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The Role of Suppression of Tumorigenicity-2 with Left Ventricular Global Strain and Aerobic Capacity in Systolic Heart Failure

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ABSTRACT

Systolic heart failure is a pathophysiological state in which, an abnormality of cardiac function is responsible for the inability of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues. It is a final condition from all heart diseases that is associated with high mortality and morbidity rates. This situation leads to the remodeling process resulting in reduced cardiac contractility as well as impaired aerobic capacity. The remodeling process is associated with an inflammatory process involving release of many inflammatory mediators as well as biomarkers. Numerous biomarkers that are released in this process can be used as a risk stratification and prognosis in patients with heart failure. One of these biomarkers is suppression of Tumorigenicity-2 (ST2). Cardiomyocytes subjected to mechanical stress express ST2 in vitro, whereas the circulating levels of soluble ST2 (sST2) are associated with left heart failure. The increased concentration of ST2 that involves Interleukin-33 (IL-33) depends on the biomechanical stress of cardiomyocytes (biomechanical strain). IL-33, as a ligand of ST2, is known to be involved in reducing tissue fibrosis and myocyte hypertrophy in mechanically strained hearts, which leads to left ventricular global strain. Thus, the present review aims to clarify the role of ST2 in systolic heart failure as a diagnostic, prognostic, and monitoring therapy.

1. Background

Systolic Heart Failure (HF) is a pathophysiological condition where abnormalities of the cardiac pump function to meet the needs of tissue metabolism (1). This situation is a late manifestation of all heart diseases with high mortality and morbidity rates amounted to 17% for hospitalized patients and 7% for outpatients within one year (2). The number of such patients increases with age; approximately 20 patients per 1,000 population aged 65 - 69 years, which increased to more than 80 patients in populations over 85 years of age (3, 4). In Indonesia, based on Riskesdas 2013 data, the highest prevalence of heart disease diagnosed at 65 - 74 years of age was 0.5%, which increased to 1.1% at ages ≥ 75 years (5).

Early diagnosis is necessary to reduce mortality and morbidity in patients with HF. Biomarkers play a key role in the risk classification and early diagnosis of patients with HF (6). Numerous studies have demonstrated that new biomarkers, such as Suppression of Tumorigenicity 2 (ST2), galectin-3, and copeptin, can be used for risk stratification in patients with HF (6). However, ST2 seems more applicable in predicting the progression of HF since this biomarker illustrates fibrosis caused by the remodeling process and can predict the incidence of HF, re-hospitalization, death, and cardiovascular adverse events (6). Monitoring ST2 levels can also facilitate assessing patients' treatment response and dynamically illustrate the clinical status of patients' progress (7).

The remodeling process of HF can lead to a decrease in cardiac muscle contraction. A simple standardized investigation performed in this contractile evaluation is echocardiography by using the Left Ventricular (LV) systolic function assessment parameters, such as Ejection Fraction (EF) and ventricular strain. Although decreased contractile function is the predominant cause of reduced Left Ventricular Ejection Fraction (LVEF), it is not necessary to assess contractile capacity for diagnosis of systolic HF. Furthermore, in experimental post-infarction

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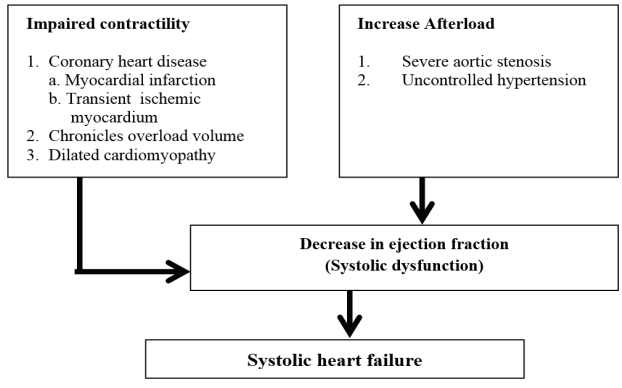
systolic HF with remodeling, myocyte contractile function may remain normal even when LVEF is reduced. Thus, assessment of LV strain gives more accurate results than EF since it can assess the overall strain on each segment of the left ventricle (8, 9).

The final condition of HF is a reduction in cardiac output, resulting in a decrease in aerobic capacity. One of modalities to evaluate the aerobic capacity is a six-Minute Walk Test (6MWT). This modality is an easy-to-do and straightforward method, which is able to assess therapeutic response and specific measurement and to determine what types of activities are capable of predicting morbidity and mortality in patients with HF (10).

Figure 1. The Conditions Causing Systolic HF.



Systolic HF is a condition caused by progression of impaired contractility and increased afterload, resulting in systolic dysfunction [1].

2. 2. Systolic Heart Failure

2.1. Definition

Systolic HF is a pathophysiological condition in which, abnormalities of the cardiac pump function to meet the needs of tissue metabolism (1). According to the American Heart Association (AHA), HF is defined as a complex clinical syndrome due to structural or functional heart abnormalities, which is related to the impairment of ventricles in blood pumping and filling (Table 1) (11).

According to the European Society of Cardiology (ESC), HF is a clinical syndrome characterized by a typical complaint, such as shortness of breath, edema of the legs, and fatigue. In addition, it may be accompanied by clinical signs, including increased jugular venous pressure, rhonchi, and peripheral edema, resulting from structural and cardiac abnormalities that lead to a decrease in cardiac output or an increase in intracardiac pressure at rest or overburden (Table 2) (12).

