

A HISTORICAL VIEW ON UNIVERSITY OF ARIZONA INVESTIGATORS'
CONTRIBUTIONS TO HEART FAILURE RESEARCH

By

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I – Abstract

Hippocrates claimed, “The physician must know what the physicians before him have known, if he does not want to deceive himself and others.” With the underlying goal of inspiring lifelong learning in pupils of the health sciences and to expound the importance of the history of medicine within medical education, this thesis will seek to define the evolution of the understanding and treatment of heart failure (HF) using the Sarver Heart Center and University of Arizona College of Medicine – Tucson (UA COM-T) investigators as a medium for displaying the progression of knowledge within the scientific community. Moreover, to be accessible and digestible to all, an explanation of basic heart function and HF pathology will be outlined. This thesis is also intended to be part of a larger output that seeks to show the importance of the humanities in the health sciences mainly by adding depth to care providers’ knowledge of treatment through history education. With hopes of stimulating students of medicine towards well-roundedness in their care, another goal for this thesis is that it may also lead to a digital media source that shares the rich history of the University of Arizona College of Medicine – Tucson in a public and accessible manner. Lastly, an overarching goal of this work is to educate those outside the university about the basic innerworkings of research in order that the public can be informed about the impact of their money and votes, as well as understand how that impact affects the overall healthcare of society due to the translation of research advancements to bedside care.

II – Introduction

Over 6 million adults in the U.S. have heart failure (HF), and in 2018 the condition was mentioned on about 380,000 death certificates (Virani, et al, 2020). “Heart failure costs the nation an estimated \$30.7 billion in 2012. This total includes the cost of health care services, medicines to treat heart failure, and missed days of work (Benjamin et al, 2019).”

HF is a public health issue worthy of considerable investment of time and resources when considering the individual scale of personal health and the nationwide impact it has with regards to public health and the economy. Although HF descriptions exist as early as in ancient Egypt, India, Rome, and Greece, few significant strides were made in the treatment of HF until thiazide diuretics, one of the first non-toxic diuretics, were produced in the mid-20th century (Davis, et al, 2000). Since the 1950s, there have been numerous landmark studies which have led to an exponential increase in the knowledge regarding HF as well treatment options more than during in any other epoch in history.

The development of many of these improvements in HF treatment and knowledge are being conducted at locations geographically closer than the public may have ever imagined. It is a given that modern medicine would not be where it is today without the collaborative efforts of investigators from around the world, but many may not realize that the university or medical center in their backyard has made significant advances to the field of medicine in which they are being treated. With more than \$24 billion of funding from the National Institutes for Health (NIH) being dispersed to more than 300,00 researchers at more than 2500 universities across the US and the world, many Americans’ homes are bound to be geographically closer to sites of medical research than they might expect (Owens, et al, 2014).

This thesis will highlight the contributions to the field of HF research from investigators at the Sarver Heart Center (SHC) and associated University of Arizona College of Medicine – Tucson faculty. As is the goal of most literature published regarding medicine, the end goal is an eventual improvement of patient care. The inner workings of the research, or bench/lab side of medicine, are often a mystery to the public, and perhaps shedding light on this side of medicine as well as the historical advancements that have occurred can benefit both the bench and the bedside realms of medicine. Let us first define various realms of the medical world: mainly the bench and the bedside of medicine. The research or lab side of medicine, colloquially referred to as the bench side of medicine, in reference to a working bench within a laboratory, focuses on investigating the underlying mechanisms of disease. This can be done with respect to full human bodily scale, specific to an organ system, at a cellular level, or even a genetic level. Research is being done on all these levels to eventually be translated into advancements in clinical care. Much collaboration has to occur in this setting in order that niche techniques, proper analysis, and clinical translation can lead to the desired outcome of better patient care. This involves primary investigators, student researchers, statisticians, clinicians, physicians, and nurses, as well as myriad of other professionals.

The application and translation of the research then informs the clinical practice of medicine. This is the medical knowledge and developed skills being used for the diagnosis, treatment, and management of patients in a clinical setting. A common setting to encounter this realm of medicine would be in a hospital, and specifically at the bedside of a patient in a hospital room, hence the common colloquialism of “bedside medicine.” Clinicians use a variety of tools and techniques to evaluate and treat patients. These include, but are not limited to, physical evaluation, imaging and laboratory tests, pharmaceuticals, procedures, and surgeries. There are

subsets within medicine that allow for specialized treatment of a particular disease or ailment, and therefore a particular patient population. The goal of a clinician should be to effectively use evidence-based medicine, from the bench side of research, to treat patients.

It is proposed that an interest in these developments within medicine could potentially spur healthcare professionals and biomedical researchers to advance their work with a greater fervor knowing that they have public support and a greater knowledge of the institutional research legacy that they may be a part of. This could occur via a shift in public approval such as an increase in zeal for the investigative side of medicine which, via voting on the destination of tax-payer dollars, donations, or social pressure could sway a variety of factors that impact today's world of medical investigations. Moreover, if one follows this linear reasoning, it can be deduced that the public's opinion has an eventual effect on the outcome of care that they may potentially receive. Therefore, it seems only fair and logical that the public be further educated on the innerworkings of research and medicine because of how directly it affects them.

One of the ways to make education to the public more appealing, given that the public will not educate themselves without a reason for doing so, is to personalize the education, or make it "close to home." Many people have a sense of connectedness to their alma mater, for example, and therefore may be more interested in what particularly their beloved universities may be taking part. Moreover, a sense of dedication and affection is also felt toward institutions that may have cured a loved one of a difficult condition or shared care for others. A personal connection with a hospital or medical center may indeed draw community members, including former patients, to want to become more educated about the research being conducted at the institution, or in the field of medicine associated with their own treatment.

For this reason, this thesis will dial in on a specific set of researchers at one academic institution, the University of Arizona, with the hopes of piquing the interest of the community. Another means to increase public education regarding health-related concepts would be to ensure that the concepts are basic enough to be fully understood by those who are not members of the scientific community. Even well-established academics know the feeling of reading a peer reviewed paper from an unfamiliar discipline and needing substantial background knowledge and additional resources to fully grasp the contents of the paper. Therefore, this thesis will begin by laying out the foundational knowledge of the function of the heart and how HF develops to its readers before scratching the surface of some of the research that has been conducted in this field. This will be followed by an exploration of some of the major advancements in the area of HF research at the University of Arizona up to this point in time and conclude with future directions for this work as well as for the field of cardiovascular medicine in general.

