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Study of Aortic Stenosis and Calcification in Patients with Chronic Kidney Disease treatedwith Hemodialysis in a Private Clinic in Puebla: Case Report

Dra. Elizabeth Báez Valbuena[1], Dra. Erika Palacios Rosas[2], Dr. Mario Jiménez Hernández[3]

[1,2,3]Universidad de las Americas Puebla

Abbreviations

Ava: aortic valve area
CDC: Center for Disease Control and PreventionD: diameter
CKD: Chronic Kidney DiseaseBMI: Body Mass Index
LGS: General Health LawN: number
WHO: World Health Organization tds: outflow tract V: velocity va: aortic valveLV: beat volume
VLas: stroke volume of ejection through aortic valveVLtds: volume beat through outflow tract
Vtds: velocity of the outgoing tractVva: aortic valve velocity
ΔP: *Transvalvular pressure*

GENERAL BACKGROUND

Chronic kidney disease (CKD) is a disease whose incidence and prevalence have increased globally, this pathology is associated with multiple morbimortalities, especially in the cardiovascular field (Ewen et al.,2019). This risk rises much more if the disease reaches terminal level with the need for the use of hemodialysis, reaching more than half of these patients with cardiac comorbidities. These cardiovascular complications are extensive, notably coronary heart disease, arrhythmias and valvular diseases that eventually lead to death. We will focus on the latter. In earlier stages, heart valves show calcification and, consequently, stenosis.It is for this reason that, according to Ewen et al. the prognosis of CKD depends on the vitality of the heart valves. Thus, in a patient with end-stage CKD, progression to significant valve destruction occurs 10 times faster than in a person with healthy kidneys. It is for these reasons that the evaluation of valvular disease, especially of the aortic valve, is of utmost importance.

Kidneys and heart are closely related, therefore, it is important to mention the significance of the concept of cardiorenal syndromes. These are defined as cardiac or renal disorders whose acute or chronic dysfunction causes another acute or chronic disorder in another system (Podkowinska and Formanowicz, 2020). The importance of this concept lies in the fact that the aforementioned cardiovascular complications are the result of these syndromes. One system is affected by the other to the same extent, therefore, the correlation between the severity of CKD and the degree of cardiac involvement is explained here. Going further into the subject of valvular involvement and taking into account the aforementioned, it is not surprising that the more advanced the CKD, the greater the degree of calcification and stenosis of the aortic valve.

Definition of Chronic Kidney Disease

CKD is defined as the gradual and progressive loss of kidney capacity. To be defined as chronic, at least 3 months must pass. To define a dysfunction in renal capacity must have these factors: glomerular filtration rate with a decrease of 40%, which translates to numbers less than 60 ml per minute per 1.73 m2 (Breyer and Susztak, 2016). This disease represents a huge risk factor for developing cardiovascular disease, with adverse cardiovascular events being the leading cause of death, according to Breyer and Susztak (2016), in these patients. However, the only treatment for this condition is dialysis (hemodialysis or peritoneal dialysis) or transplantation.

Approximately 20 million people in the United States are affected by this disease (Breyer and Susztak, 2016). Of these, half a million people have a severe form of the disease. In terms of treatment statistics, 20% need dialysis treatment while the remaining comes into debate as kidney transplantation is very limited. According to these authors, the most common cause of end-stage CKD is diabetes, with an incidence of at least 50% of cases. In second place is hypertension with an approximate 25%.

People with CKD are more at risk for progressive kidney failure, cardiovascular events and death (Ricardo, et al., 2014). In isolation, these authors were able to find simple ways to reduce the risk of progression of this disease, for example, by engaging in physical activity. This variable managed to reduce the risk of progression by 28%. In terms of atherosclerotic events,no significant changes in risk could be observed if lifestyle changes are made. This data will be useful in the course of the research work since, as can be seen, it is complicated to reduce the progression of cardiovascular disease. Regarding the causes of mortality, it was observed that constant and regular physical activity reduces the risk of death in patients with CKD. In general terms, there is a clear reduction in risk in patients who maintain correct non-pharmacological measures. In the study done by Ricardo, et.al. (2014) a 68% reduction in the risk of causes of mortality was demonstrated in patients who maintained a correct diet of a certain amount of vegetables and fruits, fish and whole grains, with a body mass index (BMI) of less than 25 kg/m2, regular exercise of moderate activity of at least 150 minutes a week and finally not having been a smoker. This shows that a healthy lifestyle results in favorable changes in the disease without the need for a pharmacological agent. The importance of mentioning these aspects is that, although CKD can be controlled with simple measures, the progression of its cardiovascular complications is another story altogether.

Hemodialysis

As mentioned above, treatment is limited to renal replacement therapy or transplantation. In this study we will focus on the former and especially on hemodialysis. Thanks to technological and medical advances in this area, the number of complications has decreased, however, the risk in hemodialysis patients has not decreased despite these advances. Few studies have focused on mortality in hemodialysis. For example, the approximate prevalence of coronary heart disease in dialysis is 40%, in contrast, the general population has a prevalence of 5-12%. The same occurs with left ventricular hypertrophy, which in dialysis has a prevalence of 75% while in healthy patients it is approximately 20% (Cases and López, 2002).

Hemodialysis is a relatively new treatment created by the efforts of Willem Kolff and Belding Scribner who treated their first patient in 1943 without success. However, in 1960 thetechnique was perfected and in 2002 they were awarded the Albert Lasker Prize for Medical Research. The number of patients receiving this treatment is constantly increasing, and with itthe complications. This therapy can save the lives of many CKD patients at the cost of hypertension and diabetes as well as exposure to toxic environments (Himmelfarb, et. al., 2020). Mortality linked to hemodialysis remains high with suboptimal outcomes and high rates of comorbidities and a far from ideal quality of life. This is why there is so much area of opportunity in this therapy. While technological advances are helping us to reduce these rates,we can focus on the management of these unexpected events.

Recall that dialysis consists of peritoneal dialysis and haemodialysis. It is noteworthy that in Latin America the percentage of hemodialysis users has increased approximately 4% annually and if we compare it with Europe or the United States it is almost double, since in these places together there has been an increase of 2% annually. It is also interesting that in general, men are the ones who resort to this treatment more than women. As for mortality, it is very high in the first 3 months of starting treatment. During the first year of treatment, about a quarter of the patients die. This is due to the fact that death comes more quickly in these patients compared to the normal population because of the above mentioned, but the remarkable thing is that the factors of this high mortality rate are not well understood, however, it is mentioned that it could be linked to poor management of comorbidities, of which the most important are cardiovascular.

Cardiovascular pathologies associated with CKD

Cardiovascular pathologies are usually present to a greater extent in patients with CKD than in the general population (150 times). The risk of dying from a cardiovascular complication is 10- 20 times higher than in the general population, being considered the main cause of death in these patients (Cases et al., 2003).

An important point is the risk factors that have been associated with these cardiovascular complications. According to Podkowinska and Formanowicz (2020), the traditional risk factors are hypertension in the first place, hypercholesterolemia, obesity and hyperhomosisteinemia. However, these factors alone do not explain the high incidence of cardiovascular pathologies in CKD. Therefore, non-traditional risk factors must be taken into account. These consist of endothelial dysfunction, valvular calcification, excess volume, oxidative stress and inflammation. It is important to mention that oxidative stress and inflammation have gained much more weight as the most important factors for the development of these pathologies. This is explained by defining these concepts. Oxidative stress is the imbalance of oxidants and antioxidants (Podkowinska and Formanowicz, 2020), this is important because CKD is also characterized by an amplification of this process and the use of treatments such as renal replacement therapy favors much more oxidative stress. It also affects the heart causing hypertension due to the process of oxidant accumulation in the kidney and vascular tissue. This hypertension promotes much more oxidative stress generating a vicious circle. Going further into the subject, all this that has already been mentioned facilitates important processes such as increased vascular permeability, leukocyte recruitment, calcification and fibrosis which generates vascular damage and remodeling of this.