2.2 Etiology and Pathophysiology

The causes of systolic HF can be divided into (1) impaired ventricular contractility and (2) increase of afterload (Figure 1) (1). Coronary heart disease is responsible for about two-thirds of cases with systolic HF, hypertension, and diabetes mellitus. Other causes include viral infections, alcohol, chemotherapy, and idiopathic cardiomyopathy (13).

A decrease in cardiac output activates the sympathetic nervous system and reduces the parasympathetic nervous system. The sympathetic nerve activation leads to an increase in norepinephrine circulating levels, which is associated with poor prognosis. In this way, the β1 adrenergic receptor will be activated, thus increasing the heart rate and myocardium contractility (13). The α1 adrenergic receptor is also activated, enhancing the inotropic effect and vasoconstriction in the peripheral arteries. This results in an increase in afterload and cardiac oxygen demand, which may trigger an ischemic condition (13-15). The heart failure condition also triggers the release of renin as a result of renal hypoperfusion (14). Activation of the Renin-Angiotensin-Aldosterone (RAAS) system leads to production of angiotensin II, which binds to type 1 (AT1) and type 2 receptors (AT2). Both of these receptor subtypes are present in the myocardium with a more significant distribution of AT2 than AT1. AT1 results in vasoconstriction, cell growth, aldosterone secretion, and catecholamine release. On the other hand, AT2 triggers vasodilatation, cell growth inhibition, natriuretic, and bradykinin release. In HF condition, AT1 receptors are reduced in the myocardium, which leads to changes in the ratio of these two receptors (13-15).

Various inflammatory mediator cytokines, such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin 1 (IL-

Table 1. The Heart Failure Classification Based on Ejection Fraction according to the American College of Cardiology Foundation (ACCF) / AHA

Classification	EF	Description
I. Heart failure with decreased ejection fraction (HF*r*EF)	≤ 40	Systolic heart failure
II. Heart failure with normal ejection fraction (HFpEF)	≥ 50	Diastolic heart failure
a. Borderline	41 - 49	Intermediate or borderline group. The characteristics, therapy, and outcomes are similar to those of the normal ejection fraction group.
b. Improved	> 40	Previously classified in HfrEF, but improved.

Abbreviations: HFrEF, heart failure with reduced EF; HFpEF, heart failure with preserved EF

Table 2. The Heart Failure Classification Based on Ejection Fraction

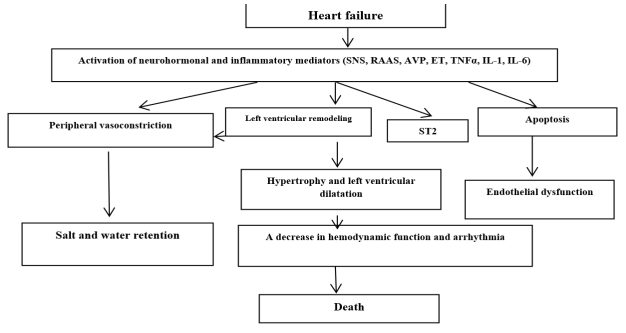
Criteria	HFrEF	HFmrEF	HFpEF
1	Symptoms ± signs	Symptoms ± signs	Symptoms ± signs
2	LVEF < 40%	LVEF 40 - 49%	LVEF ≥ 50%
3		Increased levels of *natriuretic peptides* Minimal accompanied by one of the following criteria: Structural heart disease (LVH and/or LAE) Diastolic dysfunction	Increased levels of *natriuretic peptides* Minimal accompanied by one of the following criteria: Structural heart disease (LVH and/or LAE) Diastolic dysfunction

Abbreviations: HFrEF, heart failure with reduced EF; HFmrEF, heart failure with mid range EF; HFpEF, heart failure with preserved EF

1), and Interleukin 6 (IL-6), may play an important role in aggravating HF progression. Several studies have reported that increased TNF-α and TNF-α receptors in patients with HF was associated with a poorer prognosis (15).

Remodeling stimuli, such as elevated LV wall stress, neurohormonal activation, cytokines, and oxidative stress, result in hypertrophy of the myocyte cyst, changes in interstitial matrix, and cell death. This process will eventually lead to changes in the structure and function of the left ventricle as well as myocyte damage due to either necrosis or apoptosis. As a result, it causes a decrease in cardiac muscle contractility, EF, number of contracted myocardial fibers, stroke volume, and LV dilatation (Figure 2) (16).

Figure 2. The Effects of Neurohormonal and Inflammatory Mediators on HF.



