The Molecular Mechanism and Drug Therapy of Heart Failure

Yifan Su

***Abstract*—Heart failure (HF) is a complex clinical syndrome that results from left ventricular myocardial dysfunction and contributes to dyspnea, fatigue and fluid retention. It's essential to characterize disease progression and symptoms to optimize therapy selection. Also, understanding the mechanisms of HF to guide therapy selection is of vital importance. This review focuses on the demonstrating mechanisms of HF and points out the possible pathways involved in the process. Drug therapies of HF with different effects on specific targets are analyzed. Finally, we conclude the features of the now going drugs and depict the future perspectives of drug therapy of HF, including potential new targets and new drug therapies.**

***Index Terms*—Heart failure (HF), excitation-contraction coupling (E-C coupling), drug therapy.**

I. Introduction

Heart failure (HF) is a complicated clinical syndrome. It is often characterized by serial symptoms such as dyspnea, fatigue and ankle swelling, which may be accompanied by elevated jugular venous pressure, cracked pulmonary and peripheral oedema.

Patients with HF are generally derived into two groups depended on the contractile function of the left ventricular myocardium. Patients with normal left ventricular ejection fraction (LVEF) (>50%) is heart failure with preserved ejection fraction (HFpEF),while LVEF less than 40% is heart failure with reduced ejection fraction (HFrEF). LVEF between 40-49% represents a 'gray area,' which is defined as heart failure with mid-range ejection fraction (HFmrEF). Different types of HFEF have different kind of diagnosis, in which HFpEF is more challenging than the HFrEF [1].

Patients who have HF for a long time are diagnosed to have 'chronic HF', in which symptoms remain unchanged for at least one month. If the symptoms deteriorate, it may be described as 'decompensated HF' [1].

The prevalence of HF in developed countries is approximately 1-2% of the adult population. With the rise of age, there are over 10% people with HF in people above 70 years old [2]. In addition, increasing rate of diabetes mellitus and hypertension leads to the higher prevalence of patients with HF.

The underlying mechanisms that lead to HF are usually myocardial abnormalities causing systolic or diastolic ventricular dysfunction. In addition, other abnormalities regard of valves, pericardium and endocardium may also contribute to the process. The molecular mechanisms now remain to be elusive, and the therapies of HF mainly consist of many ways which have different effects.

Manuscript received March 6, 2020; revised July 10, 2020.

Yifan Su is with the SUNY ESF, NY 13210 USA (e-mail: suyifan3@126.com).

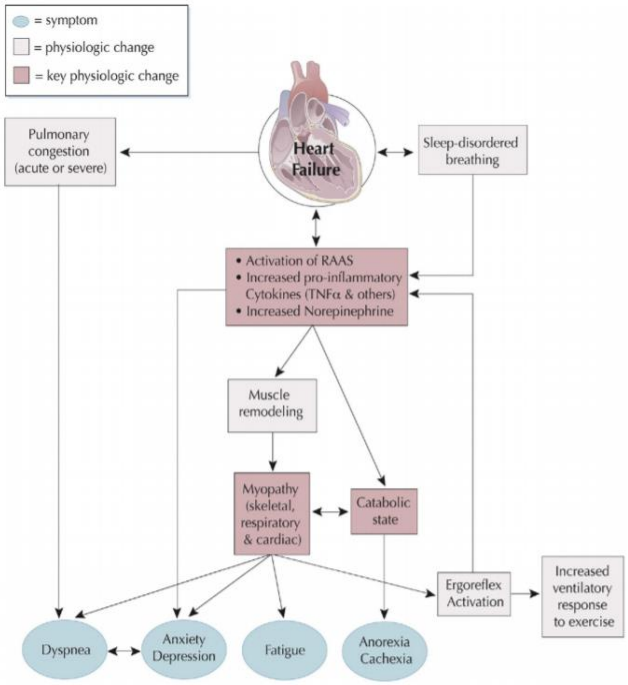

Fig. 1. Changes of recognition with the development of heart failure [1].

