CHAPTER 2

LITERATURE REVIEW

This chapter presents the fundamental anatomy and function of the cardiac and the primary clinical modalities of the cardiovascular imaging system. This chapter includes previous Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Ultrasound (US) imaging research and published studies on heart-related image registration and fusion.

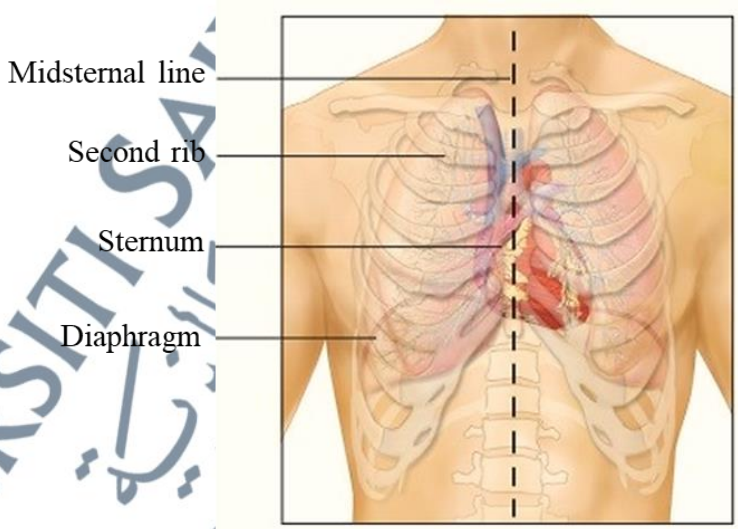
In studying cardiac imaging, it is essential to understand the basics of cardiac anatomy and physiology. Thus, Section 2.1 presents the heart's anatomy and physiology. It would provide a deeper understanding of the importance of the imaging procedure and help analyze the interpretation of the imaging outcomes. Subsequently, it is followed by the statistics and explanation of Cardiovascular Diseases (CVD) in Section 2.2. Various modalities of cardiovascular imaging, specifically US, cardiac CT, and MRI, are also addressed in Section 2.3. Lastly, image registration and fusion procedures are presented in Section 2.4, involving cardiovascular trimodality imaging. Note that this segment discusses a critical analysis of CT, MRI, and US image fusion technology.

2.1 The Heart

The cardiovascular system, also known as the circulatory system, composes the heart and blood vessels (arteries, capillaries, and veins) that carry nutrients and oxygen to the tissues and remove carbon dioxide and other wastes from them (Bit, 2020). As

the body undergoes major changes during its life cycle, the cardiovascular system's ability to meet the body's growing demands is an important condition.

The human heart is a muscular organ that comprises cardiac muscle fibers that could be thought of as a muscle rather than an organ. It is approximately the size of a man's closed fist, shaped like an upside-down pear, containing four chambers just to the left of the thoracic cavity's midline (Weinhaus, 2015). The heart can beat an average of 60-100 beats per minute (bpm) approximately 100,000 times per day (Ghuichard, 2015). The walls of the heart squeeze as the heartbeats send almost 12 pints of blood every minute throughout the body. Other than that, the blood is ejected from the heart and pushed throughout the body through the blood vessels each time the cardiac muscle contracts. It is located in the center of the chest gravity, as illustrated in Figure 2.1, which is in the mediastinum but is not specifically centered. A greater portion of the heart is on the mediastinum's left side than the right.

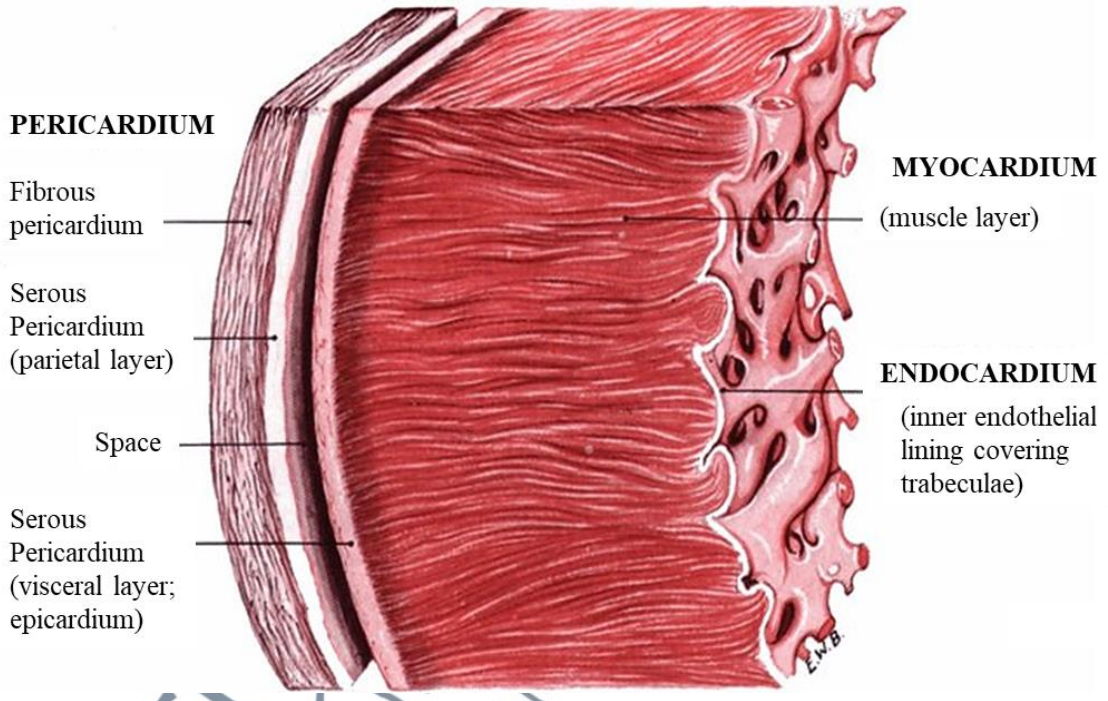


Source: Weinhaus (2015)

Figure 2.1: Position of The Heart in The Mediastinum

The human heart is located in the thorax, which serves as a protective covering for the organ, posterior to the sternum and the costal cartilage, and rests on the

diaphragm's upper surface. Two-thirds of the heart's volume is located in an oblique to the left of the thoracic midline. It resides in a space between the pleural cavities known as the middle mediastinum, the area inside the pericardium (the sac surrounding the heart), as shown in Figure 2.2. Here, a lubricating fluid is sandwiched between this serous membrane's inner and outer layers. Because of the fluid, the inner visceral pericardium can move smoothly against the outer parietal pericardium (Buckberg et al., 2018).



Source: Meo (2013)

Figure 2.2: The Heart Wall Section Displays the Components of The Cardiac Wall: The Myocardium, Pericardium, and Endocardium

The myocardium, the heart muscle that makes up the heart's four chambers, is visible inside the body. The two upper, thin-walled chambers, called atria, are primarily responsible for collecting blood. In contrast, the two lower, thick-walled chambers, called ventricles, are much more robust and responsible for blood pumping (Sliwa & Zilla, 2017). Note that blood is drawn from the body and pumped to the lungs by the

right atrium and ventricle. It is the job of the left atrium and ventricle to receive blood from the lungs and then pump it to the rest of the body. Wall thickness varies between heart chambers because of the different amounts of myocardium present, reflecting the different amounts of force each chamber must generate.

Blood circulation through the heart is governed by four valves, ensuring blood can only flow in one direction. Semilunar valves are located at the bases of the great vessels exiting the ventricles, while atrioventricular valves are located between the atria and ventricles. The bicuspid valve, also called the mitral valve, is in the left atrioventricular valve. In contrast, the tricuspid valve is in the heart's right atrium and right ventricle. The pulmonary semilunar valve describes a valve in the pulmonary trunk connecting the right ventricle to the pulmonary circulation. The aortic semilunar valve is the valve that connects the left ventricle to the aorta (Molnar & Gair, 2015). When they contract, the ventricles close atrioventricular valves to prevent blood from flowing backwards into the atria. Here, semilunar valves prevent blood from re-entering the ventricles when the ventricles relax.