Despite efforts to reduce the mortality rate of CKD patients with cardiovascular complications, these efforts have not yet been applicable to renal patients. Recommendations have been to reduce serum cholesterol levels, smoking and blood pressure (Breyer and Susztak, 2016) in a population that has not been affected by CKD. However, this is not entirely true in patients who do suffer from this pathology since the pathophysiological process of these cardiorenal syndromes that we explained above in the non-traditional risk factors, results in a large accumulation of different toxins and metabolites which contribute to this group of patientsbeing much more complex to treat and much more vulnerable to cardiac comorbidities that this whole process entails.

Valvular pathologies associated with CKD

More than half of the causes of death in patients with advanced chronic kidney disease are ischemic heart disease, sudden cardiac death and arrhythmias, infarction and peripheral arterial disease. Valvular and vessel calcification also form part of the aforementioned statistics. The most important and frequent valvular pathology in these patients is valvular calcification. In dialysis patients, the annual incidence of aortic valve calcification is approximately 25% and mitral valve calcification is 59%, while in non-dialysis patients this incidence is much lower, approximately 3.3%. It is important to mention that these affectations occur 10-20 years earlierin dialyzed patients (Ureña-Torres, et al., 2019).

Calcification of the aortic valve leads to stenosis as the pathology progresses, making patients with CKD more likely to have higher mortality rates, especially in events such as ischemic vascular events and increased complications after a surgical procedure for aortic valve replacement (Lüders et al., 2017).

Specific background

Anatomy of the aortic valve

Recall that the aortic valve is composed of three leaflets that are named according to their location with respect to the left coronary artery. Each of the leaflets has a trilaminar structure that is the one that finishes the biomechanical properties of it, these layers are the ventricularis, fibrous and spongy. The following will explain the characteristics of each of these layers according to the article by Lindman, et. al. (2016). The fibrous layer faces the aorta while the ventricularis faces the outflow tract of the left ventricle, in between these is the spongy layer. The fibrous cap has a large number of type I and III collagen fibers in a circumferential conformation. The ventricularis provides compliance, which is the ability to expand under pressure, so that the free regions of the valve can be faced and thus prevent retrograde flow of the circulation during diastole. Finally, the spongy layer is rich in proteoglycans.

In general, the valve cell population consists of valve interstitial cells, smooth muscle cells, and endothelial cells. The latter line the aortic and ventricular surface of the valve, interfacing between the blood and the valve. Valvular interstitial cells are the most prevalent. Smooth muscle cells are found at the base of the ventricularis layer.

Aortic calcification

As previously stated, aortic calcification is by far the most prevalent form of aortic stenosis in the world regardless of whether the patient is treated with hemodialysis or not. It is the cause of approximately 85,000 aortic valve replacements and 15,000 deaths annually in North America (Lindman, et. al., 2016). Calcification is given by fibrocalcific remodeling of the leaflets. The pathophysiology of the disease is divided into 2 major stages: first aortic sclerosis where the valve becomes thickened and slightly calcified, however, these changes do not cause obstruction to blood flow. The next stage is severe calcification of the valve that occurs over the years. Here there is a restriction of leaflet motion and significant obstruction to blood flow.The latter are the most important markers of aortic calcification.

The diagnostic method of choice for this type of pathology is Doppler echocardiography, which will be discussed later. It is managed by transcatheter valve therapy, a procedure that hasbecome an alternative to aortic valve replacement surgery. There is no pharmacological treatment that has proven to delay the course of the disease to stenosis, making the aforementioned surgical treatment the only two management options (Lindman, et. al., 2016).

Previously it was believed that aortic valve calcification was due to a degenerative processcaused by time-dependent wear and tear coupled with passive calcium deposition, however it is now known that there are histopathological and clinical mechanisms that show that the scoring is actually an active, multifaceted condition involving lipoprotein deposition activity, chronic inflammation and osteoblastic transition of interstitial cells in the valve and active calcification of the leaflets (Lindman, et al., 2016).

On investigation, calcified valves were found to have fibrosis and calcification which significantly alter the biomechanical properties of the leaflets. They often contain dense inflammatory infiltrates, mostly macrophages. The calcification process is itself a mineralization process, which starts with the fibrous cap. On the other hand, a small percentage of 10-15% of this process shows advanced osteogenic metaplasia with the presence of osteoblast-like cells, chondrocytes and bone marrow. All this suggests that the calcification process happens in response to damage probably unleashed by lipid-derived species and inflammation (Lindman, et. al., 2016).

The pathophysiology of calcification dictates that, thanks to these processes, there is an excessive production and disorganization of collagen fibers generating aortic valve stiffness (Lindman, et. al., 2016). This explains the relationship between calcification and subsequent stenosis.

Aortic Stenosis

Aortic stenosis is defined as the narrowing of the aortic valve which generates an obstruction of blood flow from the left ventricle to the aorta (Mourino-Alvarez, et. al., 2020). It is a chronic pathology and the most common in developed countries. Its prevalence increases with age.

For a long time, it was thought to be a passive degenerative disease, however, it is now known to be a complex pathobiological process, active and regulated by multiple events such as chronic inflammation, lipoprotein deposits, activation of the renin angiotensin system, osteoblastic differentiation of valvular interstitial cells and active calcification (Mourino- Alvarez, et. al., 2020). A very important aspect of this pathology is that there is evidence that it could possibly be preventable since it has been noted that there is an association between aortic stenosis and traditional atherosclerotic risk factors such as hypertension, smoking, diabetes, cholesterol and lipoprotein levels (Mourino-Alvarez, et. al., 2020). However, this has not been fully proven as the differences between atherosclerosis and aortic stenosis suggest that this is a much more complex scenario. For example, it has been seen that there are other factors related to stenosis such as cell signaling processes such as receptor activator nuclear kB (RANK), polymorphisms, mutations in the vitamin D receptor allele, mutations in bicuspid aortic valve disease, etc.

According to the study of Mourino-Alvarez, et. al. (2020) these patients present with symptoms such as angina, syncope or heart failure, however, half of the patients with this disease are asymptomatic at the time of diagnosis due to the discovery of a systolic murmur or abnormalities in the transthoracic echocardiogram that was initially indicated for other reasons. As for the physical examination, the findings provided by this are specific, but not sensitive for the evaluation of severity. To establish the degree of severity we must rely on the echocardiogram as this is the cornerstone for the diagnosis of aortic stenosis.

As mentioned above, approximately 50% of patients are asymptomatic even with a severe degree of stenosis, so far no exact cut-off point has been found for the optimal intervention of these patients, however, to these patients with a severe degree of stenosis compared to symptomatic patients, in 5 years it is observed that 66% of these progress while 75% die or undergo aortic valve replacement (MourinoAlvarez, et. al., 2020). It is important to know that progression is variable and unpredictable in all patients which means a risk of sudden death of 11.5% per year. On the other hand, patients with severe and symptomatic grade without treatment have a very poor prognosis, because 50% of these patients die within 1-2 years fromdiagnosis.

Treatment consists of aortic valve replacement either surgically or by catheterization. Current American and European guidelines recommend surgical replacement for those who aresymptomatic, while catheterization is reserved for those who are not candidates for surgical replacement (Mourino-Alvarez, et. al., 2020).

Echocardiogram

The use of echocardiography is a relatively new technique, with its first use of ultrasound for cardiovascular diagnosis by Edler and Hertz in 1954. For decades there has been innovation in its use and attempts have been made to standardize the basic parameters and techniques throughout the world, starting with England, Switzerland, etc. The basic usage and generalities will be briefly reviewed according to the American Society of Echocardiography guidelines inthe study by Mitchell, et. al. (2019).

