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Preventing Atrial Fibrillation in Hypertrophic Cardiomyopathy using Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)

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Abstract

Hypertrophic cardiomyopathy (HCM), a genetic cardiovascular disease, is the leading cause of cardiac death in young people, often due to atrial fibrillation (AF). AF is generally treated using antiarrhythmics and anticoagulants, which have adverse side effects after long-term use, and are therefore unsuitable for young HCM patients. AF is characterized by a rapid and irregular atrial heartbeat, marked by a short action potential duration and atrial effective refractory period in atrial cardiomyocytes. Prior studies have indicated that the renin-angiotensin system is involved in lowering both, so it has been hypothesized that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), which inhibit the renin-angiotensin system, could prevent AF. Therefore, in this study, we propose a research protocol to examine the viability of ACE inhibitors and ARBs as prophylactic measures against the development of AF in HCM patients. To test this, we suggest extracting atrial cardiomyocytes from HCM patients by performing enzyme dissociation on myocardial tissue. The isolated cardiomyocytes will then be treated *in vitro* with an ACE inhibitor, an ARB, a combination of both, or a control saline solution, and the patch-clamp technique will be used to determine the frequency and duration of their action potentials. We expect action potential duration and atrial effective refractory period to be longer in treated cells, while neither medication will provide a greater advantage, and, as prior research suggests, the combination will not yield significant benefits. The study will continue by testing the effects of ACE inhibitors and ARBs on the function of atrial myocardial organoids created from differentiated stem cells with an HCM mutation. The results of this study could present a new preventative measure against AF for HCM patients which would be safe for long-term use.

Keywords: atrial fibrillation; hypertrophic cardiomyopathy; angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; patch-clamp technique; heart organoids

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic cardiovascular disease which causes heart muscle cells, known as cardiomyocytes, to be enlarged. These irregular cardiomyocytes are not structured in the orderly patterns seen in healthy cardiac muscle and are instead disorganized and separated by fibrous scar tissue [1]. This abnormal architecture results in enlarged, or hypertrophied, cardiac muscle, often in the left ventricle and interventricular septum [1]. HCM affects roughly 1 in 500 people across all age groups, ethnicities, and genders worldwide [2]. It can be classified as obstructive or nonobstructive depending on whether excess growth prevents blood from exiting the left ventricle [1]. Although obstructive HCM is associated with worse outcomes, both forms can cause clinical presentations ranging from asymptomatic to severe shortness of breath and chest pain, and even heart failure and sudden cardiac death [3]. HCM is the leading cause of sudden cardiac death in young adults, often due to complications arising from fatal arrhythmias, most commonly atrial fibrillation (AF) [4].

AF is an irregular heart rhythm in which atrial cardiomyocytes contract rapidly and asynchronously, resulting in the atria losing their ability to pump blood [5]. This prevents blood from entering the ventricles, and the stagnant blood in the atria can clot, potentially causing heart failure and stroke [5]. In HCM patients, AF is often a direct consequence of an enlarged left atrium due to obstructions and fibrosis, which interferes with its electrophysiology: the flow of electricity through its tissue [4]. AF affects over 1 in 5 HCM patients, causing stroke in around 27% of them and often triggering symptoms of heart failure, so prompt treatment is recommended by the European Society of Cardiology whether the arrhythmia arises suddenly or is persistent [6]. Although stroke risk from AF is typically calculated using scoring systems such as CHA_2DS_2-VASc, HCM patients are younger than most other AF patients, and therefore the use of this system is not

recommended [6]. All forms of AF in HCM are treated with antiarrhythmic medications such as beta blockers and prevented with lifelong anticoagulant and antiarrhythmic treatment using vitamin K antagonists and medications such as amiodarone, which can be toxic to the liver, lungs, and thyroid after prolonged use [4,6]. Since many HCM patients are teenagers and young adults, there is a pressing need to develop new preventative treatments which do not have as many side effects.

In patients with AF, atrial cardiomyocytes, which contract upon receiving an electrical signal from pacemaker cells, show several electrophysiological abnormalities. The myocytes have a shorter action potential duration (APD), which signifies how long it takes for them to send an electrical impulse to neighbouring cells, as well as a low atrial effective refractory period (AERP), which is the length of time after sending one action potential in which an atrial cardiomyocyte cannot initiate another one [7]. Together, these changes cause cardiomyocytes to contract quickly and in rapid succession, and the electrical impulse from the heart's pacemaker flows through the atria at different speeds, resulting in the characteristic disorganized cardiac contraction of AF.

