J MEDICINE 2020; 21: 127-131

# The Potential Role of Soluble Angiotensin Converting Enzyme 2 As A Left Ventricular Dysfunction Biomarker

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**Abstract:**

*Left ventricular (LV) dysfunction is a part of the common pathophysiologic mechanism for the development of heart failure (HF). LV dysfunction can be classified into left ventricular systolic dysfunction (LVSD) and left ventricular diastolic dysfunction (LVDD). Currently, B-type Natriuretic Peptide (BNP) and N-Terminal Pro-BNP (NT-proBNP) are the most common marker used to determine HF. Both of them are used as diagnostic and prognostic marker. Angiotensin Converting Enzyme 2 (ACE2) was found as an ACE homolog, located in the cell membrane of the heart. ACE2 has a cardioprotective role in turning AngII to Ang1-7. ACE2 can be cleaved by A Disintegrin and Metalloproteinase 17 (ADAM17)/TNF-$\alpha$ converting enzyme (TACE) so that it can be detected in the plasma as soluble ACE2. Soluble ACE2 possessed a potential role as LV dysfunction diagnostic or prognostic biomarker.*

***Keywords:*** *ACE2, biological marker, left ventricular dysfunction, prognostic, renin-angiotensin-aldosterone system*

***DOI:*** *https://doi.org/10.3329/jom.v22i2.56702*



***Received:*** *20 May, 2021;* ***Accepted:*** *20 June, 2021*

## Introduction

Left ventricular (LV) dysfunction is a process known in the development of heart failure (HF) before HF occurs.[1] HF itself, has been known to be the final phase of all cardiac diseases with high morbidity, mortality, and healthcare cost.[2] The incidence of HF was reported between 500,000-600,000 cases diagnosed each year in industrialized countries with annual prevalence-based costs ranged from $868 to $25,532. The prevalence of HF was reported to be as high as 5% with 17% 30 days mortality rate with average published cost of HF hospitalization $813.[3] A better patient outcome can be achieved when the progression of HF can be detected and treated as early as possible.[4]

Angiotensin Converting Enzyme 2 (ACE2) was first identified as a homologue of ACE in a research conducted by Crackower MA et al, that was published in 2002.[5] ACE2 can be cleaved into a soluble form, soluble ACE2 and can be detected in human plasma.[6] There have been research conducted to see the role of soluble ACE2 in the pathophysiologic development of HF and the outcomes were homogeneous. This article review aimed to review the possibility of soluble ACE2 becoming a diagnostic or prognostic marker of LV dysfunction.

## LV dysfunction

LV dysfunction is a part of the common pathophysiologic mechanism for the development of HF.[1,7] The development of HF begins with the presence of risk factors for LV dysfunction including hypertension, abdominal obesity, and diabetes.[8,9] These risk factors then progress into asymptomatic changes in heart

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structure and function which finally led to overt HF.[9] Left ventricular dysfunction may be classified into left ventricular systolic dysfunction (LVSD) and left ventricular diastolic dysfunction (LVDD).[7] LVSD is determined by the impairment of pump function and enlarged end diastolic chamber volume.[10] While LVDD is determined by LV relaxation impairment with or without reduced restoring forces and early diastolic suction, and the increment of LV chamber stiffness.[11] Both of them play significant role as a process that occurs just before HF.[1]

Diagnosing LV dysfunction requires history taking, physical examination, laboratory tests, biomarkers and imaging.[12] LV dysfunction can be divided into symptomatic and asymptomatic LV dysfunction. The symptomatic LV dysfunction symptoms and signs are similar both in systolic and diastolic LV dysfunction. Exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea, pulmonary rales, elevated jugular venous pressure and lower extremity edema; while the asymptomatic LV dysfunction has no symptoms.[12,13] Nowadays, echocardiography, a noninvasive assessment of ventricular function, is considered as the method of choice in assessing the left ventricular function and remains central to modern cardiology.[14,15] However, echocardiography is not suitable to be a cost-effective screening tool due to relatively high costs.[16]