First, a window must be obtained thanks to the transducer. This can be directed anteriorly, posteriorly, superiorly, inferiorly, laterally and medially. The concept of long axis refers to thefact that the heart is being viewed in a longitudinal plane, that is to say, it is observed from the cardiac apex towards the atria, the short axis refers to the fact that a transversal cut is made. When placed in this way we obtain different windows that are described as parasternal, apical, subcostal and suprasternal depending on where the transducer is placed to obtain the images.

In order to obtain these windows correctly, the index mark of the transducer should be used as a base. It is recommended that for obtaining the left parasternal window, the patient should be placed in the left decubitus position. For the parasternal long axis, it can be observed next to the sternum with the transducer mark directed towards the patient's right shoulder. To obtain a parasternal short axis, the transducer should be placed at the same point where it was placed to obtain a parasternal long axis with the only difference that the transducer mark should be pointing to the patient's left shoulder obtaining an axial plane. The apical window is complex only because the cardiac apex is just below the breast tissue. The transducer should be placed where the apical impulse can be felt and positioned at 4 to 5 o'clock if you imagine a clock, with this position we would obtain a four-chamber view. The subcostal window is located just below the sternum. This is done by placing the patient in the supine position, the transducer is placed with the mark directed towards the left side of the patient in a position of three hours ifa clock is imagined. Finally, for the suprasternal window, the transducer is placed just above the manubrium of the sternum. A long axis view of the aortic arch is obtained. The transducermarking should be directed toward the left shoulder and placed almost parallel to the neck for the best visualization of the aortic arch.

There are different techniques or instrumentation settings in the echocardiogram, these can change by the design of the ultrasound system and cannot be changed by the operator, however, there are some modalities that can be modified during the taking of the study. To facilitate the acquisition of the echocardiogram, "presets" were developed in the equipment that are recommended and ideal for taking images for a certain type of patient, anatomical structure or blood flow. In general, all ultrasound equipment has the following modes: M-mode, two- dimensional and Doppler, from which different measurement techniques are derived and which will be explained later. The M mode refers to an image in which only grayscale images are seen without showing the complete anatomy of the heart. This is used to qualitatively and quantitatively analyze the movement of the structures. The two-dimensional mode is where, asthe name implies, the cardiac anatomy as such is observed in a two-dimensional mode. Finally, Doppler has the ability to display different parameters depending on its two submodalitiesexplained below.

In the two-dimensional mode a grayscale map is observed, the dynamic range, transducer frequency, depth and sector size and finally gain. In the case of Doppler there are two differentmodes; spectral Doppler and color Doppler. Spectral Doppler allows you to measure the velocity scale, sweep speed, sample volume, gain and tissue Doppler. While in color Doppler you can measure sector size, color gain and color map.

In this study, we will specifically use the two-dimensional mode and spectral Doppler. These modes will help us to evaluate the anatomy of the aortic valve as well as to measure velocities and diameters important in this study. As for the windows that will be used are the parasternal and apical mostly. The views are the short and long axis of the left ventricle and 4 chambers.

Statement of the problem and research question

In general, there are no studies that talk about the course that patients with chronic kidney disease who are treated with haemodialysis have in terms of the cardiovascular aspect. There are many articles and studies focused solely on the link between cardiovascular pathologiesand chronic kidney disease, such as the study "Risk Factors for Heart Failure in Patients WithChronic Kidney Disease: The CRIC (Chronic Renal Insufficiency Cohort) Study" (Jing He etal., 2017) or conferences such as "Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference" (Turakhia et al., 2018) and even the prevalence of these pathologies has been studied in other parts of the world, as for example in China with: "Prevalence and risk factors for cardiovascular disease among chronic kidney disease patients: results from the Chinese cohort study of chronic kidneydisease (C-STRIDE)" (Yuan et al., 2017). However, with regard to valvular pathologies, theliterature is reduced only to the relationship of these with chronic kidney disease, leaving aside the role played by haemodialysis, such as for example "Herzklappenvitien bei chronischer Niereninsuffuffizienz" (Ewen et al., 2019).

In our study, we will focus on valvular pathologies, specifically aortic valve calcification as it is the most prevalent valvular pathology with the highest mortality in this group of patients according to Guerraty et al. (2015), Ureña-Torres (2019), Ewen et al. (2019) and Krishna et al. (2019).

Therefore the research question is the following: How can we implement the search for valvulopathies in routine studies in patients with chronic kidney disease as part of their follow-up with hemodialysis?

Justification

More than half of the causes of death in patients with chronic kidney disease are due to cardiac pathologies and these are the ones that put the lives of patients at risk, for example according to Ewan et al (2019) the mortality of patients with chronic kidney disease rises considerably thanks to the calcification of the aortic valve, even Kirshna et al. (2019) establish that this samepathology can increase the mortality of patients 3 times. Monitoring and being able to foresee the course of cardiac affectations can provide the patient with a better quality of life since we can prevent the consequences of these pathologies or even delay their course.

Hypothesis

Does the study of aortic valve diseases provide relevant information for the patient onhaemodialysis treatment?

Objectives

Overall objective

To evaluate hemodialysis treatment and the risks and/or benefits it provides to the cardiovascular health of patients in Puebla, Mexico attending a hemodialysis clinic. By means of echocardiography to determine the changes in the architecture of the cardiac valves.

Specific objectives

To measure echocardiographic parameters for the evaluation of aortic valvular architecture and functionality in patients with CKD undergoing hemodialysis, which are:

1. Anatomical evaluation
2. Aortic Valve Peak Flow Velocity
3. Mean transvalvular pressure gradient
4. Aortic valve area

Material and methodsLocation

This study will take place in a private clinic in the city of Puebla during the approximate period of July 2021 to June 2022.

Criteria

The inclusion criteria for my study will be patients with:

- Diagnosis of chronic kidney disease o Who are treated by hemodialysis o Who agree to participate by signing the informed consent form.
- Patients who have never undergone echocardiographic studies focused on the aortic valve or, alternatively, on any valve.

As for the exclusion criteria, the following are listed:

o Patients with a diagnosis of chronic kidney disease but who have the following o Who are being treated with peritoneal dialysis o Who are transplanted or are in the process of transplantation o Who have a prosthetic heart valve.

The elimination criteria are as follows:

- Patients who do not have a diagnosis of Chronic Kidney Disease (CKD)
- Patients who revoke consent

Sample Size

N= at convenience, the number of patients treated by hemodialysis with a diagnosis of chronic kidney disease in a private clinic in the city of Puebla.

METHODS

This is a case report study, in which the importance and feasibility of the study of aortic valve disease with respect to the degree of calcification and subsequent aortic stenosis as part of routine studies of these patients will be evaluated. We report below 3 cases of patients who meet the inclusion criteria, each with different characteristics, but all studied under the same echocardiographic protocol.

Variables

The variables that will be useful for my study will be taken by echocardiography to determine the degree of calcification and aortic valve stenosis, as well as some sociodemographic variables such as sex, age, marital status and level of education as well as time since the diagnosis of chronic kidney disease and time of use of hemodialysis treatment. Before going into echocardiographic parameters, it should be mentioned that the disease should be evaluated in a comprehensive manner, therefore if we only evaluate these parameters we would not obtain an accurate measurement and therefore the evaluation of the disease would be less than ideal since it would have to be correlated with the hemodynamic parameters (Hagendorff, et. al., 2020). That said, we must obtain 3 non-echocardiographic data to complement the assessment as well as the patient's age and sex. To specifically encompass the physical examination data, we take into account 3 important data that can guide us towards the physical condition of the patient, which are the heart rate, blood pressure and weight of the patient. We will take as normal values according to the World Health Organization (WHO) the following: 60-100 beats per minute for heart rate and 90-120 for systolic pressure and 80-60 for diastolic pressure. With respect to CKD, we will also measure the time since the diagnosis of CKD and the time since the start of the use of haemodialysis.