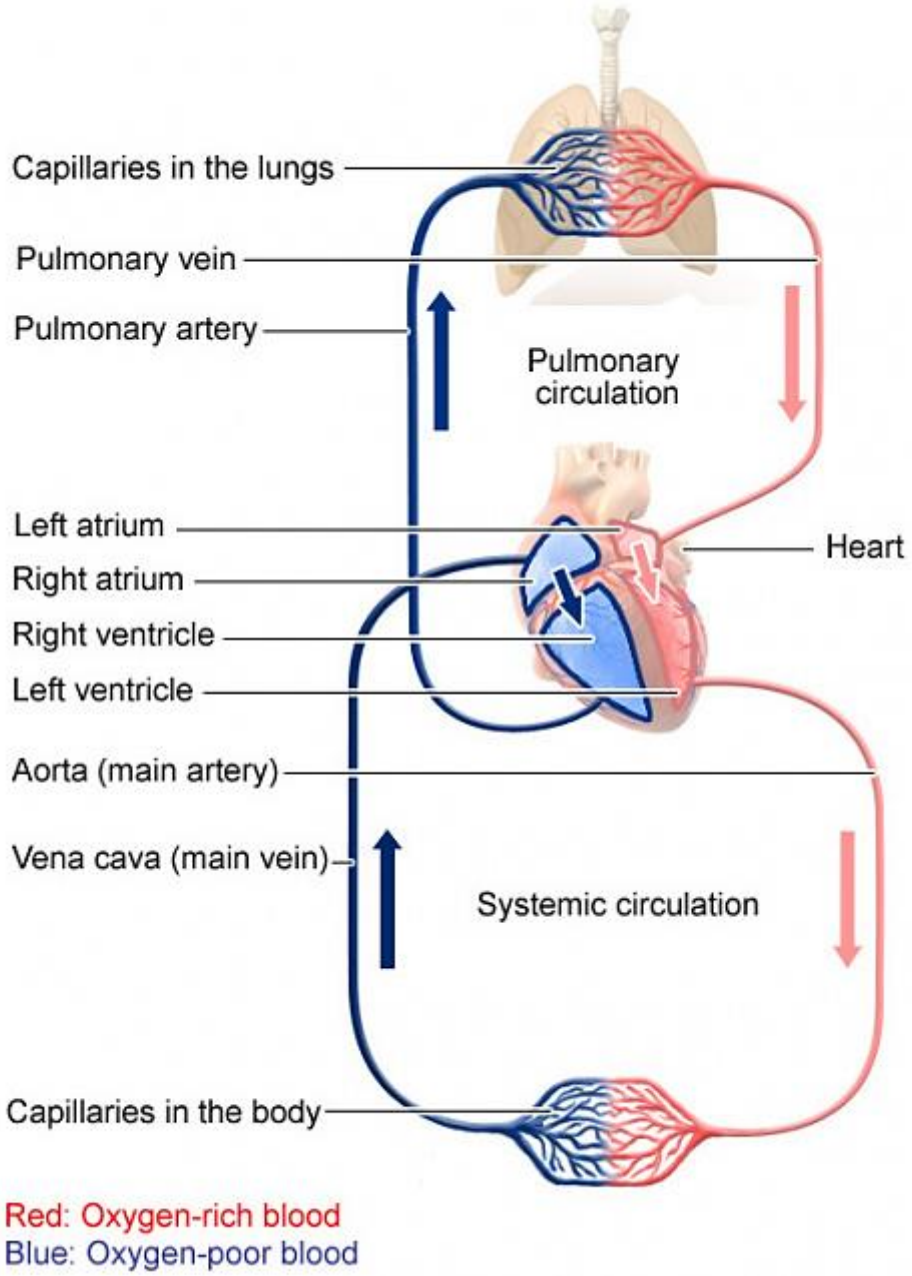
Even though the heart is full of blood, that blood does not do much to nourish or oxygenate the heart's tissues. On the other hand, heart tissues receive blood from a system of veins and arteries dedicated solely to this organ. The right and left coronary arteries originate at the base of the aorta and supply the heart with arterial blood. Meanwhile, the right atrium receives the deoxygenated blood that is returned from the cardiac veins as part of the venous drainage process.

Two main functions of the heart as a muscular pump are to assemble oxygen-poor blood from the body's tissues and pump it to the lungs to grasp oxygen and release carbon dioxide. Consequently, oxygen-rich blood will be collected from the lungs and pumped throughout the body's tissues (Biga et al., 2019). It must be noted that the blood

also circulates many other vital substances besides pumping oxygen-rich blood throughout the body's tissues to replace oxygen with carbon dioxide. Furthermore, the cardiovascular system collects waste products from the body's cells besides distributing oxygen and other nutrients, for instance, glucose and amino acids (Pittman, 2011).

2.1.1 Circulation of Blood Through The Heart

The heart is responsible for pumping blood throughout the body by forcing it through the body's blood vessels. It allows the blood to travel to all parts of the body. Blood circulation comprises two different circulatory paths: pulmonary circulation, the circuit through the lungs where oxygen is added, and systemic circulation, the circuit through the rest of the body to provide oxygenated blood (Goodwill et al., 2017). Both circulatory paths are necessary for the body to maintain oxygenated blood. The heart acts as a hub between the two systems, allowing blood to flow continuously throughout the body, as illustrated in Figure 2.3.



Source: Informedhealth.org (2019)

Figure 2.3: The Pulmonary and Systemic Pathways of The Blood Circulatory System

The process of pumping blood from the heart to the lungs for oxygenation and back to the heart is called pulmonary circulation. When oxygen-depleted blood from the body enters the right atrium via the superior and inferior vena cava, the blood exits systemic circulation and enters the pulmonary circulation instead. After that, the tricuspid valve allows the blood to be pumped into the heart's right ventricle. The

pulmonary artery receives blood pumped from the right ventricle through the pulmonary valve and branches off to supply the lungs on the right and the left. Note that the lungs serve as an exchange system, taking in oxygen and releasing carbon dioxide from the blood (Pinsky, 2016).

Systemic circulation refers to the flow of blood from the heart to the rest of the body and back again, with the latter delivering oxygen and nutrients to the body's tissues. At the same time, the former brings back waste products. From the pulmonary veins, oxygenated blood flows into the left atrium. Consequently, the blood is forced through the mitral valve and into the heart's left ventricle. The aorta is the body's largest artery, receiving blood pumped from the left ventricle through the aortic valve. Once the aorta has made its arch and divided into major arteries to the upper body, it must pass through the diaphragm before it can divide again to supply the lower body (Naeije, 2013).

2.1.2 Cycle of The Cardiac and Electrical System

Systole and diastole are the two phases of the cardiac cycle. The period of ventricular contraction is denoted by the term “systole”, whereas the period of ventricular relaxation is denoted by “diastole”. The heart's atria and ventricles are allowed to relax during diastole. Note that the pressure in the atrium is marginally higher than in the ventricle. Blood flows from the atria to the ventricles through the open tricuspid and mitral valves. The aortic and pulmonic valves close since the pulmonary artery and aortic pressures are greater than the ventricular pressures. During this phase, coronary blood flow is at its peak. The atrium contracts at the end of diastole, giving the ventricles an extra 10-20% of volume (Pollock & Makaryus, 2019).