Although AF has many possible causes, it has been hypothesized that the renin-angiotensin system (RAS), which controls local blood flow and inflammation in the heart and kidneys, contributes to its development [8]. The peptide angiotensin II, which is produced by the RAS, is thought to contribute to AF by causing atrial fibrosis, shortening APD, and shortening AERP [9-11]. In patients with left ventricular hypertrophy, as is commonly seen in HCM, decreased left ventricular volume forces blood to back up into the left atrium, enlarging it. This activates stretch receptors in the left atrium which prompt the production of angiotensin II and an increase in the number of angiotensin receptors, leading to cardiomyocyte hypertrophy and increased fibrosis [12]. In addition, a mutation in a gene encoding for angiotensin-converting enzyme (ACE) is a significant predictor of AF in HCM patients, further indicating that the RAS plays a role in its development [9].

Since the RAS is likely involved in AF, its inhibition could be a viable treatment option. In the treatment of hypertension, the RAS can be blocked with ACE inhibitors and angiotensin receptor blockers (ARBs). ACE inhibitors prevent the conversion of angiotensin I into angiotensin II, which is responsible for the structural and electrical remodelling described earlier, while ARBs block the action of angiotensin II by preventing it from binding to its receptors [13]. While ARBs are used as an alternative for individuals with ACE inhibitor intolerance, both are understood to be equally effective in reducing outcomes such as cardiovascular death, stroke, and new-onset heart failure in patients as there is no sufficient evidence to suggest otherwise [13]. Various studies have shown that ACE inhibitors and ARBs can significantly reduce the incidence of AF, particularly recurring AF, both on their own and in conjunction with antiarrhythmics [9,12,14-17]. These studies have also shown that they are most useful in vulnerable populations, such as those with hypertension or left ventricular hypertrophy, and while it is not recommended to use ACE inhibitors and ARBs solely to prevent AF in the general population, it may be considered in vulnerable populations.

ACE inhibitors and ARBs are commonly used to treat conditions such as hypertension and heart failure and are widely available, with few side effects apart from hypotension caused by an unsuitably high dose or cough caused by ACE inhibitor intolerance [18,19]. They are also frequently used as a long-term hypertension treatment, indicating that they could be safe as long-term prophylaxis against AF in young HCM patients [18,19]. Therefore, if ACE inhibitors and ARBs can be approved to prevent AF in HCM patients, millions of people worldwide will have access to long-term prophylaxis with fewer side effects than antiarrhythmic therapy, reducing the incidence of a significant cause of mortality affecting over one fifth of HCM patients [4].

However, most analyses of ACE inhibitors and ARBs are retroactive and not placebo controlled, sometimes resulting in contradictory results [14-17]. Therefore, we propose a research protocol to elucidate whether ACE inhibitors and ARBs are effective at preventing AF in HCM patients, which would address the current uncertainty of their efficacy. Since large-scale clinical trials cannot be conducted without understanding the drugs' potential effects, our study seeks to analyze the effects of ACE inhibitors and ARBs on cells and organs. If significant results are obtained, they could provide evidence to run clinical trials and potentially receive treatment approval. Our study seeks to answer the question, how effective are ACE inhibitors and ARBs as prophylactic measures against the development of AF in HCM patients at a cellular and organ level?

Methods

Our proposed study seeks to determine the effects of ACE inhibitors and ARBs in promoting electrophysiological changes which can prevent AF in cardiomyocytes and the heart as a whole. Therefore, the methodology consists of two stages: a preliminary electrophysiological analysis of atrial cardiomyocytes followed by an observation of the effects of the medications on atrial organoids.