As for the weight evaluation, we will only categorize the patient depending on their BMI. The values that will be considered normal are taken from the CDC guidelines which states that a BMI of 18.5 to 24.9 is considered normal. Remember that the formula for BMI is: weight in kg divided by the patient's height in meters squared. According to the Center for Disease Control and Prevention (CDC), we can classify a patient as underweight if their BMI is less than 18.5, overweight is when the patient is between 25-29.9, and obese is when the patient has a BMI greater than 30.

In the field of echocardiographic parameters, the following variables are needed for the assessment of involvement. The following are those proposed by the American guidelines by Baumgartner, et. al. (2017) and German by Hagendorff, et. al. (2020), which together give a series of recommendations for the measurement, performance and normal values of this pathology. Both were taken into account because together they form a comprehensive assessment of the anatomy, obstruction, velocities, gradients and areas that are of interest in this study.

We will begin by naming the necessary values and then explain the formulas and procedures that were necessary for the evaluation of aortic valve involvement. The values collected were: peak flow velocity at the aortic valve, left ventricular velocity during systole by Doppler at the beginning, middle and end of systole, aortic velocity during systole at the beginning, middle and end of systole, left ventricular outflow tract diameter for calculation of cross-sectional area and finally left ventricular outflow tract velocity measured by Doppler. It is important to mention that the latter are completely objective values to later calculate the degree of aortic stenosis, this changes in the evaluation of calcification as this is purely subjective since it is based on the clinical criteria of the operator.

Now that we have these values, we must perform 4 important assessments based on the article by Baumgartner, et al. (2017) as well as Hagendorff, et al. (2020). The first is the anatomical assessment of the aortic valve. This consists of 4 points; the first is to identify the number of valve cusps, the second is to evaluate the mobility of the cusps, the next is to assess the thickness of the leaflets and finally the assessment of calcification. The latter is of utmost importance for this study. In order to visualize this anatomy we must use a long or short parasternal window. To see the degree of calcification we must first take into account certain aspects. First, calcification is more prominent in the central part and at the bases of the cusps. The same process generates that there is no commissural fusion which generates the orifice thatis formed by systole. Having said all the above, it is important to emphasize that calcium in the echocardiogram is seen as areas of dense echogenicity and that any collection of calcium will generate an acoustic shadow in the echocardiogram. Let's remember that echogenicity is the capacity of reflection of ultrasonic waves. Now, for the classification of the degree of stenosis we will use the following scale based on the article by Baumgartner, et. al. (2017): mild if there are few areas of dense echogenicity with a little bit of acoustic overshoot, moderate if there are large multiple areas of dense echogenicity and finally severe which refers to already extensivethickening and prominent acoustic shadow. This is the only qualitative variable in this study, from here on the data is quantitative.

In this next of the 4 items mentioned is the determination of the peak flow velocity in stenosis. This is defined as the highest velocity obtained in any window and is taken using the spectral Doppler mode in multiple windows to determine the highest velocity, as shown in Figure 1. The apical and right parasternal and suprasternal windows are recommended since it has been demonstrated that this is the place where the velocities are most frequently seen, although they can also be observed more rarely in the substernal or supraclavicular windows. In the continuous wave measurement is measured using the peak of the wave, to have a correct measurement if a patient has an irregular rhythm we must obtain the measurement in at least 5 consecutive beats. This value corresponds to the velocity, therefore, its unit of measurement isin m/s. This is evaluated like the other parameters in non-significant, mild, moderate or severeaortic stenosis or high severity (Baumgartner et. al., 2017) (Hagendorff, et. al., 2020). In this specific parameter a velocity less than or equal to 2.5 m/s is non-significant, between 3.6-39. m/s is mild stenosis, 3.0-4.0 refers to moderate stenosis and finally a stenosis of equal or greater than 4 is severe.

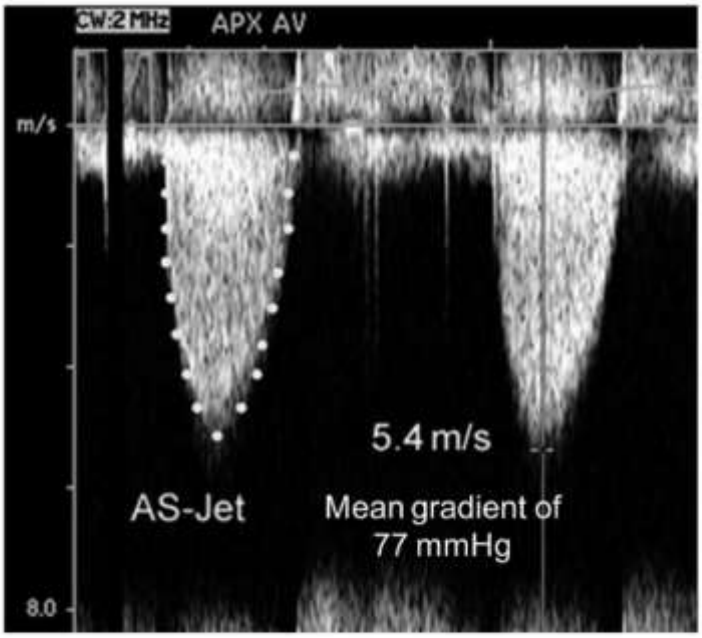

Figure 1: Continuous wave spectral Doppler, showing thepeak velocity and the points where measurements could be taken for the pressure gradient.
media (Baumgartner, et. al., 2017)

Our third parameter is to calculate the mean transvalvular pressure gradient. This is defined as the difference in pressures between the left ventricle and the aorta during systole. This gradient is calculated according to velocity by doing the Bernouilli equation, which roughly defines the behavior of a fluid through a streamline

(Mikhailov, 2005), as follows:

$\Delta P = 4$!

The average gradient is calculated by averaging the instantaneous gradients (differences) over the ejection period. This must be done in this way as it cannot be taken from the average velocity. For this measurement, we must measure only one point of the outflow tract of the left ventricle since this is where the change in velocities is generated, specifically at the valve opening site. In the spectral Doppler echocardiogram we can observe a wave that shows the flow velocity, as shown in Figure 2. The formula says that we should take several measurements during systole. An infinite number of measurements could be taken at each location on the curve, however, for practical purposes we will take only 5 points which wouldbe at the beginning and end of the curve, the midpoint and two other points. These last two points will be taken by dividing the curve in half horizontally. These 5 points are the ones chosen because with them we can make a mirror image of them and thus balance our measurements since the gradient depends on the accuracy of the velocity data.

$$\Delta P = \frac{\Sigma 4v^{!}}{N}$$

Figure 2: Left ventricular long-axis two- dimensional echocardiography showing the left ventricular outflow tract measured during mid-systole. It is measured from the anterior mitral leaflet parallel to the aortic valvular plane. At This image depicts three different measurements with the purpose of showing that all three are the same (Baumgartner, et. al...),2017)

The value obtained from this formula has m2/s2 as a unit, however, in the study of Baumgartner et. al (2017), these units would become mmHg by invasive means. Similarly, we must stage the patient, then these patients are classified as follows: if the value is less than 20 mmHg then we are talking about a mild degree, if the value is between 2040 mmHg we talk about a moderate degree and finally, if the value is equal to or greater than 40 then it is a severe degree.