In this review we will therefore focus on the molecular mechanisms and the drug therapy of heart failure.

II. Myocardial Hypertrophy in HF

Myocardial hypertrophy is an important indicator during the process of heart failure, and it is also an essential factor for subsequent heart failure diseases [3]. With the pattern of pressure and volume overload, the heart adapts to increase its output to meet the demand of body.

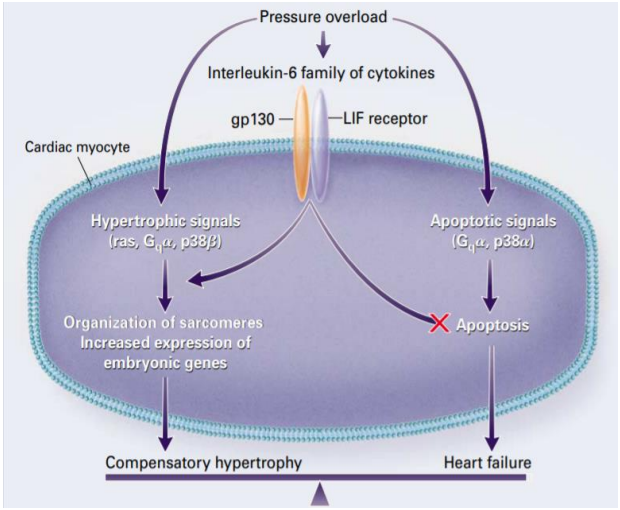

Fig. 2. Pathways during the myocardial hypertrophy as a result of biomechanical stress [3].

doi: 10.18178/ijesd.2020.11.9.1290

Myocardial hypertrophy is a complicated process in which genetic, physiologic and environmental factors are all involved [3]. Generally, hypertrophy is caused by biomechanical stress, including chronic hypertension, pressure overload and activates multiple parallel. At the cellular level, the biomechanical stress leads to overload of volume and pressure. During pressure overload, contractile-protein units will form in parallel and result in width increasing of cardiac myocytes and finally lead to hypertrophy [4].

In most cases of cardiac hypertrophy, the expression of embryonic genes plays a vital role in the process, embryonic genes including genes for natriuretic and fetal contractile proteins [4]. There are several important factors that affect the hypertrophic response, such as endothelin, insulin-like growth factor 1 and angiotensin 2. Some peptides are also implicated in hypertrophic response and react as factors mentioned above. For example, peptides stimulate G protein-coupled receptors such as endothelin-1 and angiotensin 2; interleukin-6-related cytokines and growth factors. Among these factors, the overexpression of a1b-adrenergic receptor will lead to ventricular hypertrophy, which shares common signaling pathways in cells with other hypertrophic growth factors, angiotensin II and endothelin-1 [4].

III. Excitation-Contraction Coupling

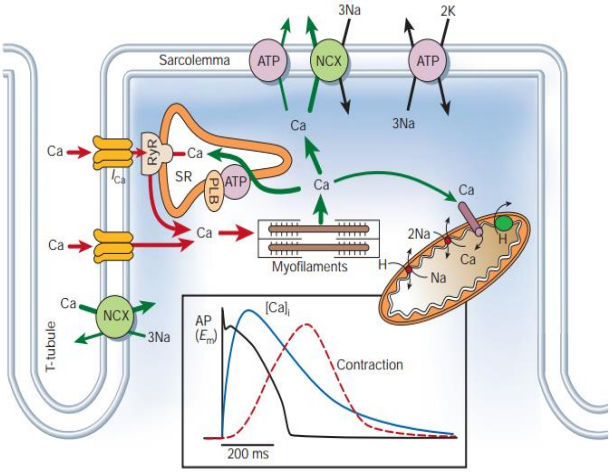

Fig. 3. The model of excitation-contraction coupling (E-C coupling) in heart [7].