III – Background

The information provided for the background information is found in long-standing textbooks like *Cardiovascular Physiology* from Elsevier (Levy, et al, 2006) The heart is ever important to the human body. Without it, all other organs in the body would be unable to function properly. It is a part of the cardiovascular system which consists of the heart, veins, arteries, capillaries and the blood. These components allow for delivery of oxygen and nutrients to, and removal of waste from, all parts of the body via blood.

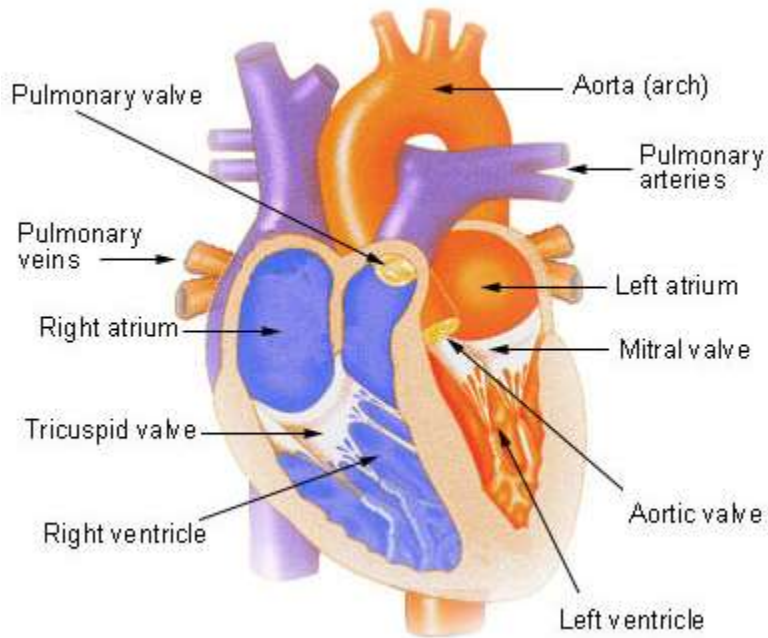


Figure 1. An illustration of the internal view of the heart, as well as nearby blood vessels, showing prominent anatomical structures. This image is adapted from the Nation Cancer Institute (SEER-NIH)

As blood approaches any valve in the heart, there is a pressure differential between the area before (preceding) and following (behind) the valve (see Fig. 1). In order for the blood to pass through the valve, and reach its next destination in the heart, the pressure in front needs to be higher than the pressure behind the valve. Only when this pressure differential is overcome, can the valve then open and allow for blood flow to the next destination. In order to move the blood from the left ventricle (LV) into the systemic system via the aorta, the ventricular pressure needs to be very high to overcome the systemic pressure, which is also very high in order to open the left semilunar valve (see Fig. 1). The heart's response to meeting a high level of pressure is to have the thickening (or hypertrophy) of the muscle that composes the wall of the LV. Once the blood enters the aorta, it is distributed throughout the body into different arteries, then arterioles, then capillaries, where nutrient and oxygen exchange takes place in body tissues. After these

exchanges, the now deoxygenated blood starts collecting from the capillaries into venules, and then into veins as it makes its way back to the right atria at which point it enters the heart. After entering the right atrium, the blood is sent through the tricuspid valve into the right ventricle which then contracts and forces the blood through the right semilunar valve, leading it eventually to the pulmonary arteries (see Fig. 1 and 2). The blood then progresses through the alveolar capillary network within the lungs. This is where gas exchange occurs. Carbon dioxide is released, and oxygen is picked up. After picking up oxygen, the blood then starts its journey back to the heart as the alveolar capillaries start to form into pulmonary venules, and then veins that then enter the left atria, which then travels through the bicuspid, or mitral valve into the LV after the left atrium contracts, in turn starting the whole circulation process over again (see Fig. 2).

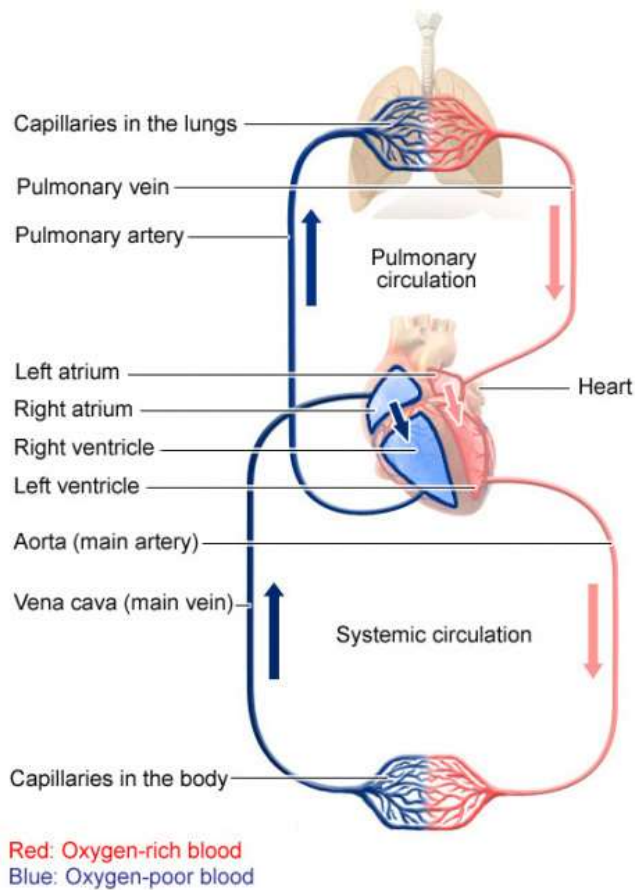


Figure 2. This image shows the heart's relation to the pulmonary and systemic circulation within the body (IQWiG)

Once the blood enters systemic circulation, there is an ever-important destination of the oxygenated blood: the heart muscle itself! The system of blood vessels responsible for delivering oxygen and nutrients to the heart muscle is known as coronary circulation. Coronary circulation consists of anastomotic channels meaning that if one of the blood vessels becomes blocked and is therefore unable to deliver enough blood to a particular area of heart tissue, there are collateral vessels that allow for bidirectional blood flow and delivery of ample oxygen and nutrients to sustain the heart tissue. The coronaries have an extensive capillary system to provide plentiful

nourishment of the heart muscle, also called myocardium. The myocardium is the thickest and middle layer of the heart (see Fig. 1). The epicardium, also called the visceral pericardium, surrounds the myocardium, and provides a layer of protection for the heart. Moreover, there is a third and innermost layer of the heart called the inner endocardium which keeps the blood within the chambers of the heart and separated from the myocardium.