The last parameter is to obtain the aortic valve area is calculated by using the continuity equation which is based on the concept that the stroke volume of ejection through the outflowtract of the left ventricle passing through the stenotic orifice, therefore, the stroke volume of the outflow tract is equivalent to the stroke volume of the aortic valve.

$VL \quad va = VL \quad vvv$

Where LV stands for beat volume, va stands for aortic valve and tds stands for outflow tract. Now, as the volume passes through a sectional area then it is equal to the same sectional volume multiplied by the flow velocity during the ejection period, therefore, the above formula can be rewritten as follows:

$$Ava \times Vva = AStds \times vvvv$$

Where AVA means aortic valve area, Vva means aortic valve velocity, AStds means sectional area of the sectional tract and Vtds means outflow tract velocity. It is cleared to finally obtain the aortic valve area by performing the following equation:

$$Ava = \frac{AStds \times Vtds}{Vva}$$

Now that we have explained how we arrived at the formula we will use, we must obtainthe values to put into the formula, which are the following: the peak aortic valve velocity (obtained in the second parameter), the diameter of the left ventricular outflow tract (for the calculation of the sectional area of the aortic valve) and the velocity in the left ventricular outflow tract measured by pulsed Doppler.

To obtain these measurements we must do the following: to obtain the diameter of the outflow tract we will measure from the inner edge of the septum to the anterior leaflet of the mitral valve at mid systole. This is best identified in the parasternal window to obtain a long axis. Usually we need the measurements of 3 beats to be sure of our measurement and in case of irregular rhythms we can obtain the measurement of 5 and obtain the average of these whether the rhythm is regular or irregular, with this we obtain the diameter of the outflow tract. To obtain the sectional area of the outflow tract is done by the following formula:

D !

$AStds = v \quad 36\ 2$

As can be seen, it is the same formula for the area of the circle. It should be noted that it has been observed that the aortic valve is not really circular but elliptical, however, for practical purposes we will take into account that the area is circular.

Finally, for the left ventricular outflow tract velocity will be taken by pulsed Doppler inapical window to visualize the 4 chambers or for a long axis where the visualization is better. In the pulsed Doppler we see waves with a well defined peak and narrow bands of velocities during systole in a healthy valve, on the other hand in the case of stenosis we see a more angular wave resulting from a spectral dispersion at this level, in this case we can move the transducer a little towards the apex to obtain a curve with a more normal morphology. Since we have calculated the area of the aortic valve, we have to stage our patient. As we are talking about area, the unit of measurement is cm2, being in this way: mild if the area is greater than 1.5, moderate if the area is between the parameters of 1.0-1.5 and finally severe if the parameter isbetter than 1.0.

Summarizing all the parameters is the following table where are the parameters, theideal windows, normal values with their staging and the formulas to obtain them.

Table 1: Variables to be measured and their characteristics

Parámetros	Ventana	Fórmula	Unidades	Valores			
				No significativa	Leve	Moderada	Grave
Evaluación anatómica	Paraesternal eje largo o corta	-	-		Pocas áreas de ecogenicidad densa con un poco de sombra acústica	Grandes áreas múltiples de ecogenicidad densa	Engrosamiento extenso y sombra acústica prominente
Velocidad pico de flujo de válvula aórtica	Paraesternal derecha Apical	-	m/s	≤ 2.5	2.6-2.9	3.0-4.0	≥ 4.0
Gradiente de presión transvalvular media	Paraesternal derecha Apical	$\Delta P = \frac{\Sigma 4v^2}{N}$	mmHg Se convierte de m/s a mmHg por medidas invasivas		<20	20-40	≥ 40
Área valvular aórtica	Paraesternal eje largo	$Ava = \frac{AStds \times Vtds}{Vva}$	cm2		>0.85	0.60-0.85	<0.6
Área seccional del tracto de salida	Paraesternal eje largo	$AStds = \pi\left(\frac{D}{2}\right)^2$	cm2				
Velocidad del tracto de salida	4 cámaras eje largo Doppler	-	m/s				

Data processing

Part of the data processing was explained above, however, to make the formulas and measurements more practical, an Excel document will be used in which by filling in the data we will obtain the values to be able to stage the patient together with the data taken from his clinical record. All these data will be collected in the Excel document mentioned above (Figure 3).

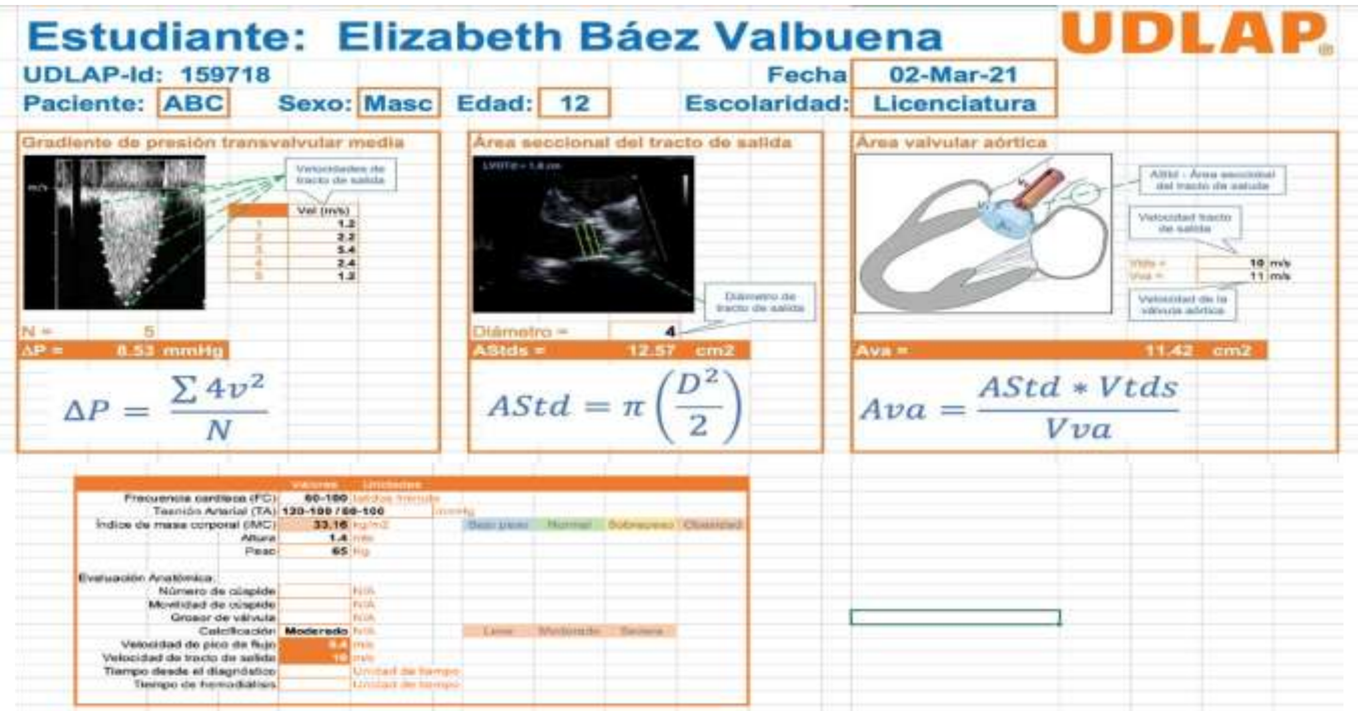

Figure : Excel table for data collection

Presentation of casesPatient 1

Male patient, 64 years old, with a master's degree. Refers to have a diagnosis of chronic kidney disease of 28 years of evolution, unknown cause. Three years ago he started hemodialysis treatment. He has a body mass index of 20.15 kg/mt2 with a height of 1.73 mt and a weight of 60.3kg, placing him in a normal weight for his size. He has been diagnosed with systemic arterial hypertension since he was 20 years old and type 2 diabetes mellitus under unspecified treatment. As for his hemodialysis treatment, he has a brachycephalic vascular access type AVF (arteriovenous fistula) and receives a weekly dose of erythropoietin of 2,000 IU/ml. He suffersfrom an unspecified cardiopathy, however, at the time of the echocardiogram a moderate hypertrophic cardiopathy was found. In our study we evaluated the anatomy of the aortic valve, where we could find the following findings: 3 cusps with adequate mobility, the thickness of the right coronary leaflet was increased as well as the annulus in smaller proportion. It was classified as a moderate calcification of these structures by the echocardiographer. As for the quantitative

values of the study, we will start with the peak flow velocity, in this patient a velocity of 9.8 m/s was obtained, which classifies it as severe aortic stenosis. The next value is the mean transvalvular pressure gradient which will define the behavior of the blood, a value of 28.6 mmHg was obtained. This places the patient in a moderate degree. The last point is the area of the aortic valve, in our patient we obtained an area of 2.86 cm2 which places the patient in a mild grade (Figure 4).