Excitation-contraction coupling (E-C coupling) is the process related to electrical excitation of the myocyte and results in contraction of the heart, in which the concentration of calcium is an essential factor [5], [6].

When cardiac action potential exists, Ca^{2+} flows into the cell through depolarization-activated Ca^{2+} channels, the minor entry of Ca^{2+} then triggers much more Ca^{2+} release from sarcoplasmic reticulum (SR). As a result, the combination effect of influx and outflow of Ca^{2+} cause the rise of Ca^{2+} concentration in cytosol and the Ca^{2+} will bound to the myofilament protein troponin C, which will then lead to the cell contraction.

Then, the concentration of Ca^{2+} will decline and protein troponin C will release Ca^{2+} when diastole happens. The whole process requires Ca^{2+} transportation from many protein gates including sarcolemma voltage-dependent Ca^{2+} channel (LCC), Ryanodine receptor 2 (RyR2), sarcolemma Na+/Ca^{2+} exchange (NCX), SR Ca^{2+}-ATPase (SEARCA), mitochondrial Ca^{2+} uniport (MCU) and sarcolemma Ca^{2+}-ATPase [7].

Disorganization of Ca^{2+} in cardiomyocytes causes contractile dysfunction and finally lead to pathophysiological conditions including hypertrophy and heart failure. Increasing of intracellular Ca^{2+} concentration will lead to defective E-C coupling, which will result in pressure overload and higher mass of cardiac muscle, finally hypertrophy [3]. So the underlying mechanism of heart failure mainly limited in disorders of E-C coupling, and it is important to find the key proteins leading to the disorder of E-C coupling to cure the disease.

IV. The Changes of E-C Coupling Related Proteins in HF

In heart failure, there are many abnormal changes of E-C coupling related proteins, which to some extent could give us the clue to cure the disease [6].

We all know the Ca^{2+} handling will alter in HF, and previously researchers found that NCX function is upregulated and the NCX expression in protein level is also typically upregulated in most HF cases [8]. Also SR Ca^{2+} content is depressed, which results from the decline of SERCA2a expression, eventually leading to the inhibition of SR Ca-ATPase function.

In HF diastolic SR Ca^{2+} leak is enhanced because of the higher open probability of RyR2. CaMKII is a part of RyR2 regulated factor [9], and the CaMKII-dependent RyR2 phosphorylation will activate RyR2 and promote diastolic SR Ca^{2+} release, which has the similar results to diastolic SR Ca^{2+} leaking [10]. In HF, CaMKII expression is increased with enhanced RyR2 activation state [8], [11].

Na-K-ATPase (NKA) expression is reduced in HF, but NKA function remains normal [12]. Protein phospholemman (PLM)expression is also reduced but with higher phosphorylated PLM in HF [12], [13]. Potassium current in HF is also altered, which will modify action potential and Ca^{2+} handling [14].

TABLE I: The Summary of Changes of E-C Coupling Key Proteins in HF

Gene/Protein	Trend	Method	Reference
NCX	Increase	Westernblot	Maier LS *et al. Cir. Res.*,1995
SERCA2a	Decrease	Westernblot	Maier LS *et al. Cir. Res.*,1995
CaMKII	Increase	Westernblot	Ai X *et al. Cir. Res.*,2005
Na-K-ATPase	Decrease	Westernblot	Bossuyt J *et al. Cir. Res.*,2005
PLM	Decrease	Westernblot	Bossuyt J *et al. Cir. Res.*,2005

V. Drug Therapy of HF

Goals of therapy in patients with HF are improving their

clinical status, functional capacity and quality of their life, preventing hospital admission then reducing mortality.