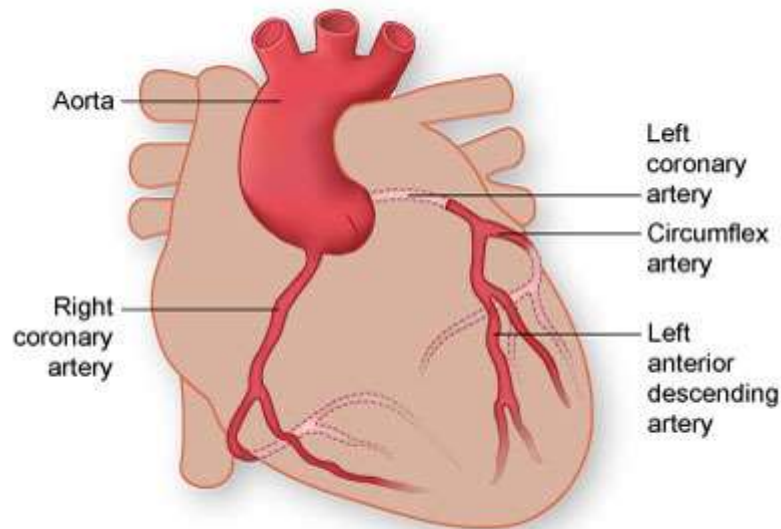


Figure 3. The coronary circulation of the heart is what supplies the heart muscle with blood.

The myocardium, or the heart muscle, is composed of cardiac myocytes (CM). These CMs are branched and are unique in the sense that they all work together, synchronously beating if they are in proximity to one another to allow for smooth and coordinated contraction throughout the whole heart. This is made possible by a combination of two types of cell connections: desmosomes which hold the CMs to each other, and gap junctions which allow adjacent CMs to be electrically connected and function as one unit (see Fig. 4). These gap junctions are located at the connection points between the cells, otherwise known as intercalated disks. Gap junctions facilitate the transmission of electrical signals between cells. Through the

direct contact of CMs via gap junctions, they can act as a functional syncytium, or a network of cells that are electrically connected and can therefore contract synchronously. This physiological structure of heart muscle allows for some chambers to contract at the same time, while others are relaxed at the same time. For instance, the atria and the ventricles do not contract at the same time. We know that the ventricle needs to be in a non-contractile state, or relaxed, while the atria is contracting to fill the ventricle with blood. Therefore, it can be deduced that not every single CM within the heart is part of the same functional syncytia unit, but rather organized into several anatomical sections. It is within reason that there would be countless functional issues if all CMs contracted at the same time at every spot in the heart.

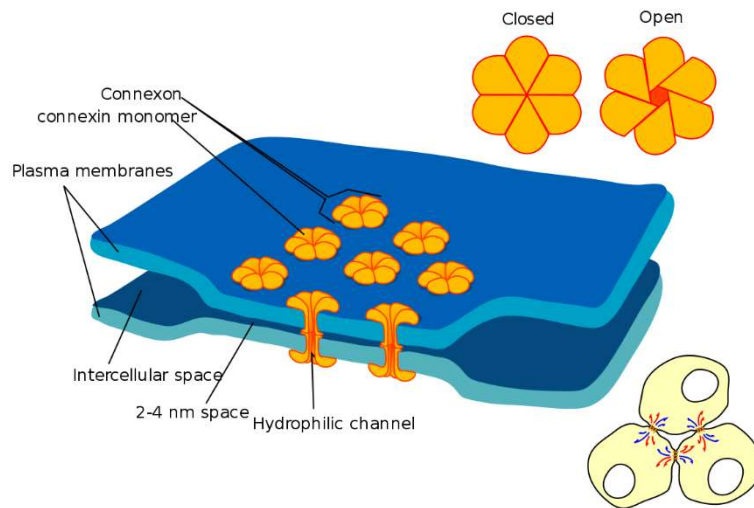


Figure 4. Gap junctions are what allow the heart muscle cells to connect to one another.

The cardiac myocytes are made of sarcomeres, or the basic contractile unit in skeletal and cardiac muscle. Knowing how sarcomeres contract, and therefore how CMs work and eventually provide pressure to move blood through the heart is an essential part in the understanding of cardiovascular physiology (see Fig. 5).