In the first stage of the study, atrial cardiomyocytes will be extracted from HCM patients, treated with medications, and analyzed using the patch-clamp method to detect changes in electrophysiology, similar to the methodology conducted by Bosch et al [11]. Many patients with HCM undergo septal myectomy surgery, which removes excess myocardial tissue from the interventricular septum and is considered the gold standard in treating

obstructive HCM [20]. It must be performed under cardiopulmonary bypass, in which cannulae are inserted into the atria to mechanically pump blood during the surgery, and excess atrial tissue discarded during cannulation will be used to provide samples for this study after obtaining patient and physician consent [21,22]. Samples will be washed with a saline solution to clean out blood and fatty tissue and stored in a 25µM KCl cardioplegic solution until they arrive at the lab [23]. Cardiomyocytes will then be extracted using enzyme dissociation, in which the extracellular matrix of the myocardial tissue is dissolved using an enzyme bath of 3.6 mg/mL collagenase B and 4.8 mg/mL collagenase D in a saline solution [23]. The samples will be cut into 1 mm cubes, fixed in 3.7% formaldehyde for 2 hours, and washed out with a saline solution before being placed in the enzyme bath at 37˚C for 24 hours with shaking 10 times every minute [23]. Dissolved cells in the solution will be extracted by transferring the solution to another tube at 4˚C and allowing the cells to settle to the bottom, and this process will be repeated until all cubes of myocardium are dissolved [23]. Based on the sample size of the study by Bosch et al., it is predicted that samples from approximately 20 patients will yield 40 cardiomyocytes for analysis [11].

Cardiomyocytes will be treated with an ACE inhibitor; an ARB; a combination of the two, whose efficacy is debated in clinical practice; or a control saline solution. The ACE inhibitor lisinopril and the ARB candesartan will be used in the study because both medications are commonly prescribed and have shown promise in cardiac studies unrelated to hypertension [24-27]. Since no prior studies have shown their effects on individual cardiomyocytes, this study will use 1 and 10µM dosages to determine whether a higher dose yields greater effects, and future studies can use these results to find dosages which are effective and clinically applicable. Each myocyte will be immersed in 2 mL of one of the 8 solutions for 30 minutes before being cultured on a petri dish. The APD and AERP of the myocytes will be measured using the patch-clamp method, specifically the whole-cell current-clamp method, which measures changes in electrical potential across a cell's membrane [28]. By fusing a micropipette filled with a conductive solution to a cardiomyocyte's cell membrane, a current will be sent through the cell at different frequencies to elicit an action potential, detected as a sudden reversal in electric potential across the membrane [28,29]. AERP will be calculated by administering a premature stimulus to a cardiomyocyte after a regular current at increasing intervals until the cell reacts, signifying the shortest time after one action potential where it is able to initiate another one [30]. APD and AERP will be calculated at frequencies of 0.5, 1.0, 1.5, and 2.0 Hz for all four treatment options, in line with similar studies [31]. In order to determine the significance of each treatment's effect on APD and AERP compared to the control, ANOVA tests will be conducted at a level of significance of 0.05 for all four current frequencies.

The second phase of the study focuses on the medications' effects on the atria by modelling with ring-shaped atrial organoids: engineered tissues which are able to contract and respond to pharmacological treatment [32]. They will be created through the process described by Goldfracht et al., which involves differentiating human pluripotent stem cells into atrial cardiomyocytes [32]. Stem cells from the freely available SCVIi001-A cell line, which are induced pluripotent stem cells from an adult HCM patient provided by Stanford Cardiovascular Institute, will be differentiated and cultured [33]. To analyze their electrophysiological properties, the organoids will be dyed using a voltage-sensitive dye, allowing for arrhythmias and normal sinus rhythm to be observed and differentiated without the use of equipment other than a microscope. A total of 40 atrial organoids in normal sinus rhythm will be immersed in 5 mL of lisinopril, candesartan, a combination, or a control saline solution at 1 or 10µM dosages and will be electrically stimulated to undergo AF. They will then be observed for 15 minutes to determine whether the medications prevent AF after the shock. The proportion of organoids which do not experience AF after 15 minutes will be recorded. Once again, an ANOVA test will be performed on the data to determine the effect of each treatment.

Anticipated Results

As indicated by prior studies, we expect ACE inhibitors and ARBs to be effective in reducing AF risk at the cellular level by lowering APD and AERP, as well as reducing AF incidence at the organ level [9,12,14-17]. The two medications are likely to show similar benefits in reducing the risk factors and incidence of AF, as seen in a 30% reduction in AF incidence in prior clinical trials [34]. The combination is not expected to show significant benefits: ACE inhibitors prevent the conversion of angiotensin I to angiotensin II while ARBs prevent angiotensin II from binding to its receptors, so it is likely that combining an ARB with an ACE inhibitor will reduce the ARB's effectiveness since there is less angiotensin II present [35].