Neuro-hormonal antagonists including Angiotensin-converting enzyme inhibitors (ACEIs), (Mineralocorticoid receptor antagonists) MRAs and beta-blockers have been shown to improve survival in patients with HF. When HF occurs, renin-angiotensin aldosterone system is activated and vasocon is restricted. Sympathetic nerve endings will release norepinephrine, which leads to myocardial hypertrophy with myocardial cell apoptosis. By using ACEIs, it can lower concentration of angiotensin aldosterone 2, relieve the load of peripheral vascular and coronary vascular resistance, and reduce myocardial fibrosis. These ACEIs related drugs including captopril, enalapril benazepril and perindopril [15], [16].

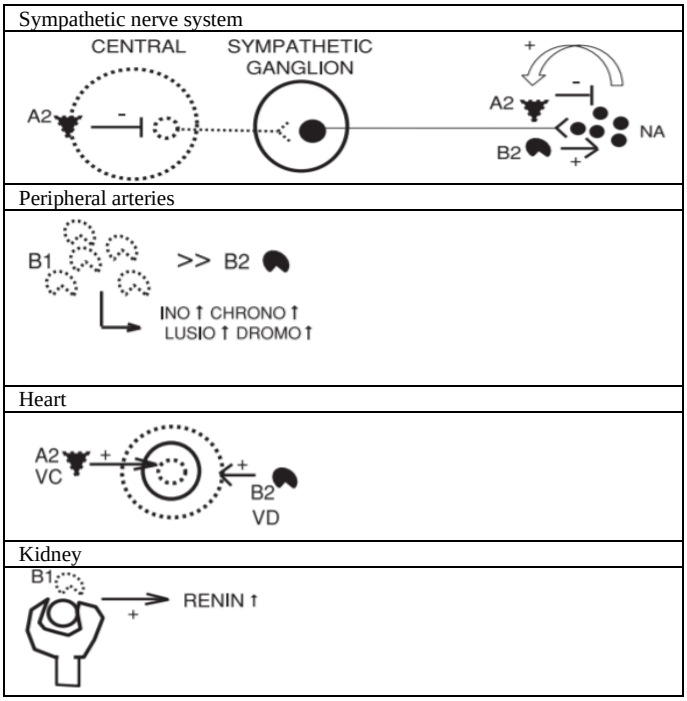

Fig. 4. Beta blockers' impact on the cardiovascular system by using catecholamines for simulation. As heterogeneous adrenoreceptors, beta blockers affect orthosympathetic nerve system, peripheral arteries, heart, and renal system [16].

Beta blockers block cardiac beta receptors and antagonize the toxic effects of excessive catecholamine on the heart, thus improving myocardial function. They also reduce renin concentration, inhibit the release of RAAS and up-regulate myocardial beta receptors to restore their signal transduction ability. As a result, the sensitivity of beta receptors to catecholamine will be improved. In short, Beta blockers work by blocking the effects of epinephrine (adrenaline), thereby decreasing the heart's demand for oxygen [14]. Atenolol, metoprolol, Sotalol hydrochloride, propranolole hydrochloride are common drugs of beta blockers.

MRAs and diuretics basically are related to function of kidney, influencing reabsorption process of water and sodium drainage, and then reduce cardiac overload [1], [15].

When aldosterone acts on the kidneys, the Na-K-ATPase activity, the ability of water reabsorption, and vascular resistance will be strengthened and heart failure will occur subsequently. MRAs can effectively prevent heart failure by preventing aldosterone from binding to salt corticosteroid receptors through competitive inhibition. MRAs drugs includes spironolactone, eplerenone, canrenone and prorenone [2], [17].

Diuretics promotes Na+ excretion and reduces the reverse exchange of Na+-Ca2+, enhancing the positive exchange of it among vascular smooth muscle cells. Thus, intracellular Ca2+ concentration declines, which in turn leads to decreased vascular wall tension and decreased peripheral resistance. As a result, diuretics promotes sodium and water drainage, and reduces blood volume, leading to the reduced cardiac overload and increasing cardiac output [2]. Diuretics consists of thiazide, loop diuretics, potassium-sparing diuretics and osmotic diuretics.

