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EDITORIAL
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A study that fails to move the needle: MATTERHORN and the confirmation of the obvious in a highly selective population

Un estudio que no cambia el juego: el MATTERHORN y la confirmación de lo obvio en una población altamente selectiva

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Keywords: functional mitral regurgitation, mitral valve, mitral valve repair, mitral valve replacement, mitral valve surgery, transcatheter edge-to-edge repair.

Palabras clave: *insuficiencia mitral funcional, válvula mitral, reparación valvular mitral, reemplazo valvular mitral, cirugía valvular mitral, reparación transcatéter borde-a-borde.*

Recently, the Matterhorn (A Multicenter, Randomized, Controlled Study to Assess Mitral vAlve reconsTrucTion for advancEd Insufficiency of Functional or iscHemic ORigiN) trial (NCT02371512) results have been released through the article by Baldus S et al.[1] In this non-inferiority randomized-controlled trial (RCT) the authors studied the efficacy of transcatheter edge-to-edge repair (TEER) compared to mitral valve (MV) surgery by the composite primary endpoint encompassing death for any-cause, rehospitalization for heart failure, stroke, reintervention, implantation of left ventricular assistant device (LVAD) at one year of follow-up in patients with functional mitral regurgitation (FMR) who are at high surgical risk. The authors concluded that TEER was non-inferior to MV surgery with respect to the primary composite endpoint efficacy at one year of follow-up.

As previously mentioned, TEER proved to be non-inferior to MV surgery in FMR, but did this study truly break new ground? Does it offer any paradigm-shifting insights?

Let us premise that it is a well-established fact that MV surgery in FMR assumes particular importance solely in the context of concomitant coronary artery bypass grafting (CABG). The recommendation is class I or IIa in the current guidelines for valvular heart disease (VHD), whereas isolated MV surgery is relegated to class IIb when CABG is not part of the therapeutic strategy.[2,3] Notably, this critical aspect was conspicuously absent from the Matterhorn trial, as reflected in the reported data from this RCT. Indeed, as detailed in *Table S2*: surgical technique provided in the supplementary material by Baldus et al,[1] no cases of concomitant CABG were reported in the surgical group. In addition, patients who had undergone CABG within the preceding month were excluded from participation.

Moreover, the study enrolled 208 patients, with 104 patients allocated to the intervention group and 104 patients assigned to the surgical group. In the surgical group, 72% of patients underwent MV repair, while 28.0% underwent MV

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replacement, at the surgeon's discretion. However, the concern arises because the absence of a clear algorithm for selecting the type of MV surgery is a significant omission, especially in a multicenter trial, such as the Matterhorn. As a point of reference, the efficacy of MV repair in FMR is contingent upon the fulfillment of rigorous echocardiographic criteria, as described by Lancellotti, et al. These criteria provide a framework for predicting MV repair success and guiding clinical decision-making.[4] The absence of standardized selection criteria for MV repair or replacement may substantially influence the constituent elements of the primary composite endpoint for efficacy, including reoperation, HFH, and stroke, as well as the components of the composite endpoint for safety (stroke, bleeding, reoperation, MR recurrence, and others), with a distinctly different impact depending on whether the procedure involves MR repair or replacement.

This trial exemplifies a flawed approach, where the lack of specific subsets (MV repair or replacement) with corresponding results, precludes the possibility of drawing meaningful conclusions under the misleading term of "mitral valve reconstruction". This term, in fact, represents a fictional construction, rather than a legitimate clinical entity which rules out MV replacement.

Although it has been consistently and concisely stated that MV replacement is superior to MV repair in FMR, with regards to the absence of MR recurrence at 1 and 2 years of follow-up, it is essential to highlight that these findings were derived from studies conducted in cohorts that incorporated CABG as a component of the therapeutic approach; that means to say, corresponding to a class I or IIa recommendation for MV surgery in FMR. Importantly, in both Cardiothoracic Surgery Network Trials, this reduced recurrence of MR did not result in improved patient survival.[5,6] In addition to this, it has been emphasized that no benefit on survival is obtained by adding MV surgery to CABG in cases with FMR ≥ 3+.[7] Survival and symptom relief are primarily determined by CABG, whereas MV surgery is centered on enhancing quality of life and alleviating symptoms.[7-9]

However, it is crucial to acknowledge that, in the context of isolated MV surgery without CABG, the indication is downgraded to class IIb. This has significant implications, as the indication for isolated MV surgery without CABG *per se* in this trial is rendered increasingly contentious, particularly when employed as a point of comparison for the concept of "non-inferiority".

Furthermore, this RCT does not provide a compelling information for upgrading TEER recommendation to a class I indication, given that the subset of FMR patients eligible for TEER or isolated MV surgery typically present with disproportionate FMR,[10] which is often a consequence of underlying coronary artery disease (CAD) necessitating concomitant CABG,[11] a scenario explicitly excluded from the Matterhorn trial. As mentioned above, no cases including CABG are reported in this RCT. At the same time, it is unknown in this RCT the proportion of patients having proportionate or disproportionate FMR, as well as the specific type of tethering, viz, symmetrical or asymmetrical tethering. This fact is commonly associated to proportionate and disproportionate FMR, respectively.[12]

Within the total population, the overall prevalence of CAD was 43.7%, yet no cases of CABG were reported. Theoretically, this implies that 43.7% of the population had ischemic dilated cardiomyopathy (IDCM). However, it is impossible to determine the exact number of cases attributable to non-ischemic dilated cardiomyopathy (NIDCM). Notably, only 46.9% of the population exhibited left ventricular tethering (Carpentier's type IIIb), whereas the remaining 53.1% had annular dilation (Carpentier's type I). Furthermore, 51% of the population had a prior history of atrial fibrillation. It can be inferred that this 51% is directly correlated with the 53.1% displaying solely annular dilation, characteristic of atrial-type FMR. In general, atrial-type FMR tends to have a more favorable prognosis compared to ventricular-type FMR, particularly following successful intervention.[13] To make matters worse, no special separate subsets of patients with these aforementioned characteristics are shown in this RCT. In other words, the Matterhorn trial's results may not be broadly applicable to everyday clinical practice, as the trial focus on dilated cardiomyopathy (not needing CABG) and atrial FMR represents a relatively narrow subset of the FMR population, which is often characterized by a more diverse range of underlying causes in real-world, spearheading the list by ventricular-type FMR mainly due to IDCM cases.[14,15]

It is widely acknowledged that the adjunctive use of MV surgery in the management of FMR, with or without concomitant CABG, primarily yields palliative benefits, improving symptoms and quality of life, whereas the survival advantage is predominantly driven by CABG.[7-9] Therefore, adding death and rehospitalization for heart failure as part of the composite primary efficacy endpoint in this RCT excluding CABG appears spurious, arbitrary and unjustified.

Since intention-to-treat (ITT) analytical approach involves assessing the outcomes of all patients who underwent randomization and were allocated to a specific treatment group, without regard to their treatment adherence, completion, or withdrawal, the results reported in the article need to be deeply analyzed. A closer examination of the Matterhorn trial's supplementary material reveals that, upon applying basic statistical by Intention-to-Treat ITT analytical approach, the only parameters that demonstrated statistically highly significant benefits favoring TEER (with p-values ranging from 0.01 to 0.001) were new-onset atrial fibrillation and bleeding complications, both of which are predictable consequences of surgical procedures *(Table 1)*.

Table 1: Statistical by intention-to-treat analytical approach regarding the primary composite endpoint for safety.

Parameter	TEER (1-year, %)	MV Surgery (1-year, %)	Difference (%)	p*
Death for any cause	8.3	10.3	2.0	0.620
Rehospitalization for any cause	24.7	39.0	14.3	0.027
Rehospitalization for HF	3.4	8.5	5.1	0.120
CV Rehospitalization	8.0	14.6	6.6	0.133
Reintervention	7.6	18.5	10.9	0.019
Stroke	1.1	4.8	3.7	0.115
VARC major bleeding	3.3	29.8	26.5	< 0.0001
Deep wound infection	1.1	4.9	3.8	0.109
AKF	4.3	10.7	6.4	0.080
New onset AF	8.7	33.3	24.6	< 0.0001
Intubation > 48 hours	4.3	11.8	7.5	0.047
Sepsis	1.1	4.8	3.7	0.115
Endocarditis	0.0	1.2	1.2	0.263

AF = atrial fibrillation. AKF = acute kidney failure. CV = cardiovascular. HF = heart failure. MV = mitral valve. TEER = transcatheter edge-to-edge repair. VARC = valvular academic research consortium.
* p values are considered as statistically highly significant as < 0.001.

It is alarming to note that the "high surgical risk" criterion was employed as a determining factor for inclusion in this trial, in direct contravention of clinical guidelines which do not recognize this parameter as a valid criterion for FMR decision-making.[2,3] Moreover, the mean STS-PROM and EuroSCORE II scores in this trial were 2.0 and 3.0, respectively, which translates to low surgical risk (≤ 3%).

In conclusion, the Matterhorn trial has succinctly illustrated that, in the realm of medical science, reality is ostensibly whatever we deem it to be. Thus, if reality does not conform to our expectations, we can simply create a new one through misleading and confusing selection criteria.

Unfortunately, the needle seems to remain largely unchanged after this trial. We would expect the authors' sound judgment to prevail, and that the utilization of this type of RCT does not unduly influence the development of forthcoming clinical guidelines.

One would hope that the authors' prudent discernment prevailed, and that the utilization of this type of RCT does not unduly influence the development of forthcoming clinical guidelines.

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ORIGINAL ARTICLE

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Left ventricular adaptive response in mechanical versus biological valves

Respuesta adaptativa ventricular izquierda en válvulas mecánicas versus biológicas

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ABSTRACT

Introduction: the most common valve pathology is severe aortic stenosis, with a prevalence of 3.9% in people in the age range of 70 to 79 years whose treatment of choice is aortic valve replacement, myocardial hypertrophy acts as a compensatory response of the left ventricle, resulting in increased wall thickness. Aortic valve replacement can reverse this hypertrophy and improve survival. **Objective:** to compare left ventricular adaptive response after aortic valve replacement surgery for severe aortic valve stenosis between mechanical vs biological prosthesis. **Material and methods:** in this observational, cross-sectional comparative and retrospective study. Patients were included from January 2019 to February 2023, with a diagnosis of severe aortic stenosis undergoing aortic valve replacement, with measurement of the adaptive response of the left ventricle, through pre- and post-surgical echocardiographic measurements. **Results:** in the biological valve replacement, an improvement in the left ventricular ejection fraction of 12.41%, a decrease in left ventricular mass of 81.09 grams was observed, for the mechanical valve an improvement in the left ventricular ejection fraction of 9.13%, a decrease in left ventricular mass of 72.82 grams ($p < 0.0001$). **Conclusions:** the left ventricular adaptive response after aortic valve replacement surgery for severe aortic valve stenosis

RESUMEN

Introducción: *la patología valvular más frecuente es la estenosis aórtica severa, con una prevalencia de 3.9% en personas en un rango de edad de 70 a 79 años cuyo tratamiento de elección es el reemplazo valvular aórtico, la hipertrofia miocárdica actúa como una respuesta compensatoria del ventrículo izquierdo, resultando en un aumento del grosor de la pared. El reemplazo valvular aórtico puede revertir esta hipertrofia y mejorar la supervivencia.* ***Objetivo:*** *comparar la respuesta adaptativa ventricular izquierda posterior a la cirugía de reemplazo valvular aórtico por estenosis valvular aórtica severa entre prótesis mecánica vs biológica.* ***Material y métodos:*** *en este estudio observacional, transversal comparativo y retrospectivo. Se incluyeron pacientes de enero 2019 a febrero 2023, con diagnóstico de estenosis aórtica severa sometidos a reemplazo valvular aórtico, con medición de la respuesta adaptativa del ventrículo izquierdo, mediante medición ecocardiográfica pre y postquirúrgico.* ***Resultados:*** *en el recambio valvular biológico, se observó una mejoría en la fracción de eyección del ventrículo izquierdo de 12.41%, una disminución de la masa del ventrículo izquierdo de 81.09 gramos, para la válvula mecánica una mejoría en la fracción de eyección del ventrículo izquierdo de 9.13%, una disminución de la masa del ventrículo izquierdo de 72.82 gramos*

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in biological and mechanical prosthesis is statistically significant. There is a greater tendency towards reduction of myocardial mass in the left ventricle with biological prostheses.

Keywords: aortic valve, aortic valve stenosis, left ventricle, surgical aortic valve replacement.

(p < 0.0001). ***Conclusiones:*** *la respuesta adaptativa ventricular izquierda posterior a la cirugía de reemplazo valvular aórtico por estenosis valvular aórtica severa en prótesis biológica y mecánica es estadísticamente significativa. Existe una mayor tendencia hacia la reducción de la masa miocárdica en el ventrículo izquierdo con las prótesis biológicas.*

Palabras clave: *válvula aórtica, estenosis aórtica, ventrículo izquierdo, cirugía de reemplazo valvular aórtico.*

Abbreviations:
AS = aortic stenosis
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
PASP = pulmonary arterial systolic pressure

INTRODUCTION

Aortic valve replacement is a crucial intervention for patients who suffer from severe aortic stenosis, a condition that significantly affects heart function. Choosing between biological and mechanical prostheses in this surgery is not a simple decision; in fact, it is a complex medical dilemma that requires careful consideration. The adaptive response of the left ventricle after surgery should be assessed for differences in adaptation between biological and mechanical prostheses, which allows us to raise fundamental questions about the long-term quality of life and continued cardiac health of patients. To date, there are few studies of left ventricular adaptive response that support the choice of valve type to be implanted according to the age, sex, and characteristics of the patients.

The prevalence reported in aortic stenosis (AS) guidelines has been 0.2% between 50 and 59 years, 1.3% between 60 and 69 years, 3.9% between 70 and 79 years, and 9.8% between 80 and 89 years. In severe AS, the rate of progression to symptoms is high, with an event-free survival rate of only 30 to 50% at 2 years. In moderate AS, the mean annual rate of progression is an increase in velocity of 0.3 m/s, an increase in the mean pressure gradient of 7 mmHg, and a decrease in valve area of 0.1 cm^2, leading to left ventricular hypertrophy. In daily practice, the choice of valve replacement treatment is between biological or mechanical prosthesis and the choice should be made as individually as possible, taking into account the decision and activities of the patient.[1]

MATERIAL AND METHODS

We conducted an observational, cross-sectional, comparative and retrospective study where the population included patients with severe AS undergoing valve replacement during the period from January 2019 to February 2023, also the inclusion criteria encompassed patients with severe AS without associated ischemic heart disease and patients with complete medical records, pre- and post-operative echocardiography studies. Patients whose records were incomplete, had associated ischemic heart disease or did not have pre- and post-operative echocardiography studies were excluded.

To conduct this research study, data were collected from patients who underwent aortic valve implantation in the adult cardiac surgery service of our institution. The source of information was taken from the clinical record from which the clinical history, preoperative note, post-operative note, and pre- and post-surgical echocardiographic reports were obtained in the period from January 2019 to February 2023.

Through the observation technique, data were collected on the clinical and demographic profile: aortic valve replacement (mechanical or biological valve), echocardiographic record, percentage of myocardial mass, ejection fraction by Simpson method, pulmonary arterial systolic pressure (PASP), New York Heart Association (NYHA) functional class, EuroSCORE II, post-operative complications, age, sex, systemic arterial hypertension, diabetes and smoking.

The study was divided into two groups, response adaptive in patients with biological valve implantation and patients with mechanical valve implantation, the data were transcribed through the collection instrument and its subsequent analysis. Within the analysis, the main objective was to analyze which type of valve has a better adaptive response of the left ventricle. Through the statistical analysis of central tendency measures, frequencies, percentages and for comparison of adaptive response, the Mann Whitney U test or Student T test was used (pre- and post-surgical measurement) according to the normal distribution of related samples. Statistical significance was considered with $p \leq 0.05$ using the SPSS 22 statistical package.

RESULTS

The study cohort consisted of 45 patients who fulfilled the inclusion criteria, with a gender distribution of 53.3% males (n = 24) and 46.7% females (n = 21). The overall mean age was 58 years, with notable differences between biological (68 years) and mechanical (48 years) valve recipients. Analysis

of preoperative NYHA functional classification revealed a predominance of class III patients (53.3%, n = 24), followed by class II (42.2%, n = 19) and class IV (4.4%, n = 2). Preoperative PASP evaluations showed that 44.4% (n = 20) of patients were not at risk for pulmonary hypertension, while 37.8% (n = 17) were at mild risk and 6.7% (n = 3) were at high risk. Comorbidities were common, with hypertension (62.2%, n = 28), diabetes mellitus (37.8%, n = 17), and smoking (26.7%, n = 12) being prevalent. Postoperative complications were infrequent, with chest bleeding and arrhythmias occurring in 4.4% (n = 2) of patients each *(Table 1)*.

The study compared mechanical and biological valve recipients, yielding the following results: sex distribution was similar between the two groups, with biological valve patients comprising 45.5% males (n = 10) and 54.5% females (n = 12), and mechanical valve patients consisting of 60.9% males (n = 14) and 39.1% females (n = 9). Statistical analysis revealed no significant difference in sex distribution between the groups (p = 0.300). Analysis of preoperative NYHA functional classification showed significant differences between biological and mechanical valve recipients. Biological valve patients were primarily classified as class II (54.5%, n = 12), whereas mechanical valve patients were mostly categorized as class III (69.6%, n = 16). This indicates that mechanical valve recipients had a higher presurgical risk profile, approaching statistical significance (p = 0.051) *(Table 2)*. Evaluation of EuroSCORE II revealed that most patients were categorized as low-risk, with a predominance of biological valve patients (81.8%, n = 18) and mechanical valve patients (69.6%, n = 16). High-risk patients were relatively rare, accounting for 9.1% (n = 2) of biological valve recipients and 4.3% (n = 1) of mechanical valve recipients. Statistical analysis showed no significant difference in risk distribution between the groups (p = 0.297). Preoperative PASP assessments revealed distinct differences in pulmonary hypertension risk between biological and mechanical valve patients. Biological valve patients showed a higher proportion without risk for pulmonary hypertension (54.5%, n = 12), whereas mechanical valve patients had a lower proportion (34.8%, n = 8). Conversely, mechanical valve patients had a higher proportion with high-risk PASP (13%, n = 3), compared to none in the biological valve group. Mild risk was observed in 45.5% (n = 10) of biological valve patients and 30.4% (n = 7) of mechanical valve patients. This difference in risk profile was statistically significant (p = 0.025), indicating a lower risk of pulmonary hypertension in biological valve patients compared to mechanical valve patients *(Table 2)*. Analysis of comorbidities revealed distinct trends between biological and mechanical valve patients. A higher proportion of biological valve patients (72.7%, n = 16) had systemic arterial hypertension, but this difference did not achieve statistical significance (p = 0.155). Biological valve patients also had a higher prevalence of diabetes mellitus (45%, n = 10), although this difference was non-significant (p = 0.299). No significant difference in smoking prevalence was observed between the groups, with 27.3% (n = 6) of biological valve patients and 26.1% (n = 6) of mechanical valve patients reporting smoking habits. Postoperative complications were relatively rare, with the majority of patients experiencing no adverse events.