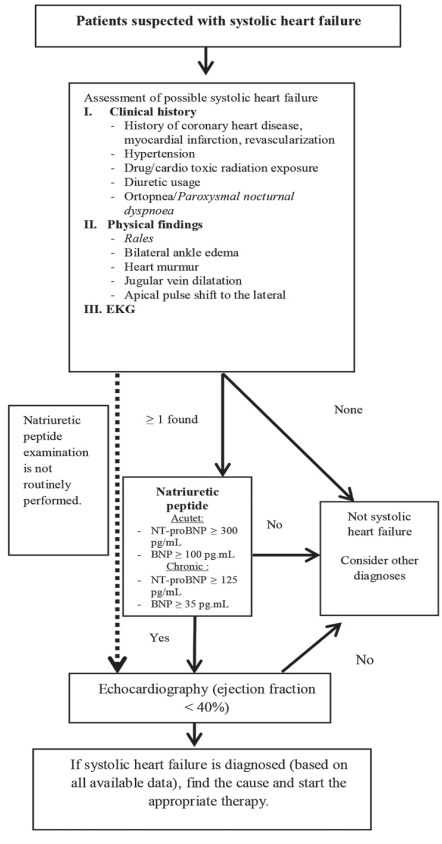
Neurohormonal and inflammatory mediators activation caused by HF play a role in triggering peripheral vasoconstriction, LV remodeling, ST2 release, and apoptosis, eventually resulting in death (6, 16).

2.3. Diagnosis of Systolic Heart Failure

HF is a clinical diagnosis. In clinical practice, however, Framingham or Boston criteria can be applied although the signs and symptoms are remarkably similar in both systolic and diastolic HF. Accordingly, the diagnosis of systolic HF is based on anamnesis, physical, and supporting examination (12). Shortness of breath is the principal symptom, which is not only associated with the increased cardiac filling pressures, but also illustrates the cardiac output limitation. Other symptoms that can be found include coughs at night, excessive satiety, swelling of particular organs (extremities or scrotum), and abdominal pain in upper right quadrant due to liver congestion. Other related symptoms, such as tachycardia, increased jugular venous pressure, loss of breath sound, Ronchi and/or wheezing, S3 gallop, ascites, and leg edema, might be found, as well (12, 17).

Beside clinical findings, numerous criteria have been proposed to distinguish between systolic and diastolic HF. For systolic HF, it is necessary to document that LVEF is less than usual. Although decreased contractile function is the predominant cause of reduced LVEF, it is not necessary to assess contractile capacity for diagnosis of systolic HF (12). Therefore, several supporting examinations, such as chest radiography, electrocardiogram, laboratory, imaging, and catheterization, need to be combined to provide the relevant information for diagnosis and treatment of patients with suspected HF. Such diagnosis is based on a combination of history, physical examination, and supporting examinations to identify or exclude HF definitely (Figure 3) (12).

Figure 3. Systolic HF Algorithm



The clinical history, physical findings, EKG, and other examinations have a pivotal role in assessment of systolic HF (12).

2.4. Heart Failure Biomarker

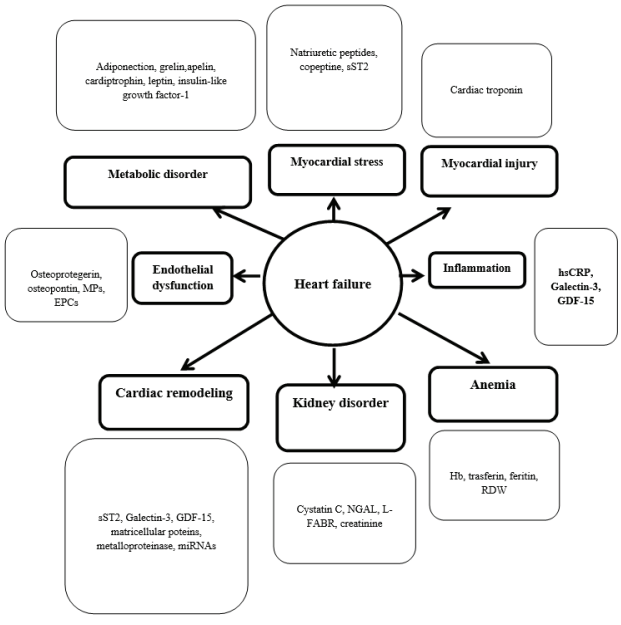
Heart failure biomarkers can be categorized empirically as neurohormonal mediators, markers of myocyte injury and remodeling, and indicators of systemic inflammation. Measurement of these biomarkers can help differentiate the condition of HF from other causes. At times the heart is stretched either by excessive pressure or volume, ischemia, inflammation, or infection, it will release some biomarkers as a compensatory mechanism. Updated clinical investigations have reported that Natriuretic Peptides (NPs), galectin-3, high-sensitivity troponin, and soluble ST2 protein were commonly used biomarkers, which remained a central part of the routine clinical practice to stratify patients at risk of HF development, first admission/readmission to the hospital, and cardiovascular death (18). Examination of these biomarkers may provide diagnostic, prognostic, and monitoring information on therapy in patients with HF (Figure 4) (18).