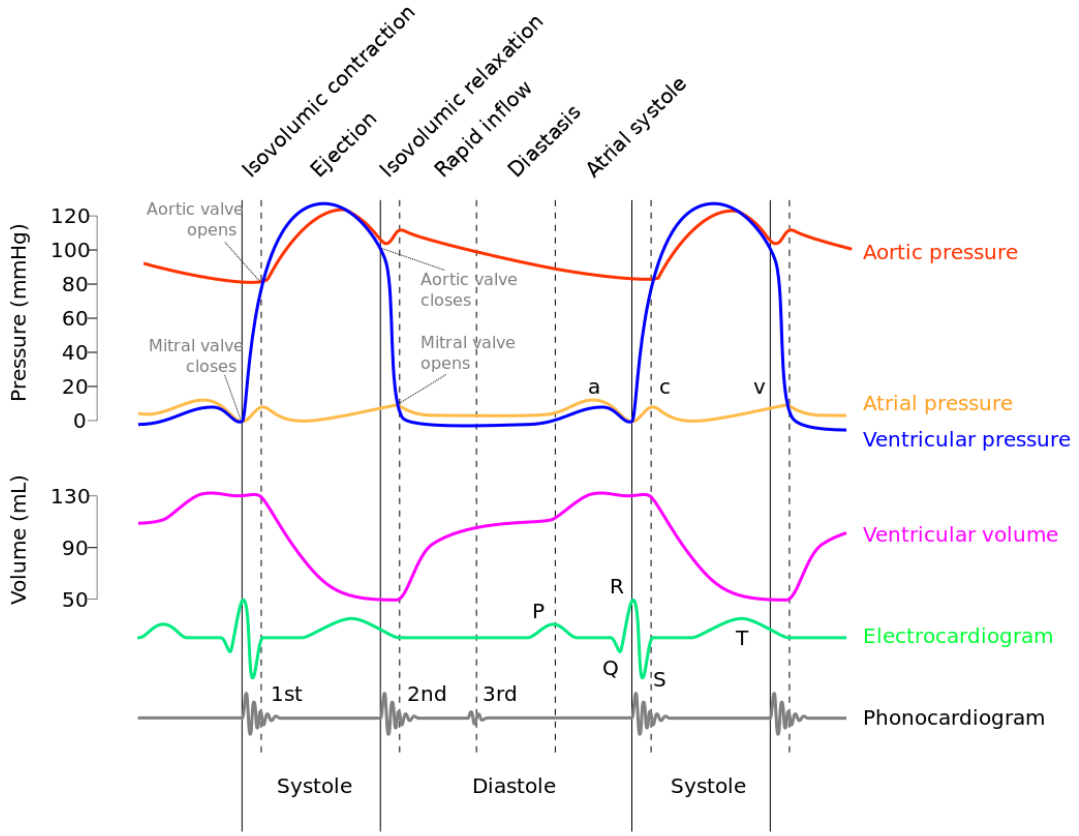
Meanwhile, in systole, the myofibrils of the ventricular myocardium contract, leading to a reduction in coronary blood flow and an elevation in pressure within the ventricle. Early in the systole cycle, the mitral and tricuspid valves will close. The next phase, isovolumetric contraction, occurs after the myofibrils have been shortened to the point where the pressure inside the ventricle is higher than the pressure inside the pulmonary artery and the aorta. The opening of the aortic and pulmonary valves and ventricular ejection follows it. Because the tricuspid and mitral valves are closed during systole, blood is allowed to return to the atria, which increases the volume and pressure of the atria. Myofibrils rapidly relax after ventricular ejection, resulting in a decrease in ventricular pressure. Once the atria are complete, the tricuspid and mitral valves open, and the aortic and pulmonary valves close. A rapid blood filling occurs during early diastole, and the filling rate gradually decreases as atrial pressure and volume decrease (Thiriet, 2014).

The mechanical reaction of myocardial cells to an electrochemical stimulus originating from the Sinoatrial (SA) node initiates cardiac systole, commonly referred to as the cardiac contraction phase. It does this by functioning as a pacemaker, which allows it to control the cardiac cycle. A depolarization wave traveling from the apex to the base of the heart sets off the heart's mechanical activation as it travels through the heart's fibrous skeleton (first the atrial mass, then the Atrioventricular (AV) node). An Electrocardiogram (ECG) reveals the fibrous skeleton's role in the conduction of electrical activity (see Figure 2.4) (Lakshmi, 2021).

Electrodes are attached to the skin to obtain the recording of the electrophysiological activity that occurs during each heartbeat. This recording is called an ECG. The P-wave, representing atrial conduction, and the PR interval, representing AV node delay, are depicted in the same figure. The QRS complex results from the

spread of electrical activity across the ventricular myocardium. The T-wave measures this process, also known as ventricular repolarization (relaxation of the muscles). Note that the ECG signal is frequently used as a gating signal in imaging devices to acquire cardiac images at various points in the cardiac cycle (Alemzadeh, 2022).

The events of the cardiac cycle in the left ventricle are depicted in Figure 2.4. A contraction of the atrium is represented by the “a” wave in the plot of atrial pressure. Meanwhile, an increase in pressure caused by the mitral valve bulging into the atrium after closure is represented by the “c” wave, and wave “v” represents passive atrial filling. During an ECG, the “P” wave represents atrial depolarization, the “QRS” wave represents ventricular depolarization, and the “T” wave represents ventricular repolarization. Blood reverberating from the sudden closure of the mitral valve (left A-V valve) makes up the 1st donates to the S1 heart sound in the phonocardiogram. On the other hand, blood reverberating from the sudden closure of the aortic valve makes up the sound labeled "2nd" and donates to the S2 heart sound (Mitchell & Wang, 2015).



Source: Lakshmi (2021)

Figure 2.4: The Electrical and Mechanical Activity of The Heart During One Complete Beat of The Heart

2.2 Cardiovascular Disease

CVD is a common term that shows conditions affecting the heart or blood vessels. It is a collection of diseases affecting the cardiovascular system. These include coronary heart diseases, stroke, aortic aneurysms and dissection, peripheral arterial disease, deep vein thrombosis, rheumatic heart disease, congenital heart disease, and other less common CVD (Westerby, 2011). Tobacco use, physical inactivity, and an unhealthy diet are the primary causes of CVD. It raises the risk of heart attack and stroke. Apart from that, CVD risk factors include diabetes, obesity, high blood pressure, and a family history of heart disease.

CVD remains the leading cause of death worldwide (Khalil et al., 2018). It accounted for approximately 58 million deaths in 2005 of all global health, with CVD estimated at 30%. This part is similar to that caused by infectious diseases, malnutrition, and a combination of maternal and perinatal conditions (World Health Organization, 2005). It is essential to realize that most of these deaths are people under 70, 46% in a more fruitful life span. Note that 79% of the disease burden is in this age group caused by CVD (Yuyun et al., 2020).

Half of the deaths caused by non-communicable diseases are due to CVD between 2006 and 2015 and are assumed to increase by 17%. Besides, death is predicted to decline by 3% from infectious diseases, malnutrition, and a combination of maternal and perinatal conditions (Reddy, 2021). Non-communicable diseases are among almost half the disease burden in low- and middle-income countries (Lopez et al., 2006; Wamai et al., 2018). CVDs, for example, heart disease and stroke, have become the world's leading causes of death and disability by 2020, with the number of deaths expected to grow to more than 20 million per year and more than 24 million per year by 2030.

Table 2.1 indicates a worldwide percentage of death causes attributable to CVDs (Karimi & Salcudean, 2020). The leading cause (42.6%) of deaths from CVD was coronary heart disease, as presented in Table 2.1, which is the disease of the blood vessels supplying the heart muscle. It was accompanied by a stroke (17.0%) triggered by blood flow damage to the brain. In addition, (10.5%) of deaths were ascribed to hypertension and (9.4%) to heart failure. Peripheral arterial diseases account for (2.9%) of CVD-related deaths due to the arteries diseases that supply blood to the arms and legs. Around (17.6%) of deaths are caused by other CVD. Hence, to improve the well-being of patients and reduce this troubling mortality, additional measures should also be directed at diagnosing and treating CVDs.

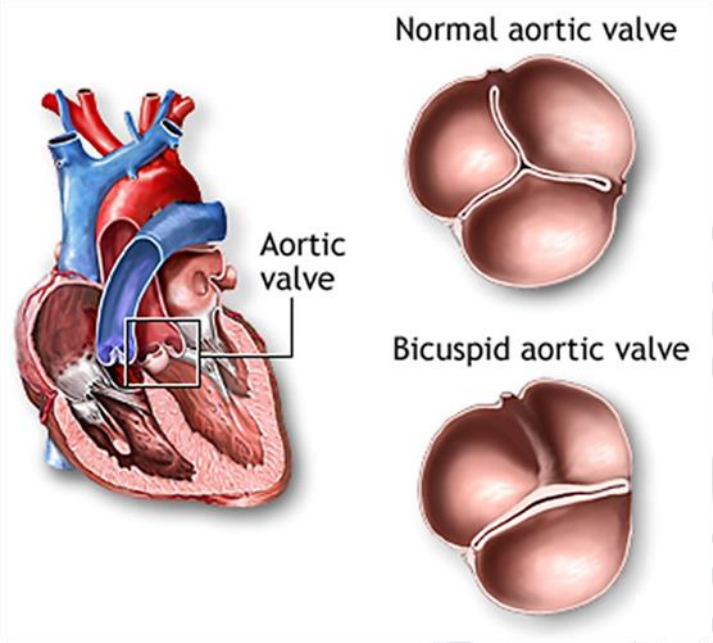
Table 2.1: Percentage of Cause of Death Attributable to CVDs in 2017

Types of CVD	Percentage cause of death (%)
Coronary heart diseases	42.6
Stroke	17.0
High blood pressure	10.5
Heart failure	9.4
Peripheral arterial diseases	2.9
Other cardiovascular diseases	17.6

Source: Virani et al. (2020)

2.2.1 Aortic Valve Disease

The aortic valve (refer to Figure 2.5), shaped like a semilunar valve, is one of the heart's valves frequently affected by CVD. It is located in an intermediate position between the left ventricle and the aorta and plays a crucial role in regulating and controlling blood flow. Its primary function is to prevent backflow and reduce pressure loss by enabling blood to flow smoothly from the heart's left ventricle to the body's tissues and organs. The leaflet of the aortic valve opens and closes approximately 100,000 times a day, equivalent to 3.7 billion times over its lifespan, placing it under tremendous tensile, shear, and bending forces (Hinton & Yutzey, 2011). Although aortic valves have often been viewed as reactive organs, they undergo a series of complex operations at the cellular and molecular levels to maintain their function. Aortic valves are exposed to extreme hemodynamic and mechanical conditions, which are now widely acknowledged.