APD is expected to increase at all frequencies, especially for the 10µM dosages. For instance, similar to the results obtained by Bosch et al, APD to 50% repolarization at 1 Hz is expected to be approximately 25 ms for the control, 35 ms for the 1µM dosages of the medications, and 45 ms for the 10µM dosages [11]. AERP is also expected to increase at all frequencies in relation to the APD increase, with the effect being more noticeable at lower frequencies [30].

It is expected that treated organoids will be less likely to experience AF because the structural and electrophysiological abnormalities caused by angiotensin II are prevented from progressing. Studies using candesartan and the ACE inhibitor enalapril found that both were able to reduce the severity of physical abnormalities such as fibrosis in the atria of animals, and this finding is likely to

apply to lisinopril as well [36,37]. However, in this case, there might be a slight difference between the efficacy of the two medications. In the atria, most angiotensin I is converted into angiotensin II by the enzyme chymase, not ACE, so the ARB may be more effective on the organoid, which only contains atrial cardiomyocytes [38].

Discussion

By investigating the effectiveness of ACE inhibitors and ARBs in preventing risk factors for AF in cardiomyocytes and organoids with an HCM mutation, they could be used in conjunction with other medications to aid vulnerable populations. For instance, a prior study using the ARB irbesartan was able to reduce AF incidence along with an antiarrhythmic, and its success was attributed to a combination of reduction of structural abnormalities as well as irbesartan's interference with potassium channels [38].

While our study uses 1 and 10μM concentrations of ACE inhibitors and ARBs as acting concentrations to determine their efficacy, it is crucial to highlight that it is difficult to compare these dosages to clinical ones. High doses of ACE inhibitors and ARBs can cause hypotension, a condition characterized by low blood pressure, which may result in symptoms such as dizziness and fainting [18]. Additionally, lisinopril has a decreased bioavailability in humans of about 25% and candesartan has a bioavailability of only 15%, indicating that the amount of drug reaching cardiomyocytes will be much lower than the prescribed dose [39,40]. Usually, lisinopril is given at dosages of 10 mg and increased to a maximum of 40 mg, but in patients without hypertension, it is important that the dosages are decreased to a suitable level above 2.5 mg [41]. Candesartan is recommended to be used at doses of 4 to 8 mg initially with a maximum dosage of 32 mg [19]. To reduce toxicity and potential side effects, when used in combination these dosages must be modified. In patients at high risk of vascular events or renal dysfunction, a combination of ACE inhibitors and ARBs is not ideal, as it could lead to more drug-related adverse events [35]. Increased risk of hyperkalemia can also occur, especially in patients with existing hypertension and diabetes mellitus [42].

Our research protocol also comes with limitations due to studying individual cells and organoids instead of observing interactions in the whole body. For instance, although retrospective analyses of humans treated with ACE inhibitors and ARBs have shown reduced incidence of AF, it is still unknown whether this is caused by interference with fibrosis or whether these medications' ability to lower blood pressure ensures that stretch receptors in the cardiac muscle are not stimulated to release angiotensin II [16,17,43]. Since our study does not model the decrease in blood pressure, it may not show these expected results. The study is also limited by the sample size; it is expected that only 40 cardiomyocytes will be viable for electrophysiological analysis and 40 organoids will be created for the second phase of the study. This means that each treatment group will contain only five measurements in both phases of the study, so outliers in the data could lead to inconclusive results in statistical analysis, especially since the cardiomyocytes will come from different patients.

Conclusions

This research protocol was designed to address the pressing need for safer prophylactic measures against AF in young patients with nonobstructive HCM. By avoiding the harmful side effects of current therapies, ACE inhibitors and ARBs provide hope for HCM patients to live longer and healthier lives.