3. ST2 Biomarker

3.1. The Biological Nature of ST2

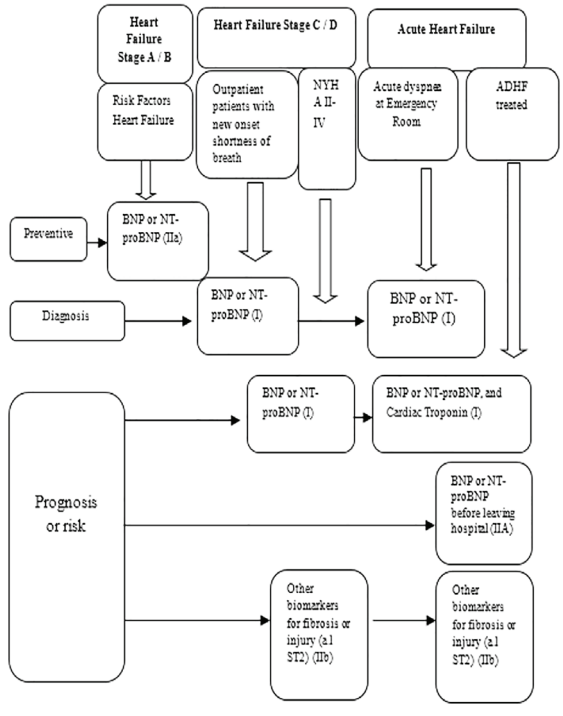
ST2 is a peptide of the Interleukin-1 (IL-1) receptor group secreted when cardiomyocytes and cardiac fibroblasts undergo mechanical strain. ST2L is a membrane-bound receptor and Interleukin-33 (IL-33) is the functional ligand

Figure 4. Biomarkers Release in HF.



HF induces the release of some biomarkers caused by metabolic disorder, myocardial stress, myocardial injury, endothelial dysfunction, inflammation, anemia, kidney disorder, and cardiac remodeling (18).

Figure 5. The Indication of Cardiac Biomarkers Usage.



The cardiac biomarkers usage depends onpatients' assessment regarding their physical findings and diagnoses (20).

for ST2L. There are three primary isoforms, namely transmembrane isoform (ST2L), secreted soluble (sST2), and variant forms of IL-1 expressed in the gastrointestinal tract (stomach, small intestine, and colon) (19). The ST2 biomarkers that trigger myocyte hypertrophy and cardiac fibrosis involve ST2L, sST2, and IL-33 ligand (19). IL-33 binds to ST2L to elicit downstream signaling pathway, leading to inflammatory gene transcription and ultimately to production of inflammatory cytokines/chemokines as well as induction of immune response (19). Thus, increased concentrations of sST2 in the circulation attenuate the systemic biological effects of IL-33. Blood concentrations of sST2 are significantly increased in inflammatory/infectious diseases, cancer, and cardiac disease, but not in chronic kidney disease (20). In patients with chronic HF, these biomarkers examinations have been considered for risk stratification (Figure 5) (20).

3.2. The Clinical Application of ST2 Measurement in Heart Failure

Dieplinger et al. reported that the reference range of ST2 was 4 - 31 ng/mL and 2 - 21 ng/mL in healthy Austrian males and females, respectively (21). A higher range of values was found in healthy American populations using the same analysis (8.6 - 49.3 ng/mL in males and 7.2 - 33.5 ng/mL in females). Indeed, the ST2 levels were not affected by age (22).

The role of ST2 as a supportive diagnostic biomarker in patients with heart disease has been widely reported. According to PRIDE study, the sST2 levels were higher in the acute HF group than in the healthy population (17). The sST2 levels were also obtained in the Acute Coronary Syndrome (ACS) population compared to the normal population (23). Measurement of sST2 in patients immediately after acute myocardial infarction can predict LV recovery time and act as an independent predictor of long-term mortality in patients with stable coronary heart disease (24, 25).

Increase of sST2 concentrations in chronic HF is closely related to severity, increased risk of death, transplantation, sudden death, and cardiovascular events such as re-hospitalization (26, 27). A study conducted by Ky et al. on patients with chronic stable HF revealed an increase in sST2 levels associated with an increased risk of death and transplantation approximately in 2.8 years (28). Major studies on sST2, including CORONA, HF-ACTION, and Val-HeFT, have also reported that increase in sST2 levels was associated with future cardiovascular events (7, 29, 30).

Therapeutic efficacy can be monitored by measuring sST2. The sST2 value changes during HF therapy can predict the incidence of mortality within 90 days (31). Bayes et al. measured both sST2 and NT-proBNP in patients with decompensated acute HF at baseline and after two weeks. The sST2 ratio was found to be associated with re-hospitalization, heart transplantation, and death within one year. A decrease in sST2 levels after 2 weeks was associated with improvement in clinical severity. Accordingly, patients without cardiovascular events had a significant reduction of sST2 from baseline within two weeks (32). The PROTECT study also assessed sST2 in patients with chronic stable HF. The results demonstrated that sST2 could provide prognostic information and predict cardiovascular events after three, six, and nine months (33).

Several studies have demonstrated a relationship between

pathophysiological mechanisms of cardiac remodeling and ST2/IL-33. A study conducted by Sanada et al. indicated the role of IL-33 and ST2 in cardiac remodeling among the rats exposed to excessive pressure (34). Miller et al. also reported a reduction in atherosclerotic plaque formation on aorta in the mice receiving a high-fat diet and IL-33 therapy. However, atherogenesis process was accelerated after ST2 administration (35). The cardioprotective effects of IL-33/ST2L on myocardial ischemia found in vitro suggested that IL-33 reduced the incidence of apoptosis in cardiac myocytes and its effect decreased by administering sST2. According to an in vivo study, rats' hearts showed a faster recovery with IL-33 administration after myocardial infarction, while ST2 slowed the treatment process down (36).