Table 1: Clinical-demographic characteristics in patients with severe aortic stenosis undergoing aortic valve replacement (N = 45).

Characteristics	n (%)
Gender	
Male	24 (53.3)
Female	21 (46.7)
Valve prostheses	
Biological	22 (48.9)
Mechanical	23 (51.1)
Pre-surgical PASP (risk)	
None	20 (44.4)
Low	17 (37.8)
Mild	5 (11.1)
Serious	3 (6.7)
Post-surgical PASP (risk)	
None	40 (88.9)
Low	3 (6.7)
Serious	2 (4.4)
Pre-surgical NYHA class	
II	19 (42.2)
III	24 (53.3)
IV	2 (4.4)
Post-surgical NYHA class	
II	45 (100.0)
EuroSCORE II (risk)	
Low	34 (75.6)
Mild	8 (17.8)
High	3 (6.7)
Systemic arterial hypertension	
Yes	28 (62.2)
No	17 (37.8)
Diabetes	
Yes	17 (37.8)
No	28 (62.2)
Smoking	
Yes	12 (26.7)
No	33 (73.3)
Post-surgical complications	
None	41 (91.1)
Bleeding	2 (4.4)
Arrythmias	2 (4.4)

EuroSCORE = European System for Cardiac Operative Risk Evaluation. NYHA = New York Heart Association. PASP = pulmonary arterial systolic pressure.

Specifically, 90.9% (n = 20) of biological valve patients and 91.3% (n = 21) of mechanical valve patients did not present any post-surgical complications. Bleeding occurred in 4.5% (n = 1) of biological valve patients and 4.3% (n = 1) of mechanical valve patients, while arrhythmias were observed in 4.5% (n = 1) and 4.3% (n = 1) of biological and mechanical valve patients, respectively. Statistical analysis confirmed no significant difference in post-operative complication rates between the groups (p = 0.999). The statistical analysis yielded a p-value greater than 0.005%, indicating a lack of statistically significant differences between the studied populations. This finding suggests that the biological and mechanical valve groups share similarities, enabling comparative analysis between the two *(Table 2)*.

Table 2: Comparison of clinical-demographic characteristics according to valve prostheses in patients with severe aortic stenosis.

Characteristics	Valve prostheses: Biological N = 22 n (%)	Valve prostheses: Mechanical N = 23 n (%)	p
Gender			0.300
Male	10 (45.5)	14 (60.9)	
Female	12 (54.5)	9 (39.1)	
Pre-surgical NYHA class			0.051
II	12 (54.5)	7 (30.4)	
III	8 (36.4)	16 (69.6)	
IV	2 (9.1)	0 (0.0)	
EuroSCORE II (risk)			0.297
Low	18 (81.8)	16 (69.6)	
Mild	2 (9.1)	6 (26.1)	
High	2 (9.1)	1 (4.3)	
Pre-surgical PASP (risk)			0.025
None	12 (54.5)	8 (34.8)	
Low	10 (45.5)	7 (30.4)	
Mild	0 (0.0)	5 (21.7)	
Serious	0 (0.0)	3 (13.0)	
Post-surgical PASP (risk)			0.315
None	20 (90.9)	20 (87.0)	
Low	2 (9.1)	1 (4.3)	
Serious	0 (0.0)	2 (8.7)	
Systemic arterial hypertension			0.155
Yes	16 (72.7)	12 (52.2)	
No	6 (27.3)	11 (47.8)	
Diabetes			0.299
Yes	10 (45.5)	7 (30.4)	
No	12 (54.5)	16 (69.6)	
Smoking			0.928
Yes	6 (27.3)	6 (26.1)	
No	16 (72.7)	17 (73.9)	
Post-surgical complications			0.999
None	20 (90.9)	21 (91.3)	
Bleeding	1 (4.5)	1 (4.3)	
Arrythmias	1 (4.5)	1 (4.3)	

EuroSCORE = European System for Cardiac Operative Risk Evaluation. NYHA = New York Heart Association. PASP = pulmonary arterial systolic pressure.

Table 3: Pre- and post-surgical echocardiographic measurements in patients with biological valve prosthesis.

Study measurements	Mean ± SD	p
LVEF (%)		0.0001
Pre-surgical	53.68 ± 12.453	
Post-surgical	63.09 ± 10.080	
LV mass (g)		0.0001
Pre-surgical	284.91 ± 94.558	
Post-surgical	203.82 ± 72.790	
LV mass index (g/m^2)		0.0001
Pre-surgical	168.86 ± 50.839	
Post-surgical	121.23 ± 35.025	
RWT		0.0001
Pre-surgical	0.600 ± 0.0895	
Post-surgical	0.488 ± 0.0939	
Septum wall (mm)		0.0001
Pre-surgical	14.91 ± 1.974	
Post-surgical	12.18 ± 1.842	
Posterior wall (mm)		0.0001
Pre-surgical	13.64 ± 2.361	
Post-surgical	11.27 ± 2.164	
PASP (mmHg)		0.001
Pre-surgical	38.95 ± 6.579	
Post-surgical	30.36 ± 5.786	

RWT = relative wall thickness. LV = left ventricle. LVEF = left ventricular ejection fraction. PASP = pulmonary arterial systolic pressure. SD = standard deviation.

Pre- and post-operative comparison in 22 biological prosthesis patients demonstrated substantial improvements in left ventricular function and remodeling. Statistically significant changes included: LVEF increase: 12.41% ($p < 0.0001$), left ventricular mass reduction: 81.09 grams ($p < 0.0001$), left ventricular mass index decrease: 47.63 g/m^2 ($p < 0.0001$), relative wall thickness decrease: 0.11 mm ($p < 0.0001$), septum wall thickness reduction: 2.72 mm ($p < 0.0001$), posterior wall thickness decrease: 1.29 mm ($p < 0.0001$), and PASP decrease: 8.59 mmHg ($p < 0.0001$). These results suggest a beneficial adaptive response of the left ventricle, with enhanced ejection fraction and decreased pulmonary hypertension risk *(Table 3)*.

A pre- and post-operative comparison in 23 patients with mechanical valves revealed significant improvements in left ventricular function and structure. Notably, the following statistically significant changes were observed: LVEF

increase: 9.13% ($p < 0.000$), left ventricular mass reduction: 72.82 grams ($p < 0.000$), left ventricular mass index decrease: 50 g/m^2 ($p < 0.000$), relative wall thickness decrease: 0.11 ($p < 0.000$), septum wall thickness reduction: 2.36 mm ($p < 0.000$), posterior wall thickness decrease: 3.08 mm ($p < 0.000$), PASP decrease: 17.39 mmHg ($p < 0.000$). These findings indicate a favorable adaptive response of the left ventricle, characterized by improved ejection fraction and reduced risk of pulmonary hypertension *(Table 4)*.

A comparative analysis of myocardial remodeling and functional variables between biological and mechanical valves revealed distinct differences in the magnitude of improvement. Notably, biological valves showed a greater tendency towards reduced left ventricular mass, with a 5.01% difference ($p = 0.324$), although this did not reach statistical significance. In contrast, mechanical valves demonstrated a greater percentage decrease in: relative wall thickness: 2.93% ($p = 0.464$), and posterior wall thickness: 3.54% ($p = 0.464$). Notably, mechanical valves exhibited a significantly greater decrease in PASP (13.75%, $p = 0.006$), indicating a more pronounced improvement in pulmonary hypertension. Although these differences suggest distinct adaptive responses between valve types, they did not reach statistical significance ($p > 0.05$) *(Table 5)*.

Analysis of myocardial remodeling by sex revealed trends towards sex-specific differences. Compared to men, women showed greater reduction in left ventricular mass: 8.82% ($p = 0.079$), greater decrease in left ventricular mass index: 7.07% ($p = 0.144$), and greater reduction in posterior wall thickness: 4.21% ($p = 0.296$). In contrast, men exhibited a greater decrease in PASP: 8.07% ($p = 0.111$). While these differences did not achieve statistical significance, they suggest potential sex-based variations in myocardial remodeling *(Table 6)*.

Table 4: Pre- and post-surgical echocardiographic measurements in patients with mechanical valve prosthesis.

Study measurements	Mean ± SD	p
LVEF (%)		0.0001
Pre-surgical	48.91 ± 15.171	
Post-surgical	58.04 ± 13.210	
LV mass (g)		0.0001
Pre-surgical	303.26 ± 98.711	
Post-surgical	227.43 ± 69.290	
LV mass index (g/m^2)		0.0002
Pre-surgical	173.61 ± 47.214	
Post-surgical	123.61 ± 35.863	
RWT		0.0001
Pre-surgical	0.559 ± 0.1126	
Post-surgical	0.440 ± 0.0870	
Septum wall (mm)		0.0001
Pre-surgical	14.41 ± 2.146	
Post-surgical	12.04 ± 2.383	
Posterior wall (mm)		0.0001
Pre-surgical	14.00 ± 3.580	
Post-surgical	10.91 ± 1.756	
PASP (mmHg)		0.0001
Pre-surgical	49.96 ± 19.848	
Post-surgical	32.57 ± 17.671	

RWT = relative wall thickness. LV = left ventricle. LVEF = left ventricular ejection fraction. PASP = pulmonary arterial systolic pressure. SD = standard deviation.

Table 5: Adaptive response in patients with severe aortic stenosis undergoing aortic valve replacement regarding the valve prostheses.

	Valve prostheses		
Echocardiographic measurements	Biological Mean ± SD	Mechanical Mean ± SD	p
LVEF difference	9.41 ± 7.36	9.13 ± 7.24	0.899
Percentage decrease in			
LV mass (g)	27.59 ± 13.49	22.58 ± 19.49	0.324
LV mass index (g/m^2)	26.22 ± 14.64	26.99 ± 17.68	0.874
RWT	17.89 ± 15.48	20.72 ± 10.70	0.464
Septum wall (mm)	17.79 ± 11.20	16.45 ± 10.08	0.689
Posterior wall (mm)	16.49 ± 13.06	20.03 ± 13.68	0.381
Average PASP (mmHg)	21.46 ± 11.01	35.21 ± 19.40	0.006

RWT = relative wall thickness. LV = left ventricle.
LVEF = left ventricular ejection fraction. PASP = pulmonary arterial systolic pressure. SD = standard deviation.

Table 6: Adaptive response in patients with severe aortic stenosis undergoing aortic valve replacement regarding gender (N = 45).

	Gender		
Echocardiographic measurements	Male n = 24 Mean ± SD	Female n = 21 Mean ± SD	p
LVEF difference	9.21 ± 7.58	9.33 ± 6.96	0.955
Percentage decrease in			
LV mass (g)	20.91 ± 16.68	29.73 ± 16.10	0.079
LV mass index (g/m^2)	23.30 ± 13.89	30.37 ± 17.89	0.144
RWT	18.05 ± 10.56	20.73 ± 15.85	0.502
Septum wall (mm)	16.58 ± 10.96	17.65 ± 10.27	0.740
Posterior wall (mm)	16.33 ± 11.95	20.54 ± 14.75	0.296
Average PASP (mmHg)	32.30 ± 19.39	24.13 ± 13.30	0.111

RWT = relative wall thickness. LV = left ventricle. LVEF = left ventricular ejection fraction. PASP = pulmonary arterial systolic pressure. SD = standard deviation.

Main differences between both groups are represented in *Figure 1*.

DISCUSSION

Aortic stenosis (AS) is the most prevalent cause of left ventricular outflow obstruction, primarily resulting from congenitally abnormal valves, calcified trileaflet valves, or rheumatic valvular disease characterized by commissural fusion and reduced central orifice area.[1] This valvular area decreases triggers pressure overload, leading to hypertrophy and increased wall stress without compromising systolic function until advanced disease stages.[2] Aortic valve replacement significantly improves survival, supporting its recommendation.[3] Surgical replacement alleviates left ventricular overload, prompting rapid remodeling visible in echocardiographic studies[4] and enhancing ejection fraction.[5] After the procedure, left ventricular mass (measured in grams per square meter, g/m^2) tends to normalize, potentially positively impacting long-term prognosis.[6] Notably, our study's average age (58 years) was lower than reported in literature. Current heart valve disease guidelines indicate AS prevalence as 0.2% (50-59 years), 1.3% (60-69 years), 3.9% (70-79 years), and 9.8% (80-89 years), respectively. Mortality rates significantly increase with cardiac symptom onset. Even mild symptoms necessitate immediate intervention, given the median survival without valve replacement is merely two to three years, with high risk of sudden death.[1] Therefore, aortic valve replacement remains the only proven treatment altering the disease's natural course. This study investigated the adaptive response of the left ventricle in patients with severe AS undergoing aortic valve replacement with either biological or mechanical valves through surgical intervention. A comparative analysis revealed significant improvements in LVEF and adaptive ventricular response, which is characterized by decreased myocardial mass, relative wall thickness, septal wall thickness, and posterior wall thickness. Notably, these changes were statistically significant in both biological and mechanical valve groups (p = 0.0001), aligning with existing literature. The enhancement in LVEF

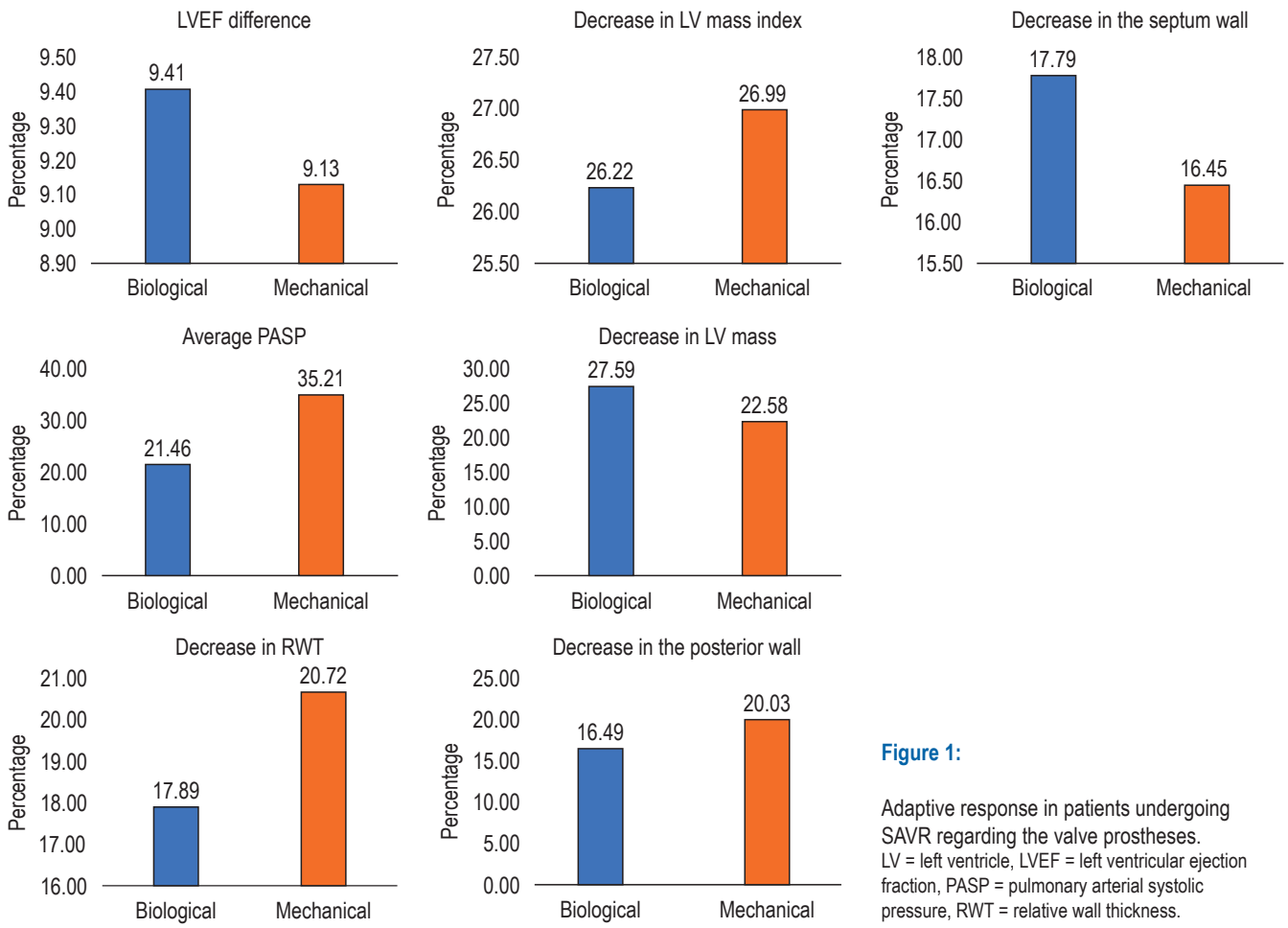

Figure 1:

Adaptive response in patients undergoing SAVR regarding the valve prostheses.
LV = left ventricle, LVEF = left ventricular ejection fraction, PASP = pulmonary arterial systolic pressure, RWT = relative wall thickness.

parallels the reduction in left ventricular hypertrophy, with men exhibiting a greater decrease.[7] This reduction predicts improved functional remodeling and increased LVEF. In this study, women demonstrated a trend towards decreased left ventricular myocardial mass, with an 8.82% reduction ($p = 0.079$), although this did not reach statistical significance. Notably, biological prostheses, specifically the Intuity Elite (Edwards Lifesciences, Irvine, CA, USA) and the Perceval S (Corcym, London, UK) rapid deployment prostheses, exhibited superior adaptive responses and contractility improvements compared to conventional prostheses. This was evidenced by greater decrease in left ventricular myocardial mass up to 21 g/m^2 (vs 9 g/m^2 and 15 g/m^2, $p < 0.001$), and consistent with this trend, a 5.01% decrease in left ventricular myocardial mass was observed ($p = 0.324$). These results indicate that biological prostheses, particularly rapid deployment models, may enhance ventricular remodeling and functional outcomes. The selection of a prosthetic heart valve for aortic valve replacement surgery requires a multidisciplinary approach, involving collaborative decision-making between cardiologists and cardiac surgeons. To ensure informed decision-making, patients should receive comprehensive information regarding indications for valve replacement, risks associated with anticoagulant therapy, and possibility as well as risks of reoperation. Furthermore, patient values and preferences should be integrated into this decision-making process, considering individual priorities and quality of life considerations.[1] According to literature, preoperative left ventricular mass rates are significantly higher in men than women. Normalization thresholds for ventricular mass index are defined as < 115 g/m^2 for men and < 95 g/m^2 for women.[8] Notably, men demonstrated a higher percentage of normalization (80.4% vs 52.4%, $p = 0.02$). This study assessed sex-based differences in left ventricular adaptive response pre- and post-operatively, revealing greater decrease in left ventricular mass in women: 8.82% ($p = 0.079$), greater decrease in left ventricular mass index in women: 7.07% ($p = 0.144$), greater decrease in posterior wall thickness in women: 4.21% ($p = 0.296$). These findings suggest that sex plays a pivotal role in adaptive response of the left ventricle to pressure overload generated by AS, and morphological and functional ventricular remodeling following sudden reduction of overload. The observed sex-based differences underscore the importance of considering gender-specific factors in the management and treatment of AS.

