seen on a microscopic level, where myocyte hypertrophy, apoptosis and increased interstitial collagen can be seen (31).

Other heart adaptations are seen when there is mild ischemia as to make sure that the supply and energy utilization is maintained and the myocardial viability is upheld, this is commonly known as "short-term hibernation". With increasing severity of ischemia, the heart will downregulate metabolism to maintain myocyte viability at the expense of its contractile function. This "hibernating myocardium" will be seen to develop a regional cellular hypertrophy like those seen in patients with advanced HF. This "stunned myocardium" may recover over a period of hours to days but a more chronic and repetitive ischemic insult will render the heart incapable of recovering between episodes of spontaneous ischemia (34). It is therefore imperative to differentiate between hibernating myocardium and ischemic fibrosis as an eventual revascularization of viable myocardium would result in an improved left ventricular function and overall survival in comparison to medical therapy alone (22, 33).

1.4.3 Neurohormonal dysregulation

A well-functioning neurohormonal activation is crucial for the maintenance of MAP as well as the compensations necessary that the heart makes in the early stages of HF. Moreover, the neurohormonal algorithm is the foundation for the therapy given to those with chronic systolic HF. Any noticeable derangements to this algorithm will cause the baroreceptors to react and increase

the sympathetic nervous activity. This in turn will cause vasoconstriction, elevate the blood pressure as well as increasing the heart rate. The increase in adrenergic tone will cascade to the activation of the renin-angiotensin-aldosterone system (RAAS) (34). These changes will consequently lead to an increase in stroke volume (SV) and total peripheral resistance (TPR), subsequently increasing MAP. The higher renin levels will increase the vascular tone and put a pressure overload on the heart causing an eventual hemodynamic injury. Furthermore, the higher level of angiotensin II will stimulate the secretion of aldosterone to a higher extent and cause a reduction in renal water and sodium excretion, increasing the retained vascular fluid volumes and lead to an excessive preload adding to the eventual hemodynamic injury posed on the heart (22, 35).

Oxidation stress is known to provoke endothelial dysfunction, which is a contributor to the development of HF. A dysfunctional endothelium will cause a distorted endothelial dependents vasodilation and at repeated episodes of ischemia and reperfusion will in the long run have decremental effects on the myocardium. These events will not only cause a change in systolic function, but also induce an increased diastolic stiffness of the heart with a diastolic dysfunction (36). These adaptations will cause a decrease of the CO through the decreased reactivity of the heart's contractility from its normal stimuli, leading to cardiac remodeling and further the myocardial dysfunction (31).

1.5 Clinical presentation

The cardinal symptoms of HF are shortness of breath while standing up, orthopnoea, paroxysmal nocturnal dyspnoea, and fatigue. All of these have their explanation in the collection of fluid in the lungs; with exception from fatigue which involve multiple mechanisms and has a complex underlying pathophysiology. Other symptoms, including GI disturbances such as bloating and indigestion, as well as right upper quadrant pain can be explained by the congestion of GI mucosa and liver, respectively. Encephalopathy can also be seen in advances cases of HF which draw its explanation from the decreased cerebral perfusion (26).

As the causes for heart failure may vary, the right side of the heart may not be able to accommodate the volume of blood returning to the hear from the vena cava. Pressing on the liver under these circumstances may increase this return of blood but the blood would instead find its way up to the jugular veins due to the hearts lack of accommodation of this extra volume of blood,

this is called the hepatojugular reflux. The jugular veins may at times be distended without the need of pressing on the liver and a jugular vein distension may be seen without the need of pressing on the liver (37). This backing up of blood can be seen due to the heart inability to accommodate the blood in its chambers. When this happens to the left ventricle, blood will start to accumulate in the lung interstitial and/or alveoli, causing lung edema. Although the lungs do possess a capacity to withstand an increase of 30mmHg of hydrostatic pressure before an extravasation of blood. This mechanism is overrun in patient with HF mostly because the lung vessels cannot dilate and accommodate more blood (38).

Considering the different etiologies of HF, various valve related murmurs can be heard that can be the cause or the consequence of heart failure. The S4 heart sound is a characteristic sound when the atrium contracts and pushes the blood into a non-compliant ventricle. While S3 heart sound happens when the blood that comes from the atria, meets a compliant ventricle. Therefore, the S4 heart sound is more specific for a diastolic heart failure. As a general guideline, peripheral edema is a pathognomonic sign of HF as its seen due to increase in hydrostatic pressure in the venous system with the consequence of fluid extravasation. It is a commonly seen sign in deambulatory patients (38).

1.6 Diagnostics

The two pillars of HF diagnostics are centred on obtaining the patients clinical history and physical examination. The history should include toxic habits, comorbidities, and cardiovascular risk factors. The symptoms can, in a broad sense, be divided into two groups, the first being pulmonary rales, pitting oedema, and tachycardia. These are classified as nonspecific in comparison to those falling into the second category, which include: jugular venous distension, gallop rhythm and displacement of the apical beat, all of which are seen in serious forms of HF (4). Naturally, several approaches have been proposed in the quest of effectively diagnosing HF and several criteria's have been suggested; one of which draws support from the Framingham study. The proposed guideline in this study includes the presence of two main or one main and two minor criteria (Table 1) (16).

Table 1. The Framingham study criteria (16).

Major criteria	Minor criteria
1. Paroxysmal nocturnal dyspnoea or orthopnoea	1. Ankle oedema
2. Distended neck vein (not counting supine position)	2. Night cough
3. Rales in presence of unexplained dyspnoea	3. Dyspnoea on ordinary exertion
4. Cardiomegaly and pulmonary hilar congestion (by X-ray in absence of left to right shunt) or increasing heart size.	4. Hepatomegaly
5. Acute pulmonary oedema described in hospital records	5. Pleural effusion
6. Ventricular gallop	6. Decreased vital capacity decreased by 1/3 from maximum records
7. Increased venous pressure (≥ 16 cm water from right atrium)	7. Tachycardia rate of ≥ 120/min
8. Circulation time (≥ 24 sec, arm to tongue)	
9. Hepatojugular reflux	**Minor or Major:** Weight loss (≥4.5 Kg) in 5 days, in response to HF Therapy
10. Autopsy shows pulmonary oedema, visceral congestion, cardiomegaly	

The European Society of Cardiology (ESC) has proposed another set of criteria for the purpose of diagnosing HF (Table 2). It takes presenting symptoms at rest and during exercise into account along with objective evidence of cardiac dysfunction at rest. The evaluation of cardiac function is also evaluated by appropriate tests (i.e., echocardiogram) (39). Diagnostic criteria one and two should be met in every case as its presented in Table 2 (40).