Source: Borger et al. (2018)

Figure 2.5: Normal and Bicuspid Aortic Valve

Although heart valve disorders can harm one's health, aortic valve diseases have severe repercussions, which consequently attaches high importance to the functions of this valve (Nishimura, 2002). Usual abnormalities in the aortic valve include narrowing the aortic valve opening during systole (aortic stenosis) and aortic regurgitation. This happens when the valve leaks to the left ventricle during diastole (Sequeira Gross et al., 2021). The overall disease burden is estimated at 3% to 4% of adults due to moderate or severe aortic stenosis and regurgitation (Coffey et al., 2021). Other than that, the prevalence of aortic stenosis and aortic regurgitation increases with age and is estimated at 1% of the population over 55. Meanwhile, 6% of the population over the age of 75 years has moderate to severe aortic stenosis or regurgitation.

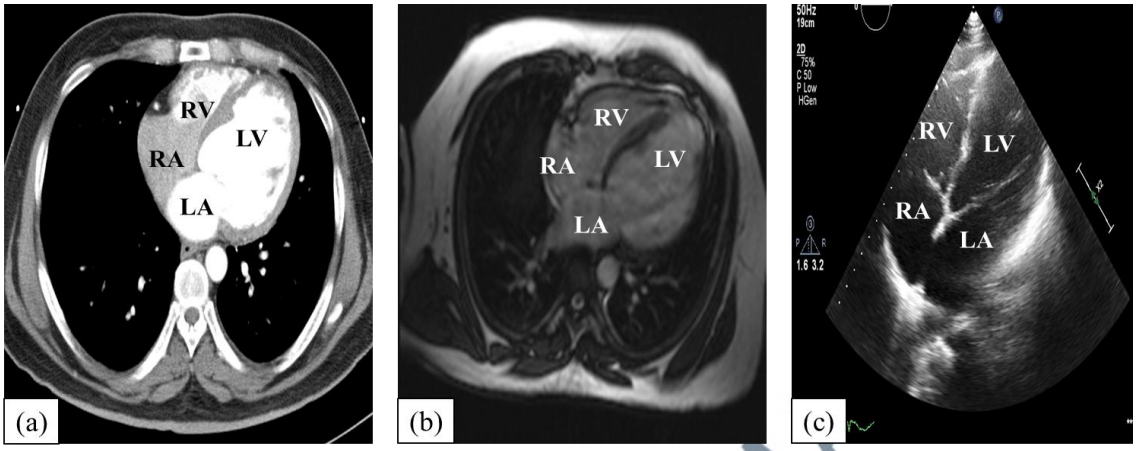
Surgery, either for replacement or repair of the aortic valve or both, is required to prevent irreversible left ventricular dysfunction. The surgery required for an aortic valve is Transcatheter Aortic Valve Replacement (TAVR) or Implantation (TAVI). This

minimally invasive procedure involves the insertion of a new valve without first removing the old, damaged one. A new valve is surgically implanted inside the damaged one (Mahmaljy & Young, 2019).

2.3 Medical Imaging Modalities for Cardiac

Medical images are used for diagnosis, planning, treatment guidance, and monitoring the progression of diseases increasingly in healthcare. In certain studies, multiple images are collected from subjects at various times and with different imaging modalities. In this study, we will use three modalities for cardiac imaging: CT, MRI, and the US. Consequently, we will employ the protocol for image registration to combine the information from all modalities.

In theory, medical image registration might entail putting all information of a given patient, irrespective of type, into a single representation of a person acting as a multimedia electronic patient record with implied information on the relationship between spatial and temporal information (Song et al., 2017). For example, Figure 2.6 illustrates the cardiac image for CT, MRI, and the US, indicating the right atrium, right ventricle, left atrium, and left ventricle. This image is obtained from a patient diagnosed with CVD in Hospital Serdang. The explanation of the outcomes of the images for all three modalities will be presented in the next subsection.



Source: Retrieve Figures from Hospital Serdang

Figure 2.6: (a) CT Cardiac, (b) MRI Cardiac, (c) Cardiac Ultrasound
Right Atrium (RA); Right Ventricle (RV); Left Atrium (LA); Left Ventricle (LV)

2.3.1 Computed Tomography (CT)

Cardiac CT provides cross-section diagrams of the heart structure. It reflects the X-ray tissue's attenuation properties (Mahesh & Cody, 2007; Franssens et al., 2017). X-ray thin radiation is used to analyze the Field of View (FOV) and calculate the yield line's attenuation at any conceivable angle of the imaging body. Note that line attenuation steps recreate a three-dimensional (3D) map of the body with a single point on the map with an X-ray attenuation value. Spiral or sequence techniques can be used to recreate the 3D image of the heart. Other than that, contrasting agents may also enhance the visualization of the blood vessel and detect the appearance of the tumor due to the disparity in the absorption of tumor contrast within the tumor and normal surrounding tissues.

Cardiac CT is commonly used as a tool for preoperative imaging, whereas multislice CT Angiography (CTA) is a good imagery procedure for patients with coronary artery disease (Ropers et al., 2003; Taron et al., 2019). Besides, in patients at risk of coronary heart disease, CT and CTA are commonly used for calcium rating (Guanyu et al., 2016). Furthermore, CT scans helped detect regional infarctions of

patients with cardiac diseases (Wong et al., 2016) and aneurysm morphodynamics (Firouzian et al., 2013) through recent developments in deformable registration techniques. In addition, volumetric CT scans provide important details, including the valve's anatomy and severity of stenosis, for treatment planning (Zhenzhen et al., 2017). However, ionizing high-dose radiation does not allow cardiac CT to be used as intraprocedural guidance in real-time. It also cannot provide hemodynamic information, including transvalvular pressure gradients, nor detect valve regurgitation (Eun et al., 2008).

According to what was discussed in the first paragraph of this section, the CT contrast indicates the amount of X-ray attenuation caused by the various types of tissue. The density of tissues and skeletal elements determines the range of attenuation coefficients. Consequently, similar tissue density and hydrogen, oxygen, and carbon atom ratios can be found in blood and soft tissue. Their X-ray attenuation properties are very similar, making them appear dark in the image. CT images demonstrate bone as brighter than blood or soft tissue because calcium in bone attenuates X-rays more than these other substances. Note that hydrogen makes up the majority of fat, and air makes up the lungs. Air has a very low physical density and appears black. When the density is higher, the structure shows up more clearly. Calcium appears to be brilliant white, whereas air appears to be black, and muscle and blood appear to be grey. Over 5,000 different shades of grey, with zero in the center, are used to create CT images (water) (Bell & Greenway, 2015). Consequently, a CT image can tell the difference between blood and air, fat, and bone, but not between blood and muscle or other soft tissues.

In areas of the body with neither air nor fat to serve as a natural contrast agent, such as the Left Ventricle (LV), injecting a radiocontrast agent to differentiate between blood and soft tissue is necessary. Similarly, the lumen and the coronary artery wall

need to be differentiated, and this can only be done with contrast enhancement. Small amounts of coronary calcium and the contrast-enhanced lumen of medium-size coronary arteries can be seen thanks to the enhanced absorption of X-rays by elements of high atomic number, such as calcium and iodine. In addition, cardiac CT scans provide stunning clarity of the heart's valves. Several cardiac CT images, including valves and surrounding structures, are displayed in Figure 2.7.