CONCLUSIONS

Following aortic valve replacement surgery for severe AS, both bioprosthetic and mechanical valves demonstrated statistically significant left ventricular adaptive responses, characterized by improved LVEF, reduced myocardial mass, decreased relative wall thickness, thinner interventricular septum and posterior walls, and lower PASP, thereby mitigating the risk of pulmonary hypertension. Notably, bioprosthetic valves tended to exhibit greater reductions in myocardial mass, whereas mechanical valves showed greater decreases in PASP, although these differences did not reach statistical significance, highlighting the need for larger sample sizes in future investigations. Furthermore, sex-based analysis revealed a greater propensity for left ventricular mass reduction in female patients. To elucidate the long-term evolution of patients following aortic valve replacement, additional echocardiographic studies are essential to expand the sample size and enhance follow-up, ultimately informing optimized patient care and guiding future research.

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CASE REPORT
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Surgery in infective endocarditis post-transcatheter aortic valve replacement in two low-risk cases

Cirugía en endocarditis infecciosa postreemplazo valvular aórtico transcatéter en dos casos de bajo riesgo

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ABSTRACT

Percutaneous aortic valve replacement has evolved from a procedure for high-risk surgical patients to an accepted procedure approved by the FDA in 2019 for patients with medium and low risk worldwide. Most cases of post-TAVI endocarditis occur within the first year of the procedure, with an incidence ranging from 0.5 to 2%. We present two cases of early-onset infective endocarditis following transcatheter aortic valve replacement in two low-risk surgical patients.

Keywords: aortic valve, complications, endocarditis, operative low-risk, TAVI, surgery.

RESUMEN

La colocación de válvulas aórticas percutáneas ha pasado de ser un procedimiento para pacientes quirúrgicos de alto riesgo a un procedimiento aceptado en 2019 por la FDA para pacientes de riesgo medio y bajo a nivel mundial. La mayoría de las endocarditis posteriores a TAVI se presentan antes del primer año del procedimiento. Su incidencia es de 0.5 a 2%. Presentamos dos casos de endocarditis infecciosa temprana postreemplazo valvular aórtico transcatéter en dos casos de bajo riesgo quirúrgico.

Palabras clave: *válvula aórtica, complicaciones, endocarditis, bajo riesgo operatorio, TAVI, cirugía.*

Abreviaturas:
CTA = computed tomography angiography
LAD = left anterior descending
LVEF = left ventricular ejection fraction
PCI = percutaneous coronary interventions
RCA = right coronary arteries
SAVR = surgical aortic valve replacement
STS = Society of Thoracic Surgeons
TAVI = transcatheter aortic valve implantation

INTRODUCTION

Recently, there has been a marked surge in Transcatheter Aortic Valve Implantation (TAVI) procedures globally, driven by the findings of clinical trials demonstrating the non-inferiority of transcatheter aortic valve replacement compared to surgical intervention in low-to-intermediate

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risk patients, as determined by the STS score and Euroscore. Paralleling this trend, an increasing number of patients are presenting with prosthetic valve endocarditis following transcatheter implantation. This represents a serious complication, with an incidence ranging from 1.7 to 2% within the first year post-implant.[1,2] Here, we present two cases of early-onset post-TAVI endocarditis, highlighting the importance of vigilance and prompt management in this patient population.

CASE DESCRIPTION

Case 1

A 63-year-old male presented with a 30-year history of smoking, arterial hypertension, and type II diabetes mellitus. In April 2023, he experienced symptoms of stable angina. Echocardiography revealed severe aortic stenosis with a valve area of 0.96 cm^2, characterized by low flow and low gradient, and a left ventricular ejection fraction (LVEF) of 34%. Coronary angiography demonstrated lesions in the left anterior descending (LAD) and right coronary arteries (RCA). Computed tomography angiography (CTA) showed an aortic valve with a 28 mm aortic annulus and suitable coronary distances for transcatheter aortic valve implantation (TAVI). The Society of Thoracic Surgeons (STS) risk score was calculated to be 1.82%. Subsequent percutaneous coronary interventions (PCI) were performed, with stent placement in the LAD and RCA on August 18, 2023. Three months later, on November 9, 2023, a percutaneous aortic valve replacement was performed via femoral access, utilizing an Evolut™ R 34 mm valve prosthesis (Medtronic, Minneapolis, MN, USA), resulting in a mild paravalvular leak in the non-coronary sinus. Four months post-TAVI, on March 10, 2024, the patient developed a febrile syndrome, petechiae on the lower limbs, decreased visual acuity in the right eye, reversible neurological deterioration, and heart failure, necessitating inotropic support and non-invasive respiratory support in the Intensive Care Unit.

Echocardiography study revealed mild aortic insufficiency with a 14% paravalvular leak, a 17 × 7 mm oscillating vegetation, and a LVEF of 53%. Additionally, anteroseptal hypokinesia, systolic and diastolic dysfunction of the left ventricle, and decreased systolic function of the right ventricle were observed. Blood cultures were positive for *Staphylococcus aureus*, and leukocytosis was present with a count of 13 × 10^9 cel/L. The patient was managed with antimicrobial therapy, and the STS risk score was calculated to be 2.53%. Due to the patient's critical condition, emergency surgery was performed 72 hours after admission. Standard central cannulation was employed, and a high transverse aortotomy was performed, revealing severe inflammatory changes in the tissues adjacent to the aorta. A central obstruction of the prosthetic valve caused by a vegetation of approximately 2 cm was identified *(Figure 1)*. The valve was

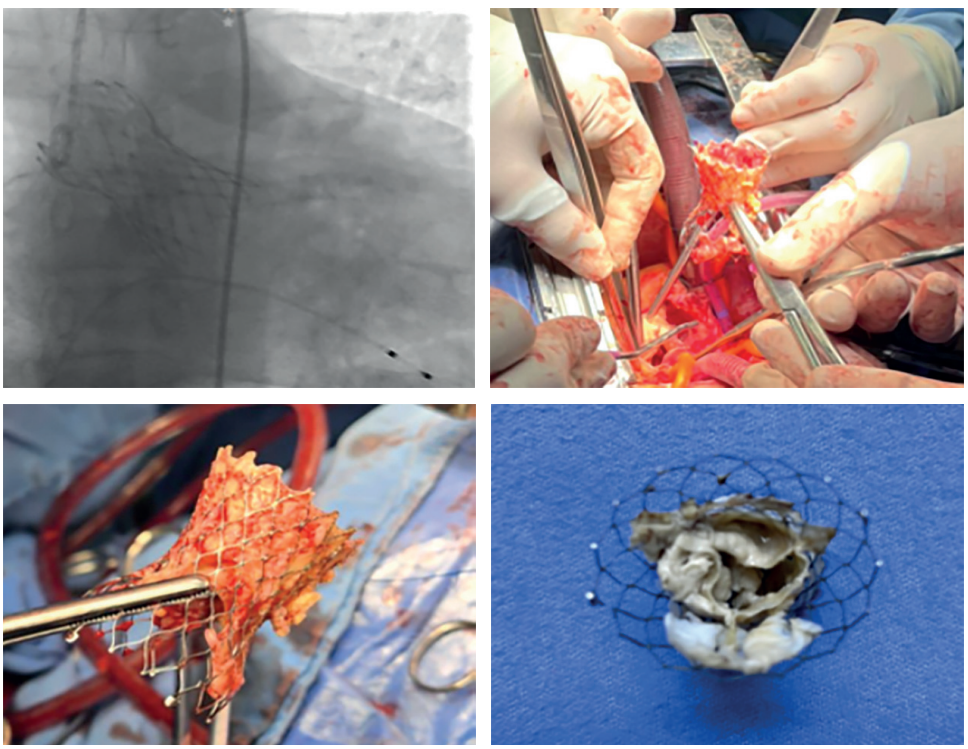

Figure 1:

Case 1. Evolut™ R 34 mm percutaneous aortic valve prosthesis (Medtronic, Minneapolis, MN, USA). A fluoroscopy view in the implant procedure, and three different views of explanted prosthesis with large vegetations.

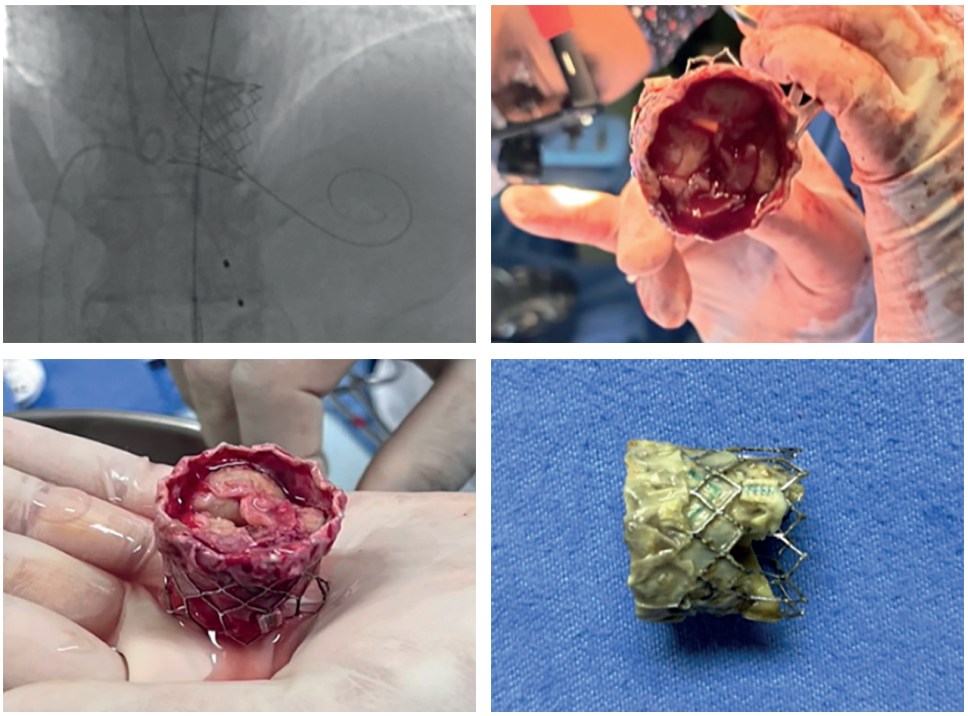

Figure 2:

Case 2. Sapiens3 29 mm percutaneous aortic valve prosthesis (Edwards Lifesciences, Irvine, California). A fluoroscopy view in the implant procedure, and three different views of explanted prosthesis with large vegetations.

carefully removed by manipulating the metal frame towards the central part of the aorta. The native aortic leaflets were excised, and part of the aortic annulus was decalcified. A No. 23 biological prosthesis was then implanted. Following aortic closure, an attempt was made to wean the patient from extracorporeal circulation. However, this was not possible due to ST segment elevation on the anterior and inferior surfaces. Consequently, two venous blood ducts were placed in the anterior descending artery and the right coronary artery, but unfortunately, this did not result in improvement, and the patient succumbed in the operating room on March 11, 2024.

Case 2

A 73-year-old male patient presented with a history of smoking, type II diabetes mellitus, and long-standing hypertension. He had suffered an inferior myocardial infarction in 2009 and remained asymptomatic until a routine check-up in 2023, which revealed an aortic murmur. Subsequent evaluation led to the diagnosis of severe aortic stenosis, with an echocardiogram on June 2, 2023, demonstrating an aortic valve area of 0.4 cm^2, maximum velocity of 4.5 m/s, mean gradient of 54 mmHg, and LVEF of 48%. Cardiac catheterization performed on the same date revealed a 90% lesion in the RCA. On February 3, 2024, a stent was placed in the middle third of the RCA. CTA showed a bileaflet aortic valve with calcification, an aortic annulus of 26.6 mm, and origins of the right and left coronary arteries at 7.7 mm and 13.4 mm, respectively. The STS risk score was calculated to be 1.56%. On June 13, 2024, a Sapiens3 29 mm percutaneous aortic prosthesis (Edwards Lifesciences, Irvine, California) was implanted via the femoral without complications, and the patient was discharged home 24 hours later. However, five days post-procedure, the patient developed signs of systemic inflammatory response, with blood cultures positive for *Staphylococcus aureus*. Despite medical treatment through five weeks, the patient's condition did not improve, and he was readmitted to the hospital on July 25, 2024, with febrile symptoms and critical hemodynamic conditions. An echocardiogram performed on August 2, 2024, revealed regurgitation/stenosis aortic, a prosthetic valve vegetation (19 × 6 mm and 7 × 14 mm), and another one of 5 × 7 mm vegetation on the anterior leaflet of the mitral valve, with leaflet perforation. The patient's condition deteriorated due to septic shock, with leucocytes count of 20 × 10^9 cel/L, and worsening renal function. Emergency surgery was performed five weeks after the onset of symptoms, on August 9, 2024, with a calculated STS risk score of 2.64%. A median sternotomy and central cannulation were performed, and the Sapiens 3 valve was explanted *(Figure 2)*. A 21 mm biological prosthesis was implanted in aortic position, and a 27 mm mitral biological prosthesis was also implanted. Additionally, repair of the left atrial roof with bovine pericardium was necessary. The patient was transferred to the Intensive Care Unit with coagulation disorders and mixed shock. Unfortunately, he died 18 hours after the operation.

COMMENT

TAVI has evolved from a procedure primarily reserved for high-risk surgical patients to a widely accepted treatment option for medium- and low-risk patients globally, following its approval by the FDA in 2019.[3] However, the ESC/EACTS 2021 Guideline for valvular heart disease recommends surgical aortic valve replacement (SAVR) for young, low-risk patients with valvular heart disease, whereas transfemoral TAVI is recommended for patients over 75 years of age or those at high surgical risk. According to the STS risk score, patients with a score < 4% are considered low-risk, as exemplified by the cases presented herein. Notably, TAVI has increasingly been adopted for low-risk patients, with current utilization rates reaching 40% of all TAVI cases in the United States and 62.5% in Asian countries. Correspondingly, mortality rates for low-risk patients undergoing TAVI have been reported to be 5.3% in the US and 3.5% in Asian countries.[4]

The majority of endocarditis cases following TAVI present within the first year after the procedure, with an incidence ranging from 0.5 to 2% for both self-expanding and balloon-expandable prostheses. Notably, the incidence of endocarditis in SAVR is 1.9%, whereas it is 1.7% after TAVI, including low-risk cases. Surgical reinterventions after TAVI are primarily driven by endocarditis, accounting for 40.7% of cases. Associated mortality rates are substantial, with intraoperative mortality reaching 18%, immediate operative mortality at 25%, and all-cause mortality up to 63.3%. Despite the high-risk nature of these patients, medical treatment is often the primary approach for endocarditis after TAVI, despite the presence of surgical indications. However, in low-risk patients, surgical intervention should not be delayed, and valve replacement should be performed promptly.[5,6] Furthermore, the removal of a TAVI prosthesis due to endocarditis is a complex and challenging procedure, frequently requiring reconstruction of the intervalvular fibrous body. Additional procedures, such as mitral valve interventions (14.7% of cases, as seen in Case II), or aortic root replacement, may also be necessary. A recent report by Takuya Ogami (2022) highlighted surgical bailout after TAVI as the most common indication for valve explant (n = 8, 47.1%), followed by infective endocarditis (n = 4, 23.5%) and paravalvular leak (n = 2, 11.8%).[7]

The European Registry of Emergency Cardiac Surgery during TAVI (EuRECS-TAVI) analyzed real-world data from 79 centers, encompassing 27,760 transfemoral TAVI procedures, and reported a slightly higher incidence of emergency conversions, at 0.76%. Single-center studies have documented emergency conversion rates ranging from 1.2 to 4.9%. The EXPLANT-TAVR registry highlights that the surgical risks associated with TAVR explant are significant and should be considered in the long-term management of aortic stenosis. Indications for explant included endocarditis (43.1%), structural valve degeneration (20.1%), paravalvular leak (18.2%), and prosthesis-patient mismatch (10.8%). Redo TAVR was not feasible due to unfavorable anatomy in 26.8% of patients. Urgent or emergency procedures were performed in 53.1% of patients, with 13.4% requiring aortic root replacement and 54.6% undergoing concomitant cardiac procedures. Overall survival at last follow-up was 76.1%. In-hospital, 30-day, and one-year mortality rates were 11.9, 13.1 and 28.5%, respectively, while stroke rates were 5.9, 8.6, and 18.7%, respectively.[8]

Although the indications for reintervention after TAVI are currently limited, this trend is expected to increase as TAVI is now considered a viable option for patients with low surgical risk in aortic stenosis. This shift in paradigm prompts reflection on the evolving role of the cardiac surgeon, as aptly noted by Tomas Modine in 2022. Cardiac surgeons possess a unique combination of skills that enable them to offer a comprehensive range of therapeutic options for structural heart disease. In addition to traditional open surgery, surgeons can provide complex transcatheter interventions, minimally invasive procedures, and redo operations for patients with valvular heart disease, thereby positioning themselves as the ultimate "valve specialist". When performing TAVI, the cardiac surgeon has the flexibility to select the optimal access site for each patient, whether it be the femoral, carotid, axillary, or transapical artery. Furthermore, given that many patients with structural heart disease present with multiple affected structures, surgeons are equipped to provide comprehensive multicomponent therapy for each of these structures in a single setting.[9]

CONCLUSIONS

The incidence of post-TAVI endocarditis requiring explantation is increasing, even among low-surgical-risk patients, and is associated with a high perioperative mortality rate, as illustrated by the two cases presented here. Notably, these findings underscore the importance of prompt surgical intervention, rather than delaying treatment with medical management alone, in order to optimize outcomes in this patient population.

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CASE REPORT
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Aortic valve migration placed by TAVI: apropos of a case

Migración valvular aórtica colocada por TAVI: a propósito de un caso

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ABSTRACT

The use of transcatheter aortic valve implantation approach (TAVI), has become popular due to its much less invasive technique. Thus, it is the treatment of choice in patients with high surgical risk. Nevertheless, the TAVI procedure represents considerable complications. We present the case of a female patient, diagnosed with severe aortic stenosis, who received a prosthetic valve through TAVI; resulting in cardiac surgery due to migration of the implanted valve to the left ventricle.

Keywords: aortic valve stenosis, complications, transcatheter aortic valve implantation, valve migration.

RESUMEN

El uso del cambio valvular aórtico transcatéter (TAVI, por sus siglas en inglés) ha tomado auge debido a ser menos invasiva y mejor tolerada que la cirugía cardíaca; posicionándose como la opción favorita en pacientes con alto riesgo quirúrgico. Sin embargo, el TAVI presenta complicaciones considerables. Se presenta el caso de una paciente con estenosis aórtica grave, intervenida a través de TAVI, presentando migración de la prótesis hacia ventrículo izquierdo, requiriendo cirugía para extracción de la misma y cambio valvular.

Palabras clave: estenosis valvular aórtica, complicaciones, implante de válvula aórtica transcatéter, migración valvular.