Table 2. European Society of Cardiology 2016 Guidelines (40).

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms +/- Signs*	Symptoms +/- Signs*	Symptoms +/- Signs*
	2	LVEF <40%	LVEF 40-49%	LVEF ≥50%
	3	-	1. Elevated levels of natriuretic peptides. 2.At least one additional criterion: a. Relevant structural heart disease (LVH and/or LAE), b. Diastolic dysfunction	

Abbreviations: HFpEF- heart failure with preserved ejection fraction, HFrEF- heart failure with reserved ejection fraction, HFmrEF- heart failure with mid-range ejection fraction, HF- heart failure, LVEF- left ventricular ejection fraction, LAE- left atrial enlargement, LVH-left ventricular hypertrophy, BNP- b-type natriuretic peptide

* Signs may not present in the early stages of HF (especially in HFpEF) and in patients being treated with diuretics.

[a] B-type natriuretic peptide - BNP > 35 pg/ml and/or NT-proBNP >125pg/ml

As it comes to be, the above-mentioned criteria are superseded by the Boston criteria in older adults, due to its validity and improved prediction of adverse outcome, furthermore, the Framingham criteria provides greater sensitivity in diagnosing HF, although the specificity and positive predictive value is higher when using the Boston criteria (Table 3) (39).

Table 3. Boston Criteria for diagnosing heart failure (38)

Category	Diagnosis	Score (points)
I	Rest dyspnoea	4
History	Orthopnoea	4
	Paroxysmal nocturnal	3
	dyspnoea	2
	Dyspnoea on walking on level	1
	Dyspnoea on climbing	
II	Heart rate abnormality (1	1-2
Physical	point for 91-110 bpm, 2points	
examination	for >110 bpm)	
	Jugular venous pressure	2-3
	elevation (2 points if >6 cm	
	H_2O, 3 points if > 6 cm H_2O	
	plus hepatomegaly or oedema)	
	Lung crackles	1-2
	Wheezing	3
	Third heart sound	3
III	Alveolar pulmonary oedema	4
Chest radiography	Interstitial pulmonary oedema	3
	Bilateral pleural effusions	3
	Cardiothoracic ratio ≥ 0.50	3
	Upper-zone flow	2
	redistribution	

No more than 4 points are allowed from each of three categories; hence the composite score (the sum of the subtotal from each category) has a possible maximum of 12 points. The diagnosis of heart failure is classified as "definite" at a score of 8 to 12 points, "possible" at a score of 5 to 7 points, and "unlikely" at a score of 4 points or less.

The confirmation or exclusion of HF is commonly supported by various other examinations and objective tests, to provide prognostic value. The B-type natriuretic peptide (BNP) and N-

terminal pro-BNP (NT-proBNP) are two of these tests that are used for the urgent and immediate diagnosis for both HFpEF and HFrEF. These two peptides are continually produced in small quantities in the heart but when sodium and water is retained in the vascular system along with activation of RAAS and the sympathetic nervous system, the action of vasopressin will lead to an increased ventricular pre-and afterload. This will elevate the wall stress which leads to production of pre-pro B-type natriuretic peptide that is eventually cleaved to BNP and NT-proBNP. The BNP promote natriuresis and vasodilation but NT-proBNP is physiologically inactive. Atrial stretch will also lead to the production of ANP (atrial natriuretic peptide) which has similar biological properties to BNP. The natriuretic peptide system will then counterbalance the detrimental effects of the RAAS that occurs in HF, along with modulating the autonomic nervous system and inhibiting the secretion of arginine vasopressin (38).

The usage of Echocardiography provides much information that is urgently needed, where information regarding the ventricles, chamber size, wall thickness and valve abnormalities are evaluated (6). After the diagnosis of HF is made, the type of HF is divided further using the most widely used method: the NYHA classification system. This system provides an outlook on prediction of mortality and can be used for monitoring the response to treatment, it describes the severity of symptoms and exercise intolerance. (2,6).

NYHA Classification - The Stages of Heart Failure:

- Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
- Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
- Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20—100 m). Comfortable only at rest.
- Class IV - Severe limitations. Experience’s symptoms even while at rest. Mostly bedbound patients.
- No NYHA class listed or unable to determine.

Of note, the severity of symptoms poorly correlates with the measures obtained reflecting LV function; although a relationship between severity of symptoms and survival exists, patients

with a classification of mild symptoms may still have an increased risk of hospitalization and furthermore, death (41-43). Patients being classified as having advanced HF may be classified as such due to patients' severe symptoms in terms of recurrent decompensation and severe cardiac dysfunction (44). Furthermore, The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) classification describes stages of HF development based on structural changes and symptoms (45):

- Stage A: High risk of HF but no structural heart disease or symptoms of HF
- Stage B: Structural heart disease but without symptoms of HF
- Stage C: Structural heart disease and symptoms of HF
- Stage D: Refractory HF requiring special interventions

1.6.1 Essential initial investigations.

Some of the essential initial investigations include natriuretic peptides, echocardiography, and electrocardiogram. If an echocardiography is for any reason is not immediately available, then a plasma concentration of natriuretic peptides (NPs) can be used as an initial diagnostic test. Elevated levels of NPs could help establish an immediate working diagnosis; help identify patients that require further cardiac investigations as well as identifying patients that do not require echocardiography based on values that fall below the cut point for the exclusion of important cardiac dysfunctions. Patients with normal plasma NP concentrations are unlikely to have HF (46). In the non-acute setting: the upper limit of normal levels for B-type natriuretic peptide (BNP) is 35 pg/mL and for N-terminal pro-BNP (NT-proBNP) it is 125 pg/mL. As for the acute setting, higher values are expected and used: BNP, 100 pg/mL, NT-proBNP , 300 pg/ mL. These diagnostic values apply in a similar fashion to HFrEF and HFpEF, although the values are expected to be lower in HFpEF than for HFrEF (47,48). The negative predictive values for these exclusionary cut points are high and similar (0.94-0.98) in both the non-acute and acute setting. Of note, the positive predictive values are lower in both the non-acute setting and in the acute setting, 0.44–0.57 and 0.66–0.67, respectively (47,49-54). Therefore, the recommendation for the usage of NPs is for ruling out HF and not for establishing HF as a diagnosis. This is supported by the fact that there are numerous cardiovascular as well as non-cardiovascular sources of elevated NPs that weaken their diagnostic usage in HF. The most important factors that impede on the utility of NPs usage as

an inclusion diagnostic test are atrial fibrillation (AF), renal failure and age (48). We find obesity on the other side of the spectrum where NP levels may be disproportionally low (55).