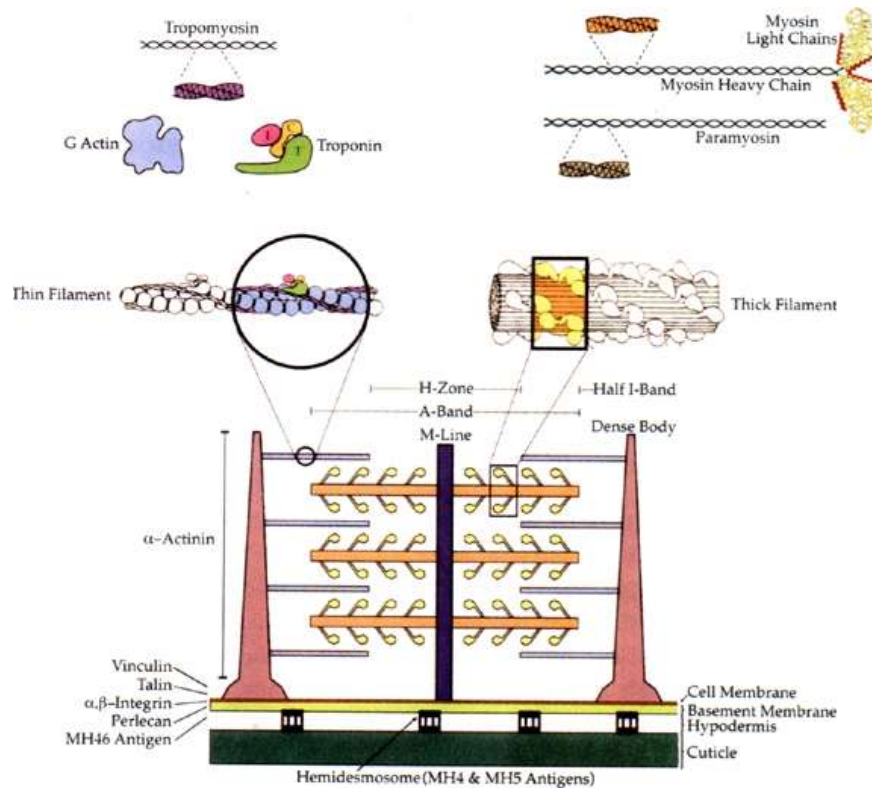


Figure 5. Sarcomeres within muscle cells have many components that allow the muscle cell to contract (Riddle, et al, 1997).

The basic structure of the sarcomere “consists of a bundle of myosin-containing thick filaments flanked and interdigitated with bundles of actin-containing thin filaments (see Fig. 5). The striated appearance of muscle results from the alternation of thick-filament-containing and thin-filament-containing regions. Refer to Figure 3 for more details regarding the physiology of a sarcomere. The energy for contraction is provided by adenosine triphosphate or ATP, the basic energy carrying molecule found within cells. The mechanism in which myosin heads bind to actin and form cross bridges to allow for contraction can only happen when calcium enters the sarcomere. Calcium enters the CMs through a series of reactions that eventually end in the sarcoplasmic reticulum releasing generous amount of Ca^{2+} within the sarcomere.

This basic cardiovascular physiology thus far has hopefully laid enough groundwork to now explore some cardiovascular pathologies. Pathology is when the structure or function is abnormal, or diseased. In the heart, pathology can present as structural, functional, or electrical abnormalities. There is a myriad of issues throughout the body that can lead to cardiovascular problems. For example, the heart can even be permanently damaged by untreated or under-treated infections like strep throat or scarlet fever. The body's immune response to these infections might unfortunately result in rheumatic heart disease where heart valves are damaged and scarred over time, leading to improper function.

Moreover, there are several arrhythmias that can occur within the heart. This means that the electrical function of the heart is not working properly. This results in abnormal heart rhythms, affecting the temporal pattern of heart muscle contractions, and affecting the proper flow of blood. Varying forms of arrhythmias can occur. Bradycardia is when the heart is beating too slowly, and on the other hand, tachycardia is when the heart is beating too quickly. Some common arrhythmias include atrial fibrillation, ventricular tachycardia, and sinus bradycardia. Many arrhythmias can lead to the symptoms of shortness of breath, fatigue, dizziness, fainting, and chest discomfort.

There are many realms of cardiovascular pathophysiology which this thesis could explore with respect to the research contributions made by University of Arizona investigators. Since the establishment of the College of Medicine – Tucson in the latter half of the 20th century, there have been substantial scientific advancements to come out of Tucson. For the sake of having a focal point and focusing on a substantial disease which the UA has had a significant stake in, this thesis will mostly discuss contributions to heart failure research, while still commenting and

showcasing research conducted in related cardiovascular fields because of the intrinsic interconnectedness of much cardiovascular pathophysiology.

Heart failure occurs on a wide spectrum. A patient with mild HF may not present with any physical symptoms in the patient. On the other hand, a patient could be experiencing a severely debilitating form of HF that extremely diminishes the patient's quality of life. In either case, there can also be accompanying comorbidities, both of cardiovascular nature and of other bodily systems which still influence the functionality of the heart. Comorbidity is the presence of a condition in addition to a primary condition. Comorbidities often complicate patient diagnosis, treatment, and management of the primary ailment. Oftentimes, diagnoses that are considered widely preventable bring with them a plethora of comorbidities. An example that one might find common in modern America is the presence of diabetes along with HF, both conditions that are often the consequence of poor diets and limited physical exercise. Moreover, cardiovascular diseases can come in pairs or trios. A patient with severe HF might also have coronary artery disease and high blood pressure, complicating the management of any three of the conditions because they are so interconnected. It is because of this interconnectedness, especially among cardiovascular comorbidities, that the research and research history discussed in this thesis will touch on several disciplines of cardiovascular study.