3.2. Cardiac Remodeling and the Role of ST2

Remodeling is an unexpected process, which is closely related to cardiac functional prognosis and worse clinical manifestations. This might be due to the loss of cardiomyocytes ability to contract in a typical cell that can be detected by a reduction of myocytes and myofilament alpha chain, change in cytoskeleton composition in cardiomyocytes, energy metabolism changes, and ß-adrenergic receptors desensitization (15).

There are two forms of pathological remodeling, namely eccentric and concentric. Eccentric remodeling refers to lengthening of myosin and sarcomere. This type is found in excessive volume load. On the other hand, concentric remodeling refers to lengthening of sarcomeres in parallel, increase in Cross-Sectional Area (CSA) of some myocytes, and thickening of the LV wall. This is found under excessive pressure load conditions (15). The remodeling process is associated with an inflammatory process involving many inflammatory mediators, including the IL-33/ST2 complex. Normally, IL-33 binds to ST2L to reduce fibrosis and myocardial hypertrophy through the NF-kB pathway. The complex activity of IL-33/ST2L involves co-receptor binding of IL-1 RAcP including toll interleukin receptor in the intracellular signaling pathway. The MyD88 adapter proteins are further involved and activation of NF-kB through IRA-1 and 4 as well as TRAF6 triggers the release of inflammatory mediators. In this context, sST2 acts as a decoy to prevent IL-33 from binding to ST2L, thus inhibiting its cardio-protective effects (Figure 6) (37).

3.3. Remodeling and Imaging Parameters

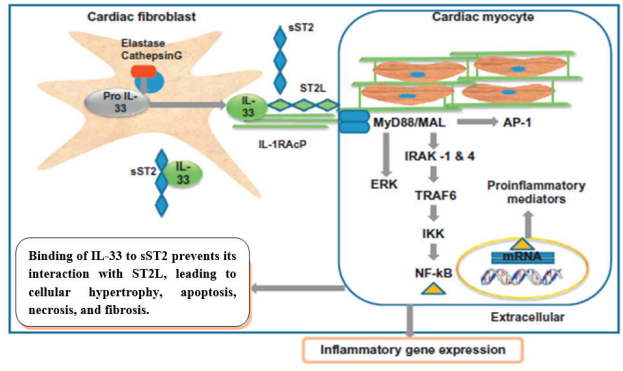
Cardiac remodeling might result in impaired LV systolic function. Cardiac remodeling can be assessed via echocardiography, radionuclide ventriculography, or Cardiac Magnetic Resonance (CMR) modalities. Echocardiography is the most commonly used modality. This examination can be performed in critically ill patients who have not received radiation exposure. The assessment parameters used in this context include EF, regional analysis of LV movement, and cardiac muscle contraction with speckle tracking (38).

4. Left Ventricular Global Strain and Aerobic Capacity

4.1. Speckle Tracking Echocardiography in Heart Failure

Echocardiography examination plays an important role in evaluation of LV function. However, this method is highly subjective due to dependence on the operator's skill and experience. Thus, we began to apply the speckle tracking method on echocardiography examination to analyze the image, quantitative measurements, and LV function (39). This technique assesses the myocardial motion based on cardiac-cycle contraction and describes strain and strain rate values multi-dimensionally so as to provide an overview of superiority of LV systolic function to EF (39).

Figure 6. The Relationship between ST2 and Cardiac Remodeling



The cellular hypertrophy, apoptosis, necrosis, and fibrosis due to the binding of IL-33 to sST2 would lead to cardiac remodeling process (37).

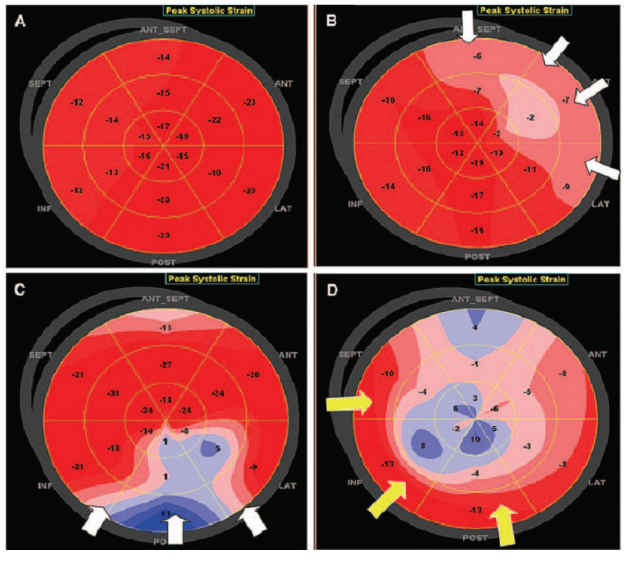
4.2. Left Ventricular Strain Rate and Strain

Strains are defined as long-term myocardial changes expressed in percentages, while strain rate refers to the speed of occurrence of long-term myocardial deformation. For clinical reasons, strain is preferred and oriented to LV coordinate system, which describes thickening and thinning longitudinally and circumferentially (39). A positive strain value indicates the myocardium thickening or lengthening, while the negative strain value describes the shortening or thinning of the myocardium. In this context, the most commonly used parameter is a longitudinal strain that can represent about 20% of the area of the left ventricle (39).