Identifying an abnormal electrocardiogram (ECG) will increase the likelihood of a correct diagnosis of HF, although it has a low specificity (56-59). An ECG can provide information about etiology (i.e., myocardial infarction) and provide indications for therapy (i.e. anticoagulation for AF). A completely normal ECG is an unlikely finding in patients suffering from HF (sensitivity 89%) (60). The routinely use of ECG is therefore recommended for the ruling out of HF (46). To establish the diagnosis and determining the appropriate treatment, the most useful modality is echocardiography. It provides an immediate information on chamber volumes, wall thickness, ventricular systolic and diastolic function, valve function as well as pulmonary hypertension. The details given by careful clinical assessment and the above tests would enable most patients to have an initial working diagnosis and treatment plan (46).

1.7 Treatment

The focus of HF treatment is aimed at improving the quality of life for the patient. An important aspect in this treatment is inhibiting cardiac remodeling by decreasing the workload of the heart. There are many drugs used for HF and among these, we find: Diuretics, ACE inhibitors, ARBs (angiotensin receptor blockers), B-blockers, MR antagonists (mineralocorticoid receptor antagonists), ARNI (angiotensin receptor-neprilysin inhibitor), Ivabradine, Digoxin and H-ISDN (hydralazine-isosorbide dinitrate).

The interventions include CRT (cardiac resynchronization therapy), LVAD (left ventricular assisting device), ICD (implantable cardioverter defibrillator) and heart transplantation. Diuretics are initially employed, as to relive signs and symptoms of congestion and in hope of reaching euvolemia. Thiazide and loop diuretics are the drug of choice as they have been shown to reduce the progression of the disease, decrease the risk of death as well as improve the exercise capacity (71,72). Another advantage is that since congestion in acute decompensated patients with HF show renal function deterioration, a fast intervention with diuretics has been found to be very useful in managing of acute decompensations in patients with HF. It effectively helps to get rid of excess fluids, edema and improve the prognosis as the degree of congestion and renal function are two significant factors of great prognostic value (73).

As mentioned above, one of the physiological adaptations is the activation of the RAAS

system. This system maintained the MAP at acceptable physiological levels but puts the cardiovascular system in a vicious circle regarding patients with HF. This system is blocked with ACE inhibitors and ARBs. These two have shown in studies that they reduce the cardiovascular mortality and morbidity (74,75). Although their concomitant use is not recommended due to hyperkalemia and hypotension, some studies suggestive of them having an additive effect (76). B-blockers act on beta receptors of the heart resulting in a negative chronotropic and ionotropic effect. Studies have shown that they reduce the mortality and morbidity in HFrEF as indicated by the COPERNICUS trial and other studies as well (77-79). The recommendation for the usage of B-blocker is in stable euvolemic patients. This is since it has a negative ionotropic effect and therefore should be used for patients with acute heart decompensations. The consensus is that B-blockers decrease the quality of life of the patient in the beginning, but this soon resolves once therapy is initiated (80).

MR antagonist's mechanism of action (MOA) is though the blocking of aldosterone receptors in the kidney, this leads to an increased sodium excretion and decreased body fluid and lower blood pressure. These drugs decrease the mortality and hospitalizations. They are also recommended when ACE, ARBs, diuretics, and B-blockers fail to help manage the disease (82).

ARNI is a drug that has double actions, it is a angiotensin receptor blocker and a neprilysin inhibitor. By inhibiting the neprilysin enzyme more NPs can be produced. ARNI reduces the mortality and hospitalizations to a higher extent than ACE inhibitors in patients with NYHA II-IV with reduced ejection fraction (82).

The "funny channels" (I_f) are responsible for the current that triggers the spontaneous depolarization of the atrioventricular node cells. Ivabradine blocks these channels in the sinoatrial node. The inhibition of this current results in a negative chronotropic effect, that will increase the time in which the ventricle is in diastole, effectively allowing more time for the blood to flow inside the coronary arteries and in that way decreasing the hearts oxygen demand. Ivabradine is most used in HFrEF with resting heart rate (HR) of $\geq$75 bpm after B-blocker optimization (83). Prognostic improvements have been shown with ivabradine (84). Digoxin is an inhibitor of the Na/K+ exchanger of the heart which leads to an accumulation of the intracellular calcium in the cardiomyocytes resulting in increased contractility. The drug has been shown to decrease hospitalizations but not mortality and it is a last line therapy (85).

H-ISDN is a combination of hydralazine and isosorbide dinitrate. Hydralazine exerts its

effects by dilating the arteriolar bed thereby decreasing the afterload and Isosorbide dinitrate produces a dilation of the venous capacitance bed thus reducing the preload. This combination will decrease the oxygen requirements of the heart. H-ISND carry no benefits in terms of mortality or hospital readmissions and any possible benefits are seen at higher doses, doses that are commonly tolerated only by young patients (86).

The CRT is done by placing two or three pacemaker leads on the heart. The first is placed in the endocardium at the distal tip of the right ventricle, the second is placed in the coronary sinus as to pace the left ventricle and the third leads placement varies among patients but may go on the right atrial appendage to pace the right atrium. The CRT is associated with lower mortality rates, cardiac readmissions and an all-cause readmission. This is used if the combination of diuretics, ACE inhibitors and MR antagonist fail a CRT is recommended if the patient is in sinus rhythm with a QRS duration of $\geq$ 130ms (87). A study compared optimal medical therapy alone or optimal medical therapy combined with CRT or CRT-D (CRT with a cardioverted defibrillator) and showed that the implantation of a cardioverter defibrillator reduced mortality and cardiovascular readmissions although CRT-D shows a better survival advantage (88).