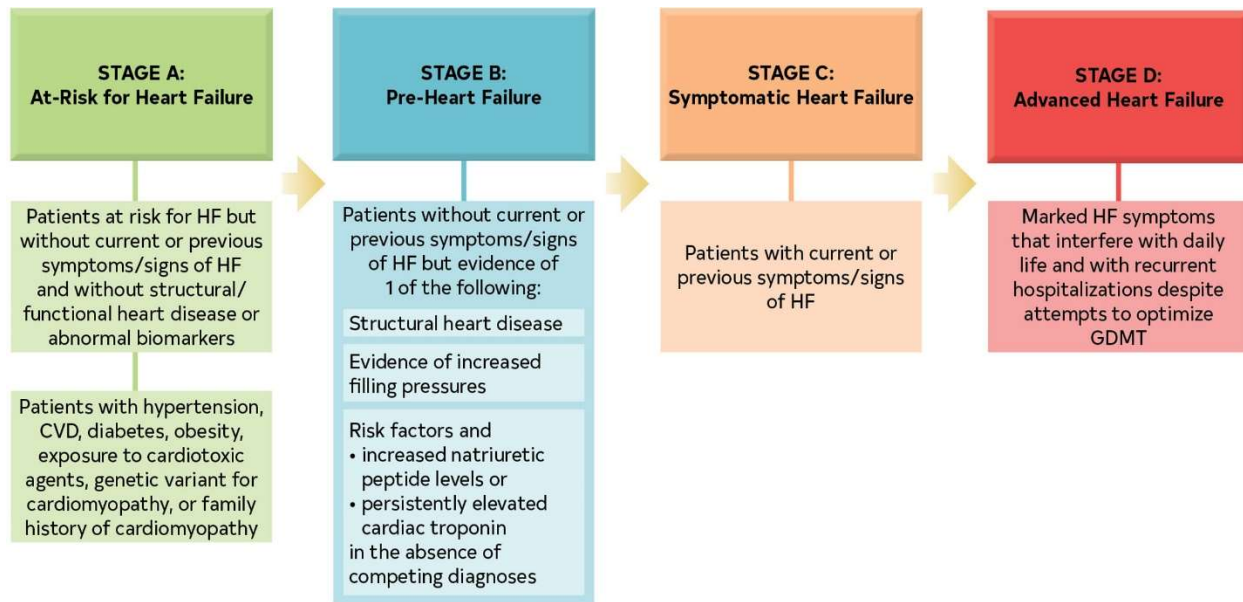


Figure 6. There are 4 stages of HF as defined by the American College of Cardiology and the American Heart Association (AHA).

The American Heart Association defines heart failure (HF) as “a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood (AHA)” (see Fig. 6). In other words, HF is defined as the heart’s inability to deliver the proper amount of blood, and therefore oxygen and nutrients, to the organs of the body. HF is a chronic condition with no definite cure at our present time. It is rather a condition that can be managed with varying levels of treatment aimed at stopping the progression of the disease and improving the patient’s quality of life. Treatments for HF can include surgical procedures, administration of medications, and lifestyle changes. These varying levels of treatment and symptom management are some of the advancements that have come out of the University of Arizona. Depending on the stage of a patient’s HF, the disease can range from being silent and presenting with no symptoms all the way to the absolute need for life-support in a hospital setting without which would lead to death. These stages of HF are

delineated by the American College of Cardiology and the American Heart Association indicating both severity and symptoms (see Fig. 6)

IV – Chronology of HF Research

The following section explores two main historical contributions from the University of Arizona to the field of cardiovascular research. These two main areas of research cover two ends of the University of Arizona College of Medicine – Tucson history spectrum. The first is a dive into an advancement that came out of UA COM-T that has most likely saved more lives than any other advancement or venture. The second is an analysis of exciting work that is in its infancy, the impact it has had thus far, and the potential for its benefits in the field of HF in the years to come.

The figure below (Fig. 7) is a timeline depicting both worldwide and University of Arizona contributions to the field of cardiovascular research. (Originally presented as a poster spring 2023). It is important to note that no realm of biomedical research would be where it is today without the collaborative efforts of multidisciplinary researchers within one institution, as well as the cross-institution collaboration that has occurred nation and worldwide. When recognizing the historical contributions of research movements, it is also important to expound the efforts of the group. Rather than praising a sole researcher for leading the way, there is great benefit in recognizing others that contributed to any success. To begin with, it is simply professional courtesy and allows for credibility of the work. Additionally, it can spur less experienced collaborators to continue their work in the field. It can also foster professional

note that there was very little basic scientific improvement in the field of cardiovascular health until the 1950's, i.e., the start of this timeline. Until about the mid-20th century, the treatment for HF was bedrest, that is, if anyone were to even live long enough to have diagnosable HF.

Before discussing the research that has been done at the institution in question, a brief history of the College of Medicine – Tucson and the Sarver Heart Center, the affiliated heart research center on the same campus is provided. After much political tension regarding the home of Arizona's first medical school, the College of Medicine – Tucson has its first class of medical students in 1967. In 1986, Drs. Jack Copeland and Eugene Morkin founded the “University Heart Center” with only a few other members. The center was renamed the Sarver Heart Center in recognition of a gift from the Sarver family and the center dedicated its new home in 2000, a 30,000 square foot addition to the College of Medicine. The Center is now composed of more than 150 physicians and scientists who collaborate on all things cardiovascular, working “toward a future free of heart disease, vascular disease, and stroke (Sarver Heart Center).”

Cardiopulmonary Resuscitation

The first area of research explored here is the advancement of administering cardiopulmonary resuscitation (CPR). The technique developed by researchers at the UA goes by many names: Chest Compression-Only Cardiopulmonary Resuscitation (CCO CPR), Continuous-Chest Compression Cardiopulmonary Resuscitation (CCC CPR), and hands-only CPR. As mentioned beforehand, the forefront of research in this area of cardiovascular studies has most likely saved more lives than any combination of other research advancements in this field of study that came from UA COM-T, having saved at least 6,980 lives (AZDHS, 2023).

Before getting into the history of CCC CPR, the connection between CPR and HF is first considered.

Heart failure, in essence, can lead to cardiac arrest. Cardiac arrest is when the heart stops beating all together and when CPR must be performed. The occurrence of cardiac arrest is extremely detrimental to one's body as oxygen and nutrients cannot reach the body's target tissues when the heart stops beating. One of the more severe consequences of cardiac arrest can be the irreversible damage to brain tissue caused by lack of oxygen possibly resulting in intellectual disabilities. In severe cases of HF, the heart can stop pumping all together. This could be due to electrical malfunction of the heart from diseases like atrial or ventricular fibrillation. Fibrillation is defined by rapid or uncoordinated contractions of the heart muscle. Fibrillation can often cause shortness of breath, chest pain, and lightheadedness. HF is a risk factor for both arrhythmias because it often changes the structure of the heart, making it more susceptible to developing abnormal heart rhythm. When structural changes from HF occur in the atria of the heart, atrial fibrillation can result, and conversely, when structural changes from HF occur in the ventricles, ventricular fibrillation can occur. Ventricular fibrillation is often considered more fatal and has a greater chance of leading to death compared to atrial fibrillation which can eventually lead to mortality, but in shorter time frames leads to blood clots and stroke.

One can imagine that it is of the utmost importance to return blood flow to the vital organs as soon after one has experienced cardiac arrest as possible. The ultimate way to restart and reset the electrical activity of the heart is to shock it back into sinus, or a normal rhythm using an automated external defibrillator (AED). Effective use of an AED will often result in the re-establishing of an effective rhythm for the heart to work on its own. The question then remains. What then is someone to do until an AED is available for use? The answer is

cardiopulmonary resuscitation. CPR works by manually compressing the chest, and thereby indirectly compressing the heart itself, to make blood flow while the native function of the heart cannot sufficiently pump blood for the needs of the body (see Fig. 8). Compressing the chest 2 inches about 100 to 120 times a minute will give the person experiencing cardiac arrest the highest chance of survival until an AED can be administered. This rate of compression allows for blood to continue flowing to the brain and vital organs.