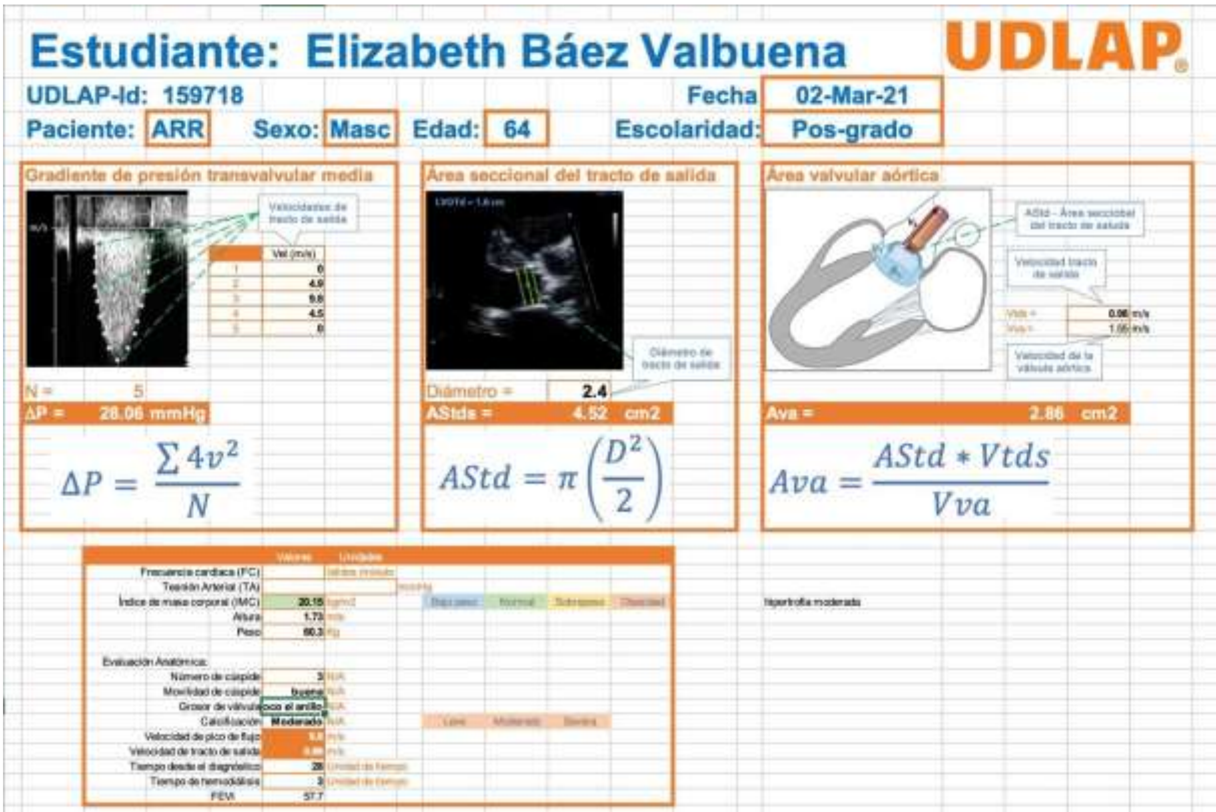

Figure 4: Patient 1 data in the Excel data collection table

Patient 2

Female patient, 69 years old, with a bachelor's degree as schooling. She suffers from systemic arterial hypertension and diabetes mellitus controlled with metformin without specifying dose. She has a history of having suffered COVID-19 in 2020, for which she was admitted to the intensive care unit due to complications caused by comorbidities, without the need for intubation, but with a stay of several days. As for her anthropometric measurements; she has aheight of 1.54 mt and a weight of 60 kg which gives us as a result a BMI of 25.3 kg/m2, classifying her as overweight. She has known her diagnosis of chronic kidney disease for 6 years, however since her infection with COVID-19 she requires hemodialysis. She has been on this treatment for 2 years through a jugular tunneled venous access, receiving weekly erythropoietin doses of 4,000 IU/ml. When evaluating the anatomical characteristics of the aortic valve, he found 3 cusps of good mobility and thickness, with mild calcification. In the evaluation of quantitative parameters, the peak flow velocity obtained was 11.4 m/s which places the patient in a severe degree. The mean transvalvular pressure gradient was 37.07 mmHg, which places the patient in a borderline moderate grade. The aortic valve area is 1.7 cm2, which translates to a mild degree (Figure 5).