There are different ventricular assisting devices, and they are usually subdivided into LVAD (left ventricular assisting device), RVAD (right ventricular assisting device) and BIVAD (biventricular assisting device) which is a combination of RVAD and LVAD. The RVAD helps the right ventricle to pump blood into the pulmonary artery but is not commonly used and the LVAD help the left ventricle push blood into the aorta. The LVAD is most used in clinical practice. The LVAD is used in end-stage HF if all other options have failed. It is used as a bridging therapy (in the wait for a heart transplant) or a destination therapy. The reason it is sometimes used as a destination therapy, and used though out life, is that the patient is not eligible for a heart transplant. This can be due to irreversible pulmonary hypertension/elevated pulmonary vascular resistance, an active systemic infection, or an active malignancy (89).

Heart transplant is the treatments of choice for eligible patients with end-stage HF that remain symptomatic despite optimal medical therapy (90). The American College of Cardiology/American Heart Association (ACC/AHA) have postulated the following guidelines for heart transplantation (91):

- Refractory cardiogenic shock requiring intra-aortic balloon pump counter pulsation or left ventricular assist device.
- Cardiogenic shock requiring continuous intravenous inotropic therapy (i.e., dobutamine, milrinone, etc.).
- Peak VO_2 (VO_{2max}) less than 10 mL/kg per min.
- NYHA class of III or IV despite maximized medical and resynchronization therapy.
- Recurrent life-threatening left ventricular arrhythmias despite an implantable cardiac defibrillator, antiarrhythmic therapy, or catheter-based ablation.
- End-stage congenital HF with no evidence of pulmonary hypertension.
- Refractory angina without potential medical or surgical therapeutic options.

1.8 Mechanical ventilation in the CICU

Contemporary cardiac intensive care units (CICU's) provide care for an increasingly complex patient population, which is partly driven by increasing age and increasing population proportion with respiratory failure needing non-or invasive positive pressure ventilation (PPV). PPV play many times an important role in cardiogenic patients. Non-invasive PPV may improve survival and reduce the need for invasive PPV when appropriately applied. While invasive PPV can be lifesaving, the modality does carry risk of complications that can influence CICU mortality. This modality has both favorable and unfavorable interactions with LV and RV physiology. A good level of understanding of the underlying cardiac and pulmonary pathophysiology is required for the effective application of PPV as to be proficient with the appropriate selection, potential cardiopulmonary interactions, indications and complications of PPV; but also, to be able to tailor the specific ventilatory strategies to a patient underlying cardiovascular condition (92).

1.8.1 Basics of pulmonary mechanics

The cardiovascular and pulmonary systems have a close working relationship, meaning that change that happens in one system often affects the other (93,94). Intrapleural pressure ($P_{pleural}$) influences cardiovascular physiology and is determined by two opposing forces: the thoracic wall

with its tendency to spring outward and the alveolar units with their tendency to collapse. During spontaneous inspiration, contraction of the respiratory muscles will render $P_{pleural}$ more negative. $P_{pleural}$ becomes less negative during passive expiration that occurs through alveoli and chest wall recoil (92).

Two parameters of further importance are respiratory compliance and airway resistance. These two components play a role in spontaneous breathing and PPV. Total compliance includes lung parenchymal and chest wall compliance. Chest wall compliance is under the influence of extrapulmonary factors, such as obesity, rib/thoracic cage deformity and intraabdominal pressure, as well as medication (e.g., Fentanyl-induced chest wall rigidity (95). Plateau pressure (P_{plat})is relevant in patients undergoing PPV, it refers to the alveolar pressure (P_{alv}) at end-inspiration and is the maximal P_{alv} during the respiratory cycle. In ventilated patients the P_{plat} is measured during and end- inspiratory pause when there is zero flow, this value can be used to estimate total lung compliance by the equation: volume / [P_{plat} - positive end-expiratory pressure]. The airway resistance is related to the diameter of the airways and is explained by Ohm's law (resistance = ΔP/flow), an increased airway resistance will decrease dynamic lung compliance (92).

Four additional PPV parameters require definition. First is the positive end-expiratory pressure (PEEP) which is a pressure that is kept slightly above atmospheric pressure throughout the respiratory cycle. This helps to recruit more alveoli in every respiration and prevent them from collapsing at end-expiration. Second, mean airway pressure which is the arithmetic average pressure over the entire ventilatory cycle. Third, is the transpulmonary pressure which is the difference of P_{alv} and $P_{pleural}$ (P_{alv} - $P_{pleural}$). This pressure influences the hemodynamics of the LV and RV. Of note, PPV increases both these parameters and is therefore difficult to accurately estimate the transpulmonary pressure when a patient is being treated with PPV (92). For more advanced providers, an esophageal balloon can be used to estimate $P_{pleural}$ and calculate the transpulmonary pressure if so needed (96). Fourth, peak airway pressure is the pressure needed to overcome the airways resistance and generate the tidal volume (TV), so when TV and lung compliance are constant then peak airway pressure correlates with airway resistance. However, if the lung compliance is decreased the peak pressures will increase (92). See table 4 for key concepts regarding these parameters and their cardiopulmonary interactions.

Table 4. Basic pulmonary physiology and cardiopulmonary interactions (92).

$P_{pleural}$ Affects RV and LV Preload and Afterload
1. $P_{pleural}$ is determined by the balance of the tendency of alveolar units toward collapse (elastic recoil) versus of the thoracic wall to spring outwards and action of respiratory muscles
2. Changes in $P_{pleural}$ generally influence RV *inflow* and LV *outflow*, while changes in transpulmonary pressure (P_{alv}-$P_{pleural}$) influence RV *outflow* and LV *inflow.*
3. Negative $P_{pleural}$ a) increases venous return and preload; b) decreases RV afterload; and c) increases LV afterload.
4. Positive pressure ventilation increases $P_{pleural}$ and a) decreases preload; b) increases RV afterload; and c) decreases LV afterload
5. Large shifts in $P_{pleural}$ (e.g., respiratory distress) can significantly increase LV afterload.
PEEP Affects RV and LV Hemodynamic
1. Total PEEP is the sum of extrinsic PEEP (generated by the ventilator) and intrinsic or auto-PEEP (due to incomplete exhalation).
2. Extrinsic PEEP is commonly used in the CICU for its beneficial effects on oxygenation, alveolar recruitment, airway patency, and preload.
3. PEEP: a) increases pulmonary vascular resistance; b) decreases RV and LV preload; c) decreases LV afterload; and d) reduces LV compliance through interventricular dependence.
4. The effect of PEEP on cardiac output varies with preload dependence and LV contractility and compliance.