The results of this proposed study could prompt future studies on model organisms to determine the ability of ACE inhibitors and ARBs to prevent AF in whole organisms with HCM. If successful, researchers could consider analyzing AF prevalence in HCM patients who take these medications for conditions such as hypertension, and if there appears to be a negative correlation between ACE inhibitor or ARB use and AF incidence, clinical trials can be started to bring these treatments one step closer to patients who need them. It may also be of interest to investigate the effectiveness of different ACE inhibitors (i.e. enalapril) and ARBs (i.e. losartan), including the clinical relevance of ACE inhibitor classifications such as sulfhydryl, phosphinyl, and carboxyl. Additionally, exploring whether a combination of ACE inhibitors, ARBs, and antiarrhythmics offer more beneficial outcomes compared to individual treatments can allow doctors to prescribe optimal dosages of these medications to suit each patient's needs. This will guide us towards safer treatments and personalized care for HCM patients, ultimately optimizing their cardiovascular well-being.

List of Abbreviations Used

HCM: hypertrophic cardiomyopathy
AF: atrial fibrillation
APD: action potential duration
AERP: atrial effective refractory period
RAS: renin-angiotensin system
ACE: angiotensin-converting enzyme
ARB: angiotensin receptor blocker

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

The protocol outlined in this article requires samples of human heart tissue, which may only be obtained with the consent of HCM patients undergoing septal myectomy and the surgeons performing the procedure. Adult stem cells from the SCVIi001-A cell line, which have been given ethical approval by the Administrative Panel on Human Subjects in Medical Research at Stanford University and are approved for research by third parties, will be obtained from the Stanford Heart Institute and used to generate organoids.

Authors' Contributions
AK: contributed to the protocol design, reviewed current literature, assisted in writing the manuscript, and gave final approval of the version to be published.
AN: contributed to the protocol design, researched relevant literature, drafted the manuscript, and gave final approval of the version to be published.

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References
[1] Marian AJ, Braunwald E. Hypertrophic cardiomyopathy: Genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. Circulation Research. 2017 Sep 15;121(7):749–70. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5654557/
[2] Du M, Wang X, Zhang A, Li F, Yi M. Prognostic effect of atrial fibrillation on survival in patients with hypertrophic cardiomyopathy: A meta-analysis. Journal of Cardiothoracic Surgery. 2023 Jun 20;18(1). https://doi.org/10.1186%2Fs13019-023-02299-x
[3] Popa-Fotea NM, Micheu MM, Bataila V, Scafa-Udriste A, Dorobantu L, Scarlatescu AI, et al. Exploring the continuum of hypertrophic cardiomyopathy—From DNA to clinical expression. Medicina. 2019 Jun 23;55(6):299. https://doi.org/10.3390%2Fmedicina55060299