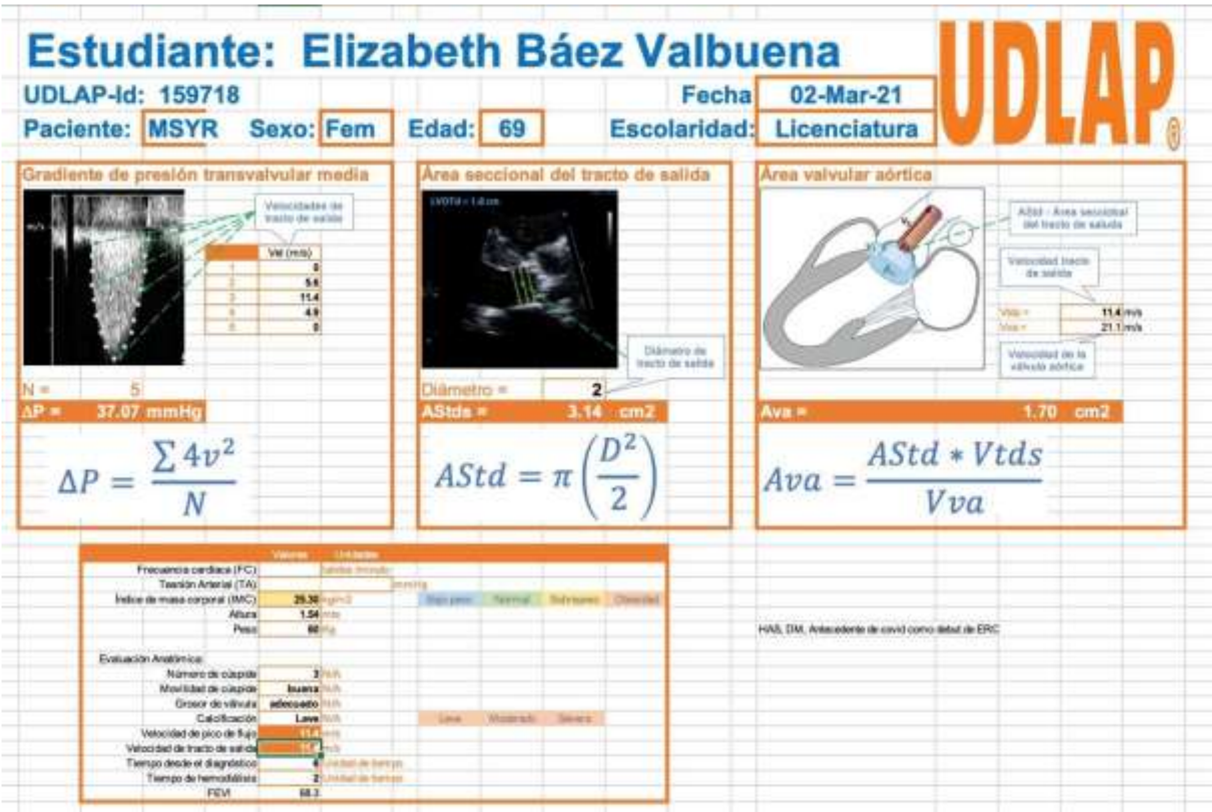

Figure 5: Patient 2 Data in the Excel Data Collection Table

Patient 3

Female patient, 69 years old, with a bachelor's degree. She suffers from systemic arterial hypertension and type 2 diabetes mellitus of more than 10 years of evolution. She also has difficulty with mobility, so she moves around in a wheelchair and is dependent on a cane for ambulation. Her height is 1.61 mt and her weight is 89 kg which classifies her as a grade I obese according to the WHO as she has a BMI of 34.3 kg/m2. She has known her diagnosis ofchronic kidney disease for 17 years, however, she has only been on hemodialysis for 7 years. She has a jugular tunneled vascular access and in her case no treatment with erythropoietin is provided. At the time of the echocardiogram it was found that she also suffers from severe hypertrophic heart disease. At the time of the anatomical evaluation of his aortic valve was found with 3 cusps with good mobility. Thickening was found in the non-coronary and right coronary leaflets as well as moderate calcification in both. For quantitative values, the peak flow velocity in this patient was 9.3 m/s which places her in a severe grade. The mean transvalvular pressure gradient obtained was 24.02 mmHg, which translates to a moderate grade. Finally, the aortic valve area in this patient was 1.79 cm2 which means a mild grade. (Figure 6).

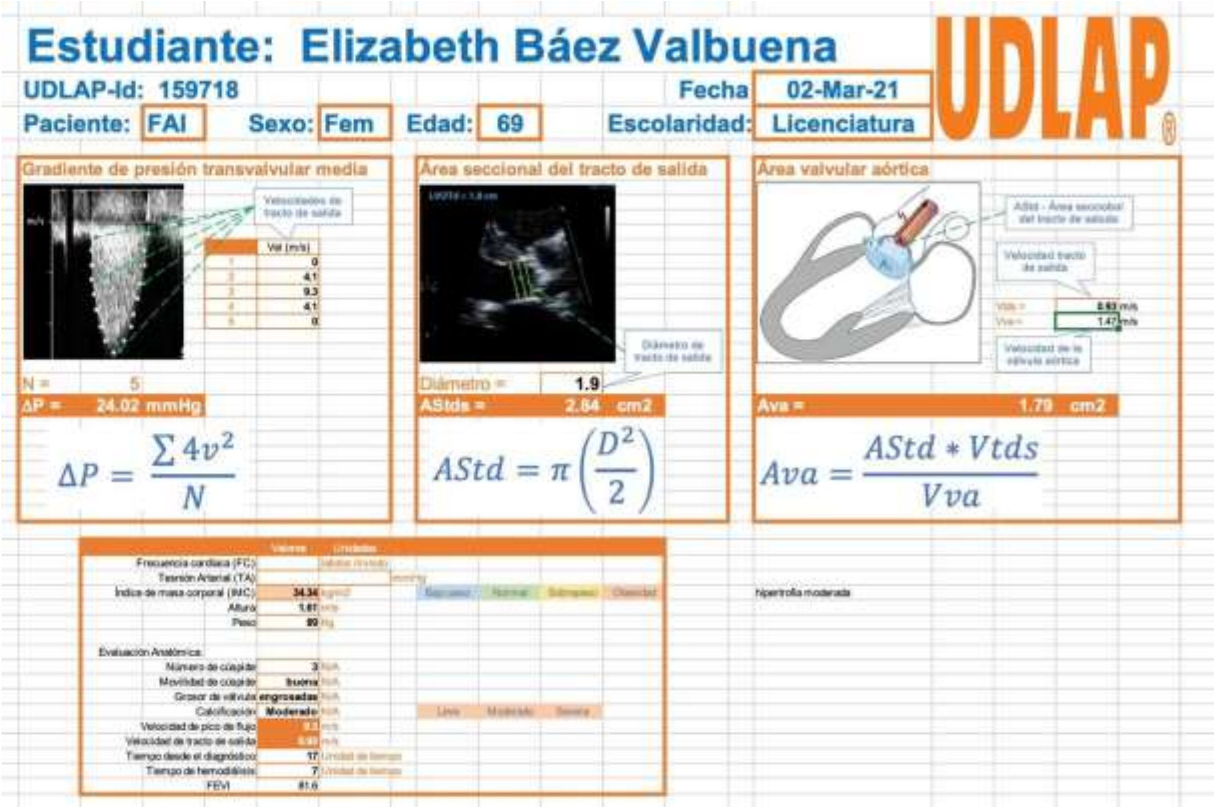

Figure 6: Patient 3 data in the **Excel** data collection table

DISCUSSION

Echocardiographic measurement of these 3 patients provides us with valuable information about cardiac involvement secondary to renal disease. As mentioned above, this relationship is well known, however, it is not routine to evaluate our parameters in the aortic valve.

Taking into account the consequences that the state of the aortic valve represents, it is important to measure the proposed parameters to prevent more serious consequences or to predict them in order to be able to take action in the face of such a complication. In our 3 patients, although the difference in the time with the diagnosis of renal disease and the time of hemodialysis treatment is significant, we found relatively similar parameters (Table 2).

Table 2: Evaluation of echocardiographic and non-echocardiographic data of our patients withtheir interpretation.

Paciente	Años con diagnóstico	Años con hemodiálisis	Calcificación	Velocidad pico de flujo	Gradiente transvalvular	Área valvular aórtica
1	28	3	Moderada	Severa	Moderada	Leve
2	6	2	Leve	Severo	Moderado	Leve
3	17	7	Moderada	Severo	Moderado	Leve

The ESC 2012 guidelines definition of severe aortic stenosis states that it must meet the following: o Peak velocities >4 m/s o Mean pressure gradient >40 mmHg o Aortic valve area
<1 cm2 o Aortic valve area <0.6 cm2 if adjusted to body surface area

Originally the mean pressure gradient had not been taken into account, so it was decided to take it as another variable and calculate it in our patients, which can be measured directly in the echocardiogram. Putting the definition in context with our patients we can conclude the following (Table 3)

Table 3: Quantitative patient data

Paciente	Velocidad pico	Gradiente medio	Área valvular aórtica
1	9.8 m/s	50 mmHg	2.86 cm2
2	11.4 m/s	90 mmHg	1.70 cm2
3	9.3 m/s	40 mmHg	1.79 cm2

The 3 patients comply with 2 of the 3 parameters except for the aortic valve area, which in all of them is greater than 1 cm2, therefore, despite the time on hemodialysis and the time with the diagnosis of chronic kidney disease, they cannot be classified as severe stenosis.

We will begin to analyze the measured parameters and compare them with the literature to get a broader picture of the importance of these measurements.