Airway Pressure Influences Hemodynamic Via its Impact on Alveolar Pressure and Pleural Pressure

1. Airway pressure is determined by the flow, airway resistance, tidal volume, compliance of the chest wall and lung parenchyma, and the total end-expiratory pressure.
2. Positive pressure ventilation exerts its effects on cardiovascular hemodynamic principally through its impact on P_{alv} and $P_{pleural}$.
3. In poorly compliant lungs, changes in intrathoracic pressure will have more pronounced effects on hemodynamic.

Abbreviations: $P_{pleural}$ - intrapleural pressure, RV - right ventricle, LV - left ventricle, P_{alv} - alveolar pressure, PEEP - positive end-expiratory pressure, CICU - Contemporary cardiac intensive care unit

1.8.2 The application of positive pressure ventilation (PPV)

The role of the positive pressure ventilation (PPV) is to move air in and out of the lungs and effectively creating a pressure gradient between the ventilator and the patient. The total positive end-expiratory pressure ($PEEP_T$) is the sum of extrinsic PEEP ($PEEP_{ex}$), which is generated by the ventilator, and the intrinsic PEEP ($PEEP_{in}$). $PEEP_{ex}$ is commonly used in the CICU due to its linear relation between it and partial pressure of oxygen in the blood. It has therefore a beneficial effect on oxygenation, airway patency, preload, and alveolar recruitment (97,98). There are no established optimal PEEP values, but low values (5 cmH_2O) are commonly used in intubated patients to maintain airway patency and avoid atelectasis and higher levers of PEEP can be useful for conditions such as noncardiogenic pulmonary edema and HF (98,99). When considering of applying PPV in a cardiac patient the fundamental concepts the patient's airways should be considered. The underlying lung characteristics such as lung compliance and resistance determine the relationship between the set parameters of the PPV and resultant pressures, flows and volumes. The net effect of PEEP on CO is dependent on LV/RV function, as well as ventricular interdependence, preload, and afterload. In patients with RV failure an elevated PEEP (5-15 cmH_2O) may in fact decrease RV CO. while in patients with LV failure an elevated PEEP (10-15 cmH_2O) may in fact improve CO (100).

1.8.3 PPV and LV physiology

The cardiovascular hemodynamics are principally affected through P_{alv} and $P_{pleural}$ two of the parameters that PPV effect. Of note, the transpulmonary pressure also affects the LV and RV. In a broad sense, changes to the $P_{pleural}$ will affect the inflow to the RV and outflow to the LV, while the transpulmonary pressure will influence the inflow to the LV and outflow from the RV. It does so by affecting the pulmonary vasculature. So, a decrease $P_{pleural}$ will cause the LV systolic pressure to become lower relative the systemic circulation and therefore increase the afterload. While and increase in $P_{pleural}$ will initially cause in increase in aortic pressure, which will trigger the peripheral baroreceptors autoregulation and lower the systemic vascular resistance and LV afterload, improving CO (99,101). The effect of PPV and RV can be influencing the LV through ventricular interdependence. A pressure overload and a dilated RV can displace the interventricular septum toward the LV and reduce the LV preload and stroke volume. The net effect is change in CO (92,102,103).

1.8.4 PPV and RV physiology

During spontaneous breathing a negative $P_{pleural}$ contributes to the venous return, RV filling and preload, therefore PPV may have important effects on these parameters including myocardial perfusion (104). The pressure gradient between the venous circulation and RV is normally around 4 – 8 mmHg, so small changes to this value can have big effects on the venous return as well as the CO (104, 105). PEEP generates positive airway pressure (P_{aw}) that is transmitted to P_{alv} and $P_{pleural}$ generating a decrease in RV preload and increase in RV afterload. At appropriate PEEP levels the pressure may relive atelectasis, open alveoli, enhance lung volume, favorably tether blood vessels and decreasing pulmonary vascular resistance. All this will improve blood flow (106). If the PEEP levels are on the other hand to high, then the pressure will lead to an alveolar overdistension and compress the extra alveolar vessels. This leads to an increase in PVR and redirects the blood to poorly ventilated areas of the lunch increasing a V/Q mismatch resulting in hypoxia and hypercarbia (107).

The RV has a limited myocardial mass that is sensitive to pressure changes. It is more sensitive to changes in afterload than to changes in preload (101). PPV effects RV pressure, aortic pressure and $P_{pleural}$, myocardial perfusion is in turn dependent on an optimal interaction between

these parameters. IT is therefore of outmost importance to take the potential adverse effect into consideration when using different PEEP levels in patients with RV failure (101). See Figure 3 for the relationship between alveolar /volume/pressure and PVR effected by PEEP.

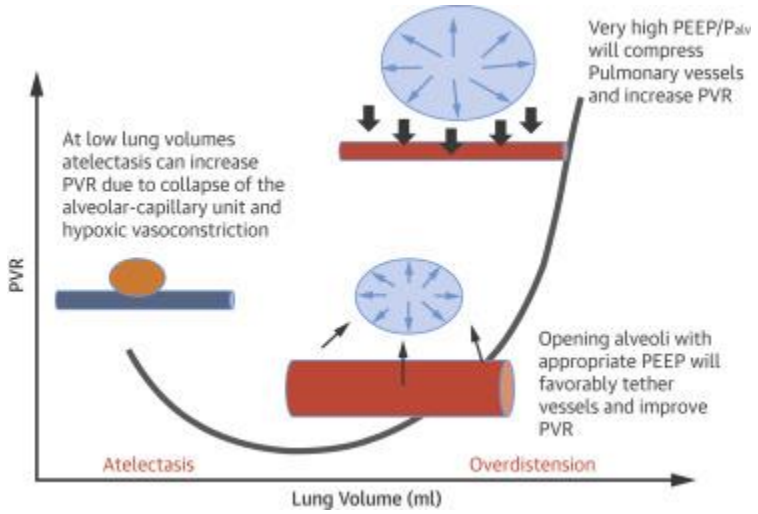


Figure 3. The relationship between alveolar /volume/pressure and pulmonary vascular pressure (109). PEEP = positive end-expiratory pressure, PVR = pulmonary vascular resistance, P_{alv} alveolar pressure

Taken from: Adapted from West JB, Luks AM. West's Respiratory Physiology: The Essentials. Philadelphia, PA: Wolters Kluwer Health Ed. 2015. p. 92.