INTRODUCTION

Worldwide, the aortic stenosis is the most common valve disease in elderly patients.[1] In this group, even up to 60% of symptomatic patients have a moderate-high surgical risk, and up to a 30% of patients were not considered candidates for cardiac surgery, because of a considerable high surgical risk. Due to the necessity to ensure a safer approach to these patients, the transcatheter aortic valve implantation (TAVI), appeared as an alternative for these patients.[2]

Nowadays, the evolution of TAVI in the clinical practice, shows an improvement of the results, reaching a 94% of success procedures. Also, different studies agree in the fact that after 2014, the patients treated trough TAVI remained less time in the hospital, the mortality cases dropped 30%, and had less cases of procedures converted to cardiac surgery. Nevertheless, the incidence of acute kidney injury, major bleeding and post-implantation dilatation of the aortic ring, have increased. Which, altogether, increases the incidence of major complications in the patient.[3]

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CASE DESCRIPTION

A 59-year-old female patient with a history of systemic hypertension presented to the emergency room with moderate chest pain and a single episode of syncope during physical activity. Echocardiography revealed concentric left ventricular hypertrophy, a left ventricular ejection fraction of 69%, aortic valve fusion, an aortic ring diameter of 20.8 mm, a maximum transvalvular aortic gradient of 99 mmHg, and a mean gradient of 25 mmHg. The patient was diagnosed with severe aortic stenosis and referred to the cardiothoracic surgery department.

The patient was deemed a suitable candidate for valve replacement via cardiac surgery. However, to expedite treatment, a TAVI approach was employed. During the procedure, an Accurate Neo 2S 23 mm prosthesis (ACURATE neo2™, Boston Scientific, Marlborough, MA, USA), was implanted, but a residual valvular gradient of 25 mmHg was observed due to incomplete prosthesis deployment. To achieve optimal deployment, a post-implant dilatation of the aortic ring was performed, but a gradient of 20 mmHg persisted. Consequently, a second Accurate Neo 2S 23 mm prosthesis was implanted using the TAVI-in-TAVI technique. Unfortunately, during the second implantation, the first prosthetic valve migrated into the left ventricle *(Figure 1)*.

Due to this complication, the patient was taken to the operating room for extraction of the migrated valve and aortic valve replacement. Under cardiopulmonary bypass, the migrated valve was extracted from the left ventricle,

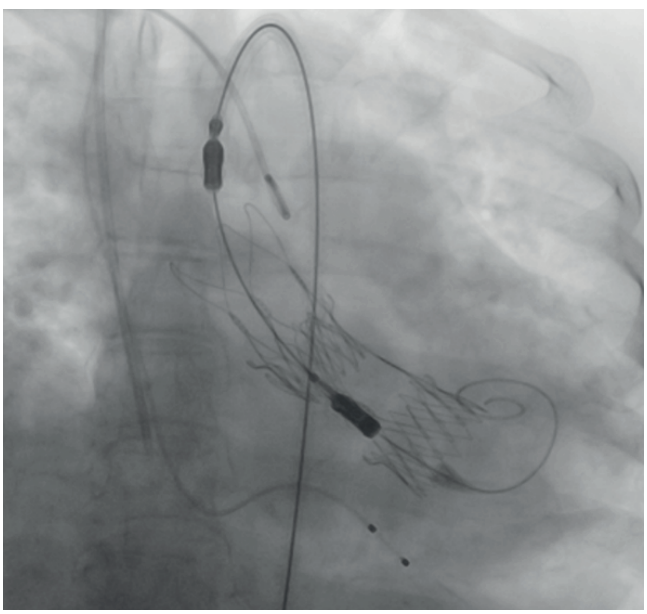

Figure 1: Migration of the transcatheter prosthesis to left ventricle, after failed TAVI-in-TAVI approach.
TAVI = transcatheter aortic valve implant.

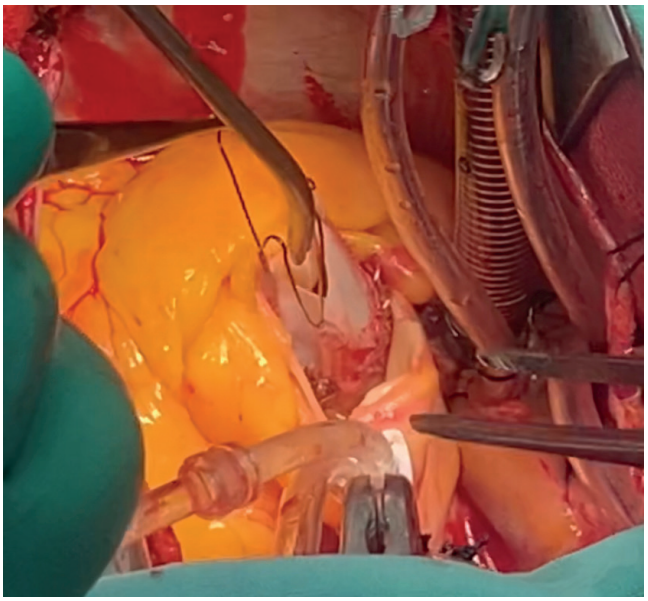

Figure 2: Extraction of the migrated prosthesis from the left ventricle.

along with the second implanted prosthesis *(Figures 2 and 3)*. Subsequently, an aortic ring enlargement using the Nicks technique was performed, and the valve was replaced with a SJM™ Masters Series 21 mm (St Jude Medical, Inc., USA) mechanical prosthesis. Finally, a chest drainage tube was placed in the retrosternal space, and the procedure was completed without complications, with a total cardiopulmonary bypass time of 115 minutes and an aortic clamping time of 94 minutes.

In the immediate postoperative period, the patient exhibited satisfactory progress, with a well-functioning aortic valve, mean trans-prosthetic gradient of 10 mmHg, maximum velocity of 2.2 m/s, and preserved left ventricular ejection fraction *(Figure 4)*. The patient required nitroglycerin dosed at 116 µg/minute due to a systemic hypertensive peak. Following the fast-track algorithm, the patient was weaned from invasive mechanical ventilation, demonstrating a good respiratory pattern and parameters, as well as a good cognitive response.

On the second postoperative day, supplemental oxygen and nitroglycerin were discontinued. Given the patient's favorable clinical condition, they were transferred to a non-intensive care unit for continued observation. The drainage was removed on the fourth postoperative day, and the patient was discharged home on the eighth postoperative day free from any complications.

COMMENTARY

Like any other procedure, the TAVI approach is not devoid of risks; in fact, 2-8% of patients develop major or life-

threatening complications. The most common complication of TAVI is peripheral vascular injury, particularly at the catheter entry point, which can result in limb ischemia or hemorrhage.[1] The second most common complication is rhythm disorders, usually due to left bundle branch block (65% of cases) and complete atrioventricular block (10% of cases), which necessitates lifelong permanent pacemaker implantation.[1]

Prosthetic migration to the left ventricle is observed in 7% of cases, where extracorporeal membrane oxygenation may be required as a bridge while the patient undergoes urgent cardiac surgery.[2] It is concerning that up to 84% of post-TAVI patients exhibit cerebral embolism, although only 10% of these cases present clinical signs of brain damage. Aortic valve regurgitation of any grade is reported in 70% of all patients, with significant paravalvular regurgitation in 20% of all post-TAVI patients.[2]

Furthermore, up to 20% of post-TAVI patients develop acute kidney injury, and 5% of these require renal replacement therapy.[1] Compared to cardiac surgery, post-TAVI patients require permanent pacemaker implantation more frequently, especially in cases where aortic ring dilatation was necessary, due to an increased risk of conduction system injury. This is commonly observed in patients with bicuspid aortic valves, such as the case reported.[2] The incidence of conduction system injury has increased, as newer TAVI prosthesis models have a lower incidence of valvular regurgitation, at the expense of a higher incidence of rhythm disorders.[4]

Despite being considered a safer approach, mortality rates for post-TAVI and post-cardiac surgery patients are equal at 24 months post-procedure.[2] Due to this high complication rate, new techniques have been explored, such as overestimating aortic ring size by up to 20% and using self-expanding prostheses.[5] However, implanting a significantly larger prosthesis must be done with extreme caution, due to the risk of aortic ring rupture.[1]

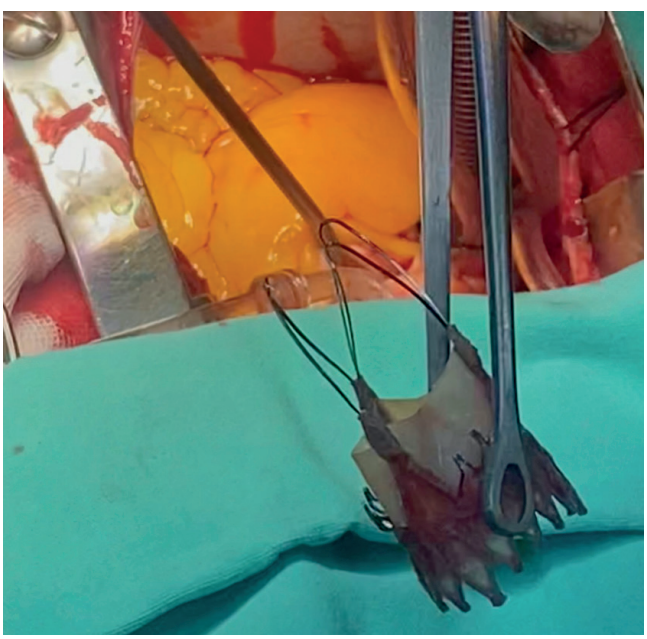

Figure 3: Extraction of the second implanted prostheses from the aortic ring.

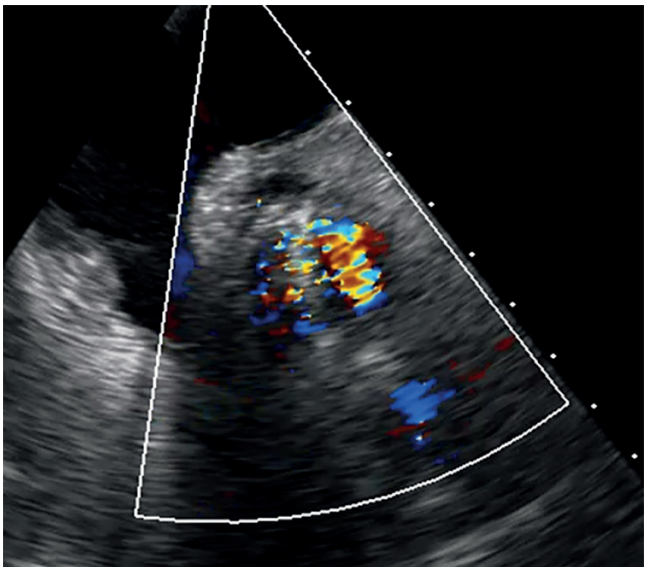

Figure 4: Echocardiographic image of the replaced mechanical aortic valve.

Finally, there has been growing interest in achieving correct commissural alignment between the prosthetic and native valves; as a strategy to reduce the incidence of coronary ostial impingement and prosthetic misplacement. Correct valve implantation also reduces valvular gradient and blood stasis in the Valsalva sinuses, thereby reducing valve degeneration and extending prosthesis lifespan. However, achieving correct alignment with current TAVI systems is extremely challenging, requiring detailed procedure planning and aortic root study.[6] This renders TAVI an expensive and slow procedure, reducing the opportunity of using it in emergency cases.

CONCLUSIONS

TAVI has emerged as a widely accepted procedure for aortic valve replacement in patients with high surgical risk, where the potential benefits of intervention outweigh the risks. However, it is crucial to acknowledge that this approach is not devoid of significant complications. Consequently, TAVI should not be performed in patients with low-to-mild surgical risk, as the technique and equipment are not yet sufficiently refined to guarantee optimal outcomes. Therefore, in patients with a life expectancy exceeding 5 years and mild surgical risk, cardiac surgery is strongly recommended.[2]

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Direct to the heart: ventricular injury due to percutaneous thoracic catheter

Directo al corazón: lesión ventricular por catéter torácico percutáneo

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ABSTRACT

We present the case of a male patient who was treated in the emergency department for left pleural effusion by means of a thoracic drain. After placement, immediate blood output was obtained. A chest CT scan was performed, as well as an echocardiogram which showed the position of the drainage tube in the left ventricle. Surgical intervention was performed to remove the catheter by left anterior thoracotomy with successful extraction.

Keywords: ventricular perforation, endopleural tube, percutaneous drainage, heart, complication.

RESUMEN

Presentamos el caso de un paciente masculino quien fue tratado en el departamento de urgencias por derrame pleural izquierdo mediante un drenaje torácico. Posterior a la colocación se obtuvo gasto hemático inmediato. Se realizó tomografía de tórax, así como ecocardiograma que evidenció posición de tubo de drenaje en ventrículo izquierdo. Se realizó intervención quirúrgica para el retiro de catéter mediante toracotomía anterior izquierda con extracción exitosa.

Palabras clave: *perforación ventricular, tubo endopleural, drenaje percutáneo, corazón, complicación.*

INTRODUCTION

Pleural effusion is a common complication, occurring in 41% of patients admitted to the intensive care unit and 21% of all hospitalizations.[1] Chest tube placement is a frequently performed procedure in the hospital setting, ranging from emergency situations to postoperative chest drains for elective surgery. Despite its numerous indications and patient benefits, chest tube placement is associated with various complications. These complications can be categorized into early (< 24 hours after placement), occurring in 3% of cases, and late (> 24 hours after placement), occurring in 8-10% of procedures. Organ-specific complications, including esophageal, gastric, intestinal, hepatic, splenic, and diaphragmatic injuries, have been reported. Pulmonary injury is the most frequent complication, and excessive suction can lead to pulmonary infarction. Another serious injury is cannulation of a pulmonary artery, which necessitates surgical repair of the injured vessel.[2]

Percutaneous pleural drainage is one of the most commonly performed procedures in the intensive care unit, ranking among the top three invasive procedures, alongside vascular catheterization and endotracheal intubation.[2] Thoracic ultrasound has emerged as a valuable adjunctive tool, enabling physicians to enhance the success rate of the procedure while minimizing complications.

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Minimally invasive percutaneous thoracic drainage systems have become an essential tool in in-hospital practice. The UNICO® catheter placement is a viable alternative for performing minimally invasive procedures, including thoracentesis, pneumothorax interventions, hemothorax management, and drainage of pleural effusions of neoplastic origin or other fluid collections. The UNICO® system (Redax S.p.A., Poggio Rusco, Italy) comprises a fenestrated polyurethane catheter nested within another catheter, an extension line, an adapter for connection to any chest drainage system, a collection bag, and a set of two syringes. Its innovative two-valve design enables the unidirectional flow of air and fluids out of the cavity, preventing re-entry. This design eliminates the need for the traditional three-way stopcock previously used during fluid evacuation. Notably, the UNICO® system facilitates a minimally invasive approach, allowing for easy bedside placement without requiring operating room positioning.

Filosso et al. presented preliminary results on the placement of small-caliber chest drainage in a specific population with malignant pleural effusion. The study analyzed the placement of UNICO® catheters in seven patients, all of whom had undergone previous thoracentesis for pleural effusion. The procedures were performed at the bedside, and no complications were reported following drain insertion. The median dwell time for the chest tube was 7.2 ± 2.7 days, ranging from 4 to 11 days. Radiographic evidence of lung re-expansion was observed in all patients. Notably, there were no instances of wound infection, displacement, or alteration of drainage. The unique design and characteristics of the UNICO® catheter makes it a safer option for this patient population.[1]

CASE DESCRIPTION

We report the case of a 76-year-old male patient with a 30-year history of type II diabetes and end-stage renal disease (KIDGO G5), managed with hemodialysis. His current presentation began with a generalized tonic-clonic seizure at home, following which he was admitted to a private institution and initiated on diphenylhydantoin. Subsequent to hospitalization, a thoracic computed tomography (CT) scan was performed, revealing radiographic findings consistent with pneumonia and left pleural effusion. The CT report noted a massive left pleural effusion and moderate pericardial effusion. Pulmonology service chose to place a UNICO® percutaneous drainage catheter. Immediately following catheter placement, the output was reported to be completely hemolytic. A follow-up chest CT scan revealed the presence of the catheter in the left ventricle *(Figure 1)*. Upon discovery of this complication, the patient was transferred to the general hospital for further management by the cardiothoracic surgery service.

The patient underwent evaluation by the cardiology service, which included a 2D transthoracic echocardiogram with pulsed Doppler. The echocardiogram revealed left ventricular perforation by the endopleural probe through the lateral wall, with the probe tip extending into the left atrium. Additionally, the mitral valve was compromised by the pleural probe, resulting in moderate insufficiency. The left ventricular ejection fraction was reported as 39%. Global and segmental mobility were abnormal due to global hypokinesia. A severe global pericardial effusion was also noted, with a separation of 34 mm and an approximate volume of 900 ml, indicating tamponade *(Figure 2)*.

After evaluation by the cardiothoracic service, it was decided to perform surgery. A left anterior thoracotomy approach was performed due to the position of the catheter

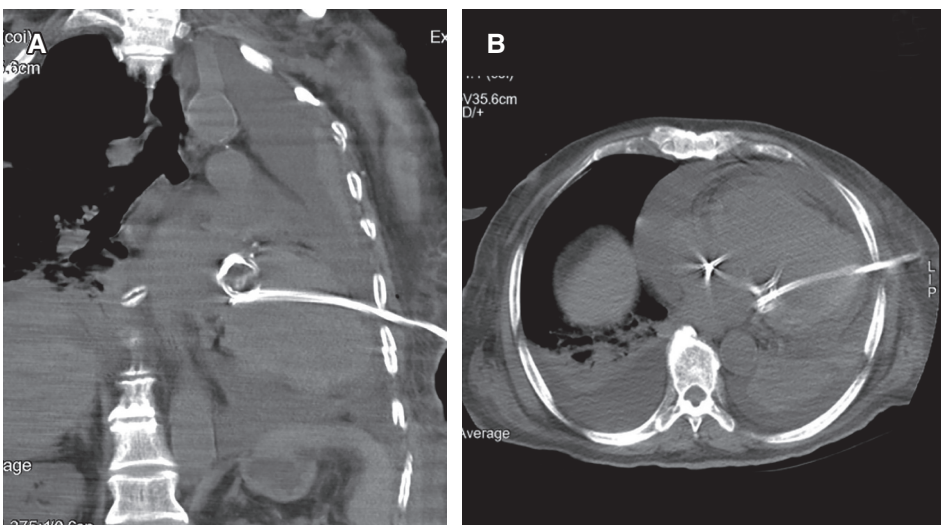

Figure 1:

Tomographic slices showing catheter in ventricular position. **A)** Coronal section. **B)** Cross section, showing the presence of intracardiac catheter.