**Soluble ACE2**

ACE2 is a zinc metalloproteinase and a homologue of ACE. The first 17 out of 18 exons of ACE2 gene is similar to ACE. ACE2 can be found in several organ systems including cardiovascular, kidneys, lungs, and brain. Specifically in the cardiovascular system, ACE2 is expressed in the coronary vascular endothelium, cardiomyocytes, and cardiac fibroblast.[17] In cellular level, ACE2 is anchored to the plasma membrane.[18] ACE2 role is related closely with RAAS, where it act as a novel endogenous inhibitor of the RAAS by counteracting the effects of Ang II that promotes hypertension, cardiac hypertrophy and adrenergic activity.[5,6] The counteract occurred by converting Ang II to Ang 1-7.[6]

ACE2 is cleaved into its soluble form (soluble ACE2) by two enzymes A Disintegrin and Metalloproteinase 10 (ADAM10) and A Disintegrin and Metalloproteinase 17 (ADAM17). ADAM10 cleaved ACE2 to soluble ACE2 in airway cell types, while ADAM17 cleaved ACE2 to soluble ACE2 in nonairway cell types.[19] ADAM17 or also known as TNF-á converting enzyme (TACE) is firstly known for its ability in shedding the formation of cytokines especially TNF-á but later on it is proven to have further role in cardiovascular system. Its activity is known to be affected by the Angiotensin II type 1 receptor (AT1R).[20] The illustration of ACE2 cleaving process can be seen in figure 1. The increase activity of ADAM17 resulted in elevated soluble ACE2 which represents the loss of protective effect from ACE2 in the heart.[21] Therefore, the low level of ACE2 and the high level soluble ACE2 represent an increasing activity of RAAS which is harmful to multiple organ systems including the cardiovascular system.

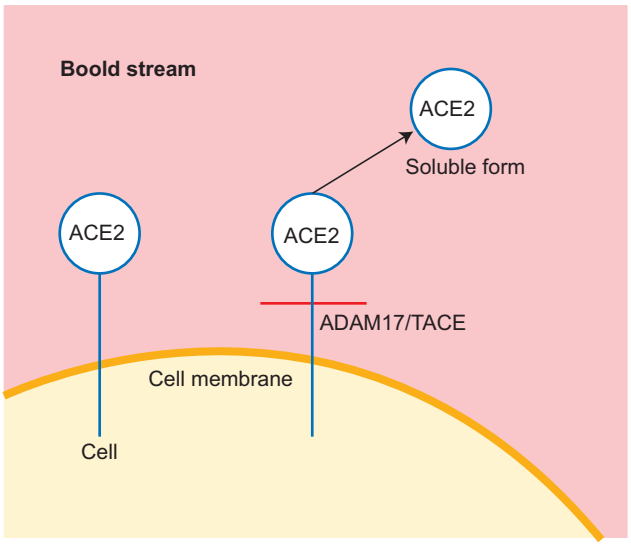


**Figure 1.** Illustration of ACE2 cleaving process by ADAM17/TACE

Different from ACE2, soluble ACE2 ability in converting Ang II into Ang 1-7 remain unclear but it was suggested by Xu J et al that most likely it is less effective compared to ACE2 because structural change or decrease in local metabolism.[20] Further research is needed in order to figure out the exact role of soluble ACE2. However, in several studies related to cardiovascular diseases, soluble ACE2 level have been known to increase, which suggest it may be the cause or effect of adaptive or maladaptive process.[18] The increasing level of soluble ACE2 in LV dysfunction possessed potential to become either diagnostic or prognostic biomarker.

**Soluble ACE2 measurement**

Plasma or serum is required in measuring the soluble ACE2. The protocol of measuring soluble ACE2 has been established and become standardized. The protocol name is ACE2 fluorescent enzymatic assay protocol which uses quenched fluorescent substrate. The substrate is widely available and produced by several companies. The details of the protocol can be seen in previous studies including

Epelman et al[6,22], Ortiz-Pérez et al[23], Úri K et al[24], and Shao Z et al[25].