4.3. Clinical Applications of Left Ventricular Strain Imaging

Strains assessment is ideal for measuring regional myocardial function. In the longitudinal direction, the Global Longitudinal Strain (GLS) reflects the mean deformation value along the entire LV wall seen through a combination of three apical views of echocardiography. The study by Ying Chon Charoen et al. reported that the average values of GLS were -15 - 22%, with -19% being the mean measurement (39, 40). More positive GLS values indicate more severe myocardial contraction disorder and can predict the location of stenosis in coronary arteries (Figure 7) (41). GLS values also provide prognostic predictions of HF, coronary heart disease, heart valve abnormalities, and cardiomyopathy (42, 43). Stanton's study revealed that GLS was superior to LVEF and Wall Motion Score Index (WMSI) as a predictor of mortality in patients with coronary heart disease (44).

Figure 7. An Overview of Bull's Eyes LV Strain Analysis Calculation Program Using 2D Speckle Tracking Echocardiography Technique (41)



A: Normal strain; B: A patient with myocardial infarction (LAD occlusion) with decreased strains in the anterior and lateral regions; C: A patient with myocardial infarction (LCX occlusion) with reduced strains in the inferior and inferolateral regions; D: A patient with non-ischemic cardiomyopathy with reduced strains in almost the entire left ventricle.

4.3. Aerobic Capacity in Heart Failure

Physical activity level is positively related to aerobic capacity, which is the product of the capacity of the cardiorespiratory system to supply oxygen (i.e., cardiac output) and the capacity of the skeletal muscle to utilize oxygen (i.e., arterial-venous oxygen difference). Therefore, it is not surprising that sustained physical inactivity (deconditioning) as in heart disease induces a reduction in aerobic capacity (45-47).

Aerobic capacity is a measure of fitness and could be a predictor of mortality. Aerobic capacity is considered abnormal if the maximum aerobic capacity is less than 85% of the predicted age (48). Several studies have noticed that exercise training led to a significant increase in aerobic muscle capacities, with a dramatic increase in myofibril cross-sectional area, mitochondrial density, volume density of cytochrome c oxidase-positive mitochondria, and capillary density (49, 50). These modifications appeared even with low-intensity endurance exercise training (i.e., 40% of peak VO2) and allowed a significant improvement in both peak VO2 and ventilatory threshold (49, 50).

Decreased systolic function leads to a decrease in the quality of life of patients suffering from HF due to reduced exercise capacity. Several studies have found that GLS was superior to EF in assessing the functional capacity and prognosis of patients with HF. A study conducted by Rampengan et al. on patients suffering from HF indicated that the incidence rates of re-hospitalization and unstable angina pectoris were 71% and 21%, respectively. However, no significant correlations ($P > 0.05$) were observed between distance in the 6MWT and EF (51). In contrast, Hasselberg et al. reported that GLS was associated with maximum O2 consumption and decreased aerobic capacity in patients with systolic and diastolic HF (52). Similar results were also reported by Petersen et al., indicating a linear correlation between global and regional LV function and functional capacity in patients with and without preserved EF based on echocardiography speckle tracking (53).

Aerobic capacity assessment can be carried out by a cardiac test method facilitated with a treadmill or ergometer bike test. However, this assessment requires specialized facilities and equipment, which is quite expensive and often not available in all hospitals. Submaximal practice test with the 6MWT is another alternative that can be used for the initial assessment. This technique is easy to practice mainly in patients who are unable to do treadmill or ergometer bike, is not costly, can provide a picture of disease severity as well as prognosis, and can monitor the success of treatment (53). Several studies have assessed the prognostic function, mortality prediction, and re-hospitalization of the 6MWT in patients undergoing HF treatment. The Study Of Left Ventricular Dysfunction (SOLVD) by Bitner reported the mortality rate of approximately 10.23% at a distance less than 350 meters and 2.99% at a distance over 450 meters in the 6MWT (54). Moreover, Santos et al. showed that the 6MWT correlated with quality of life in patients with HF. Accordingly, quality of life decreased significantly based on the functional capacity and distance in the 6MWT (55).

5. Occlusion

Systolic HF is a major cardiovascular problem with high mortality and morbidity rates. The remodeling process in systolic HF leads to a decrease in EF and impaired myocardial contractility, resulting in decreased aerobic capacity. One of the remodeling biomarkers in this condition is ST2. ST2 examination can provide diagnostic information, prognosis, and therapy monitoring. Evaluation of systolic cardiac function with global LV strain measurement also provides an effective overview of LV contractility. Furthermore, the 6MWT may be used as a supporting examination to assess the exercise ability in patients with HF. All these modalities are expected to enhance life expectancy and quality of life in patients with HF.

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Authors' Contribution

Starry Homenta Rampengan developed the original idea, study concept and design, and the protocol, abstracted and analyzed the data, wrote the manuscript, and is the guarantor. Nancy Lampus contributed to development of the protocol, abstracted the data, and prepared the manuscript. Johan Gunadi analyzed and interpreted the data.