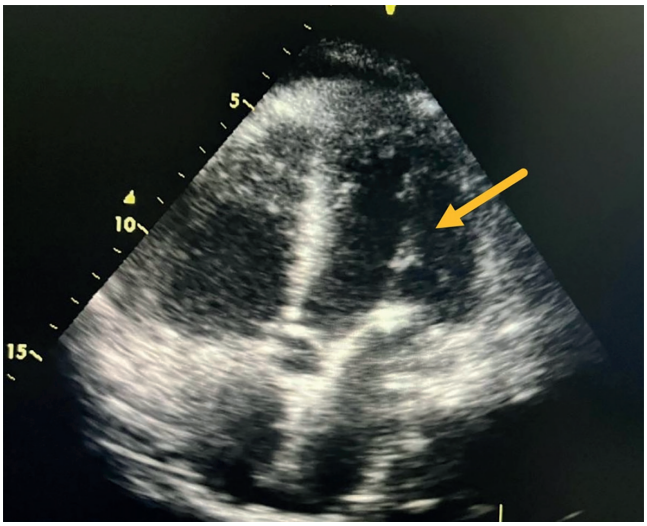

Figure 2: Echocardiogram with evidence of mitral valve lesion and pericardial effusion.

(Figure 3A). The catheter was located in the anterior axillary line, at the level of the intercostal space, visualizing a catheter with a pulsatile trajectory. An incision was made at the level of the sixth intercostal space. Dissection by planes was performed. Pericardium was opened and serohematic liquid was obtained. We visualized a single 12 FR catheter in the lateral wall of the left ventricle at 1cm from the anterior descending artery, without active bleeding *(Figure 3B)*. For catheter removal, two 4-0 polypropylene stitches were placed with 20 × 10 mm Bard® PTFE Felt Pledget Teflon patches. Two mattress stitches with patches were placed around the puncture site. The first stitch *(Figure 4A)* was adjusted prior to placement of the contralateral patch. Once adequate adjustment of both stitches with patch is verified *(Figure 4B)*, the caterpillar is removed while sutures are kept under tension and knots are tied. Adequate hemostasis of the perforation site is observed, adequate closure *(Figure 4C)*. Cardiopulmonary bypass was not required. Subsequently, a Coseal® type surgical sealant was placed. Pericardium is closed and then drains are placed. Conventional plane closure was performed.

After surgery, the patient was transferred to the intensive care unit of the hospital for hospitalization. Transthoracic echocardiographic tracing is performed, showing pericardial effusion with posterior predominance, with 16 mm leaflet separation. Left ventricular ejection fraction of 56% is reported. With preserved mobility. During the stay in the intensive care unit, he was kept under mechanical ventilation, presented with upper gastrointestinal tract bleeding, refractory atrial fibrillation and vasopressor support. He died three days after surgery due to pneumonia and septic shock in intensive care.

COMMENT

Injuries to the left ventricle following chest tube placement are rare, but their occurrence can be lethal. Complications as common as infection, bleeding, and even life-threatening injury to adjacent organs can occur.

Pleural drain placement procedures are the most common procedures performed at the patient's bedside, in the emergency department and even in intensive care. It is important to remember that, despite being a common procedure, it is necessary to follow a process of preparation of the patient, the area where the procedure will be performed and the equipment to be used.[3]

Several cases of ventricular injury due to chest drain placement have been described in the literature. The case reported by Haron H, et al.,[4] involves a patient where the patient suffered ventricular injury with catheter mobility during systole and diastole. A 20 fr chest tube with a sharp metal-tipped trocar was placed. The repair was performed with double sutures. In this case the patient was young with no comorbidities, the treatment was successful and the patient was discharged from the hospital. In the report of Goltz JP, et al.[5] where the lesion involved the anterolateral wall of the left ventricle, crossing the ventricle through the mitral valve, to the left atrium and into the contralateral lung. The tube used in this case was Pleuracan® (B. Braun, Melsungen, Alemania). A left anterolateral thoracotomy was performed, not specifying the approach. Although the patient was older (ninth decade of life), he was successfully discharged from the hospital. Kim D, et al.,[6] reported a case where a Prime-S® (Sungwon Medical, Cheongju, Corea) catheter was used, which does not contain a metallic trocar. In this case a lesion was reported in the left ventricle, crossing the aortic valve, with the tip located in the ascending aorta. In this case, open mini-thoracotomy was performed, the catheter was removed, but the myocardium was not repaired. Hospital evolution was hindered by pneumonia and prolonged mechanical ventilation. The patient died. Ahn S, et al.,[7] reported a right ventricular injury, with injury to the hepatic vein via the inferior vena cava. In this case a Thal-Quick® (Cook Medical, Bloomington, USA) chest tube was used. This type of catheter consists of an introducer needle. The resolution of this case was performed by interventionism, where an Amplatzer® (Abbott Medical, Nathan Lane North Plymouth, MN, USA) device was used as a vascular plug.

Injuries caused by percutaneous catheters or chest tubes are rare. The prevalence of these injuries depends on the preparation and careful technique of the physician performing the procedure. Injuries that are usually significant and life-threatening involve injuries to the lungs, cardiac structures, neighboring organs such as the liver, diaphragm, stomach or spleen.[5]

Since Beck, in 1926, described the physiology of the cardiac buffering triad, the diagnosis of cardiac injury has evolved. Ventricular lesions represent a challenge. Repair

can be complicated by tachycardia due to bleeding. It is suggested that 2-0, 3-0 or 4-0 polypropylene sutures be used for ventricular repairs. The sutures should contain folding. In lesions proximal to the coronary arteries, mattress sutures are used to ensure hemostasis.[8] In our case, mattress stitches were performed during the approach in order to achieve hemostasis. In our reported case no coronary artery injury was involved.

The repair of ventricular lesions depends on the rapid identification of the lesion and the appropriate protocol. The success of the treatment is determined from the transfer of the patient to an adequate hospital, access to necessary resources, such as blood bank, supplies, operating room and prepared equipment. Coordination between the surgical and resuscitation teams is a key point for success.[9] The cardiothoracic surgeon is a fundamental part in these cases. The preparation and experience is fundamental in this case to achieve a surgical plan that will be successful.

CONCLUSIONS

Ventricular injury following chest tube insertion is rare but lethal when it occurs. Although it is a procedure that is performed numerous times in hospitals, it usually has a minimal percentage of minor complications. Even in inexperienced hands the occurrence of these injuries is extremely rare. The presentation of this case highlights the

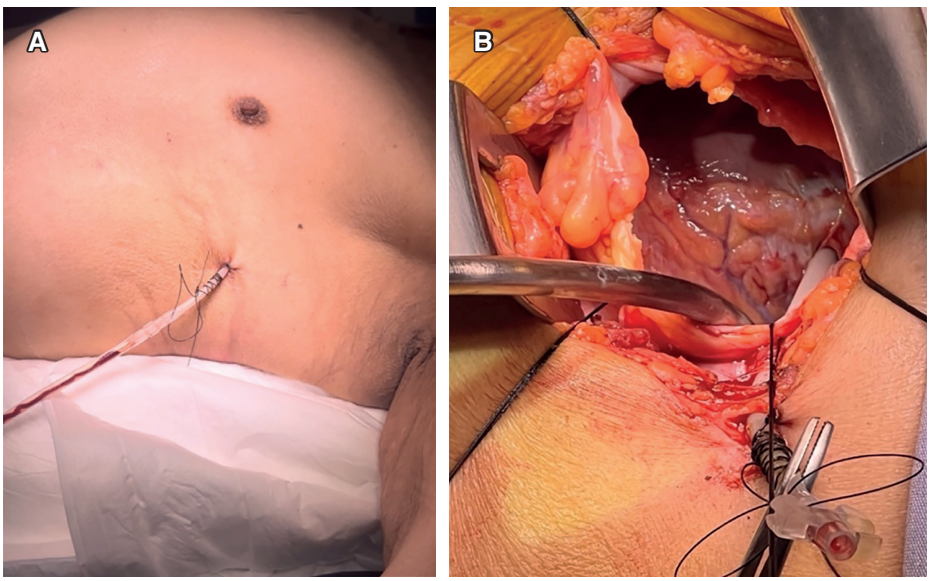

Figure 3:

A) Catheter with pulsatile trajectory.
B) Catheter in ventricular position.

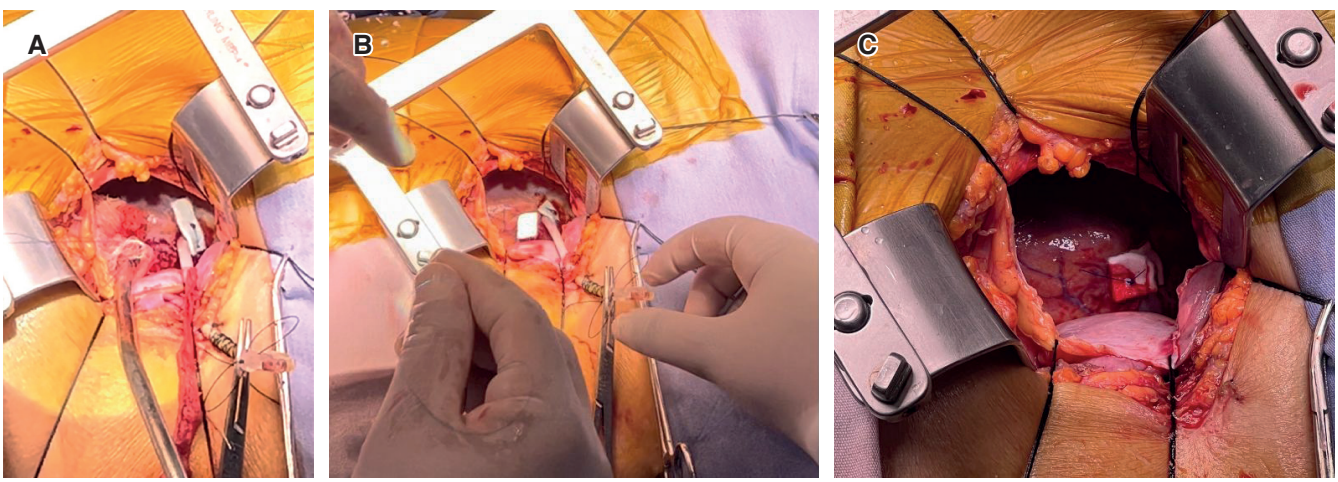

Figure 4: A) First mattress point with pledgeted. **B)** Second contralateral mattress point. **C)** Verification of hemostasis following mattress point adjustment.

importance of knowing the proper technique for chest tube insertion, as well as the identification of the classic safety points. This report serves as a reminder to trainee physicians of the critical importance of theoretical knowledge and fundamental skills in clinical practice.

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CASE REPORT
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Aortopulmonary window: diagnosis in the operating room

Ventana aortopulmonar: diagnóstico en quirófano

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ABSTRACT

Aortopulmonary window is a rare congenital defect that affects about 0.2% of the population. It is diagnosed and corrected during the first weeks of life. In adulthood it is rare and involves a high mortality. We present the case of a 17-year-old female, since the first years of life presents distal cyanosis and systolic murmur. Fixed fibrous subaortic stenosis, ventricular septal defect and severe mitral insufficiency were diagnosed. Surgical resolution was performed where aortopulmonary window was diagnosed in the operating room.

Keywords: congenital defect, aortopulmonary window, pulmonary hypertension.

RESUMEN

La ventana aortopulmonar es un defecto congénito infrecuente que afecta alrededor de 0.2% de la población. Se diagnostica y corrige durante las primeras semanas de vida. En la edad adulta es rara e implica una alta mortalidad. Presentamos el caso de paciente femenino de 17 años, desde los primeros años de vida presentó cianosis distal y soplo sistólico. Se diagnosticó estenosis subaórtica fibrosa fija, comunicación interventricular e insuficiencia mitral severa. Se realizó resolución quirúrgica donde se diagnosticó ventana aortopulmonar en el quirófano.

Palabras clave: *defecto congénito, ventana aortopulmonar, hipertensión pulmonar.*

Abbreviations:
APW = aortopulmonary window
CT = computed tomography
ECOTT = transthoracic two-dimensional echocardiography
FSSSA = fixed fibrous spur type subaortic stenosis
PDA = persistent ductus arteriosus

INTRODUCTION

Aortopulmonary window (APW), also referred as aortopulmonary septal defect, is a rare congenital heart defect. It is defined as abnormal communication between ascending aorta and pulmonary trunk, with the presence of separate semilunar valves.[1] Regarding the incidence of this defect, several authors present different figures ranging from 0.1-0.25%.[2] Others suggest figures of 0.2 to 0.6% of all congenital heart defects.[3]

Presentation of APW during adulthood is usually rare, being surgically corrected during early childhood.[1] If surgical repair is not performed during the first months of life, mortality in the first year of life is between 40 and 50%.[4] Patients in whom incidental diagnosis of APW is found during adulthood often present with pulmonary hypertension.[5] The progression of the disease is caused by increased pulmonary flow due to the presence of left-right shunt, generating irreversible pulmonary vascular obstructive disease, as well as congestive heart failure symptoms and the development of Eisenmenger's syndrome.[6]

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The earliest classification of APW was described in 1978 by Katsuhiko Mori in a series of 14 cases. This paper provided a classification of three types.[7] Subsequently, in 2000, members of the STS-Congenital Heart Surgery Database Committee and representatives of the European Association for Cardiothoracic Surgery took up the classification established by Mori in 1978 to establish a new nomenclature for APW. Currently, 4 types of aortopulmonary septal defects have been described: type 1 or proximal defect. In the posteromedial wall of the ascending aorta, over the sinus of Valsalva, a few millimeters above the semilunar leaflets. With a sufficient superior border, but a few millimeters inferior border, which separates the APW from the semilunar valves. Type 2 or distal defect. This type of APW location is situated in the superior portion of the ascending aorta. It presents a sufficiently large inferior border and a scarce superior border. Type 3 or total defect. It is a defect that extends over most of the ascending aorta, with poorly marked superior and inferior borders. Type 4 or intermediate type. It is a defect that extends mostly in the portion of the ascending aorta, like type 3 or total defect, but presents superior and inferior borders of adequate size.[8]

The aortopulmonary septal defect can be isolated, meaning that APW alone is present, or complex and accompanied by other cardiac defects. It has been reported that the association with other defects is 25 to 35%.[9] Some of them are persistent ductus arteriosus (PDA), interrupted aortic arch, severe coarctation, tetralogy of Fallot, aortic atresia, and ventricular septal defects.[10] Coexistence of interrupted aortic arch is more frequently found.[11]

The diagnosis is made by transthoracic ultrasound with Doppler, which is key and confirmatory for the detection of the defect.[2] This defect may go undetected by ultrasound, so other imaging tests may be used to confirm the diagnosis such as computed tomography angiography (CT) or cardiac catheterization. Once the diagnosis is established, it is important that correction of the defect is performed surgically as early as possible. Several studies have shown that closure using a patch through a transaortic approach is possible.[12]

Subaortic stenosis, also called subvalvular aortic stenosis, is a congenital heart disease resulting from the formation of fibromembranous tissue.[13] It is one of the most common cardiopathies in the aorta, with a prevalence of 6.5%; it is the second most common type of aortic stenosis. This formation of fibrotic tissue generates an increased pressure gradient in the outflow tract of the left ventricle due to a fixed obstruction in blood flow. It is associated with other defects such as ventricular septal defect, patent ductus arteriosus, coarctation of the aorta, bicuspid aortic valve, abnormal left ventricular papillary muscle and/or atrioventricular septal defect, among others.[14] The diagnosis is made by echocardiogram. Clinically they remain asymptomatic; however, symptoms can appear when performing activities that generate physical stress or during pregnancy.[10]

CASE DESCRIPTION

We present the case of a 17-year-old female patient, whose pathology began at birth, with development of cardiac symptoms, presenting distal cyanosis and heart murmur without follow-up and without treatment. She began her follow-up until the age of 13 years when she went to the health center for presenting grade III malnutrition, where

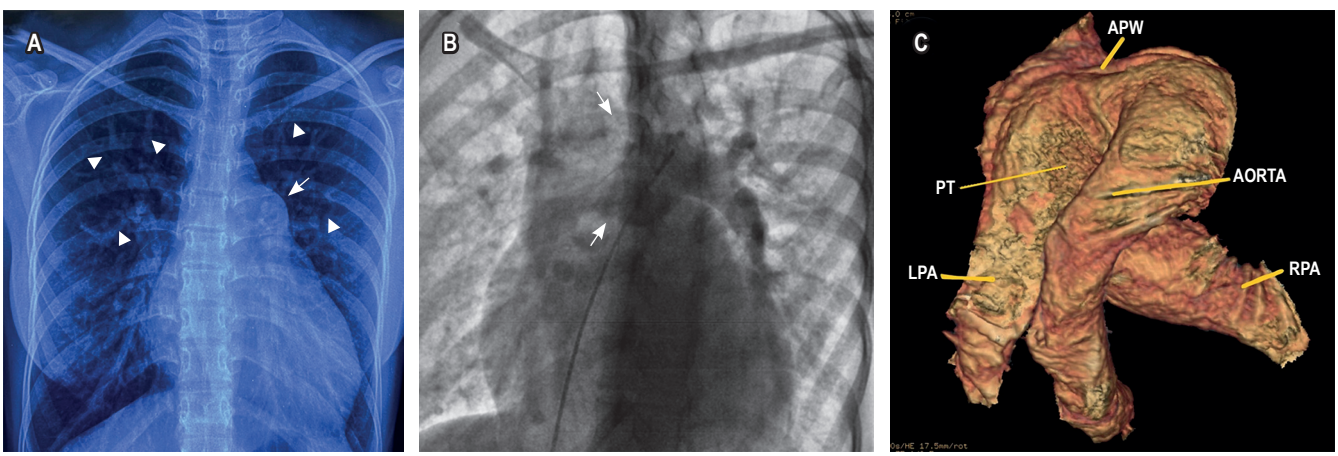

Figure 1: A) Chest X-Ray performed prior to surgery, showing dilatation of the pulmonary artery trunk (arrow), increased pulmonary flow, which identifies the increase of the bronchovascular network by veno-capillary congestion in both hemithorax (arrowhead). **B)** Pre-surgical diagnostic right catheterization where the filling phase of the pulmonary artery is identified where a slight image of leakage through the APW is identified. **C)** Angiotomography, pre-surgical reconstruction of great vessels where communication between the pulmonary and aorta is identified.
APW = aortopulmonary window. LPA = left pulmonary artery. PT = pulmonary trunk. RPA = right pulmonary artery.

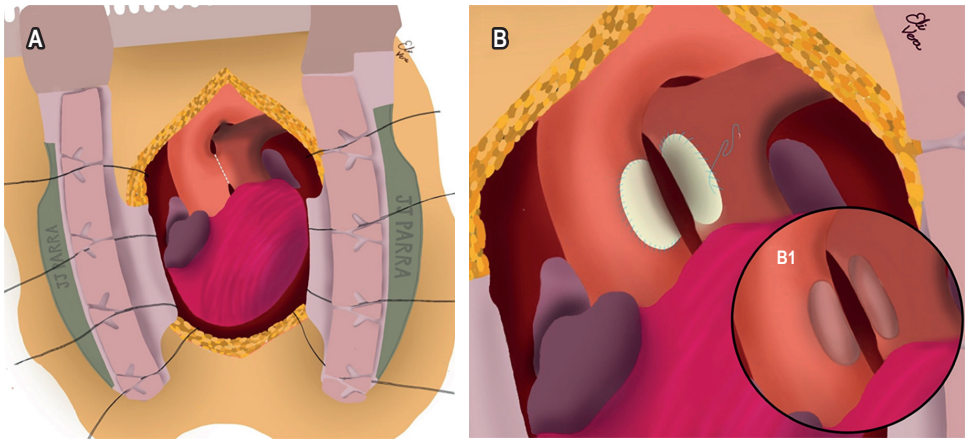

Figure 2:

A) Representation of median approach before median sternotomy. Incision is made over the anterior wall of the defect. **B)** Illustration depicting the separation of the structures and placement of pericardial patch on each structure.

she was evaluated and sent to pediatric cardiology due to the presence of a murmur.