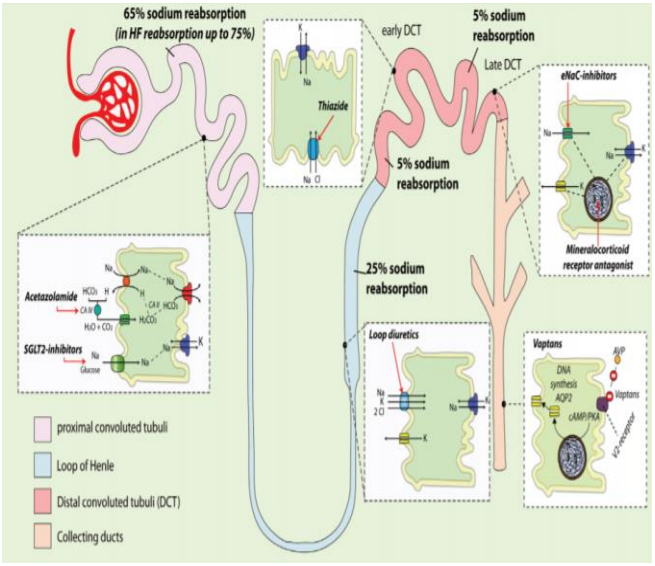

Fig. 5. Functions of different diuretics on several sites regarding sodium reabsorption in kidney [2].

Since intracellular Ca^{2+} concentration of cardiomyocyte is a hallmark in heart failure symptoms and is essential for homeostasis in HF patients, it's important to adjust aberrant Ca^{2+} condition in curing HF. Drugs to normalize cardiomyocyte Ca^{2+} include Cardiac Glycosides, Istaroxime, Ca^{2+} channel blockers and Ranolazine [18].

Cardiac Glycosides is a widely used drug which mainly inhibits the Na+/K+-ATPase and elevates intracellular Na+. It then reverses the NCX and results in Ca^{2+} influx. Istaroxime is a dual-action steroid derivative and increases contractility of cardiomyocyte in a similar way with Cardiac Glycosides. Ranolazine will inhibit late Na+ current and prevent it from accumulation. Finally, electrochemical gradient of NCX is shifted and Ca^{2+} in diastolic period is reduced [18].

VI. The Development of the Drug Therapy

As we have discussed many pharmacological therapies to HF such as Diuretics, ACEIs, ARBs and MRAs, they are always effective ways to work as therapy in HF. However, the use of some drugs is not always effective and the effect sometimes is limited.

The beta-blockers mentioned above are less effective in reducing systolic blood pressure (SPB). In addition, the

effective drug diuretic will be misused in increasing the risk of hemorrhage with NOACs when treating patient with renal dysfunction. Consequently, in treating HF, some cardiac biomarkers should be considered such as natriuretic peptides, high-sensitivity troponin, galectin-3 and cystatin-C. Furthermore, classifying the types of HF such as HFrEF and HFpEF is also important in making decisions [19], [20].

Also, there are other approaches that provide future perspectives of drug therapies. It is useful to have higher doses instead of standard doses of existing drugs for therapy. For instance, the higher doses of ARB losartan proved to be better procedures for patients [21].

There are also therapies based on different types of HF. For patients with Acute Decompensated Heart Failure (ADHF), stimulation of the β-adrenergic receptor can be implicated in the procedure [21]. The future study also includes the use of vasodilators and natriuretic peptides for ADHF patients. However, for HFPEF patients trial data are limited. Though we know that β-blockers are useful to diastolic dysfunction, other therapies such as ARBs are not as effective as β-blockers.