[4] Falasconi G, Pannone L, Slavich M, Margonato A, Fragasso G, Spoladore R. Atrial fibrillation in hypertrophic cardiomyopathy: Pathophysiology, diagnosis and management. American Journal of Cardiovascular Disease. 2020 Oct 15;10(4):409–18. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7675160/
[5] Roka A, Burright I. Remodeling in persistent atrial fibrillation: Pathophysiology and therapeutic targets—A systematic review. Physiologia. 2023 Jan 9;3(1):43–72. https://doi.org/10.3390/physiologia3010004
[6] Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The task force for the diagnosis and management of hypertrophic cardiomyopathy of the European society of cardiology (ESC). Eur Heart J. 2014;35(39):2733–79. https://doi.org/10.1093/eurheartj/ehu284
[7] Bosch R. Cellular electrophysiology of atrial fibrillation. Cardiovascular Research. 2002 May;54(2):259–69. https://doi.org/10.1016/S0008-6363(01)00529-6
[8] Martyniak A, Tomasik PJ. A new perspective on the renin-angiotensin system. Diagnostics. 2022 Dec 21;13(1):16. https://doi.org/10.3390%2Fdiagnostics13010016
[9] Novo G, Guttilla D, Fazio G, Cooper D, Novo S. The role of the renin-angiotensin system in atrial fibrillation and the therapeutic effects of ACE-Is and ARBS. British Journal of Clinical Pharmacology. 2008 Sep;66(3):345–51. https://doi.org/10.1111/j.1365-2125.2008.03234.x
[10] Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. Circulation. 2000 Jun 6;101(22):2612–7. https://doi.org/10.1161/01.cir.101.22.2612
[11] Bosch RF, Milek IV, Popovic K, Mermi J, Mewis C, Kühlkamp V, et al. Ambasilide prolongs the action potential and blocks multiple potassium currents in human atrium. Journal of Cardiovascular Pharmacology. 1999 May 1;33(5):762–71. https://doi.org/10.1097/00005344-199905000-00013
[12] Kuzniatsova N, Shantsila E, Lip GY. Atrial fibrillation: Blockade of the renin-angiotensin system in atrial fibrillation. Nat Rev Cardiol. 2010 Aug;7(8):428-30. https://doi.org/10.1038/nrcardio.2010.103
[13] Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin-converting enzyme inhibitors in hypertension: To use or not to use? Journal of the American College of Cardiology. 2018;71(13):1474–82. https://doi.org/10.1016/j.jacc.2018.01.058
[14] Jancin B. Angiotensin receptor blocker cuts atrial fibrillation: Val-HeFT and life trials. Family Practice News [Internet]. 2004 Feb 1;34(3). Available from: https://link.gale.com/apps/doc/A113852702/AONE?u=ko_k12hs_d73&sid=bookmark-AONE&xid=1960e366
[15] Morganti A. Angiotensin receptor blockers and atrial fibrillation. High Blood Pressure & Cardiovascular Prevention [Internet]. 2011 Apr 1;18(2). Available from: https://link.gale.com/apps/doc/A264365634/AONE?u=ko_k12hs_d73&sid=bookmark-AONE&xid=d030e43b
[16] Boos CJ, Lip GYH. Targeting the renin–angiotensin–aldosterone system in atrial fibrillation: From pathophysiology to clinical trials. Journal of Human Hypertension. 2005 Aug 11;19(11):855–9. https://doi.org/10.1038/sj.jhh.1001933
[17] Lévy S. Drug insight: Angiotensin-converting-enzyme inhibitors and atrial fibrillation—indications and contraindications. Nature Clinical Practice Cardiovascular Medicine. 2006 Apr;3(4):220–5. https://doi.org/10.1038/ncpcardio0480
[18] Goyal A, Cusick AS, Thielemier B. ACE Inhibitors [Internet]. StatPearls Publishing; 2023 [cited 2024 Feb 29]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430896/