2. OBJECTIVES

The aim of this study is to try to identify differences between the characteristics and biomarkers in patients with HF. Furthermore, additional aim is to explore if these differences could be used as an early indication as to whom an early application of ventilatory support would benefit the most.

Hypotheses of this study are:

- Most patients with HF that are put on mechanical ventilation have more comorbidities than the control group.
- Most patients with HF that are put on mechanical ventilation have higher laboratory values.
- Patients with HF that are put on mechanical ventilation have higher mortality than the control group.

3. MATERIALS AND METHODS

3.1 Study design

The study is a retrospective study. The patients were selected based on our inclusion/exclusion criteria for the year 2020 from the coronary care unit from hospitals in Križine and Firule in Split, Croatia.

3.2 Inclusion and exclusion criteria

Inclusion criteria for this study are patients that present to the hospital with a primary diagnosis of HF when admitted to the hospital.

Exclusion criteria for this study are patients that do not fulfill the criteria of having a primary diagnosis of HF when admitted to the hospital.

3.3 Data extraction

Discharge letters were extracted from the databases of Križine and Firule hospital in Split. A total of 96 discharge letters were obtained from Križine hospital and 26 discharge letters were obtained from Firule hospital, but 108 discharge letters were used in the study due to some patients being admitted more than once during the year and effectively qualifying into both the focus group and control group. These last-mentioned patients were for that matter excluded from the study. The data was extracted under the guidance and ethical approval warranted by Ethical Committee of University Hospital of Split, Class: 500-03/18/01/81, Number: 2181-147-01/06/M.S.-18-2, Split, 20th December 2018.

3.4 Data analysis

The raw data from said discharge letters were categorized specifying gender, age, biomarkers, comorbidities, ejection fraction, if they underwent ventilatory support, how long the patients were hospitalized, and endpoints defined as death or alive.

3.5 Statistical analysis

SPSS (Statistical Package for the Social Sciences) program was used for the analysis and management of the statistical analysis in this study. Numbers as well as percentages were used for the qualitative data description and chi-square tests were used for testing the differences in categorical variables in the focus group and control group. Continuous variables were analyzed using means and standard deviation presenting them using students t-test. Categorical variables were presented analyzing whole numbers and percentages presenting them using Chi-square test. The statistical significance breakpoint in this study is $P<0,05$.

4. RESULTS

4.1 Descriptive statistics and description of population used

The study included N =108 patients in total. The patients in this study were hospitalized during the year 2020 and were stratified based on age, sex, comorbidities and whether the patients required ventilatory support. Biochemical markers were analyzed and functional parameters, i.e., ejection fraction, were extracted from the discharge letters. These were analyzed for their significance in an early recognition for eventual ventilatory support. The mean age for the patients was 76 years ± 10 years with a span from 43 years to 95 years. The patients selected showed a gender distribution of 46 (43%) being women and 62 (57%) being men. The control group showed a slightly lower number of comorbidities compared to the focus group, which was three and four, respectively. The control group consisted of 76 (70%) patients, while the focus group that received ventilatory support consisted of 32 (30%) patients. The endpoints were defined as in-hospital deaths and reached a value of 27.8%.

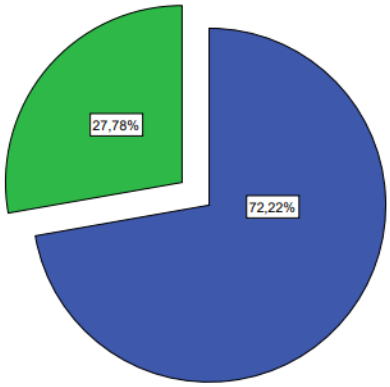


Figure 4. Endpoints represented by hospital deaths. Green color represents total patients that died in the hospital, around 27.8 %. Blue color represents patients that survived which was around 72.2%.

Table 5 embodies the descriptive statistics for the given parameters and biomarkers analyzed.

Table 5. Descriptive statistics for the biomarkers analyzed

Parameter	Study population (n= 108)	Mean ± SD
Age (years)	108	76.0 ± 10.1
Length of stay (days)	108	8.7 ± 6.9
Creatinine (micromoles/L)	101	139.1 ± 68.7
AST (IU/L)	95	94.7 ± 284.0
ALT (IU/L)	94	94.4 ± 365.3
CRP (mg/L)	91	38.9 ± 52.1
Sodium (mmol/L)	103	139.0 ± 4.8
Potassium (mmol/L)	103	4.2 ± 0.6
Chloride (mmol/L)	85	99.4 ± 5.5
hs-cTnT (pg/mL)	81	328.0 ± 836.9
NT-proBNP (pmol/L)	91	11540.6 ± 14403.5
LVEF (%)	70	40.7 ± 12.3
Number of comorbidities	108	3.6 ± 1.9

Data were presented as mean ± standard deviation. Abbreciations: AST – aspartate aminotransferase, ALT – alanine aminotransferase, CRP – c-reactive protein, hs-cTnT – high-sensitive cardiac troponin T, NT-proBNP – N-terminal pro hormone B-type natriuretic peptide, LVEF – left ventricle ejection fraction

4.2 Difference in parameters between those without mechanical ventilation vs. those that underwent mechanical ventilation with respect to continuous variables

The difference in parameters posed for the control group in comparison to the focus group are depicted below in table 6. The table also reproduces the statistical significance for each of the parameters analyzed with respect to continuous variables. The variables age, length of stay in the hospital, Creatinine (micromoles/L), AST (IU/L) ALT (IU/L), CRP (mg/L), Sodium (mmol/L),

Chloride (mmol/L), hs-cTnT (pg/mL), NT-proBNP (pmol/L) and number of comorbidities all showed to be statistically significant between the control group and the group that got mechanical ventilation ($p<0.05$). The two variable that did not show any statistically significant values were Potassium (mmol/L) and LVEF (%). Potassium showed a mean value of 4,2 mmol/L in the control group while the focus group had a mean value of 4.4 mmol/L. This gave us a p-value of 0.198 and was therefore not statistically significant. The mean LVEF was 41.3 % in the control group and 38.9 % in the focus group, which gave us as p-value of 0.510 and was therefore statistically insignificant.