Source: Bennett et al. (2012)

Figure 2.7: Anatomy of the Aortic Root as Seen on A 64-Channel Dual-Source Cardiac CT scan with ECG Gating
(a) Right (R), Left (L), and Noncoronary (N) Cusps are Visible in This Double Oblique CT Image of The Aortic Valve
(b) The Right (White Arrow) and Left (Black Arrow) Main Coronary Arteries Can Be Seen as They Originate in This Double Oblique CT Image Taken from A Slightly More Craniocaudal Angle
(c) The Three-Chamber View of a Cardiac CT Image Obtained After Long-Axis Reformatting Is Analogous to Parasternal Long-Axis Images Obtained During The US Ascending Aorta (AA); Anterior Leaflet of The Mitral Valve (ALMV); Left Atrium (LA); Left Ventricular Outflow Tract (LVOT); Right Ventricular Outflow Tract (RVOT); Sinuses of Valsalva (SOV); Sino Tubular Junction (STJ)

Cardiac CT is not considered the definitive method for assessing heart valves. Generally, it offers higher resolution than cardiac MRI, allowing for visualization of valve leaflet movement and as a supplementary tool to US and MRI. However, there are significant drawbacks to using retrospective ECG-gated CT due to its reliance on ionizing radiation to evaluate valve structure and function. Unlike coronary artery assessment, which can be performed at specific points in the heart's cycle, valve

function assessment with CT requires imaging throughout the cardiac cycle, leading to increased radiation exposure. As a result, cardiac CT for valve evaluation is typically reserved for specific cases, such as patients with metal implants or pacemakers who cannot undergo MRI for medical reasons (Feuchtner, 2013). In cases of patients undergoing cardiac valve procedures, preoperative CT can be beneficial as it allows simultaneous evaluation of coronary arteries to identify any significant arterial narrowing. Additionally, postoperative patients with prosthetic valves may find CT angiography valuable if US and MRI fail to provide sufficient information.

2.3.2 Magnetic Resonance Imaging (MRI)

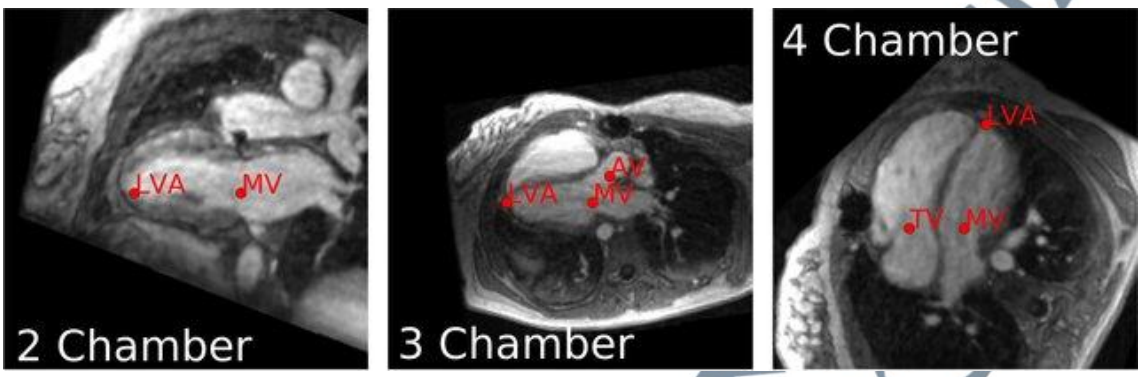
Cardiac MRI generates three-dimensional cross-sectional images comparable to those produced by cardiac CT. MRI experiments utilize powerful magnetic fields to generate visual representations of atomic nuclei, including water molecules, hydrogen atoms, or fat molecules within the body (Constantinides, 2017). The spin of the atomic nucleus can be seen as a magnet vector, making the proton look like a magnet. The initial sequence of thrilling pulses and recording signals are essential for acquiring the image. The amplitude of the signal is then used to create maps showing the heart's structure. Note that MRI provides a high resolution and tissue contrast images that are useful for the examination of the heart chamber (Tavakoli et al., 2013), the heart valves (Dowsey et al., 2006), the size and flux of the main arteries (Bustamante et al., 2015) as well as surrounding structures (Zhuang et al., 2010). The pericardium MRI diagnoses several CVD, such as inflammatory conditions and tumors (Wang et al., 2011; Weissler et al., 2015).

In a study conducted by Guang et al. (2017), MRI was used to evaluate the impact of coronary artery disease, including inadequate blood flow to the heart muscle and

scarring within the heart muscle resulting from a heart attack. Additionally, MRI has been employed for preoperative planning procedures, as discussed by Washburn et al. (2017). It also tracks the progression of certain disorders over time, as Molko et al. (2002) highlighted. Furthermore, MRI enables the assessment of the cardiovascular anatomy and blood vessels, as demonstrated by Gilbert et al. (2014), and the examination of the effects of surgical interventions, particularly in congenital cardiovascular patients, as Hamon et al. (2007) mentioned. Moreover, MRI provides valuable information on heart necrosis and fibrosis using late gadolinium, enhancing imaging capabilities, monitoring iron overload, and characterizing myocardial tissues through relaxometry, as Santarelli et al. (2015) noted. However, it is important to consider that MRI tests are considerably more expensive and contraindicated for patients with metallic implants such as graft stents, cardiac pacemakers, or hemodynamic devices than cardiac CT. Meanwhile, MRI is considered the gold standard for cardiac assessment. Nevertheless, it still has limitations in resolving valve leaflet details. Therefore, MRI may not be a practical option for surgical planning related to valve diseases.

In recent studies on MR imaging of the aortic valve, the application of Steady-State Free Precession (SSFP) acquisitions with ECG gating has been utilized (Le et al., 2017). These acquisitions have been employed to assess the structure of the valve as well as the size of the valve orifice. Typically, phased-array coils are employed. MR imaging parameters can differ depending on the manufacturer of the MR imaging system. However, they are typically optimized to provide the highest possible spatial resolution. The section thickness was 8 mm, with a 0-2 mm gap. Images in orthogonal planes, such as two-chamber, four-chamber, and long-axis (occasionally referred to as

three-chamber) views, as portrayed in Figure 2.8, are generally obtained during the diagnostic process.



Source: Le et al. (2017)

Figure 2.8: MRI Images in Two-Chamber, Three-Chamber, and Four-Chamber
Aortic Valve (AV); Mitral Valve (MV); Left Ventricle Apex (LVA); Tricuspid Valve (TV)

A turbulent flow is the result of stenosis and regurgitation of the aorta. Signal voids are created when intravoxel phase dispersion occurs in turbulent flow regions. These signal voids appear like dark "jets" coming from the valve. When attempting to diagnose aortic stenosis or regurgitation, discovering a jet can be of assistance. On the other hand, the echo time, flip angle, and imaging plane contribute to how large a jet appears. As a result, the size of a jet cannot be used to measure the degree to which stenosis or regurgitation is present (Nayak et al., 2015).

Aneurysmal dilatation can often be detected by imaging the ascending aorta, which can be done with or without contrast material. Imaging myocardial enhancement delayed from its normal acquisition time may help characterize left ventricular fibrosis in the presence of aortic stenosis. Preliminary research suggests that the degree of improvement in left ventricular function following aortic valve replacement is inversely related to the extent of delayed enhancement.

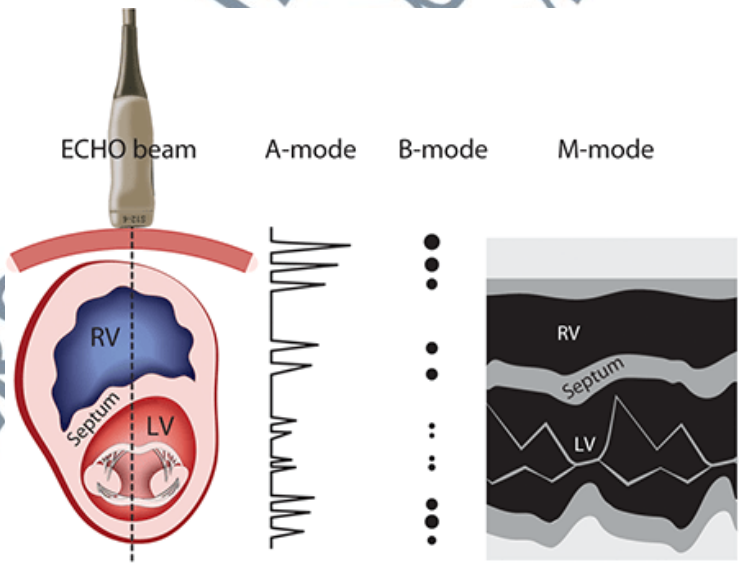
2.3.3 Ultrasound (US)

A US image of the heart is called echocardiography. It is a crucial imaging test for detecting cardiac disease. The basic principle of US is that a US probe generates high-frequency sound waves directed toward the tissue. As the waves reach tissue limits with different reflective indices, a portion of the sound waves that penetrate the tissue reflects the transducer. Consequently, the reflected signals are identified and analyzed using a US device to recreate images of the cardiac structure. The US in two-dimensional (2D) is currently the most common preoperative imaging technique for cardiac pathology (Ahmed & Sasikumar, 2022).