Figure 8. Drs. Ewy, Kern, and their team teach CCO CPR in McKale Center before a University of Arizona basketball game.

It has traditionally been taught to give 2 rescue breaths, otherwise known as mouth-to-mouth ventilation, after 30 chest compressions based on the logic that the breaths will replenish the body with more oxygen by supplying the lungs with a new breath of air. The administrator of

CPR if giving rescue breaths is instructed to tilt the person's head back, lift their chin, pinch their nose shut, cover their mouth with yours making a tight seal, and give two breaths while watching the person's chest rise. CCO CPR is more effective in keeping the person's vital organs viable during cardiac arrest because there is sufficient oxygen in the blood to supply the body in time for an AED to arrive; brain death does not occur until it has not received oxygen for 10 minutes (Cleveland Clinic). It was the Resuscitation Research Group at the Sarver Heart Center and the University of Arizona that was one of the leading voices in the charge for CCO CPR.

The University of Arizona Sarver Heart Center Resuscitation Research Group was a collection of community members headed by Drs. Gordon Ewy and Karl Kern who advocated for CCO CPR. By the mid-1990s, the group was recommending CCO CPR because they had conducted research that showed that CCO CPR resulted in better survival than traditional CPR in out-of-hospital settings. (Ewy, et al, 2011) Moreover, they found that promoting CCO CPR increased chances of survival because bystanders were less likely to administer any form of CPR if they felt less prepared and comfortable to do so. It was found the mouth-to-mouth ventilation was often a barrier to bystanders performing CPR. It was for this reason that the group promoted CCO CPR because any CPR bettered the chances of survival compared to no CPR (Ewy et al 2011).

As CPR research had progressed and showed that CCO CPR was at least as effective as traditional CPR, the Resuscitation Research Group began heavily advocating for individuals with primary cardiac arrest (an unexpected, witnessed collapse in an individual who is not responsive). Education in Tucson was pushed out on a wide-scale community level. In 2004, the campaign for CCO CPR helped educate the community with flyers, newspaper articles, school demonstrations, and celebrity endorsements. Throughout the analysis, the greatest finding was

that individuals who received CCO CPR had almost twice the chance of survival compared to individuals who had either no CPR administered, or standard CPR administered after having experienced cardiac arrest due to a shockable rhythm (Ewy, Sanders, Kern, 2011) (See Fig. 9).

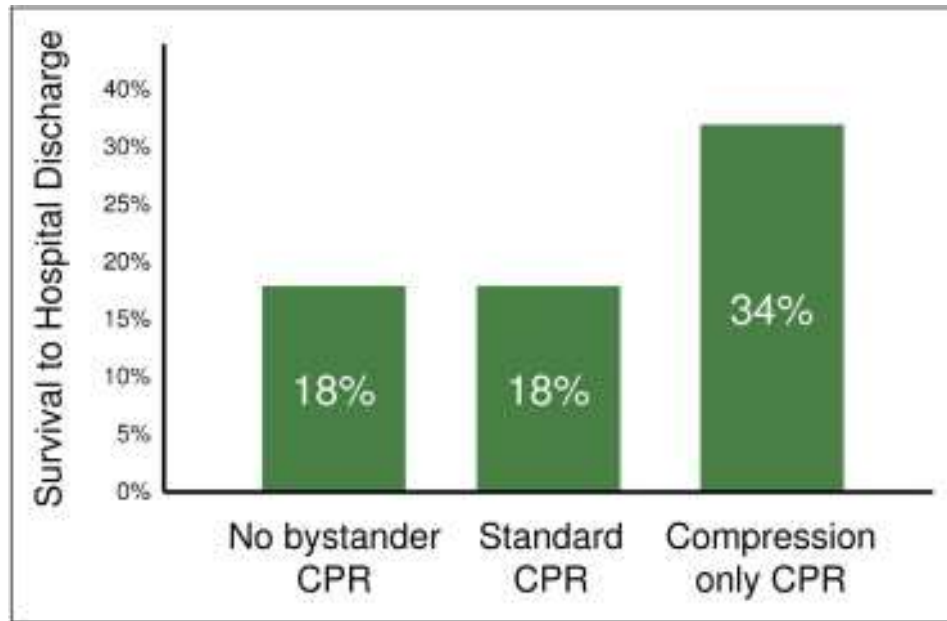


Figure 9. Chest Compression Only Cardiopulmonary Resuscitation showed to almost double the chances of survival for individuals who went into cardiac arrest (Ewy, Sanders, Kern, 2011).

These amazing results were also paired with a “significant increase in the incidence of bystander cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest (28%-40%), an increase in the likelihood of bystanders performing compression-only cardiopulmonary resuscitation (20%-76%), and an overall survival difference of 4% with conventional cardiopulmonary resuscitation compared with 10% with compression-only cardiopulmonary resuscitation.” Moreover, this monumental group in the area of CPR research proposed an integrated approach to cardiac arrest that involves more than just the bystander. “The New CPR”

guidelines, or cardiocerebral resuscitation, as it is referred to by the group, advocates for pre-hospital and hospital engagement in the treatment of primary cardiac arrest (Ewy, Sanders, Kern, 2011) (See Fig. 10).