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References

1. Miranda D, Lewis G, Fifer M. Heart failure in Lilly L. *Pathophysiology of heart disease*. 6 ed. Philadelphia: Lippincott Williams & Wilkins; 2011. p. 220-48.
2. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, *et al*. EUREObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail*. 2013;**15**(7):808-17.
3. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, *et al*. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*. 2013;**127**(1):e6-e245.
4. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, *et al*. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004;**292**(3):344-50.
5. Ministry of Health, Republic of Indonesia. Report of national basic health research (Riskesdas 2013). Jakarta, Indonesia; 2013 [updated 2013; cited]; Available from: http://www.litbang.depkes.go.id/riskesnas.
6. Daniels LB, Bayes-Genis A. Using ST2 in cardiovascular patients: a review. *Future Cardiology*. 2014;**10**(4):525-39.
7. Felker GM, Fiuzat M, Thompson V, Shaw LK, Neely ML, Adams KF, *et al*. Soluble ST2 in ambulatory patients with heart failure: Association with functional capacity and long-term outcomes. *Circ Heart Fail*. 2013;**6**(6):1172-9.
8. D'Hooge J, Heimdal A, Jamal F, Kukulski T, Bijnens B, Rademakers F, *et al*. Regional strain and strain rate measurements by cardiac ultrasound: principles, implementation and limitations. *Eur J Echocardiogr*. 2000;**1**(3):154-70.
9. Geyer H, Caracciolo G, Abe H, Wilansky S, Carerj S, Gentile F, *et al*. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. *J Am Soc Echocardiogr*. 2010;**23**(4):351-69; quiz 453-5.
10. Berisha V, Bajraktari G, Dobra D, Haliti E, Bajrami R, Elezi S. Echocardiography and 6-minute walk test in left ventricular systolic dysfunction. *Arq Bras Cardiol*. 2009;**92**(2):121-34.
11. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, *et al*. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;**62**(16):e147-239.
12. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, *et al*. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;**37**(27):2129-200.
13. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, *et al*. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Heart Rhythm*. 2011;**8**(8):1308-39.
14. McMurray JJ. Clinical practice. Systolic heart failure. *N Engl J Med*. 2010;**362**(3):228-38.
15. Mann D, Zipes D, Libby P. Mann DL, Pathophysiology of heart failure in Bonow RO. In: Hasenfuss G, editor. *Braunwald's heart disease*. 10 ed. Philadelphia: Elseiver; 2015. p. 454-72.
16. Aronow WS. Epidemiology, pathophysiology, prognosis, and treatment of systolic and diastolic heart failure. *Cardiol Rev*. 2006;**14**(3):108-24.
17. Januzzi JL, Jr., Peacock WF, Maisel AS, Chae CU, Jesse RL, Baggish AL, *et al*. Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) study. *J Am Coll Cardiol*. 2007;**50**(7):607-13.
18. Berezin A. Utility of Biomarkers in Contemporary Management of Chronic Heart Failure. *Annals of Clinical and Laboratory Research, iMedPub Journals*. 2015;**3**(2):16-28.
19. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. *Nat Rev Drug Discov*. 2008;**7**(10):827-40.
20. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, *et al*. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;**136**(6):e137-e61.
21. Dieplinger B, Januzzi JL, Jr., Steinmair M, Gabriel C, Poelz W, Haltmayer M, *et al*. Analytical and clinical evaluation of a novel high-sensitivity assay for measurement of soluble ST2 in human plasma--the Presage ST2 assay. *Clin Chim Acta*. 2009;**409**(1-2):33-40.
22. Lu J, Snider JV, Grenache DG. Establishment of reference intervals for soluble ST2 from a United States population. *Clin Chim Acta*. 2010;**411**(21-22):1825-6.
23. Demyanets S, Speidl WS, Tentzeris I, Jarai R, Katsaros KM, Farhan S, *et al*. Soluble ST2 and interleukin-33 levels in coronary artery disease: relation to disease activity and adverse outcome. *PLoS One*. 2014;**9**(4):e95055.
24. Dieplinger B, Egger M, Haltmayer M, Kleber ME, Scharnagl H, Silbernagel G, *et al*. Increased soluble ST2 predicts long-term mortality in patients with stable coronary artery disease: results from the Ludwigshafen risk and cardiovascular health study. *Clin Chem*. 2014;**60**(3):530-40.
25. Weir RA, Miller AM, Murphy GE, Clements S, Steedman T, Connell JM, *et al*. Serum soluble ST2: a potential novel mediator in left ventricular and infarct remodeling after acute myocardial infarction. *J Am Coll Cardiol*. 2010;**55**(3):243-50.
26. Wojtczak-Soska K, Pietrucha T, Sakowicz A, Lelonek M. Soluble ST2 protein in chronic heart failure is independent of traditional factors. *Arch Med Sci*. 2013;**9**(1):21-6.
27. Wojtczak-Soska K, Sakowicz A, Pietrucha T, Lelonek M. Soluble ST2 protein in the short-term prognosis after hospitalisation in chronic systolic heart failure. *Kardiol Pol*. 2014;**72**(8):725-34.
28. Ky B, French B, McCloskey K, Rame JE, McIntosh E, Shahi P, *et al*. High-sensitivity ST2 for prediction of adverse outcomes in chronic heart failure. *Circ Heart Fail*. 2011;**4**(2):180-7.
29. Anand IS, Rector TS, Kuskowski M, Snider J, Cohn JN. Prognostic value of soluble ST2 in the Valsartan Heart Failure Trial. *Circ Heart Fail*. 2014;**7**(3):418-26.
30. Broch K, Ueland T, Nymo SH, Kjekshus J, Hulthe J, Muntendam P, *et al*. Soluble ST2 is associated with adverse outcome in patients with heart failure of ischaemic aetiology. *Eur J Heart Fail*. 2012;**14**(3):268-77.
31. Boisot S, Beede J, Isakson S, Chiu A, Clopton P, Januzzi J, *et al*. Serial sampling of ST2 predicts 90-day mortality following destabilized heart failure. *J Card Fail*. 2008;**14**(9):732-8.
32. Bayes-Genis A, Pascual-Figal D, Januzzi JL, Maisel A, Casas T, Valdes Chavarri M, *et al*. Soluble ST2 monitoring provides additional risk stratification for outpatients with decompensated heart failure. *Rev Esp Cardiol*. 2010;**63**(10):1171-8.
33. Gaggin HK, Szymonifka J, Bhardwaj A, Belcher A, De Berardinis B, Motiwala S, *et al*. Head-to-head comparison of serial soluble ST2, growth differentiation factor-15, and highly-sensitive troponin T measurements in patients with chronic heart failure. *JACC Heart Fail*. 2014;**2**(1):65-72.
34. Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie AN, Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. *The Journal of clinical investigation*. 2007;**117**(6):1538-49.
35. Miller AM, Xu D, Asquith DL, Denby L, Li Y, Sattar N, *et al*. IL-33 reduces the development of atherosclerosis. *J Exp Med*. 2008;**205**(2):339-46.
36. Seki K, Sanada S, Kudinova AY, Steinhauser ML, Handa V, Gannon J, *et al*. Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarction through ST2 signaling. *Circ Heart Fail*. 2009;**2**(6):684-91.
37. Lupu S, Agoston-Coldea L. Soluble ST2 in Ventricular Dysfunction. *Adv Clin Chem*. 2015;**69**:139-59.
38. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. *JACC Cardiovasc Imaging*. 2011;**4**(1):98-108.
39. Mirea O, Duchenne J, Voigt JU. Recent advances in echocardiography: strain and strain rate imaging. *F1000Res*. 2016;**5**.
40. Yingchoncharoen T, Agarwal S, Popovic ZB, Marwick TH.