At 14 years of age, she was evaluated annually by pediatric cardiology with suspicion of congenital heart disease. On physical examination, she presented as acyanotic with no evidence of respiratory distress. Auscultation at the precordial level identified a grade II/VI systolic ejection murmur in the second intercostal space, increased volume in the left hemithorax, normal pulses in the extremities. Cardiomegaly grade I at chest X-Ray. Electrocardiogram with no important alterations.

During follow-up, at the age of 17 years there was clinical progression with the development of dyspnea on moderate efforts. Auscultation identified progression of systolic murmur to grade III/VI. A chest X-Ray was performed showing increased bronchopulmonary tract in both hemithoraces and prominence of the pulmonary artery silhouette *(Figure 1A)*.

A transthoracic echocardiogram was performed with the following findings: perimembranous ventricular septal defect of 7 mm, aortic insufficiency jet of 3 mm, fixed fibrous spur type subaortic stenosis (FSSSA) with maximum gradient of 35 mmHg and mean of 19 mmHg, moderate to severe mitral insufficiency with max gradient of 12 mmHg and mean of 19 mmHg (double mitral lesion), right ventricular systolic pressure of 40 mmHg, pulmonary artery systolic pressure of 50 mmHg, left ventricular ejection fraction of 78%, with important left-sided cavities dilatation.

Diagnostic cardiac catheterization was performed, where the following findings were found as follows: pulmonary artery pressure of 100/70 mmHg, mean 87 mmHg; aorta 111/57 mmHg, mean 80 mmHg; right atrium 4/0 mmHg, mean 6 mmHg, maximum peak-to-peak gradient: 5 mmHg; right ventricle 95/25 mmHg, telediastolic 14 mmHg; left ventricle 98/3 mmHg, telediastolic 7 mmHg, maximum peak-to-peak gradient 13 mmHg. Severe pulmonary hypertension and small ventricular septal defect of 7 mm. Initially there was no evidence of left-right shunt in the catheterization. Subsequent analysis allows us to identify it *(Figure 1B)*.

In addition to the previous studies, CT angiography was performed, which was not useful due to poor radiological technique. Therefore, the defect is not evidenced by this imaging study. However, a reconstruction of the CT angiography was requested *(Figure 1C)*.

The patient was scheduled for operation in our service for closure of ventricular septal defect, mitral valve replacement with a mechanical prosthesis and subaortic stenosis resection.

Surgical correction was performed by median sternotomy with extracorporeal circulation. On opening the pericardium, as an operative finding, aortopulmonary communication was observed *(Figure 2A)*. At that time the diagnosis of aortopulmonary window is made in the operating room.

Correction was performed by initiating aortic cannulation with purse-string suture 3-0 polypropylene and superior and inferior vena cava cannulation with purse-string suture 4-0 polypropylene. Subsequently, heparinization with 15,000 IU was performed and cardiopulmonary bypass was started. Double aorta and APW clamping is performed. Cardioplegia is administered in the first half via the aortic root. Second half is administered through left and right ostium until electromechanical arrest.

For resolution of PDA, a pericardial patch is placed. To begin the resolution of the defect, the aortopulmonary window section was performed. The aim of the correction was to achieve complete separation of the pulmonary trunk and the aorta. This separation allowed for the individual repair of each structure. Two pericardial patches were placed to perform the plasty of the involved structures. One of the patches was placed in the aortic mouth of the defect and the second was placed in the pulmonary trunk *(Figure 2B)*. After correction of the aortopulmonary window defect, subaortic stenosis resection was performed.

For valve replacement, a transseptal approach is used. A 25mm mechanical valve was placed in the mitral position. The interatrial septum is closed with prolene 4-0 surjete. Finally, cavity purging and aortic unclamping are performed. We searched for previously reported interventricular septal defect without finding evidence of the defect. The time of extracorporeal circulation was 3 hours. The aortic clamp time was 2 hours and 34 minutes.

The day after surgery, a new control echocardiogram was performed, where the following findings were reported: FSSSA resection in good condition, recording a peak aortic outflow gradient of 8 mmHg and mean of 4 mmHg; mechanical mitral valve is observed in proper position with an opening area of 1.7 cm^2 and a peak gradient of 6 mmHg and mean of 3 mmHg, right ventricle systolic pressure 6 mmHg, pulmonary artery systolic pressure 16 mmHg, left ventricle ejection fraction 62%. Length of stay in the Intensive Care Unit of 3 days. Postoperative course uneventful. In-hospital discharge on the fourth postoperative day.

A postoperative tomography was performed to corroborate the correction of the defect, which reported cardiomegaly, pulmonary arteries at the level of the root of the right pulmonary branch with a decrease in its caliber of 9 mm, adequate course of contrast medium without leaks. Ascending aorta, arch and the descending aorta with adequate diameters and no filling defects were detected *(Figure 3)*.

COMMENT

The presentation of this case description has different situations that are of interest for analysis and review. We present the case of a 17-year-old female patient with an initial diagnosis of fixed spur type subaortic stenosis, moderate to severe mitral insufficiency and 7 mm perimembranous ventricular septal defect. In relation to the literature and the latest classification established in the Congenital Heart Surgery Database and Nomenclature Project: aortopulmonary window, a type II APW associated with ductus arteriosus was presented.[8]

The diagnosis, as has been demonstrated in several case series, is performed by transthoracic two-dimensional echocardiography (ECOTT) with Doppler.[1] Among other utilities of ECOTT is the establishment of the degree of pulmonary hypertension. In the case of our patient, last ECOTT demonstrated a pulmonary artery systolic pressure of 50 mmHg. By non-invasive methods, such as echocardiography, the average in healthy adolescents is a normal range of 20 mmHg.[15] In the cardiac catheterization performed months before surgery, severe pulmonary hypertension was evidenced. In our case, different echocardiograms were performed at different times, and the main abnormality, APW, went unnoticed. Therefore, the diagnosis of APW was made in the operating room. There are other studies that support the diagnosis, such as catheterization and CT angiography. In our case, both studies were performed. The quality of the CT angiographic study was not significant to make the diagnosis. On the other hand, catheterization did not show clear images to make a clear diagnosis. In such a way that it was decided to opt for surgical intervention presenting the diagnoses of FSSSA, severe mitral insufficiency and ventricular septal defect.

In a study conducted in 2019 by El Dick et al.[1] a cohort of 62 adult patients was studied; 41 patients presented type I proximal, 13 type II distal, 8 type III total defects. In the case presented here, we can make the correlation with

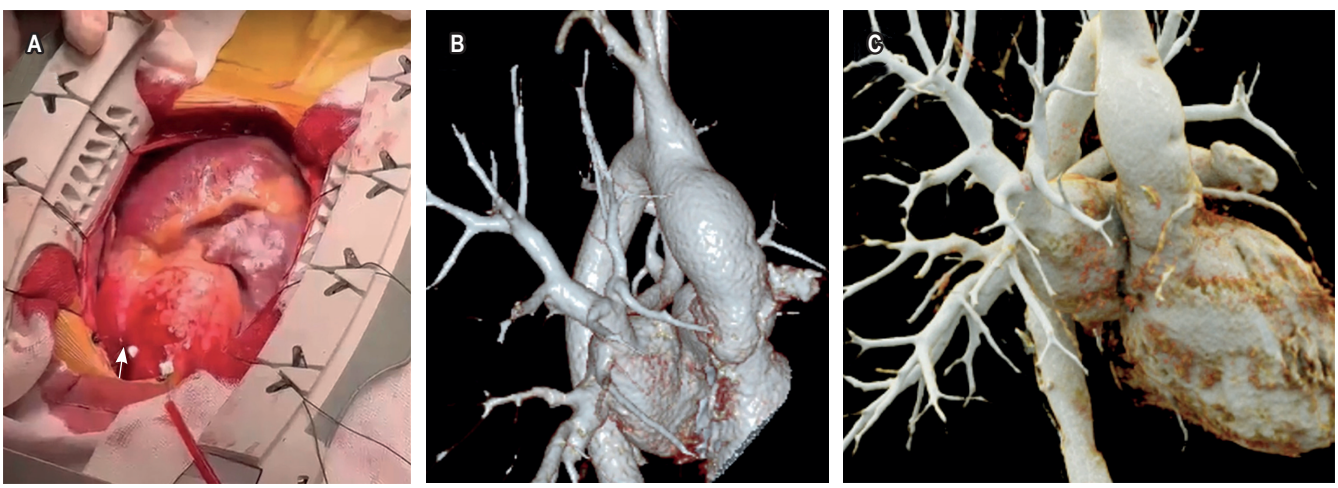

Figure 3: A) Image of the defect when opening the cavity. **B-C)** Antiotomography images after surgery with reconstruction, showing the closure of both vessels without defects.

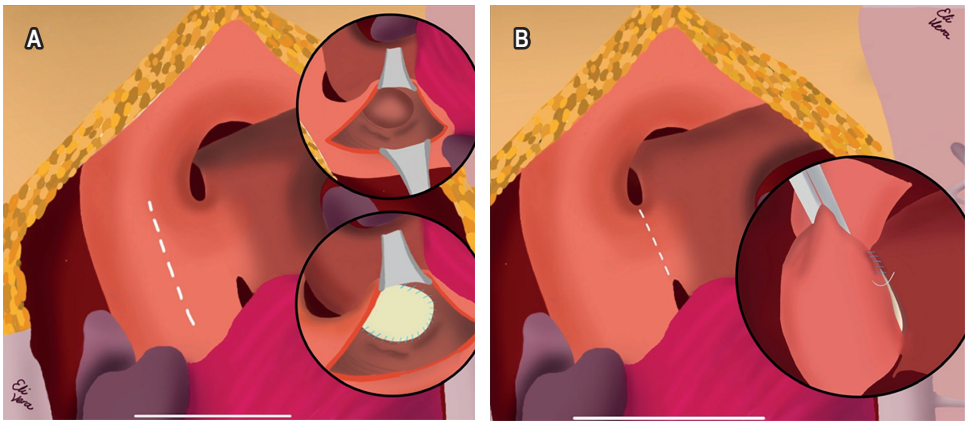

Figure 4:

A) Illustration showing the transaortic approach and suturing of the patch over the defect through the incision. **B)** Illustration showing the transpulmonary approach and sandwich patch suture.

respect to the last classification. Our patient presented a type II or distal defect.

According to a study published in 2020 by Bin-Moallim et al.[9] where 20 patients aged from 4.8 to 5.8 months were analyzed, 2 patients presented simple APW while 18 patients were associated with other malformations. In this study, the most frequently associated defect was atrial septal defect in 40% of the studied population. In relation to the PDA they reported in 40% of the patients. It is worth mentioning that in 2/3 of the patients with PDA they found interruption of the aortic arch. Regarding the complications presented during a follow-up of 4.5 years, 85% of the patients in the cohort studied remained asymptomatic without residual APW and did not require reintervention. Complications occurred in three patients which included mild residual lesions, including mild supra-pulmonary valvular stenosis, leakage through the APW patch and mild pulmonary artery stenosis.[9]

The resolution of the defect can be done through several approaches. The approach conventionally used is the transaortic approach *(Figure 4A)*. It is useful for the variant of the defect where a more extensive part of the aorta is involved. It is useful in cases where the defect extends to the right pulmonary artery. Allows better visualization of the posterior portion of the aorta.[16] The anterior approach consists of vertical opening of the anterior wall of the defect. It is performed using the anterior sandwich patch technique. The inferior, posterior and superior border of the defect is sutured. When the incision is closed, the patch is incorporated into the suture line *(Figure 4B)*. A transpulmonary approach can be performed. This is performed when visualization of the coronary ostia is difficult. It consists of opening the pulmonary artery and placing a patch through it. A pulmonary artery flap can be performed. The latter approach is not routinely recommended due to the risk of reoperation for severe pulmonary artery stenosis.[17]

CONCLUSIONS

The surgical correction in our patient involved a challenge during the intervention because prior to the procedure, the presence of APW was not contemplated. Once surgery was performed, the aorto-pulmonary window was divided by placing two patches, one in each structure (aorta and pulmonary artery), thus avoiding the risk of fistulas or residual communications. One of the complications that our patient presented, as described in some case series, is mild supra-pulmonary stenosis.[9] The technique used in our case has been described as a variant of the anterior approach. The only disadvantage described to this approach is the time that the surgeon will invest in performing it. Generates good benefits for the patient and few or mild complications.[17]

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HISTORICAL NOTES
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Michael Servetus: unveiling the secrets of pulmonary circulation

Miguel Servet: descubriendo los secretos de la circulación pulmonar

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ABSTRACT

The 16th century, an era marked by turmoil and transformation, witnessed a significant breakthrough in the field of anatomy and medicine. It was during this period that the dissection of human cadavers, previously considered a sacrilegious and forbidden act by the Holy Inquisition, began to be accepted as a fundamental tool for the study of the human body. This new approach enabled anatomists and physicians of the time, such as Andreas Vesalius, to make groundbreaking discoveries that would lay the foundations for modern medicine. Among these advances, the discovery of blood circulation, made by William Harvey in 1628, stands out particularly, revolutionizing our understanding of the human body's functioning. However, it is surprising that very few historians and medical scholars have highlighted the important discovery of pulmonary circulation made by Spanish physician Miguel Servetus in 1553. It is possible that this is due to the fact that his description of pulmonary circulation was embedded in Book V of his theological work *"Christianismi Restitutio"*, which may have reduced the visibility of his contribution to the field of medicine. Nevertheless, it is essential to recognize Servetus' pioneering role in understanding blood circulation and his influence on Harvey's subsequent discoveries. Our attention will turn to the prominent figure of Michael Servetus, a pivotal character in the history of medicine and theology. This article will delve into his life, works, and notable contributions, with particular emphasis on his groundbreaking description of the lesser or pulmonary circulation.

Keywords: history, Miguel Servet, Michael Servetus, pulmonary circulation, theology, 16th century.

RESUMEN

El siglo XVI, una época marcada por la convulsión y el cambio, fue testigo de un importante avance en el campo de la anatomía y medicina. Fue en este periodo cuando la disección de cadáveres humanos, hasta entonces considerada un acto impío y prohibido por el Santo Oficio Inquisitorial, comenzó a ser aceptada como una herramienta fundamental para el estudio del cuerpo humano. Este nuevo enfoque permitió a los anatomistas y médicos de la época, como Andreas Vesalio, realizar importantes descubrimientos que sentarían las bases para la medicina moderna. Entre estos avances destaca especialmente el descubrimiento de la circulación sanguínea, realizado por William Harvey en 1628, que revolucionaría la comprensión del funcionamiento del cuerpo humano. Sin embargo, es sorprendente que muy pocos historiadores y estudiosos de la Medicina hayan destacado el importante descubrimiento de la circulación pulmonar realizado por el médico español Miguel Servet en 1553. Es posible que esto se deba a que su descripción de la circulación pulmonar se encontraba inserta en el libro V de su obra teológica "Christianismi Restitutio", lo que podría haber restado visibilidad a su campo de contribución en el campo de la medicina. No obstante, es fundamental reconocer el papel pionero de Servet en la comprensión de la circulación sanguínea y su influencia en los descubrimientos posteriores de Harvey. A continuación, nos enfocaremos en la figura protagónica de Miguel Servet, un personaje clave en la historia de la medicina y teología. En este artículo exploraremos su vida, su obra y sus contribuciones significativas, destacando especialmente su papel como pionero en la descripción de la circulación menor o pulmonar.

Palabras clave: *historia, Miguel Servet, Michael Servetus, circulación pulmonar, teología, siglo XVI.*

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Qui ambulat in tenebris, nescit quo vadat

Michael Servetus was a Spanish theologian, physician and humanist. He is considered one of the most important figures in the Protestant Reformation and a pioneer in modern medicine. The relationship between Michael Servetus' discoveries and the work of William Harvey is a topic of debate among medical historians. Although Harvey does not explicitly mention Servetus in his work *De Motu Cordis* (1628), it is possible that he was influenced by Servetus' ideas. Servetus had described the pulmonary circulation in his work *Christianismi Restitutio* (1553), and it is possible that Harvey had access to this information through indirect sources. The discovery of the pulmonary circulation is described in Book V of the *Christianismi Restitutio* by Michael Servetus.

However, this fact went practically unnoticed through time because of its theological content, this work was included in the index of prohibited and censored books by the Holy Inquisition. However, some surviving copies that managed to escape the fire suggest that Harvey may have had access to this document, which reinforces the theory that Servetus was a pioneer in the description of pulmonary circulation.

We will proceed to analyze the chain of events that culminated in this discovery of pulmonary circulation by Michael Servetus.

The life of Michael Servetus is an enigma wrapped in contradictions. His birth, a mystery. Aragon or Navarre? 1506 or 1511? Servetus' answers fade away like smoke in the wind, leaving behind a large amount of uncertainty. This ambiguity is largely due to the inquisitorial processes he faced. To protect himself from persecution, Servetus provided changing information about his identity and age at different times, which has led to confusion among historians.

However, according to historical records, *Michael Servetus Conesa* was born in Villanueva de Sijena, a small town in the province of Huesca, in the kingdom of Aragon (Spain) on September 29, 1511.[1] This date and place of birth are considered the most accurate, despite the contradictions and ambiguities surrounding the life of this historical figure *(Figure 1)*.

In 1526 he entered the University of Zaragoza to study philosophy and literature. In 1528 he moved to the University of Toulouse in the province of Languedoc (France) to study Roman and canon law, as well as the Old and New Testament.[2] It should be noted that at that time, the Council of Toulouse prohibited the reading of biblical texts to lay people.[3] He was also interested in theology and the Religious Reformation, developing his own ideas about faith and the Church. In 1529, he suddenly returned to Spain, because the Inquisition in Toulouse issued an edict of persecution against a list of 40 fugitives, spearheaded by Michael Servetus.[4]

From 1525 he had been accepted as a page and personal assistant to Friar Juan de Quintana. Between 1529 and 1530, his presence was requested by Friar Juan de Quintana, confessor of Emperor Charles V, to travel with Charles V's entourage to Bologna (Italy) to be crowned Emperor of the Holy Roman Empire by Pope Clement VII.[5] On October 25, 1530, Servetus arrived in Basel, a vibrant Swiss city that was an important cultural center and a breeding ground for innovative theological debates. This city, located in the heart of Europe, became a key stage for Servetus' intellectual and spiritual development.[6] In 1531, Servetus published *"De Trinitatis Erroribus"*, a theological treatise that revealed his profound erudition and his ability to question the established theological doctrines of the time.[7]

In Servetus' time, Strasbourg (region of Alsace, France) was an important center of the Protestant Reformation and had become a refuge for Protestants persecuted in other parts of Europe. Thus, it was the home of many theologians and reformers. In 1532, in Strasbourg he published *"Dialogorum de Trinitate"*.[8] Both were signed by Servetus with his real name as *"Michaelem Servet, alias Reves ab Aragonia Hispanum"*. In both texts he questioned and sharply rejected the concept of the Trinity of scholastic theology. These two productions are important because they constituted the embryo of his major work, the *"Christianismi Restitutio",* which will be discussed later.