Table 6. The difference in parameters posed for the control group that did not receive ventilatory support in comparison to the focus group that received ventilatory support.

Parameter	**Mechanical ventilation group (n=32)**	**Control group (n=76)**	**P-value***
Age (years)	73.0 ± 10.8	77.3 ± 9.5	*0.042*
Length of stay (days)	11.0 ± 10.2	7.8 ± 4.6	*0.023*
Creatinine (micromoles/L)	164.0 ± 65.9	127.5 ± 67.4	*0.012*
AST (IU/L).	232.9 ± 481.5	30.9 ± 18.1	*0.001*
ALT (IU/L)	25.7 ± 630.6	32.8 ± 43.7	*0.016*
CRP (mg/L	58.4 ± 64.9	29.7 ± 42.4	*0.014*
Sodium (mmol/L)	140.9 ± 5.2	138.2 ± 4.4	*0.010*
Potassium (mmol/L	4.3 ± .8	4.2 ± .5	*0.198*
Chloride (mmol/L	101.5 ± 6.2	98.5 ± 5.0	*0.026*
hs-cTnT (pg/mL)	770.5 ± 1306.1	94.2 ± 174.8	*<0.001*
NT-proBNP (pmol/L)	16521.4 ± 21840.8	9327.0 ± 8788.5	*0.027*
LVEF (%)	38.9 ± 13.4	41.2 ± 12,0	*0.510*
Number of comorbidities	4.2 ± 2.4	3.3 ± 1.6	*0.037*

*Student's t-test. Data were presented as mean ± standard deviation. Abbreviations: AST - aspartate aminotransferase, ALT – alanine aminotransferase, CRP – c-reactive protein, hs-cTnT –

high-sensitive cardiac troponin T, NT-proBNP – N-terminal pro hormone B-type natriuretic peptide, LVEF – left ventricle ejection fraction.

4.3 Difference in parameters between those without mechanical ventilation vs. those that underwent mechanical ventilation with respect to categorical variables

The difference in parameters between those without mechanical ventilation vs. those that underwent mechanical ventilation with respect to categorical variables are stated in table 7. The parameters: Male sex, in-hospital deaths and previous myocardial infarction showed to be statistically significant and overrepresented in the group that received mechanical ventilation. The parameter: atrial fibrillation also showed to be statistically significant but overrepresented in the control group. The parameters: diabetes mellitus, arterial hypertension, COPD, ischemic cardiomyopathy pulmonary hypertension all showed not to be statistically significant.

Table 7. Comparison of categorical data between mechanical ventilation group and control group.

Parameter	Mechanical ventilation group (n=32)	Control group (n=76)	P-value*
Male sex	24 (75%)	38 (50%)	*0.016*
In-hospital death	21 (65.6%)	9 (11.8%)	*<0.001*
Atrial fibrillation	4 (12.5%)	43 (56.6%)	*<0.001*
Previous myocardial infarction	8 (25.0%)	4 (5.3%)	*0,003*
Diabetes mellitus	10 (31.3%)	24 (31.6%)	*0.973*
Arterial hypertension	9 (28.1%)	35 (46.1%)	*0.083*
COPD	3 (9.4%)	7 (9.2%)	*0.979*
Ischemic cardiomyopathy	4 (12.5%)	7 (9.2%)	*0.606*
Pulmonary hypertension	5 (15.6%)	8 (10.5%)	*0.457*

*Pearson Chi-Square test. Data were presented as n (%). Abbreviations: COPD – chronic obstructive pulmonary disease. Significant p-value in this study is <0,005.

5. DISCUSSION

Many differences were identified and most of them where statistically significant between the control group and the focus group, except for potassium and LVEF. The fact that almost all of them showed to be statistically significant between the groups, points to the reality that the characteristics and biomarkers used in this study could not be used for an early prediction for an eventual ventilatory support, either as standalone or in combination with each other. This fact does not mean that they can be excluded in a further review of them or that we here are claiming that a more extensive study has not or is not being done, but it highlights the aspects of the study itself. This could in other words just be an indication that the study sample may have been too small.

Our hypothesis regarding the patients that received mechanical ventilation had more comorbidities could on the other hand be answered by the study. The control group showed a lower number of comorbidities in comparison to the focus group with the difference being three and four, respectively.

Our study could also show that the laboratory values were in fact higher in the focus group in comparison to the control group. This was true for all the biomarkers chosen except for potassium and LVEF, where the difference of being significant was not proven.

We also could answer our third hypothesis, showing that the focus group did in fact have a higher mortality rate in comparison with the control group when receiving mechanical ventilation. Where around 66% of patients died from the population included in the focus group, in comparison to 12% of patients died from the control group when receiving mechanical ventilatory support. This can be hypothesized being due to our two positively answered hypothesis, but not concluded here to be due to that fact. If the cause of them dying were to be due to them receiving mechanical ventilation was not studied here but is of interest for future studies. It is known that there are many challenges in weaning patients of mechanical ventilation which initially presents with severe heart failure. One study could for example not show predicting values of spontaneous breathing trials (SBT) using NT-proBNP and echocardiographic indices before SBT in the hopes of predicting SBT outcomes (110). So further studies in this area are needed.