Normal ranges of left ventricular strain: a meta-analysis. *J Am Soc Echocardiogr*. 2013;**26**(2):185-91.
41. Abraham TP, Dimaano VL, Liang HY. Role of tissue Doppler and strain echocardiography in current clinical practice. *Circulation*. 2007;**116**(22):2597-609.
42. Bertini M, Ng AC, Antoni ML, Nucifora G, Ewe SH, Auger D*, et al*. Global longitudinal strain predicts long-term survival in patients with chronic ischemic cardiomyopathy. *Circ Cardiovasc Imaging*. 2012;**5**(3):383-91.
43. Zhang KW, French B, May Khan A, Plappert T, Fang JC, Sweitzer NK*, et al*. Strain improves risk prediction beyond ejection fraction in chronic systolic heart failure. *J Am Heart Assoc*. 2014;**3**(1):e000550.
44. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. *Circ Cardiovasc Imaging*. 2009;**2**(5):356-64.
45. Marchionni N, Fattirolli F, Fumagalli S, Oldridge NB, Del Lungo F, Bonechi F*, et al*. Determinants of exercise tolerance after acute myocardial infarction in older persons. *Journal of the American Geriatrics Society*. 2000;**48**(2):146-53.
46. Raven PB, Welch-O'Connor RM, Shi X. Cardiovascular function following reduced aerobic activity. *Med Sci Sports Exerc*. 1998;**30**(7):1041-52.
47. American College of Sports Medicine. Lippincott Williams & Wilkins. Philadelphia: PA; 2000.
48. ATS Statement. *American Journal of Respiratory and Critical Care Medicine*. 2002;**166**(1):111-7.
49. Belardinelli R, Georgiou D, Scocco V, Barstow TJ, Purcaro A. Low intensity exercise training in patients with chronic heart failure. *J Am Coll Cardiol*. 1995;**26**(4):975-82.
50. Hambrecht R, Niebauer J, Fiehn E, Kalberer B, Offner B, Hauer K*, et al*. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *J Am Coll Cardiol*. 1995;**25**(6):1239-49.
51. Prasad A, Kumar S. Mortality due to rheumatic heart disease in developing world. *Journal of Clinical & Experimental Cardiology*. 2016;**07**(12).
52. Hasselberg NE, Haugaa KH, Sarvari SI, Gullestad L, Andreassen AK, Smiseth OA*, et al*. Left ventricular global longitudinal strain is associated with exercise capacity in failing hearts with preserved and reduced ejection fraction. *Eur Heart J Cardiovasc Imaging*. 2015;**16**(2):217-24.
53. Petersen JW, Nazir TF, Lee L, Garvan CS, Karimi A. Speckle tracking echocardiography-determined measures of global and regional left ventricular function correlate with functional capacity in patients with and without preserved ejection fraction. *Cardiovasc Ultrasound*. 2013;**11**:20.
54. Bittner V, Weiner DH, Yusuf S, Rogers WJ, McIntyre KM, Bangdiwala SI*, et al*. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. SOLVD Investigators. *JAMA*. 1993;**270**(14):1702-7.
55. Santos J, Brofman P. Six minute walk test and quality of life in heart failure a correlative study with a Brazilian sample. *Insuf Card*. 2008;**3**(2):72-5.