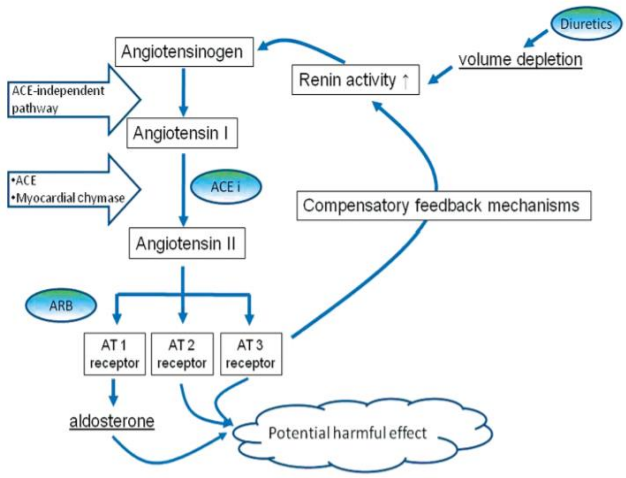

Fig. 6. Mechanisms of renin-angiotensin-aldosterone system (RAAS) retention in heart failure, with diuretics involved in changing renin activity [21].

Moreover, new drugs can act on novel targets of critical intracellular signaling pathways. Direct renin inhibitors (DRIs) offer an additional means of suppressing the RAAS to inhibit the rate-limiting step in RAAS cascade, and then induce the rain inhibition [22]. Furthermore, since hyperaldosteronism in HF is a severe problem, the aldosterone-receptor blocker was assessed to be safe and efficient to inhibit the release of aldosterone.

New drugs can be applied in dealing with the cardio-renal-anemia syndrome of HF. In improving renal function, adenosine antagonist is the novel agent that can inhibit adenosine receptors and promote diuresis. Rolofylline is also an intravenous adenosine receptor antagonist that facilitates diuresis and preserve renal function. Relaxin plays a crucial role in the hemodynamic and renovascular changes in HF. Urodilatin and adrenomedullin are two peptides that regulate renal function [23]. To correct anemia, drugs can be applied in controlling the level of the erythropoietin (EPO), increase the synthesis of EPO and iron supply.

VII. Conclusion and Future Directions

Heart failure is a complicated disease and has a significant threat to human health, and it is important to have a deep investigation to the underlying mechanism. E-C coupling is the fundamental mechanism of the normal function of cardiomyocytes, it would be abnormal in heart failure which results from the altered expression level of key proteins in the process. However, there are lot of proteins which have a different expression level pattern when heart failure happens, and the key factors leading to the disease are still unknown. So, it is key to figure out the truly or the governing ones in the process so that it can provide the new therapy target to cure the heart failure.

Drug therapy is one of the important ways to cure heart failure, and now the traditional popular drugs used in the clinical are ACE inhibitors, angiotensin II receptor blockers, beta blockers and diuretics.

The ACE inhibitors and angiotensin II receptor blockers are vasodilators, which can widen the vessels and the blood pressure would lower down so that the heart workload is decreased. Beta blockers can directly target on the heart reducing the blood pressure and slowing heart rate. Diuretic works through promoting fluid flow outside and without collecting in body so as to reduce the pressure of heart. Although the traditional drugs show the positive effect on the heart failure, they still have many limits, namely that patients must have the drugs in a long time, and side effects such as loss of potassium and magnesium make patient keep many other drugs or supplements at the same time.

Sometimes drug therapy cannot stable the disease and another therapy such as medical devices should be adopted. So, a comprehensive drug that have few side effects and much more effective must be created.

As there are many different kinds of heart failure, and each one has different symptom, and it is necessary to have specific drug for each kind of heart failure since the underlying mechanism of heart failure is also different. So, the future drug therapy should consider all of the above factors to make the patients have a better life.

Regarding the future development of heart failure therapy, in addition to combine all the existing drugs, researchers should also take advantage of the fantastic techniques developed in biotechnology area.

CRISPER-Cas9 technique is n new fantastic gene editing technology, which was applied in many area, especially the cancer therapy.