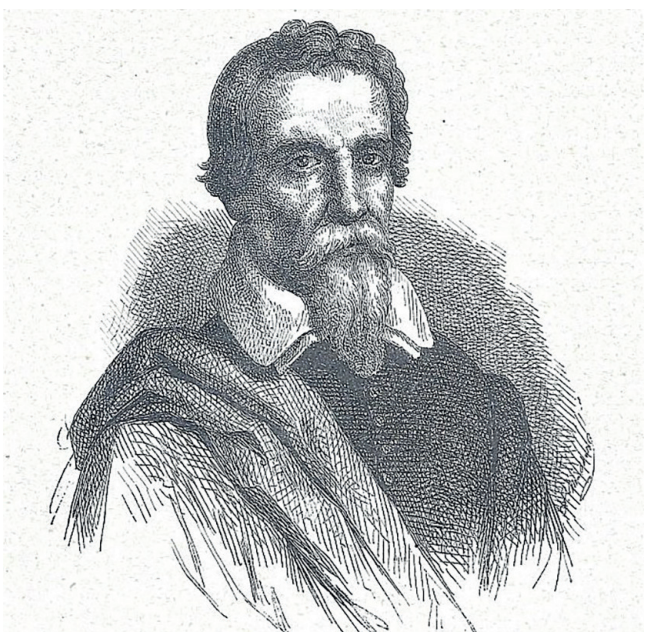


Figure 1: Portrait of Michael Servetus (Servet-Michele-ritratto).
Credit: Albertomos-Own work. Created in 1894. Albertomos, CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0>, via Wikimedia Commons. This file is licensed under the Creative Commons Attribution-Share Alike 4.0 International license. https://upload.wikimedia.org/wikipedia/commons/3/3a/Servet-Michele-ritratto.jpg

The publication of *"De Trinitatis Erroribus"* had serious consequences for its author, since on May 24, 1532, the Spanish Inquisition in Medina del Campo began an investigation against Servetus, prohibiting the circulation of his work and summoning him to appear before the Holy Inquisition.[9]

It was highly likely the persecution of the Spanish Inquisition that pushed him to move and settle in Lyon (France). There, he published in 1535 *"The Geography of Ptolemy",* now under the name of *Miguel de Villanueva (Micheal Villanovani)*, making an impeccable translation from Greek to Latin.[10] Servetus' decision to change his name could be motivated by the edict of persecution of the Spanish Inquisition. This circumstance could have contributed to the confusion about his place of birth, which some historians place in Tudela (Navarre, Spain).[1]

In Lyon he met Symphorian Champier, a physician and humanist, who convinced him to study medicine. He studied the works of Galen, Hippocrates, and Avicenna, among others. He relied heavily on observation as a basic cornerstone of medical practice.

Servetus subsequently moved to the University of Paris, where he enrolled in the Faculty of Medicine in 1537. There, he had the opportunity to learn from leading experts in the field, such as Jacques Dubois, known as Jacob Sylvius, and John Gunther d'Andernach,[11] a renowned German anatomist who had published the treatise "*Institutiones anatomicae"* in 1536, one of the first texts with detailed drawings of dissection on human cadavers, which would become a fundamental classic for the teaching of anatomy in Europe for a quite long time.[12] Sylvius wrote *"I had as assistants Vesalius, a very diligent young man in Anatomy, and then Michael Villanovanus, a man eminent in all letters and none inferior in the doctrine of Galen".*[13] Under the mentorship of both, Servetus became familiar with the practice of dissection on human cadavers, which instilled in him a deep-seated interest in human anatomy. He also investigated the circulation of blood alongside Vesalius and laid the foundations for the further discovery and publication of pulmonary circulation in 1553.[14-16] He fought against the conventional medical uses and behaviors of the period, such as bloodletting, which was totally useless. He said *"it is necessary to cure the sick without making him suffer"*.

In 1537 published in Paris the Syruporum universa ratio ad Galeni censuram, the only book in Servet's entire oeuvre with an exclusively medical character.[17,18]

The true passion of Michael Servetus was not only medicine, but also theology. He had a great knowledge and mastery of Hebrew, Greek and Latin. It is very likely that from a very young age, Servetus received his basic knowledge through his stay at the monastery of Villanueva, as well as at the monastery of Montearagón, where his mentor, Friar Juan de Quintana, was the abbot. At that time, the monastic schools were the main cultural centers. The *Seven Liberal Arts* were taught in them: the *Tribium* or sermonical arts (grammar, dialectic and rhetoric), and the *Quiadrivium* or real arts (arithmetic, geometry, music and astronomy/astrology).[19]

Michael Servetus had a deep knowledge in astrology. At the University of Paris in the time of Michael Servetus, astrology was taught in the Faculty of Arts. The Faculty of Arts was one of the four faculties of the University of Paris (Law, Medicine, Theology, and Liberal Arts), and was responsible for teaching the Liberal Arts. Astrology was considered an important part of education in the Middle Ages and the Renaissance, and was taught as a tool to understand the movements of celestial bodies and their influence on human life. All were permitted by the Inquisition. The only one that was not permitted was *divinatrix* or judicial astrology *(qua ex astris praedicit)*, which, based on the contemplation of planetary positions, determined conclusions regarding what could happen on a social or political level. It was punishable by burned at the stake.[20]

In his lecture on astrology at the Faculty of Arts of the University of Paris, Servetus predicted the eclipse of the Moon with Mars on February 13, 1538. Obviously, this was an astronomical phenomenon. The problem developed because Servetus turned this fact into judicial or predictive astrology by adding *"princes will be induced to warlike enterprises, and many countries will be devastated…."*.[21]

He was then ordered to discontinue his lecture in astrology at the University of Paris. In response he wrote and published a 16-page pamphlet entitled *"Michaelis Villanovani in quendam medicum apologetica discrepatio pro Astrologia"* (Apologetic Discourse of Michael de Villanova on Astrology against a Certain Physician Objector).[22] All this led to his being denounced before the procurator general of King Francis I. The trial before the parliament of Paris took place on March 18, 1538. The trial is recorded in the minutes of the Faculty of Medicine of the University of Paris, vol. V, 1538, page 97 and 98. Thanks to the influence of John Thiebalut, a Protestant physician and physician to the chamber of Francis I, who had also been physician and astrologer to Charles V, and to the participation in his favor of his friend the physician and astrologer Heinrich Cornelius Agrippa, the condemnation was very light and lenient : withdraw the pamphlets and obey the Faculty of Medicine and its Doctors.[23]

After this incident, he decided to leave Paris and move to Charlieu (France), where he developed as a doctor for almost three years. He did not yet have a medical degree, which he apparently could have obtained at the University of Montpellier in 1540.[24]

However, since 1541 he lived in the Dauphiné of Vienne (France), invited by the Archbishop of the Dauphiné Pierre Palmier, who had attended Servetus' astrology lectures at the

University of Paris. Archbishop Palmier awarded him the title of physician of the Dauphiné of Vienne from 1541 to 1553.

Servetus met Pagnini in Lyon. Santes Pagnini was a disciple of the reformist and Protestant friar from Ferrara (Italy) Girolamo Savonarola. Pagnini left all his notes to Servetus when he died in 1536. Based on these notes, Servetus proceeded with the aforementioned printing of Pagnini's Bible in seven volumes.[25]

Between 1542 and 1545, Servetus was hired by the Compagnie des Libraires de Lyon, and he produced three editions of Bibles, which he enriched with annotations and new translations from Hebrew and Greek. In 1542, the *Bible ex Santes Pagnini*, in Lyon, and as editor Huge de la Porte.[25] This was put on the list of books prohibited by the Holy Inquisition in Spain. In 1542, the *Bible Sacra ex postremis Doctorum*, a reduced version of the previous one.[26] In 1545, the *Bible Sacra cum glosis*. It took him 5 years to edit it. This last edition of the Bible is the most enriched by the annotations and corrections of Servetus, who signs under the pseudonym of *Michel De Villeneuve*. It is a reinterpretation of the Bible of Melchior Novesianus published in Cologne (Germany) in 1541.[27]

In 1553, in the Dauphiné of Vienne (France), he published his masterpiece of unparalleled, and the most heretical of all his literary production: the *"Christianismi Restitutio"*.[28] It took him almost 10 years to write it. It consists essentially of four parts, two of which are the most relevant: Servetus' theological ideas contrary to traditional theological scholastic doctrine, and the lesser or pulmonary circulation of the blood. The fact that these medical descriptions are within the theological texts of the *Christianismi Restitutio* is because for Servetus, the divine spirit (the soul) is in the blood and spreads throughout the body.

Analyzing this work deeply, Michael Servetus was the first European to discover pulmonary circulation. There is no evidence that he was aware of the discovery of the physician Ibn Al-Nafis in 1212,[29] since the work was forgotten until it was accidentally rediscovered by the Egyptian physician Muhyo Al-Deen Altawi in 1924.[30]

The publication of *Christianismi Restitutio* turned out to be too problematic. It was carried out clandestinely, on the outskirts of the Dauphiné, with Balthazar Arnoullet and Guillaume Guéroult taking over as editors.[31]

The *Christianismi Restitutio* presents several interesting facts. For example, it circulated in manuscript form from 1546, although incompletely due to the constant additions and revisions it underwent. Later, in 1551, the printers and editors Arnoullet and Gueroult agreed to print the book. For this purpose, they established a clandestine printing press on the outskirts of Vienne, in the Dauphiné. Printing began in 1552 and was completed in 1553. The conditions that the printers set for printing were specific: they demanded that the book be printed in the French Dauphiné of Vienne, possibly to have the support of Archbishop Pierre Palmier, a friend and protector of Servetus. In addition, Servetus took charge of all expenses, personally corrected the proofs and took charge of the distribution and sale of the book.[32]

In an edition of 800 copies, unbound to maintain discretion, the books were distributed as bales of paper. To avoid arousing suspicion, the first shipment was made clandestinely on 03 January 1553, and was sent hidden among bales of hay to the Frankfurt fair. Another was sent to Geneva, both destroyed on the orders of John Calvin. The third bale was sent to Lyon, then returned to Vienne, to be burned by the Holy Inquisition in Toulouse along with the effigy of Servetus. Currently, only two copies of the original first edition of *Christianismi Restitutio* have survived intact to this day. One of these valuable books is in the National Library of Austria in Vienna and another in the National Library of France in Paris. Another book is in the Library of the University of Edinburgh, but this one is missing the title page and the first 16 pages. In 1791, a reprint of *Christianismi Restitutio* was made in Nuremberg. Only four copies of this second edition have survived to this day, one in the Bibliothèque Nationale in Paris, one in the Bibliothèque Nationale in Geneva, and two in the Yale University Library. In addition, another copy is suspected to exist in the Vatican Library, although its existence has not yet been confirmed.[32] The 1553 edition was published anonymously, with no author credits or information about the printer. The only clue is the signature "MSV", believed to be that of *Miguel Serveto de Villanueva*.[31,33] *(Figure 2)*.

To understand Servetus, it is necessary to understand the historical context dominated by Galenic physiology. Claudius Galen (129-216), a physician, surgeon and philosopher of the Roman Empire, was one of the most prominent medical researchers of the Ancient Age, whose ideas dominated European medicine for more than a millennium. According to Galen, the functioning of the body is based on the interaction between three fundamental concepts: spirits, virtues and operations. Spirits *(spiritus or pneuma)* are subtle materials that activate the organs of a cavity. In this context, virtues refer to the forces that drive the functioning of organs, and are identified with the Latin term vis, equivalent to the Greek *dy'namis*. The relationship between spirits and virtues is fundamental, since spirits trigger the virtues of organs, which combine to give rise to an operation. This operation is the specific action performed by a certain organ, and may involve several coordinated virtues. In short, the spirits are those that trigger the virtues of the organs, and the virtues are identified with the forces that make the organs function.

Furthermore, Galen classified spirits into three categories, corresponding to the three types of soul (understood as the principle of movement and change in living beings). These three types of *spirits or pneumas* are the natural or vegetative

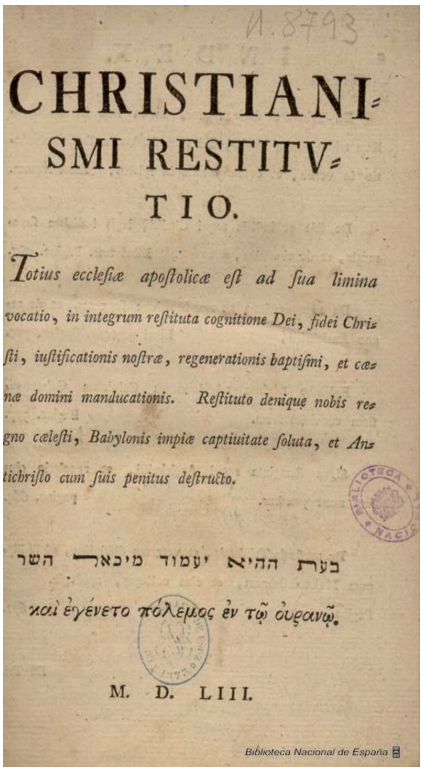


Figure 2:

Cover of Christianismi Restitutio. The reproduced work belongs to the collection of the National Library of Spain.

spirit, based in the liver; the vital spirit, located in the thorax, with the heart as its fundamental organ and which also includes the lungs; and the animal spirit, the highest, based in the brain, and responsible for the most complex mental functions that characterize the human being. The natural spirit would spread from the liver through the veins and reach the heart. There, it would be transformed into the vital spirit, responsible for maintaining life through functions such as breathing, heartbeat and pulse. This would imply that the blood with the natural spirit, which reached the right heart, crossed the interventricular septum through invisible pores to end up in the left heart, where it finally mixed with air and created the vital spirit that was subsequently distributed throughout the body.[34-36]

However, it is important to note that in Galen's time, human anatomy was a little-explored field, as there were no authorized dissections on human cadavers. In fact, Galen's masterpiece, "De anatomicis administrationibus", is a collection of lectures on anatomy given in Rome around 177 AD. In them, Galen based himself on the dissection of monkeys, assuming a close similarity between animal and human anatomy.[37]

In the Middle Ages, the University of Bologna pioneered the practice of dissection of human bodies. Mondino de Luzzi (1275-1326) wrote the first anatomy book based on human dissections, *"Anathomia"*. This groundbreaking work demonstrated human anatomy in a practical way and lasted for more than two centuries. Mondino describes a three-day dissection, devoting one day to each major body cavity (abdomen, thorax, and head), and mentions the possibility of a fourth day for the extremities.[38-40]

Servetus' work, *"Christianismi Restitutio"*, marked a milestone in the history of medicine by questioning the teachings of Galen, which had dominated the field for centuries. However, it was his experience in human dissections, acquired at the University of Paris, that allowed him to make important observations about pulmonary circulation and challenge Galenic theories.[11,13]

Servetus' true passion was theology, and to reduce him solely to a visionary physician who discovered pulmonary circulation is to simplify his legacy. The essence of his work reflects an inquisitive mind and a deep search for truth. In Servetus's vision, medicine and human anatomy were merely tools to discover "divine philosophy" or "sacred physiology", a deeper understanding of creation and the divine design underlying the human condition.

In Servetus's view, the divine breath was the essence of life, residing in the blood. To keep the human organism alive, this vital breath had to circulate freely through the body, carrying with it its vital spirit. It was this passionate search to understand the intrinsic connection between the divine breath and human life that prompted Servetus to discover pulmonary circulation. In this context, Servetus combined his medical-anatomical knowledge with his theological training.

Firstly, Servetus was based on various biblical texts, pointing out that life is in the blood, and that blood is life. However, it is interesting to note that the author was more interested in the journey of the soul than in the route of the blood. Furthermore, for Servetus, the soul resided in the blood, creating a unique and singular vision that combines theological and physiological elements.

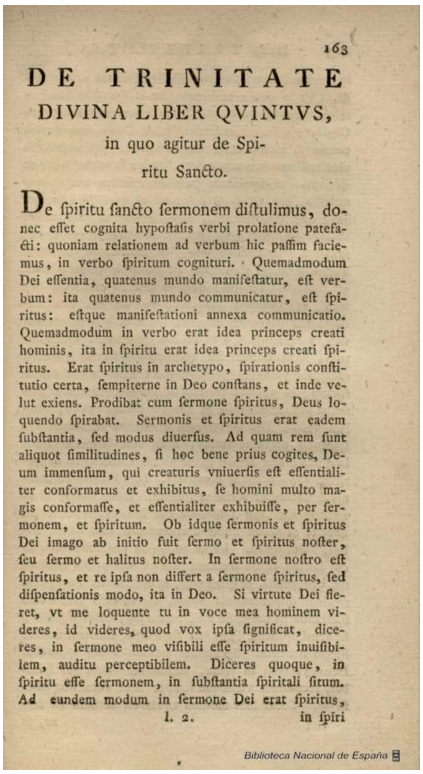
Book V of *Christianismi Restitutio* contains the passage describing the pulmonary circulation[28] *(Figure 3)*. The key in establishing the concept of pulmonary circulation was the understanding that blood flows from the pulmonary artery to the pulmonary veins. This implied that blood leaves the right heart through the pulmonary artery, returns to the left heart through the pulmonary veins [*et à venâ arteriosâ in arteriam venosam transfunditur……and is transferred from the arterial vein (pulmonary artery) to the venous artery (pulmonary veins)]* and then leaves the heart again. In this way, a circuit or circulation is formed or established. It was Servetus who first conceived this revolutionary idea.[41]

He established substantial differences regarding the formation of spirits, compared to the traditional Galenist concept, which we have already described above. Given the historical and medical importance of the text, I faithfully transcribe it in its original version in classical Latin (with its

corresponding translation), taken directly from Book V of *Christianismi Restitutio*[28] *(Figure 4)*.

Servetus begins by giving an explanation, different from the traditional Galenic concept, about the different types of spirits, the soul, and the blood; this is what finally led him to describe the pulmonary circulation: *"Dicitur in nobis ex trium superiorum elementorum substantia esse spiritus triplex, naturalis, vitalis et animalis. Tres spiritus vocat Aphrodisaeus. Vere non fiunt tres, fed denuo spiritus distincti. Vitalis est spiritus, qui per anastomoses ab arteriis communicator venis, in quibus dicitur naturalis. Primus ergo est sanguis, cuius sedes est in hepate, et corpis venis. Secundus, est spiritus vitalis, cuius sedes est in corde, et corporis arteriis. Tertius est spiritus animalis, quasi lucis radius, cuius sedes est in cerebro, et corporis neuris. In his omnibus est vnius spiritus et lucis Dei energia.*

Quod a corde communicetur hepati spiritus ille naturalis, docet hominis formatio ab utero. Nam arteria mittitur iuneta venae per ipsus foetus umbilicum: itidemque in nobis postea semper iunguntur arteria et vena. In cor est prius,quem in hepar, a Deo inspirata Adae anima, et ab eo hepati communicata. Per inspirationem in os et nares, est vere inducta anima: inspiratio autem at cor tendit. Cor est primus viuens, fons caloirs in medio corpore. Ab hepate sumit liquiorem vitae, quasi materiam, et eum vice versa viuificat: ficut aquea liquor superioribus elementis materiam



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DE TRINITATE
DIVINA LIBER QVINTVS,
in quo agitur de Spiritu Sancto.