**Soluble ACE2 as diagnostic marker of LV dysfunction**

The neurohormonal sub-study of Assessment of Doppler Echocardiography in Prognosis and Therapy (ADEPT) study found that increased soluble ACE2 activity has significant association with LV and RV systolic dysfunction, and LV dilatation. LV systolic dysfunction remained associated independently with soluble ACE2 activity after multivariate regression analysis with p=0.047. This study also found that there was no relationship between soluble ACE2 activity and systemic inflammation (represent by hsCRP or MPO levels).[6] The fact that soluble ACE2 activity is associated independently with LV systolic dysfunction and independent from systemic inflammation suggest a potential role as diagnostic marker for LV dysfunction. In the future, as a diagnostic marker, soluble ACE2 can be measured in patients with LV dysfunction risk factors (hypertension, high blood glucose and abdominal obesity). The early diagnosis of LV dysfunction represented by the high level of soluble ACE2 allow cardiologist to give a more aggressive treatment in preventing the development of heart failure.

**Soluble ACE2 as prognostic marker of LV dysfunction**

NYHA class, LV ejection fraction and B-type natriuretic peptide was correlated to soluble ACE2 activity. A compensatory mechanism to limit LV dysfunction was the reason behind the increment of soluble ACE2 activity.[23] The higher the soluble ACE2 activity correlated strongly with the worsening clinical conditions of patients (NYHA class) with severe HF before and after the pacemaker implantation. The soluble ACE2 activity was higher in HF patients than hypertensive patients, and the soluble ACE2 activity was higher in hypertensive patients than in healthy individuals, which may suggest soluble ACE2 activity can be a biomarker of cardiovascular disease or imminent HF.[24]

The ADEPT neurohormonal sub-study also found that after a mean follow-up time of 34±17 months, 23% patients experienced death or cardiac implantation, and 29% experienced the combined end-point of death, cardiac transplantation or HF hospitalization. Patients with increased soluble ACE2 and NT-proBNP levels had significantly worse clinical outcomes than those with low soluble ACE2 and NT-proBNP levels. In a comparison with a low likelihood of adverse events patients (NT-proBNP belom the median), those with increased soluble ACE2 activity (>28.3 ng/ml) had a significantly increased event rate ($p<0.05$).[6] In line with the finding, Úri K et al found that soluble ACE2 activity positively correlated to NT-proBNP levels in HF patients before and after cardiac resynchronization therapy (CRT), and there was no correlation between them in individuals with normal LV systolic function.[24] In accordance to the previous study, a study conducted by Epelman S et al also concluded that soluble ACE2 activity was correlated with a worsening LVEF and increasing BNP levels.[22] However, a further study conducted by Úri K et al found that NT-proBNP as a rather general biomarker for HF, while soluble ACE2 activity is selective biomarker for systolic dysfunction.[26] The summary of soluble ACE2 findings from previous studies that enhances its possibility to become LV dysfunction marker can be seen in figure 2.