This modality enables clinicians to determine the degree of valve regurgitation or stenosis, the size of the valve annular, leaflet involvement, the structural integrity of the chordal and papillary muscles, and the total Left Ventricular (LV) size and LV systolic activity in valvular disease (Li et al., 2015b). In hypertensive patients, the US plays a vital role by presenting information on LV mass (Dey et al., 2010), the function of LV systolic, damaged LV diastolic function, and also the function and size of the Left Atrium (LA) (Barbosa et al., 2010). Besides, the Intravascular US (IVUS) technology can also recognize coronary artery diseases (Alavi & Masaeli, 2016). US offers surveillance for early detection of heart disease and intervention in rheumatic heart disease and ischemic heart disease (Beaton et al., 2012; Andrea et al., 2020). It can also be utilized for postoperatively imaging guidance to help doctors in operations due to its real-time capacity without ionizing radiation (Li et al., 2015). Other than that, it is also a low-priced choice compared with other imaging modalities (Grewal et al., 2009; Brien et al., 2020). Nevertheless, due to speckle noise and restricted FOV, the quality of US images is lower than the other imaging modalities, such as cardiac CT and MRI (Hareendranathan et al., 2018).

Various US modes are used for imaging, including A-mode, B-mode (2D echocardiography), M-mode, and Doppler mode. M-mode US, called motion-mode US, provides a one-dimensional (1D) view of reflectors along a single US line. By employing M-mode, physicians can observe the motion of cardiac structures such as valves. This technique also enables more accurate measurements of chamber size, wall thickness, and linear dimensions (Mohamed et al., 2010).

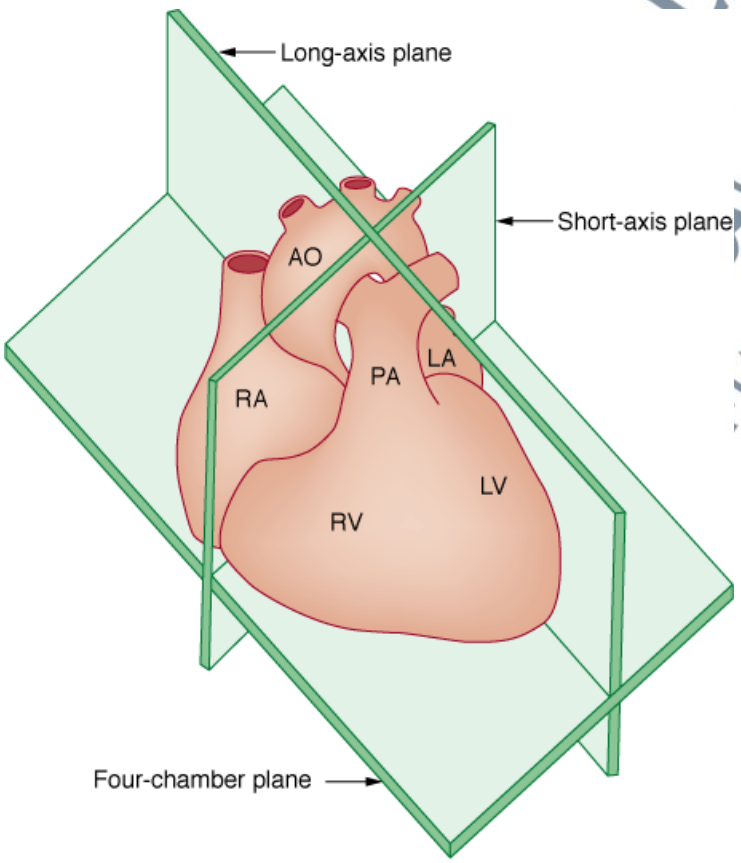
The amplitude-modulated display, also known as the A-mode display, was the initial mode of the display. On the screen, a positive deflection (spike) indicates the presence of a "structure" in the path of the US beam, and the height (amplitude) of the spike indicates the strength of the returning signal in A-mode. Signals are transformed from spikes to dots in the intensity-modulated display, called B-mode (B = brightness). Note that the dots are brighter and more visible when the spikes are higher (indicating a stronger signal). It is the fundamental concept behind M-mode and 2D imaging (see Figure 2.9) (Siassi et al., 2019).



Source: Siassi et al. (2019)

Figure 2.9: 2D Parasternal Short-Axis View of The Heart at The Level of The Mitral Valve Leaflet Tips, With A-Mode, B-Mode, And M-Mode Schematics Depicted for Clarity (Assuming A Single US Beam)
Right Ventricle (RV); Left Ventricle (LV)

High-resolution images of the heart's structure and function can be obtained in real-time using 2D US, also known as B-mode imaging. The long parasternal axis, short parasternal axis, and apical four-chamber views are the three fundamental imaging planes utilized in the heart (see Figure 2.10) (Fuster & Narula, 2022). Note that the long parasternal axis view images the heart from the aorta to the apex.



Source: Fuster & Narula (2022)

Figure 2.10: The Three Fundamental Planes Of Tomographic Imaging Utilized In US Aorta (AO); Left Atrium (LA); Left Ventricle (LV); Pulmonary Artery (PA); Right Atrium (RA); Right Ventricle (RV)

2.4 Image Registration

The process of capturing and analyzing medical images is essential for clinical uses. Medical imaging is often used throughout the clinical workflow, from the initial diagnosis to planning to the actual intervention. Because it provides physicians with a visual of structures they otherwise would not be able to see, medical imaging is

particularly important in procedures for minimally invasive treatment. When describing a particular clinical case, referring to multiple images acquired at various time points or viewed from various angles is common. Images captured with various imaging techniques can also be included. Therefore, image registration is a technique that frequently proves helpful in integrating various information sources.

Image registration of the same or different modalities is essential in providing additional details to the physician that could not be obtained from a single modality alone. Other than that, image registration helps practitioners combine data from different sources and offers a second opinion on disease diagnosis and treatment. Integrating all imaging modalities from image registration for spatial alignment is the most critical stage of the fusion process (Alam & Rahman, 2019).

2.4.1 Theoretical Background

Image registration is a vital technology that has benefited from 20 years of medical image analysis development (Razzak et al., 2018). It is a method for determining the correspondence of features between images taken at different times or with various imaging modalities. The correspondences can be used to change the appearance of one image such that it strongly matches another by rotating, translating, stretching, and other methods. Consequently, the pairs can be compared, mixed, or evaluated directly. The most intuitive application of registration is to improve the various locations of the patient between scans (Crum et al., 2004; Dong et al., 2019).

What we mean by “image registration” is the process of determining a transformation that moves features from one coordinate space to another. It allows one to transfer information between the two different coordinate spaces. Extracting features, defining geometric transformations, measuring similarities, and optimizing the process

are typical first steps in image registration workflows. Note that the chosen feature for mapping is first extracted in feature space. Second, the search space determines how much the images need to be changed to align (Zitova, 2019).

For the sake of argument, let us say we need to spatially register two images, one of which is a moving image $A(x)$ defined over a domain $x \in V_A$, and the other a fixed image $B(x)$ defined over a domain $x \in V_B$. The points in $A(x)$ are transformed to their equivalents in $B(x)$ using the transformation $C(x)$, as illustrated in Figure 2.11. Transformations such as the affine, curved, projective, and rigid varieties are frequently employed. The quality of the estimated similarity between the original still image and the transformed moving image is determined by a similarity measure. Hence, determining the transformation parameters necessary for spatially aligning the images can be achieved by optimizing a similarity measure. This measure is derived from various features within the image, such as the voxel intensities, and involves maximizing or minimizing it to find the optimal alignment. It will allow the search for the optimal transformation parameters to be completed. According to the optimization strategy, the search process will continue until convergence. At this point, the transformation parameters will have been discovered to minimize or maximize the similarity measure.