We will first analyze the time of evolution of aortic stenosis along with the variable of hemodialysis and thus compare with the literature if our patients meet the norm or are exceptions. Ureña-Torres et al. mention that (2019) regarding calcification; patients show a survival after diagnosis of 1- 2.6 years without mentioning the level of valve calcification. However, in our study 2 of the 3 patients had moderate aortic calcification, both with more than 2 years of hemodialysis. However, none of the patients mentioned having knowledge of this condition, except patient 1 who had a previous diagnosis of hypertrophic heart disease, although this condition has no relevance in calcification. Therefore, in these cases, the three patients exceeded the life expectancy proposed by the author.

The same author emphasizes the treatment of concomitant hypertension in these patients since, as such, there is no specific treatment for aortic calcification except for its replacement. It is a progressive and chronic pathology, for this reason he recommends the control of aggravating factors of calcification, the most important being systemic arterial hypertension, which is suffered by all 3 patients and all 3 have a treatment plan. This point is important because it mentions that antihypertensive drugs were previously considered contraindicated in aortic stenosis, a premise that has been refuted by the new evidence.

Hypertension increases the diastolic transvalvular pressure gradient across the aortic valve, the leaflets undergo remodeling with collagen deposition, inflammation and endothelial dysfunction (Ureña-Torres et al., 2019). The control of this comorbidity, improves the aforementioned and blocks the renin-angiotensin-aldosterone axis which prevents the progression of stenosis in human and animal clinical trials.

Going further into the subject of comorbidities, the onset of calcification and subsequent aortic stenosis goes hand in hand with the presence of concomitant diseases, the most representative being diabetic neuropathy and a history of ischemic heart disease. In the case of our patients, only patient 1 had a history of heart disease. However, all 3 already had mild to moderate calcification even without these risk factors (Kurasawa et al., 2021). It is also mentioned that the use of some antihypertensive drugs is associated with the progression of calcification, which it is very likely that some of the patients have consumed throughout the history of hypertension control, which may justify the degree of calcification in which we found our patients. It is reported that at the time of diagnosis the degree of calcification is more prevalent and severe as time on hemodialysis and age increase. In our case, this is true, patient 1 and 3 are those who were classified with a moderate degree of calcification, they have also been on hemodialysis for more than 3 years which may not seem very important, but they have been diagnosed with chronic kidney disease for more than 15 years of evolution. The variable of age is not fulfilled one hundred percent since the three patients have a similar age, therefore we cannot make a frank comparison, what is evident is that they belong to the third age of life having all three over 60 years of age, which may have predisposed in a greater way its onset and progression. Kurasawa et al. (2021) mention that the fact of having a diagnosis of aortic stenosis and mild to moderate calcification is not a marker as such of cardiovascular pathology, despite this it is clinically useful because it is possible to evaluate more completely the risk of mortality in these patients to avoid sudden cardiac death due to heart failure. Similarly, concomitant adverse events such as heart failure itself can trigger inflammation which aggravates renal pathology and therefore the number of deaths increases due to the deterioration of the patient's condition.

According to the European Society of Cardiology and the European Association of Cardiothoracic Surgery, the new indications for valve replacement and management are the following: symptomatic patients with severe aortic stenosis, aortic stenosis with high gradient(mean gradient >40 mmHg or peak flow velocity >4m/s)
(Ureña-Torres et al., 2019). These data are expressed in Table 4.

Table 4: Mean gradient and peak flow velocity data of our patients

Paciente	Gradiente medio	Velocidad pico de flujo
1	50 mmHg	9.8 m/s
2	90 mmHg	11.4 m/s
3	40 mmHg	9.3 m/s

As can be seen, the three patients comply with the echocardiographic parameters, however, none of them present symptoms, therefore they do not comply with the indications for valve replacement. It is also mentioned that these indications are not completely reliable due to the lack of evidence in renal patients or patients with renal replacement therapy such as hemodialysis. In the event that some of the patients do comply with all the indications, the use of biological valves is discussed since it is not considered a contraindication to be a hemodialysis patient. In addition, it is evident that these patients have a higher postoperative mortality.

Another important point is that ischemic cardiac events as well as those related to the aortic valve occur in 39% of asymptomatic patients with progressive aortic stenosis over a 4-year period (Horiguchi et al., 2021). This data supports the importance of screening by echocardiography for the evaluation of aortic valve pathology and to prevent the aforementioned risks.

CONCLUSIONS

After carrying out our study with the parameters established in the American and European guidelines for the anatomical and structural evaluation of the aortic valve and applying them to Mexican patients, we can conclude that these measures can be modified at the patient's convenience.

That is, in the application of the protocol we find the mean pressure gradient parameter much more useful than any other parameter. We had not considered it as a variable at the beginning of our protocol, so now we can realize that it provides a lot of information without the need to interpret or place it in formulas like our other variables. It is important to emphasize that thanks to the implementation of this screening we can actually see the real usefulness of certain parameters and variables.

Now we know that the variables that really serve us and have transcendence are the following:

- Anatomical evaluation o Cusp mobility o Number of cusps o Valve thickness
- Degree of calcification o Peak flow velocity o Pressure gradient o Aorticvalve area

We reaffirmed the importance of the non-quantitative variables in our study since there are no quantitative parameters for measuring them, however, remember that these are dependent operator, therefore we still recommend that they be evaluated by expert eyes on the subject.

We realized that the other variables are not really of vital importance for a study of this type, we do not dismiss their usefulness for more precise studies, however in this protocol we can obtain more relevant information in a simpler way with other types of measurements.

It is important to mention that none of our 3 patients reported any complaints during the echocardiogram, and the average time of the study was approximately 10 minutes. Patients were asked about discomfort immediately after the study, and the answer was negative in 100%of the cases.

We propose to take up these findings to add them to the routine studies of patients with chronickidney disease treated with hemodialysis because they provide important information about thecardiovascular health of patients as we have been mentioning throughout this text. Likewise, these measurements do not take more than 10 minutes to perform and the information they provide is of great importance. Considering these measurements in this type of patients as recurrent studies to find affectation or to monitor its evolution if any already exists, gives us anew perspective on a structure previously not taken into account. As a side note, our patients showed a genuine interest in their own health in the context of this protocol and requested a follow-up at their next routine check-up to evaluate their progression.

Bioethical Considerations

The protocol will be carried out in accordance with the principles of the Declaration of Helsinkiand with the General Health Law, Title Two: Ethical Aspects of Research on Human Beings.

CHAPTER I: Common Provisions. Article 13 and 14.- In all research in which the human being is the subject of study, the criterion of respect for his dignity and the protection of his rights and welfare shall prevail.

Likewise, the stipulations of Title Five of the General Health Law (LGS) regarding health research will be respected, which stipulates that health research includes the development of actions that contribute: To the knowledge of biological and psychological processes in human beings; to the knowledge of the links between the causes of disease, medical practice and social structure; to the prevention and control of health problems that are considered a priority for the population; to the knowledge and control of the harmful effects of the environment on health; to the study of techniques and methods that are recommended or used for the provision of healthservices, and to the national production of inputs for health.

Likewise, according to the Federal Law on Personal Data Protection, in all personal data processing, it is presumed that there is a reasonable expectation of privacy, understood as the trust that any person places in another, regarding that the personal data provided between them will be treated in accordance with what the parties agreed in the terms established by law.

Finally, as indicated in Article 8 of the Federal Law on Personal Data Protection, consent may be revoked at any time without retroactive effect. To revoke consent, the data controller must, in the privacy notice, establish the mechanisms and procedures to do so.

For this research protocol it will be necessary the use of informed consent since being a prospective study, I will have direct contact with the patient at the time of performing the echocardiogram, also clinical records will be used so the researcher presents a letter of confidentiality (Annex 1) to be presented and delivered to the private hemodialysis clinic before starting the data collection for research, in order to commit to maintain confidentiality and to give a good data management.

This study has no conflict of interest on the part of the author or any of her advisors.

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