The study was conducted during a peculiar year that was characterized by a global pandemic. The regulations that came from that global pandemic affected the hospitals admissions in different ways in a general manner and specific manners throughout the year

itself. This may have been a contributing fact to the total number of patients that fell into and were excluded by our inclusion and exclusion criteria. How it affected the study specifically will not be discussed as that is not the focus here and is more of a political discussion and beyond the scope of this study. The limitations of this study were its sample size. We believe that a bigger sample size would show a more defining indication as to what biomarker in isolation or in conjunction with other markers and/or characteristics would in an early stage indicate the necessity for mechanical ventilation. This is something we could not show with our study.

6. CONCLUSION

Based on the study results, we can conclude the following:

1. The study sample was too small to determine if the biomarkers and characteristics measured and seen in patients could be used for an early beneficial prediction of ventilatory support.
2. Patients with heart failure that end up needing ventilatory support tend to have more comorbidities and overall higher laboratory values than those seen in patients that do not end up needing ventilatory support.
3. Patients that show higher laboratory values and end up needing ventilatory support have a higher mortality rate than those patients that have lower laboratory values and end up needing ventilatory support.

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8. SUMMARY

Aim: The aim of this study was to try to identify differences between the characteristics and biomarkers in patients with HF. Furthermore, to explore if these differences could be used as an early indication as to whom an early application of ventilatory support would benefit the most.

Methods: We did a retrospective study analyzing characteristics and biomarkers in patients with a primary diagnosis of heart failure, that were admitted to the hospitals in Firule and Križine in Split, during the year of 2020. We scanned the hospitals registries for patients falling into our inclusion and exclusion criteria, subdividing them into categorical groups and further analyzing numerical values that were pertinent and of interest to our study. The categorical and numerical groups were statistically analyzed with the program SPSS.

Results: The mean age for the patients was 76 years (SD±10 years) with a span from 43 years to 95 years. The patients selected showed a gender distribution of 46 (43%) being women and 62 (57%) being men. The control group showed a slightly lower number of comorbidities compared to the focus group, which was three and four, respectively. The control group consisted of 76 (70%) patients, while the focus group that received ventilatory support consisted of 32 (30%) patients. The endpoints were defined as in-hospital deaths and reached a value of 27.8% in total, were the focus group showed higher mortality in comparison to the control group that did not receive ventilatory support, which was around 66% and 12% respectively. The variables age, length of stay in the hospital, creatinine (micromoles/L), AST (IU/L) ALT (IU/L), CRP (mg/L), sodium (mmol/L), chloride (mmol/L), hs-cTnT (pg/mL), NT-proBNP (pmol/L) and number of comorbidities all showed to be statistically significant between the control group and the group that got mechanical ventilatory support ($p<0.05$). The two variables that did not show any statistically significant values were potassium (mmol/L) and LVEF (%).

Conclusion: The study sample was too small to determine if the biomarkers and characteristics measured and seen in patients could be used for an early beneficial prediction of ventilatory support. As almost all the parameters analyzed, except for potassium and LVEF, showed to be significant between the focus group and the control group meant that not one nor more than one parameter could be used alone or in conjunction with each other for an early prediction as to whom a ventilatory support would benefit the most.

9. CROATIAN SUMMARY

Naslov: Obilježja i biomarkeri u bolesnika sa zatajivanjem srca kao pokazatelji potrebe za mehaničkom ventilacijom

Cilj: Cilj ove studije bio je pokušati otkriti moguće razlike kod bolesnika sa zatajivanjem srca obzirom na obilježja i biomarkere. Nadalje, istraživanje ovih razlika, moglo bi se koristiti kao rani indikator za procjenu potrebe kome će rana primjena mehaničke ventilacije donjeti najveću korist.

Metode: Izvršena je retrospektivna studija kako bi analizirali obilježja i biomarkere u bolesnika sa primarnom dijagnozom zatajivanja srca koji su zaprimljeni u KBC Split (lokalitet Firule i Križine) tijekom 2020. godine. Istraživani su podaci iz Registra pacijenata sa zatajivanjem srca kako bi analizirali pacijente prema zadatim uključnim i isključnim kriterijima, svrstavajući ih prema odabranim skupinama, te kako bi analizirali numeričke vrijednosti koji su važne i od interesa za našu studiju. Katagoričke i numeričke grupe analizirane su statistički prema programu SPSS.

Rezultati: Srednja dob bolesnika iznosila je 76 godina (SD±10 godina) sa rasponom od 43 do 95 godina. Odabrani pacijenti imali su sljedeću spolnu distribuciju: 46 (43%) su bile žene i 62 (57%) muškarci. Kontrolna skupina je imala malo niži broj komorbiditeta u usporedbi s ciljnom skupinom, što je iznosilo 3 i 4, usporedno. Kontrolna grupa se sastojala od 76 (70%) pacijenata, dok se ciljna grupa, koja je bila na mehaničkoj ventilaciji, sastojala od 32 (30%) pacijenta. Definirani ciljevi bili su bolnička smrtnost koja je iznosila ukupno 27,8%, dok je ciljna skupina pokazla veći mortalitet u usporedbi sa kontrolnom skupinom koja nije bila na mehaničkoj ventilaciji, što je iznosilo 66% i 12%. Varijable dob, dužina boravka u bolnici, kreatinin (mikromoli/ L), AST (IU/L) ALT (IU/L), CRP (mg/L), natrij (mmol/L), kloridi (mmol/L), hs-cTnT (pg/mL), NT-proBNP (pmol/L) i broj komorbiditeta, svi pokazuju statistički značajnu razliku između kontrolne skupine i grupe koja je bila na mehaničkoj ventilaciji ($p<0,05$). Dvije varijable koje nisu pokazale statističku signifikantnost bile su kalij (mmol/L) i LVEF (%).

Zaključak: Studijska grupa je bila premala kako bi se odredilo da li bi se mjereni biomarkeri i karakteristike naših pacijenata mogli upotrebljavati za rano-pravovremeno predviđanje potrebe za mehaničkom potporom.Gotovo svi analizirani parametri, osim kalija i LVEF, pokazali su značajne vrijednosti, ukoliko se usporedi promatrana skupina s mehaničkom ventilacijom i kontrolna, što govori u prilog tome da se ne samo jedan već više paramatra mogu koristiti, pojedinačno ili zajedno, za rano otkrivanje kome će mehanička potpora najviše pomoći.

10. CURRICULUM VITAE

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