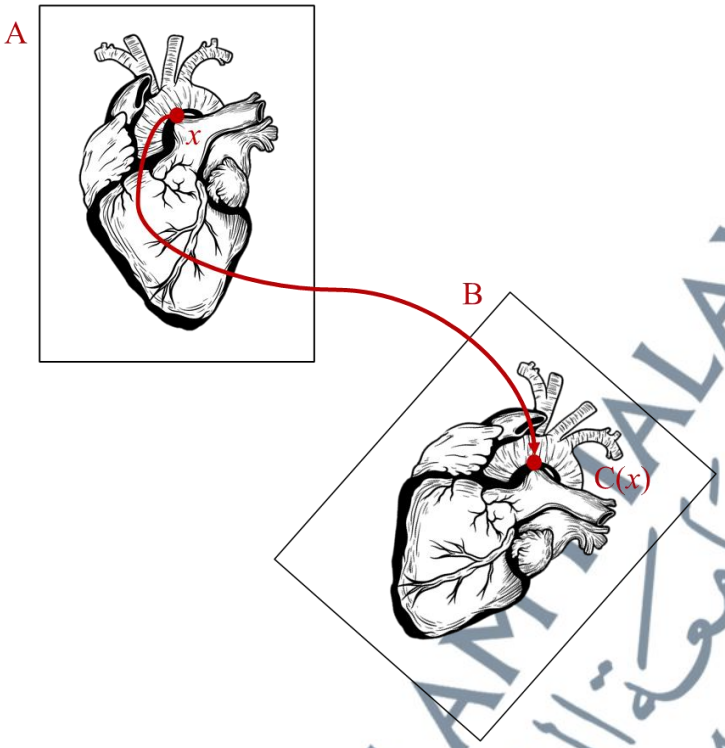


Figure 2.11: *C*(*x*) is A Mapping Function That Locates in The Fixed Image *B* The Position That Corresponds to The Point *x* in The Moving Image *A*

Figure 2.12 illustrates the typical workflow for image registration as well as the primary components that make up these pipelines. Image 2, the static image, is fed into the registration algorithm alongside Image 1, the dynamic image, and some initial transform estimates. During registration, points from the static image are converted to the dynamic image to apply the similarity measure or metric. It is necessary to use an interpolator to estimate the voxel intensities at the transformed points if they do not fall precisely on the discrete grid positions that define the dynamic image.

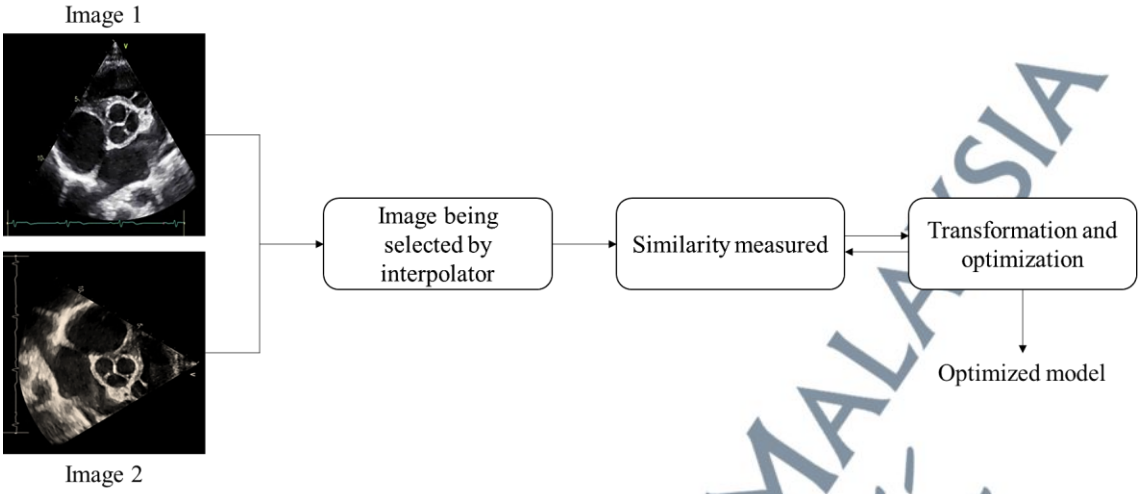


Figure 2.12: Standard Procedure for Image Registration Pipelines

Image registration is an active area of study. Image registration can be defined as the overlay of two or more images taken from various points of view or by multiple sensors on the same scene at different times (Nag, 2017). It aligns two images geometrically, which are static and dynamic images. Most of the early work in medical image registration was collected with multiple modalities, for instance, MRI and CT or Positron Emission Tomography (PET), when registering brain images of the same subject (Pelizzari et al., 1989; Hill et al., 1991). Due to various imaging conditions, the present variations between images are introduced.

Multimodal image registration is essential in informing the physician that they cannot only get through a single modality alone. The image fusions allow a physician to quickly incorporate data from the modalities and assist them in diagnosing and treating the patients' diseases in their decision. Other than that, multimodal image registration requires two or more modalities to fuse them so the physician may interpret the details from the superimposed or side-by-side images. The fusion could also be done using static images, such as CT and MRI, or Single Photon Emission Computed Tomography (SPECT) and PET images, which will result in static fusion (Liu et al.,

2014). Besides, it can also be performed with a real-time modality, such as US with static images, for instance, US and CT or US and MRI, that will result in real-time fusion (Punithakumar et al., 2014).

2.4.2 Image Registration for Cardiovascular

Registration of cardiac images is a more nuanced process compared to the other parts of the body, precisely due to nonrigid imaging and associated motions of the heart and thoracic structures (Mäkelä et al., 2002). In addition, cardiac images are typically taken in less resolution than any other organ image. Several works on image registration of cardiovascular have been published prior to medical image registration. Gilardi et al. (1996) have studied the methods and clinical applications to incorporate multimodal biomedical images of the heart. Apart from that, the aspects of cardiac PET and MRI correlation were briefly explored by Habboosh (1992).

Other than that, few studies are associated with the cardiac structure with multimodality fusion, such as using CT and MR images discussed by Carminati et al. (2012) and MR and SPECT images studied by Santarelli et al. (2001). However, these studies only result in static image fusion, which is lacking in providing real-time information. Utilizing US in imaging the heart will allow the physician to assess the anatomical information and the functional changes of the heart. Moreover, several works use US fusing with another modality, such as US with MR images (Kiss et al., 2012; 2013). The cardiac application also included US fusion with CT images (Giessen et al., 2010).

2.4.3 Trimodality Image Registration

In two separate panels, two pairs of registered images are obtained using three different sets of images: axial, coronal, and sagittal views from various modalities. In existing Treatment Planning Systems (TPS), dual-modality image fusion techniques can merge and present two sets of images in a single panel and operation. Nevertheless, surgeons still require additional details from other modalities for treatment procedures (Lahat et al., 2015), and the current setup lacks convenience in providing real-time information (Khalil et al., 2018). This study focuses on developing trimodality image registration techniques to enhance image registration performance. These techniques enable the merging and simultaneous display of all image sets involving three modalities (CT, MRI, and US) within a single panel and operation for patients with CVD.

In previous research, trimodality image fusion techniques have been employed in the context of radiotherapy treatment. Guo et al., (2014) focused on brain tumors as a disease where trimodality techniques involving MRI, CT, and PET were utilized. They developed a method for trimodality image fusion using a commercial system called Advantage Workstation by GE Healthcare, Milwaukee, WI. This technique enables the registration of PET/CT + MRI trimodality images within a single application, facilitating the diagnosis of brain and body imaging. The study demonstrated that trimodality image fusion techniques positively impact radiotherapy treatment planning for brain tumors. It was observed that these techniques reduced inter-observer variation in the shapes of Gross Tumor Volumes (GTV) and intra-observer variation in GTV volumes for brain tumors. Therefore, the findings suggest that this method can be useful in radiotherapy treatment planning, reducing uncertainties associated with brain tumors.

Samarin et al. (2015) proposed a theory on the registration accuracy of image fusion in two distinct contexts: a trimodality PET/CT + MR system and a SPECT + CT system. Their research aimed to determine how well different scanners can be integrated into a single workflow using a patient shuttle system that allows seamless patient transfer without repositioning. In their proposal for trimodal PET/CT + MR imaging fusion from 2015, Samarin et al. noted that a shared coordinate system eliminated the need for software-based or manual registration correction between the CT and MR data sets. Consequently, it is possible to perform sequential PET/CT + MR and SPECT + CT imaging by utilizing an in-house solution for a dedicated patient shuttle system that was recently developed.