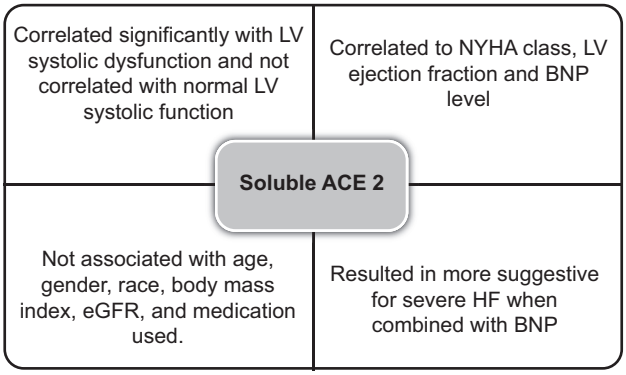


**Figure 2.** Soluble ACE2 findings from previous studies

**Current Biomarker**

B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) are two biomarkers that will be useful to support clinical decision making for ambulatory and hospitalized patients with dyspnea.[7] BNP can also be useful to predict LVSD and left ventricular remodeling after AMI, even though it cannot be considered as a replacement for echocardiography.[14] A study conducted by Bellagavi AC et al also support that levels of NT-proBNP had a good correlation with LVEF worsening in elderly patients. A total of 100 patients who presented to the ED with shortness of breath were evaluated with echocardiography and NT-proBNP levels. 58% patients with normal ejection fraction (EF) had a mean NT-proBNP level of 891.75 pg/ml (cut off <1000pg/ml), 3% with mild LV dysfunction with EF between 40-49% had a mean 1359 pg/ml, 17% with moderate LV dysfunction with EF 30-39% had mean of 2092.35 pg/ml and 19% with severe LV dysfunction with EF <30% had a mean 2763.95 pg/ml. Patients with LV dysfunction as a final diagnosis had significantly higher levels of NT-proBNP than those without LV dysfunction ($p<0.001$).[27]

A systematic review by Latour-Pérez J et al concluded BNP

levels are more useful in ruling out HF, while the capacity of identifying patients with ventricular systolic dysfunction is limited. The ability of BNP to differentiate patients with and without ventricular dysfunction is moderate, this may be caused by its physiopathology of natriuretic secretion, where high ventricular diastolic pressure and ventricular distention were associated with higher levels of BNP than in patients with asymptomatic compensated ventricular dysfunction.[28] The use of BNP or NT-proBNP has les utility in detecting left ventricular dysfunction. From the Framingham study that included 3177 asymptomatic participants, both BNP measurement and echocardiography were performed with the area under the curve (AUC) for the receiver-operating characteristic (ROC) for detection of left ventricular hypertrophy or LVSD was 0.75.[29]

BNP levels were different in acute and non-acute settings, the levels were higher in the first than the latter.[30] Higher levels of BNP was the strongest predictor of increased risk for death among patients without HF and the second strongest predictor, behind age, among patients with HF.[30] Several inflammatory and systemic disease such as sepsis, systemic lupus erythematous and cancer can affect natriuretic peptide value.[31–33]

**Future direction and limitations**

The increasing level of soluble ACE2 may represent the decreasing level of ACE2 (as a result of ACE2 shedding) which suggest the occurrence of LV dysfunction while also represent a worse outcome. Soluble ACE2 activity correlated with LV structural and functional parameter, while BNP level correlated with both LV and RV. The activity of soluble ACE2 was not associated with age, gender, race, body mass index (BMI), estimated glomerular filtration rate (eGFR) and medication use, but was positively correlated with plasma BNP levels.[25] Plasma ACE2 activity was as potent as BNP to predict cardiac death and heart transplantation.[34] Future studies are needed to determine the cut off point for soluble ACE2. In using soluble ACE2 as a biomarker, one should be cautious in interpreting the result of increasing level of soluble ACE2 because as mentioned previously, ACE2 is expressed in multiple organ systems so that change/disease in one of the organ systems may altered soluble ACE2 level.

**Conclusion**

Soluble ACE2 possessed a potential role as LV dysfunction diagnostic or prognostic biomarker. The role of soluble ACE2 in progression of HF from LV dysfunction risk factors is clear, the increasing level of soluble ACE2 in patients with LV dysfunction has been proven, the increasing level of soluble ACE2 is associated with poorer outcome, and no association found between soluble ACE2 level with age, gender, race, BMI, eGFR and medication use. However, further studies are needed to determine the cut-off points and one should be aware that beside LV dysfunction there are other conditions that can also affect soluble ACE2 level.

**Funding**

None related to this manuscript.

**Acknowledgement**

The authors thank all who supported this article review.

**Conflict of Interest**

The authors declare no conflict of interest.

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