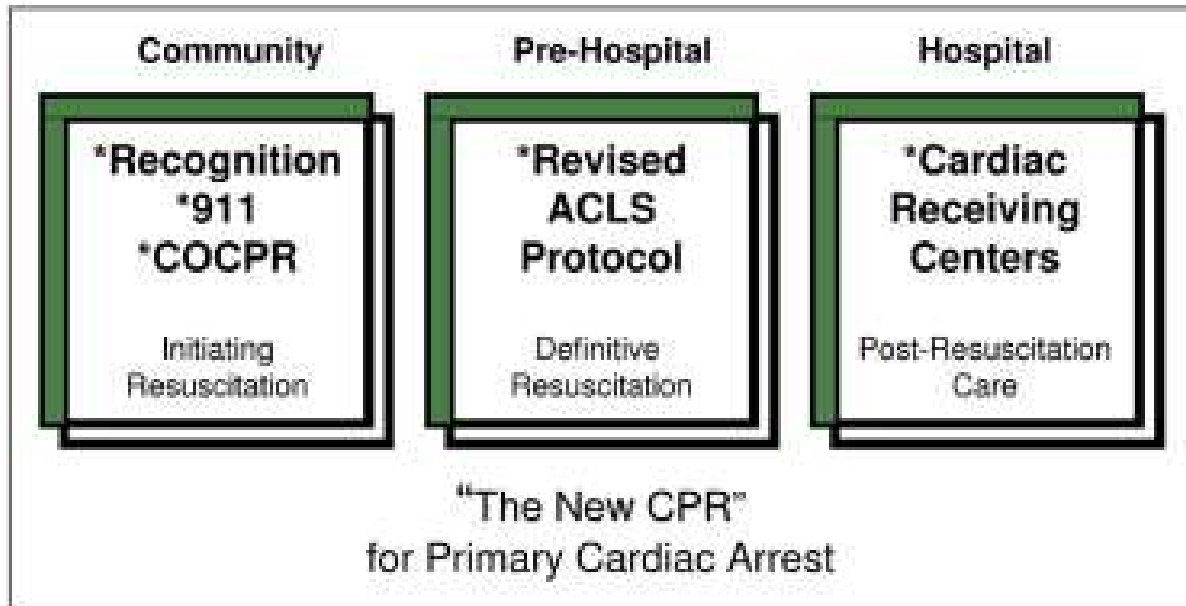


Figure 10. The Research Resuscitation Group at Sarver Heart Center advocates for a revised way to approach primary cardiac arrest (Ewy, Sanders, Kern, 2011).

In 2011, the group projected that 58,000 lives a year could be saved in the United States if cardiocerebral resuscitation were implemented nationwide. 58,00 lives saved would surely be a conservative estimate given the aging population and the equally, if not more, prevalent cases of preventable cardiovascular diseases based on today's numbers (Ewy, Sanders, Kern, 2011).



Figure 11. Drs. Ewy and Kern pose with Wilbur and Wilma after teaching CCO CPR in McKale Center before a University of Arizona basketball game.

There is no wonder why the research group here has given so much time and energy into educating the public about their findings. The data are what the data are. Because of these evidence-based practices, community organizations, corporate bodies, and other institutions have been able to train countless people on life-saving techniques. An amazingly effective approach to this education is simply training and increasing familiarity with these methods in addition to certifications. CPR certifications may be inconvenient or expensive for many members of the community. However, because of varying modes of informal training, a non-certified lay individual may feel more confident in their ability to perform CCO CPR and therefore potentially save someone's life. Informal training sessions such as the one before a basketball game in Fig. 8 are a great example of community education. Groups like Resuscitation Education

and CPR Training Group (REACT), led by UA COM-T medical students hold many community-education events at high schools, elderly homes, and for administrative staff on campus.

Regenerative Medicine

The next historical exploration within this thesis is from much more recent history. It is one step closer to a category of therapies that many believe could be the cure-all for HF. This new realm of cardiovascular therapy is referred to as regenerative medicine. The topic of tissue regeneration is one under great controversy and discussion within biomedical research. It has traditionally been theorized that there are several tissue types that have a set number of cells once an organ has reached maturation. Some of these categories of tissue are neurons, cardiac muscle, the lens of the eye, and cartilage. Because of the importance of each of these tissue types, significant funding and time has gone into research regarding the restoration, regeneration, and maintenance because the body cannot naturally restore naïve function by itself once damage has been done. The tissue in focus here is predictably cardiac muscle.

Cardiac muscle has a limited ability to regenerate. After sustaining damage to the heart muscle, mainly after a heart attack, it is thought that damaged tissue is replaced by scar tissue. Unlike skeletal muscle, the muscle within the heart cannot restore its own function after damage. Dead heart cells affect the ability of the heart to pump blood in two main ways. Dead or damaged cells are often not able to contract properly, and their ability to successfully transmit electrical signals in the heart has been diminished. Some of the novel therapies being investigated to combat this pathology would be the use of stem cell therapeutics and using growth factors to stimulate the growth of new heart muscle cells. Much research is looking into

both of these therapeutic options, especially at the combination of the two because stem cells have been shown to secrete growth factors.

To begin exploring this new world of treatment for HF, and potentially many other cardiovascular diseases, I will start by considering a landmark study to have come out of the Goldman Lab within the Sarver Heart Center (SHC). The publication is titled An Electrically Coupled Tissue Engineered Cardiomyocyte Scaffold Improves Cardiac Function in Rats with Chronic Heart Failure (Goldman, et al, 2014). As indicated by the title, this is a complex issue, involving considerable scientific details and jargon. To enable understanding by the public, the research involved is broken down here.

To begin with, the study is an examination of a patch (see Fig. 12) that is used to treat heart tissue that has undergone infarction, or a heart attack (or myocardial cell death). Heart attacks can lead to heart failure if a significant amount of tissue is damaged. The 2014 paper assesses the use of a patch from that lab that was constructed of neonatal cardiomyocytes, or heart muscle cells, on a three-dimensional fibroblast construct. Fibroblasts are connective tissue cells, and in the heart, they play a crucial role in contributing to the structure, function, and maintenance of the extracellular matrix of cardiomyocytes.

When the team constructed this patch for the first time, promising results were discovered. The cell-to-cell connectivity in the patch was extremely extensive. Because of this connectivity, the patch of heart muscle could smoothly transmit electrical signals which allowed the patch to spontaneously and synchronously contract.