Some genes have been the targets of the gene editing in heart disease therapy. HCM is a disease of cardiac muscle that results in ventricular hypertrophy and has a propensity for arrhythmias, syncope, and heart failure. Mutations in *MYBPC3* account for approximately one-third of all HCM in humans, as well as a significant number of cases of inherited dilated and noncompaction cardiomyopathy. the successful correction of a MYBPC3 mutation in human germ cells using CRISPR-Cas9 was already reported, which indicating that this approach can be a potential one to cure HCM.

So CRISPER-Cas9 technique, one of the gene editing

methods, can be a potential way to cure heart failure and the similar cardiovascular diseases. Of course, any new useful technique like CRISPER-Cas9 will be helpful, and many genes targets will be definitely found in the near future.

Conflict of Interest

The author declares no conflict of interest.

Author Contributions

Yifan Su is the sole author of this article, who searched for information, had it compiled, and wrote the paper.

Acknowledgment

I would like to express my special thanks of gratitude to my instructor Qianjin Guo, who guided me in topic selection and schedule planning. He also provided me with golden suggestions in references and article polishing, and I am really thankful to him.

References

[1] D. Snipelisky, S. P. Chaudhry, and G. C. Stewart, "The many faces of heart failure," *Cardiac Electrophysiology Clinics*, vol. 11, pp. 11-20, 2019.

[2] P. Ponikowski, A. A. Voors, S. D. Anker, H. Bueno, J. G. Cleland, A. J. Coats, V. Falk, J. R. González-Juanatey, V. P. Harjola, and E. A. Jankowska, "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," *European Journal of Heart Failure*, vol. 18, pp. 891-975, 2016.

[3] J. J. Hunter and K. R. Chien, "Signaling pathways for cardiac hypertrophy and failure," *New England Journal of Medicine*, vol. 341, pp. 1276-1283, 1999.

[4] A. Baartscheer, C. Schumacher C. Belterman, R. Coronel, and J. Fiolet, "[Na+] i and the driving force of the Na+/Ca2+-exchanger in heart failure," *Cardiovascular Research*, vol. 57, pp. 986-995, 2003.

[5] D. A. Eisner, J. L. Caldwell, K. Kistamás, and A. W. Trafford, "Calcium and excitation-contraction coupling in the heart," *Circulation Research*, vol. 121, pp. 181-195, 2017.

[6] D. M. Bers, "Altered cardiac myocyte Ca regulation in heart failure," *Physiology*, vol. 21, pp. 380-387, 2006.

[7] D. M. Bers, "Cardiac excitation–contraction coupling," *Nature*, vol. 415, p. 198, 2002.

[8] L. S. Maier, T. Zhang, L. Chen, J. DeSantiago, J. H. Brown, and D. M. Bers. "Transgenic CaMKIIδC overexpression uniquely alters cardiac myocyte Ca2+ handling: Reduced SR Ca2+ load and activated SR Ca2+ release," *Circulation Research*, vol. 92, pp. 904-911, 2003.

[9] X. Ai, J. W. Curran, T. R. Shannon, D. M. Bers, and S. M. Pogwizd, "Ca2+/calmodulin–dependent protein kinase modulates cardiac ryanodine receptor phosphorylation and sarcoplasmic reticulum Ca2+ leak in heart failure," *Circulation Research*, vol. 97, pp. 1314-1322, 2005.

[10] M. T. Jiang, A. J. Lokuta, E. F. Farrell, M. R. Wolff, R. A. Haworth, and H. Valdivia, "Abnormal Ca2+ release, but normal ryanodine receptors, in canine and human heart failure," *Circulation Research*, vol. 91, pp. 1015-1022, 2002.

[11] D. M. Bers, "Macromolecular complexes regulating cardiac ryanodine receptor function," *Journal of Molecular and Cellular Cardiology*, vol. 37, pp. 417-429, 2004.