[19] Hill RD, Vaidya PN. Angiotensin II Receptor Blockers (ARB, ARb) [Internet]. StatPearls Publishing; 2020 [cited 2024 Feb 29]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537027/
[20] Knyshov G, Lazoryshynets VV, Rudenko KV, Kravchuk BB, Beshlyaga VM, V. Zalevsky, et al. Is surgery the gold standard in the treatment of obstructive hypertrophic cardiomyopathy? Interactive Cardiovascular and Thoracic Surgery. 2012 Sep 30;16(1):5–9. https://doi.org/10.1093/icvts/ivs352
[21] Septal myectomy [Internet]. Johns Hopkins Medicine. 2019 [cited 2024 Feb 29]. Available from: https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/septal-myectomy
[22] Ismail A, Semien G, Miskolczi SY. Cardiopulmonary bypass [Internet]. StatPearls Publishing; 2020 [cited 2024 Feb 29]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482190/
[23] Liu H, Bersell K, Bernhard Kühn. Isolation and characterization of intact cardiomyocytes from frozen and fresh human myocardium and mouse hearts. Methods in Molecular Biology. 2020 Aug 29;2158:199–210. https://doi.org/10.1007/978-1-0716-0668-1_15
[24] Podzolkov VI, Tarzimanova AI, Gataulin RG. Cardioprotective properties of lisinopril: New possibilities. Rational Pharmacotherapy in Cardiology. 2018 Jul 5;14(3):319–23. https://doi.org/10.20996/1819-6446-2018-14-3-319-323
[25] Chang G, Yeh Y, Chen W, Ko Y, Lai Y, Lee Y. Candesartan cilexetil attenuates arrhythmogenicity following pressure overload in rats via the modulation of cardiac electrical and structural remodeling and calcium handling dysfunction. Journal of the American Heart Association. 2022 Aug 2;11(15). https://doi.org/10.1161/jaha.121.024285
[26] Packer M, Poole-Wilson PA, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation. 1999 Dec 7;100(23):2312–8. https://doi.org/10.1161/01.cir.100.23.2312
[27] Ostergren J. Candesartan for the treatment of hypertension and heart failure. Expert Opinion on Pharmacotherapy. 2004 Jul 1;5(7):1589–97. https://doi.org/10.1517/14656566.5.7.1589
[28] Veitinger S, DeRose J, Greb C. The patch-clamp technique [Internet]. Leica Microsystems. 2011 [cited 2024 Feb 29]. Available from: https://www.leica-microsystems.com/science-lab/life-science/the-patch-clamp-technique/
[29] Britannica. Action potential [Internet]. Encyclopedia Britannica. 2022 [cited 2024 Feb 29]. Available from: https://www.britannica.com/science/action-potential
[30] Takanaka C, Sarma JSM, Singh BN. Electrophysiologic effects of ambasilide (LU 47110), a novel class III antiarrhythmic agent, on the properties of isolated rabbit and canine cardiac muscle. Journal of Cardiovascular Pharmacology. 1992 Feb 1;19(2):290. https://doi.org/10.1097/00005344-199202000-00018
[31] Bosch RF, Zeng X, Grammer JB, Popovic K, Mewis C, Kühlkamp V. Ionic mechanisms of electrical remodeling in human atrial fibrillation. Cardiovascular Research. 1999 Oct;44(1):121–31. https://doi.org/10.1016/s0008-6363(99)00178-9
[32] Goldfracht I, Protze S, Shiti A, Setter N, Gruber A, Shaheen N, et al. Generating ring-shaped engineered heart tissues from ventricular and atrial human pluripotent stem cell-derived cardiomyocytes. Nature Communications. 2020 Jan 7;11(1). https://doi.org/10.1038/s41467-019-13868-x
[33] Liu L, Shenoy SP, Jahng JWS, Liu Y, Knowles JW, Zhuge Y, et al. Generation of two heterozygous MYBPC3 mutation-carrying human iPSC lines, SCVIi001-A and SCVIi002-A, for modeling hypertrophic cardiomyopathy. Stem Cell Research. 2021 May;53:102279. https://doi.org/10.1016/j.scr.2021.102279
[34] Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Journal of the American College of Cardiology. 2005 Jun;45(11):1832–9. https://doi.org/10.1016/j.jacc.2004.11.070
[35] Misra S, Stevermer JJ. ACE inhibitors and ARBs: One or the other—not both—for high-risk patients. The Journal of Family Practice. 2009 Jan 1;58(1):24–7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3183919/
[36] Li D, Shinagawa K, Pang L, Tack Ki Leung, Cardin S, Wang Z, et al. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing–induced congestive heart failure. Circulation. 2001 Nov 20;104(21):2608–14. https://doi.org/10.1161/hc4601.099402
[37] Okazaki H, Minamino T, Tsukamoto O, Kim J, Okada K, Myoishi M, et al. Angiotensin II type 1 receptor blocker prevents atrial structural remodeling in rats with hypertension induced by chronic nitric oxide inhibition. Hypertension Research. 2006 Apr 1;29(4):277–84. https://doi.org/10.1291/hypres.29.277
[38] Madrid AH, Marín IM, Cervantes CE, Morell EB, Estévez JE, Moreno G, et al. Prevention of recurrences in patients with lone atrial fibrillation. The dose-dependent effect of angiotensin II receptor blockers. Journal of the Renin-Angiotensin-Aldosterone System. 2004 Sep 1;5(3):114–20. https://doi.org/10.3317/jraas.2004.027

[39] Beermann B. Pharmacokinetics of lisinopril. The American Journal of Medicine. 1988 Sep 23;85(3B):25–30. https://doi.org/10.1016/0002-9343(88)90346-4
[40] Atacand [Internet]. Food and Drug Administration. 2005 [cited 2024 Feb 29]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020838s026lbl.pdf
[41] Olvera Lopez E, Parmar M, Terrell JM. Lisinopril [Internet]. StatPearls Publishing; 2020 [cited 2024 Feb 29]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482230/
[42] Momoniat T, Ilyas D, Bhandari S. ACE inhibitors and ARBs: Managing potassium and renal function. Cleveland Clinic Journal of Medicine. 2019 Sep 1;86(9):601–7. https://doi.org/10.3949/ccjm.86a.18024
[43] Vermes E, Tardif JC, Bourassa MG, Racine N, Levesque S, White M, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction. Circulation. 2003 Jun 17;107(23):2926–31. https://doi.org/10.1161/01.cir.0000072793.81076.d4

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