According to the findings above, much work has been done in the medical field. However, the significance of trimodality imaging in cardiovascular and treatment procedures and its application in cardiac valves has not been fully discussed. These registration frameworks were developed to guide treatment for CVD, particularly on the aortic valve. They also serve as a potential tool for use during intraprocedural navigation for CVD treatment.

The CT scan and MRI procedure are essential to diagnose cardiovascular-related diseases. The ability to produce cross-sectional images of the heart provides the physician with complete anatomical information is advantageous to the physician. However, due to high radiation, it is impossible for CT to undergo real-time imaging (Gonzalez et al., 2008; Sun, 2013) and MRI, which requires a more extended period for image acquisition. On the other hand, echocardiography is the US imaging of the heart. It provides real-time imaging of the heart structure, allowing the physician to assess its anatomical, functional, and hemodynamic changes.

Nevertheless, the constraint of US is due to the limited FOV and lower detail in the display of the images (Otto, 2007; Ewertsen et al., 2013) .To compensate for the limitation of CT, MRI, and US, a fusion of the three modalities will help the physician obtain complete information from these modalities. It will be helpful in guided image intervention related to the treatment of the heart. A programming language named Matrix Laboratory (MATLAB) (vR2020b, MathWorks, Natick, USA) is recently available in radiology and consists of an image processing toolbox. It can provide US/CT + US/MR trimodality image registration in one application for optimized cardiac and body imaging.

This study will set the US image as the primary image since it is a 2D planar US image frame with an opaque background surface. In contrast, CT/MRI images will be the proximity of semi-transparent surfaces. The general idea of trimodality algorithm registration (Guo et al., 2014) is represented in Figure 2.13 and formulated in Equation 2.1 based on the computer graphics' transparency model.

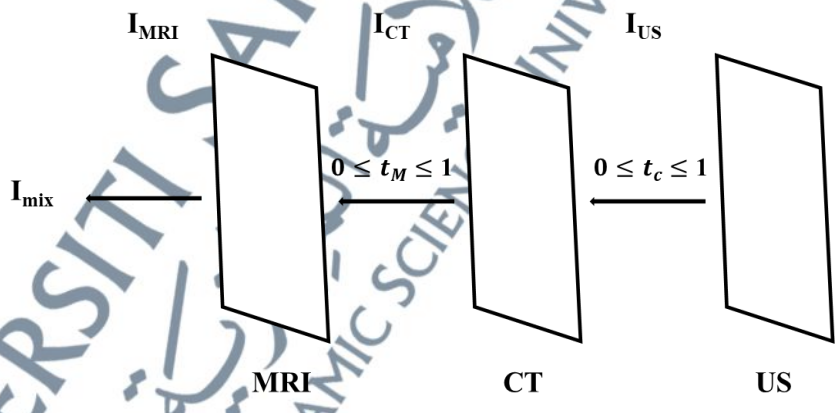


Figure 2.13: Illustration of Trimodality Image Registration

$$I_{mix} = t_M I_{MRI} + (1 - t_M)[t_C I_{CT} + (1 - t_C) I_{US}] \; 0 \leq t_M, t_C \leq 1 \quad (2.1)$$

In Equation 2.1, I_{mix} represent a pixel of the intensity value in the registered image, while I_{MRI}, I_{CT}, I_{US} represent the corresponding pixels of the intensity values in MRI, CT, and US images, respectively. Subsequently, the transparency factor of CT and MRI images will be interpreted as t_M and t_C, respectively, in which the user can customize according to each modality's wanted transparency weight. The display of the registered image will vary in line with the change in the transparency factor ($t_M,\ t_C$).

Therefore, our main interest in this study is to enhance the study of trimodality image registration in treatment planning, as it is useful in treatment procedures. The present work aims to investigate the trimodality image registration system for guiding CVD treatment procedures. This trimodality system will be varied to study its guidance in CVD treatment via temporal registration system, spatial registration system, and validation techniques, which are qualitatively and quantitatively, to determine its potential usability in the future.

2.5 Demographics of Patients

The prevalence of CVD is responsible for almost half of all Noncommunicable Diseases (NCDs). Meanwhile, Communicable Diseases (CDs) were once the primary global cause of death. They have been surpassed by NCDs, with CVD remaining the leading cause. It leads to approximately 17.3 million deaths annually, projected to increase to over 23.6 million by 2030. Among individuals diagnosed with CVD, there has been an upward trend in the number of patients who undergo all three imaging procedures—namely, the US, CT, and MRI—for diagnosis and treatment. Figure 2.14 illustrates the graph depicting the growth in the utilization of US, CT, and MRI procedures among patients with CVD at Hospital Serdang, Selangor, Malaysia, for five years (2015-2020).

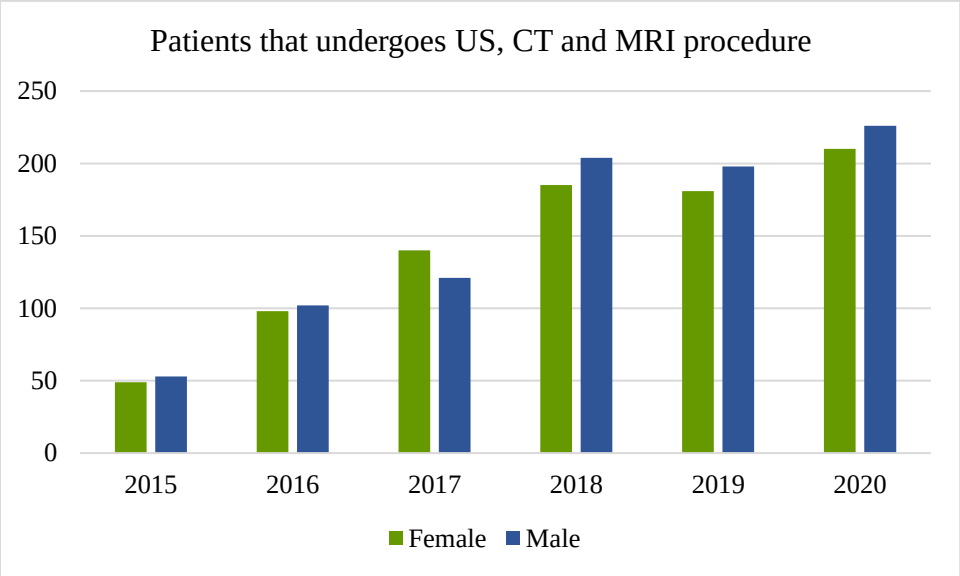


Figure 2.14: Graph of Patients with CVD That Undergo US, CT, and MRI Procedures in Hospital Serdang, Selangor, Malaysia, Within 5 Years (2015 – 2020)

The graph in Figure 2.14 illustrates an upward trend in the number of male and female patients who have undergone all three diagnostic procedures between 2015 and 2020. In 2015, the number of male and female patients undergoing the treatment was 48 and 52, respectively. However, by 2020, the number of male and female patients undergoing treatment with all three diagnostic modalities had remarkably increased by 210 and 230, respectively. This increase in patients requiring US, CT, and MRI for cardiovascular treatment is due to each modality's unique and essential contribution to enhancing diagnostic accuracy during cardiovascular procedures. For example, this includes TAVI and TAVR for the aortic valve.

Figure 2.14 indicates that all three diagnostic procedures, including US, CT, and MRI, are essential in accurately diagnosing and treating CVD. Patients are required to undergo all three procedures to provide the attending physicians with all the relevant and necessary information during the operation. As a result, having access to data from all three modalities makes it easier for doctors to make informed patient treatment decisions.

2.6 Summary

Recent research analysis reveals a scarcity of studies on the spatial alignment of 2D US with volumetric data from cardiac CT and MRI, primarily due to the coarse resolution and the requirement of an optical tracker device for clinical application. Although dual-modality fusion and registration are widely employed for multimodality data visualization, registering and fusing three modalities becomes paramount when examining a disease using three distinct images. The trimodality image registration system aims to address temporal synchronization and spatial orientation issues in relocating heart images. This is done by offering innovative techniques for integrating composite structural information and valuable insights across all modalities. Despite its potential, limited research has been conducted thus far to explore the benefits and challenges of this novel approach to trimodality image registration.