[12] J. Bossuyt, X. Ai, R. Moorman, S. Pogwizd, and D. Bers, "Altered phospholemman (PLM) expression and phosphorylation in a non-ischemic, arrhythmogenic rabbit heart failure model," *Circ Res.*, vol. 97, pp. 558-565, 2005.

[13] K. J. Sweadner and E. Rael, "The FXYD gene family of small ion transport regulators or channels: cDNA sequence, protein signature sequence, and expression," *Genomics*, vol. 68, pp. 41-56, 2000.

[14] R. Sah, R. J. Ramirez, G. Y. Oudit, D. Gidrewicz, M. G. Trivieri, C. Zobel, and P. H. Backx, "Regulation of cardiac excitation–contraction coupling by action potential repolarization: Role of the transient outward potassium current (Ito)," *The Journal of Physiology*, vol. 546, pp. 5-18, 2003.

[15] J. K. Rogers, J. J. McMurray, S. J. Pocock, F. Zannad, H. Krum, D. J. van Veldhuisen, K. Swedberg, H. Shi, J. Vincent, and B. Pitt, "Eplerenone in patients with systolic heart failure and mild symptoms: analysis of repeat hospitalizations," *Circulation*, vol. 126, pp. 2317-2323, 2012.

[16] F. Gorre and H. Vandekerckhove, "Beta-blockers: Focus on mechanism of action which beta-blocker, when and why?" *Acta Cardiologica*, vol. 65, pp. 565-570, 2010.

[17] D. A. Sica, "Mineralocorticoid receptor antagonists for treatment of hypertension and heart failure," *Methodist DeBakey Cardiovascular Journal*, vol. 11, p. 235, 2015.

[18] D. Peana and T. L. Domeier, "Cardiomyocyte Ca2+ homeostasis as a therapeutic target in heart failure with reduced and preserved ejection fraction," *Current Opinion in Pharmacology*, vol. 33, pp. 17-26, 2017.

[19] G. Mancia, "Management of arterial hypertension of the European society of hypertension; European society of cardiology 2007 guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)," *J Hypertens*, vol. 25, pp. 1105-1187, 2007.

[20] Y. Sakata, N. Shiba, J. Takahashi, S. Miyata, K. Nochioka, M. Miura T. Takada, C. Saga, T. Shinozaki, and M. Sugi, "Clinical impacts of additive use of olmesartan in hypertensive patients with chronic heart failure: the supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial," *European Heart Journal*, vol. 36, pp. 915-923, 2015.

[21] Y. Sata and H. Krum, "The future of pharmacological therapy for heart failure," *Circulation Journal*, pp. 1004130687-1004130687, 2010.

[22] U. Elkayam, G. Tasissa, C. Binanay, L. W. Stevenson, M. Gheorghiade, J. W. Warnica, J. B. Young, B. K. Rayburn, J. G. Rogers, and T. DeMarco, "Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure," *American Heart Journal*, vol. 153, pp. 98-104, 2007.

[23] G. Cotter, H. C. Dittrich, B. D. Weatherley, D. M. Bloomfield, C. M. O'connor, M. Metra, B. M. Massie, and P. S. Committee, "The PROTECT pilot study: A randomized, placebo-controlled, dose-finding study of the adenosine A1 receptor antagonist rolofylline in patients with acute heart failure and renal impairment," *Journal of Cardiac Failure*, vol. 14, pp. 631-640, 2008.

Yifan Su was born on August 21, 1998, in Wuhan, China. Yifan Su majors in the Biological Engineering Department of Beijing University of Chemical Technology, Beijing, China. Then, she studies in SUNY ESF of the USA for further undergraduate learning as a transfer student.

As an undergraduate, she worked in DNV's equipment and engineering department. Besides, she completed the equipment and operation standards of the Petroleum Tarim Oilfield Company, China. The standard include quality control standard for the 3rd party testing of 140Mpa ultra-high pressure manifold.

.