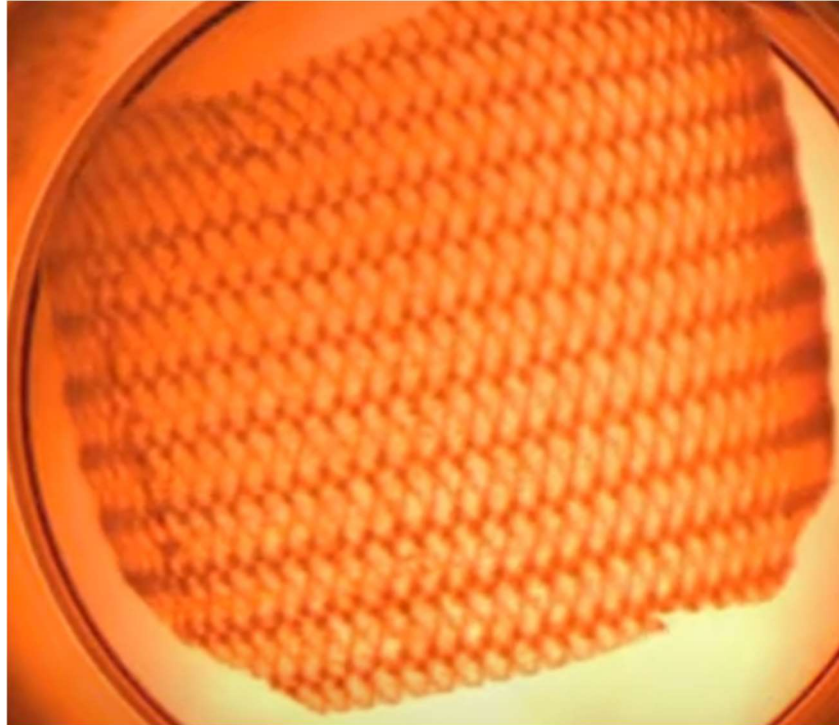


Figure 12. An image of a patch produced by the Goldman lab. The QR is a link to a video showing the patch synchronously and spontaneously contracting.



Another interesting find from the Goldman, et al, 2014 publication is that the patch could be electrically paced (or activated) at near physiological rates. This is great information because it means that if it were to be placed in vitro, or in a living animal or human, it could withstand the pace at which a heart might be beating. Other results of the study showed promising findings regarding the function of the heart after the patch had been placed. The patch showed increased function after placement of the heart at short term (3 weeks) and long term (18 weeks) time periods. In both time periods, it increased ejection fraction by 26% at 3 weeks and 54% at 18 weeks. Ejection fraction is the measurement used to assess the heart's left ventricle ability to contract and how much blood is pumped out of the heart during a heartbeat. It also showed a lower end diastolic pressure, which is important because it allows the heart to relax and fill blood

properly during the diastolic phase, which is the stage where the heart is relaxed and refilling with blood before the next contraction. The end diastolic pressure decreased 38%. One more significant finding was that this set of cells adhered to the heart had angiogenic cytokines which means that new blood vessels were formed in the tissue which supported blood flow in the heart muscle.

The patch constructed by the Goldman lab was one of the first of its kind. It is still one of the few patches that successfully promotes new blood vessel growth within the heart muscle, which is crucial in the field of tissue regeneration because any new tissue that has the possibility to be developed needs oxygen and nutrients from the blood to properly grow. Since the lab's production of the patch in the 2014 paper, many new iterations have been produced. Labs across the globe, including the Goldman lab, are constructing similar patches with cells engineered to secrete different cytokines and cell signaling proteins in an attempt to best restore heart function after damage.

The potential for regenerative therapies based on the work like that done in the Goldman lab is seemingly endless. There are exponential combinations of new and varied cell types and secretion factors that can be constructed into a cardiac patch to make it more effective. There are now several investigators working alongside Dr. Goldman to advance this research as far as it can go. Moreover, one can imagine that there is talk about regenerative therapies in other tissue because of the success in heart muscle in studies like this one.

V – Acknowledgements

I would first like to thank the many that have gone before me in the field of medicine. From Hippocrates to my principal investigator, Dr. Steve Goldman, there have been countless people to go before me. I truly do believe that in all fields, we are standing on the shoulders of giants and will continue needing to do so to make any advances in our respective fields.

Embarking on this project has been a particular treat because of all the rich stories I have been able to hear. The historical research advancements developed from my home institution have surely been amazing to learn about and I feel very proud to be a part of the legacy of investigators who developed them, but just as much as that, I loved hearing the very personal stories that make the history heart warming and personable. It's stories like those I heard from some of the founding memories of the College of Medicine – Tucson that make history come to life. There are countless stories about the community support and excitement for the establishment of the College of Medicine in Tucson. One of the stories that has been passed down in the medical school is that of the founding dean, Dr. Merlin K. 'Monte' DuVal who went to fill up his vehicle at a local Tucson gas station and the attendant recognized him as the person fronting the mission to establish the medical school. From there the attendant thanked him for his efforts to bring better healthcare to his community and asked Mr. DuVal to stay put as the attendant went to fetch something from the station. Upon the attendant's return to the gas pump, he gave Dr. DuVal a tin can filled with coins and dollars, totaling maybe only \$100 or so. He told Dr. DuVal that community members who used this gas station were so excited at the prospect of receiving a medical school and new hospital in Tucson that they had been pitching in a little bit of money to help fund the medical school every time that they had used the gas station.

Below are a few quotes from members of the University of Arizona College of Medicine – Tucson community who have been extremely influential in the development of the college. The hope is to honor them in recording their stories or saying, as well as potentially impart their wisdom to others by capturing it in writing.

From a Founding Radiology Faculty Member

We came (to Arizona to establish the medical school) because of friendship.

I had to meet with the president (University of Arizona, President Harvill) one-on-one, and he made it very clear what's expected of us to start this school.

I'm only in my 93rd year, so unless Steve (Dr. Steve Goldman) comes up with some better tissue than what we have for cardiac transplant, I don't expect to be around for too many more years, but nevertheless...

I started academia in 1948 when I started undergraduate school and I've been in academia ever since because I love the students.

From a Principal Investigator in Sarver Heart Center

The data are what the data are.

A lack of planning on your end does not constitute an emergency on my end.

A promise made is a debt unpaid.

Lastly, I would like to thank everyone in the Goldman lab for their support. Thank you to Adrian Grijalva for helping me format the history timeline as well as Dr. Jordan Lancaster and other lab members for suggesting ideas regarding the poster and presenting. I am thankful for the

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VI – Sources

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