De ſpiritu ſancto ſermonem diſtulimus, donec eſſet cognita hypoſtaſis verbi prolatione pateface-ti: quoniam relationem ad verbum hic paſſim faciemus, in verbo ſpiritum cogniturí. Quemadmodum Dei eſſentia, quatenus mundo manifeſtatur, eſt verbum: ita quatenus mundo communicatur, eſt ſpiritus: eſtque manifeſtationi annexa communicatio. Quemadmodum in verbo erat idea princeps creati hominis, ita in ſpiritu erat idea princeps creati ſpiritus. Erat ſpiritus in archetypo, ſpirationis conſtitutio certa, ſempiterne in Deo conſtans, et inde velut exiens. Prodibat cum ſermone ſpiritus, Deus loquendo ſpirabat. Sermonis et ſpiritus erat eadem ſubſtantia, ſed modus diuerſus. Ad quam rem ſunt aliquot ſimilitudines, ſi hoc bene prius cogites, Deum immenſum, qui creaturis vniuerſis eſt eſſentialiter conformatus et exhibitus, ſe homini multo magis conformaſſe, et eſſentialiter exhibuiſſe, per ſermonem, et ſpiritum. Ob idque ſermonis et ſpiritus Dei imago ab initio fuit ſermo et ſpiritus noſter, ſeu ſermo et halitus noſter. In ſermone noſtro eſt ſpiritus, et re ipſa non differt a ſermone ſpiritus, ſed diſpenſationis modo, ita in Deo. Si virtute Dei fieret, vt me loquente tu in voce mea hominem videres, id videres, quod vox ipſa ſignificat, diceres, in ſermone meo viſibili eſſe ſpiritum inuiſibilem, auditu perceptibilem. Diceres quoque, in ſpiritu eſſe ſermonem, in ſubſtantia ſpiritali ſitum. Ad eundem modum in ſermone Dei erat ſpiritus,

l. 2. in ſpiri

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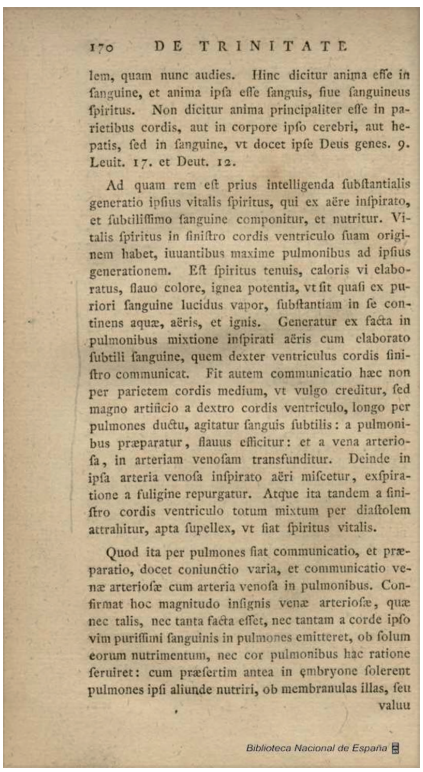
Figure 4:

Page 170 of Christianismi Restitutio containing the famous passage describing the pulmonary circulation. The reproduced work belongs to the collection of the National Library of Spain.



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lem, quam nunc audies. Hinc dicitur anima eſſe in ſanguine, et anima ipſa eſſe ſanguis, ſiue ſanguineus ſpiritus. Non dicitur anima principaliter eſſe in parietibus cordis, aut in corpore ipſo cerebri, aut hepatis, ſed in ſanguine, vt docet ipſe Deus genes. 9. Leuit. 17. et Deut. 12.

Ad quam rem eſt prius intelligenda ſubſtantialis generatio ipſius vitalis ſpiritus, qui ex aëre inſpirato, et ſubtiliſſimo ſanguine componitur, et nutritur. Vitalis ſpiritus in ſiniſtro cordis ventriculo ſuam originem habet, iuuantibus maxime pulmonibus ad ipſius generationem. Eſt ſpiritus tenuis, caloris vi elaboratus, flauo colore, ignea potentia, vt ſit quaſi ex puriori ſanguine lucidus vapor, ſubſtantiam in ſe continens aquæ, aëris, et ignis. Generatur ex facta in pulmonibus mixtione inſpirati aëris cum elaborato ſubtili ſanguine, quem dexter ventriculus cordis ſiniſtro communicat. Fit autem communicatio hæc non per parietem cordis medium, vt vulgo creditur, ſed magno artificio a dextro cordis ventriculo, longo per pulmones ductu, agitatur ſanguis ſubtilis: a pulmonibus præparatur, flauus efficitur: et a vena arteriosa, in arteriam venoſam transfunditur. Deinde in ipſa arteria venoſa inſpirato aëri miſcetur, exſpiratione a fuligine repurgatur. Atque ita tandem a ſiniſtro cordis ventriculo totum mixtum per diaſtolem attrahitur, apta ſupellex, vt fiat ſpiritus vitalis.

Quod ita per pulmones fiat communicatio, et præparatio, docet coniunctio varia, et communicatio venæ arterioſæ cum arteria venoſa in pulmonibus. Confirmat hoc magnitudo inſignis venæ arterioſæ, quæ nec talis, nec tanta facta eſſet, nec tantam a corde ipſo vim puriſſimi ſanguinis in pulmones emitteret, ob ſolum eorum nutrimentum, nec cor pulmonibus hac ratione ſeruiret: cum præſertim antea in embryone ſolerent pulmones ipſi aliunde nutriri, ob membranulas illas, ſeu valuu

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Figure 3:

Book V of Christianismi Restitutio. The reproduced work belongs to the collection of the National Library of Spain.

suppeditat, et ab eis, iuneta luce, ad vegetandum vivificatur. Ex hepaits sanguine est animae materia, per elaborationem mirabilem quam nune audies. HInc dicitur anima effe in sanguine, et anima ipfa effe sanguis siue sanguineus spiritus. Non dicitur anima principaliter effe in perietibus cordis, aut in corpore ipso cerebri, aut hepatis, sed in sanguine, ut docet ipse Deus Genes. 9. Leuit.17 et Deut. 12.

Ad quam rem est prius intelligenda substantialis generatio ipsus vitalis spiritus, qui ex aere inspirato, et subtilissimo sanguine componitur, et nutitur. Vitalis spiritus in sinistro cordis ventriculo suam originem habet, iuuantibus maxime pulmonibus ad ipsus genertionem. Est spiritus tenuis, caloris vi elaboratus, siau colore, ignea potentia, ut sit quasi ex puriori sanguine lucidus vapor, substantiam in se continens aqua, aeris, et ignis. ***Generatur ex facta in pulmonibus mixtione inspirati aeris cum elaborato sibtili sanguine, quem dexter ventriculus cordis sinistro communicat. Fit autem communicatio haec non per parietem cordis medium, ut vulgo creditur, fed magno artificio a dextro cordis venticulo, longo per pulmones ductu, agitatur sanguis subtilis: a pulmonibus preparatur, flauus efficitur: et a vena arteriosa, in arteriam venosa transfunditur.***

Deinde, in ipsa arteria venosa inspiratio aeri miscetur, exspiratione a fuligine repurgatur. Atque ita tandem a sinistro cordis ventriculo totum mixtum per disstolem attrahitur, apta fupellex, ut siat spitirus vitalis. Quod ita per pulmones

fiat communicatio, et praeparatio, docet coniunctio varia, et communication venae arteriosae cum arteria venosa in pulmonibus.

Confirmat hoc magnitudo insignis venae arteriosae, qua nec talis nec tanta facta effet, nec tantam a corde ipso vim puriffimi sanguinis in pulmones emitteret, ob folum eorum nutrimentum, nec cor pulmonibus hac ratione seruiret: cum praesertim antea in embryone folerent pulmones ipsi aliunde nutriri, ob membranulas illas, feu valuulas cordis usque ad horam natiutatis nindum apertas, ut docet Galenus. Ergo ad alium ufum effunditur sanguis a corde in pulmones hora ipsa natiutatis, et tam copiosus.

Item a pulmonibus ad cor non simplex aer, fed mixtus sanguine mittitur per arteria venosam: ergo in oulmonibus fit mixtio. Flauus ille color a pulmonibus datur sanguini spirituoso, non a corde. In sinistri cordis ventnriculo non est locus capax tantae, et tam copiosa mixitions, nec ad flauum elaboratio illa sufficiens. Demum, paries ille medius, cum fit vasorum et facultatum expers, non est aptus ad communicationem et elaborationem illam, licet aliquid resudare posit.

Eodem artificio, quo in hepate fit transfusio a vena porta ad venam cauam propter sanguinem, fit etian in pulmone transfusio a vena arteriosa as arteriam venosam propter spiritum. Si quis haec conferat cum iis, quae feribit Galenus lib 6. et 7. de usu partium, veritatm penitus intelliget, ab ipso Galeno non animaduersam.

Ille itaque spiritus vitalis, a sinistro cordis ventriculo, in arterias totius corporis deinde transfunditur, ita ut qui tenuior est, superiora petat, vbi magis adhuc elaboratur, praecipue in plexu retiformi, sub basi cerebri sito, in quo ex vitali fieri incipit animalis, ad propriam rationalis animae sedem accedens.

Iterum ille fortis mentis ignea vi tenuatur, elaboratur, et perficitur, in tenuissimis vasis, seu capillaribus arteriis, quae in plexibus choroidibus sitae sunt, et ipsissimam mentem continent. Hi plexus intima omnia cerebri penetrant, et ipsos cerebri ventriculos interne fuccingunt, vasa illa secum complicata, et contexta seruantes, usque ad neuronum origines ut in eos sentiendi et mouendi facultas inducatur. Vasa illa miraculo magno tenuissime contexta, tametfi arteriae dicantur, sunt tamen fines arteriarum tendentes ad originem neuronum, ministerio meningum. Est nouum quoddam genus vasorum.

Nam ficut in transfusione a venis in arterias, est in pulmone nouum genus vasorum, ex vena et arteria: ita in transfusione ab arteriis in neuros est nouum quoddam genus vasorum ex arteriae tunica in meninge: cum praeseritim meninges ipsae fuas in neuris tunicas seruent. Sensus neuroum non est in molli illa eorum materia, sicut in cerebro. Neuri omnes in membranarum filamenta definunt, exquisitissimum sensum habentia, ad quae ob id semper spiritus mittitur.

Ab illis itaque meningum seu choroidum vasculis, velut a fonte, lucidus animalis spiritus veluti radius per neuros essunditur in oculos, et alia sensoria organa. Via edaem, vice versa, aduenientes extrinsecus sensatarum rerum lucidae imagines, ad fontem eundem mittuntur, quasi per lucidum medium intro penetrantes.

Hinc quoque fit, ut praedictis vasis communem membranae tunicam in interna cauitate feruent nerui ad fidam spiritus custodiam: idque a tenui meninge, ficut et externam aliam tunicam habent a crassa. Illa etiam ventriculorum cerebri spatia inania, quae, philosophi et medici admirantur, nihil minus continent, quam animam.

Sed prima ratione facti sunt ventriculi illi as expurgamenta cerebri recipienda, veluti cloacae, ut probant excrementa ibi recepta, et meatus ad palatum et nares, a quibus desuxiones morbofae nafcuntur. Et quando ventriculi ita opplentur pituita, ut arteriae ipsae choroidis ea immergantur, tunc subito genetaur apoplexia" (It is said that in us, out of the substance of the three higher elements, there is a triple spirit, natural, vital and animal. Aphrodisius calls them three spirits. In truth, they are not three flowing spirits, but they are also distinct spirits. It is the vital spirit, which communicates through anastomosis of the arteries to the veins, in what is called natural. The first, then, is the blood, whose source is in the liver and veins of the body. The second is the vital spirit, whose seat is in the heart and organs of the body. The third is the animal spirit, like a ray of light, whose seat is in the brain and nerves of the body. In all of them there is one spirit and the energy of the light of God.

That this natural spirit communicates from the heart to the liver is shown by the formation of man from the mother's uterus. For the artery is sent united to the vein through the umbilical cord of the same fetus; and in us the artery and vein are always united afterwards. Adam's soul was inspired by God into the heart before it entered the liver, and was communicated by Him to the liver. By inspiration in the mouth and nostrils the soul is truly introduced; but inspiration tends to the heart. The heart is the first living being, the source of heat in the middle part of the body. From the liver it takes the liquid of life, so to speak matter, and in turn gives it life: just as the watery liquid supplies matter to the higher elements, and by them, united with light, is quickened to vegetate. From the blood of the liver comes the matter of the soul, through a wonderful elaboration which you will now hear. Therefore, it is said that the soul is in the blood, and the soul itself is the blood or the bloody spirit. It is not said that the soul resides primarily in the organs of the heart, or in the body itself, the brain or the liver, but in the blood, as God Himself teaches in Genesis. 9. Leviticus 17 and Deut. 12.

To this end, it is necessary first to understand the substantial generation of the vital spirit itself, which is composed and nourished by the inspired air and the subtler blood. The vital

spirit has its origin in the left ventricle of the heart, and the lungs especially assist in its generation. It is a subtle spirit, elaborated by the force of heat, or color, and the fiery power, so that it is like a luminous vapor of the purest blood, containing in itself the substance of water, air, and fire. It is generated from the mixture of the air inspired by the lungs with the blood being produced by the lungs, which the right ventricle of the heart communicates with the left. **This communication is not made by the middle wall of the heart, as is commonly believed, but by a great artifice from the right ventricle of the heart. After a long passage through the lungs, the subtle blood is agitated: it is prepared by the lungs, it becomes yellow and is transported from the arterial vein to the venous artery**.

Then, in the venous artery itself, the inspiration mixes with the air, and the exhalation purifies it from soot. And so finally the whole mixture is drawn out of the left ventricle of the heart through the diastole, a suitable vessel, so that it becomes the vital spirit. That the communication and preparation take place through the lungs is shown by the various connections and communications of the arterial vein with the venous artery in the lungs.

This is confirmed by the remarkable size of the vena arteriosa (pulmonary artery), which could not be made so large, nor could it send such a force of the purest blood from the heart itself to the lungs for their nourishment, nor does the heart serve the lungs in this way, especially since already in the embryo the lungs were nourished from another source, and because of these membranes the valves of the heart are not opened until the hour of birth, as Galen teaches. Therefore, for another purpose, blood is poured from the heart into the lungs at the very hour of birth, so copiously.

In the same way, from the lungs to the heart, not only air is sent, but mixed with blood, through the venous artery: thus, a mixture is produced in the lungs. The yellow color is given to the spirituous blood by the lungs, not by the heart. In the left ventricle of the heart there is no space capable of containing such a large and copious mixture, nor is such a preparation sufficient for the yellows. Finally, this intermediate wall, when it is deprived of vessels and resources, is not suitable for this communication and preparation, although it may perhaps produce something.

By the same way in which in the liver a transfusion is made from the portal vein to the vena cava for blood, in the lung a transfusion is made from the arterial vein (pulmonary artery) to the venous artery (pulmonary veins) for respiration. If someone compares this with what Galen states in Books 6 and 7 on the usefulness of the parts *(De Usu Partium),* he will fully understand the truth, which Galen himself did not notice.

This vital spirit, then, from the left ventricle of the heart, is then transfused into the arteries of the whole body, so that the subtler it is, the higher it seeks, where it is most elaborated, especially in the reticular plexus, situated under the base of the brain, in which the vital begins to become animal, to approach the proper seat of the rational soul.

Furthermore, this powerful fiery force of the mind is maintained, developed and perfected in the thinnest vessels, or capillary arteries, which are situated in the choroid plexuses and contain the mind itself. These plexuses penetrate all the innermost parts of the brain, and internally line the ventricles of the brain itself, keeping these vessels folded and intertwined with them, up to the origins of the neurons, so that the capacity to feel and move is induced in them. These vessels, interwoven with great miracle, are called arteries, and yet they are the ends of the arteries that tend to the origin of the neurons, serving the meninges. It is a new type of vessels.

Just as in the transfusion of veins into arteries there is a new type of vessel in the lung, from the vein and the artery, so also in the transfusion of arteries into nerves there is a new kind of vessel from the tunic of the artery into the meninges: for the meninges themselves especially preserve their sheaths in the nerves. The sense of the nerves is not in their soft matter, as in the brain. All nerves are defined by filaments of membranes, having the most exquisite sensation, to which the spirit is therefore always sent.

From these small vessels of the meninges or choroid, therefore, as from a fountain, the luminous spirit of the animal, like a ray, pours itself through the nerves into the eyes and other sensory organs. Just as, on the contrary, the luminous images of perceived things arriving from without are sent back to the same fountain, as if they penetrated into the interior through a luminous medium.

From these destinations it follows that that soft and frequent mass is not properly the seat of a rational soul, for it is cold and devoid of feeling. But it is like the dust of these vessels, so that they do not break; and it is the guardian of the animal spirit, so that it does not disintegrate, when it is to be communicated to the nerves; and it is cold to temper that burning heat contained within the vessels. Hence it also happens that the nerves, for the reliable preservation of respiration, form a common membranous layer in the internal cavity of the above-mentioned vessels: and this because of the thin meninges, since they have a different outer layer from the thick one. Even those empty spaces of the ventricles of the brain, which astonish philosophers and physicians, contain nothing less than the soul. But for the first reason, these ventricles were made to receive the expurgations of the brain, like cloacae, as is proved by the excrements received there and the passages to the palate and nasal cavities, from which the discharges of diseases arise. And when the ventricles are so full of phlegm that the very arteries of the choroid are submerged in it, then apoplexy suddenly occurs).

Finally, he ends by saying *"…… Spiritus ille nequam, cuius potestas est aeris, una cum inspirato a*

nobis aere, lacunas illas libere ingreditur et egreditur, ut ibi cum spiritu nostro, intra vasa illa, velut in arce collocato, iugiter, dimicet. Imo eum ita undique obsidet, ut vix illi liceat respirare, nisi quando superueniens lux spiritus Dei malum spiritum fugat" (…That evil spirit, whose power is in the air, together with the air we breathe, freely enters and leaves these holes, to constantly fight there with our spirit, placed within these vessels, as in a fortress. In fact, it besieges it on all sides, so that it is hardly allowed to breathe, except when the light of the Spirit of God, descending upon it, drives away the evil spirit).[28]

This discovery of the pulmonary or lesser circulation went unnoticed for many years because it was found in a fundamentally theological work. The appearance of a scientific discovery in a theological book may seem unusual, but in the context of Servetus' integrative thought, it is perfectly logical. For him, theology, medicine and philosophy were interconnected disciplines that complemented each other. Moreover, since the information on pulmonary circulation was burned together with the theological work of Michael Servetus, the discovery of pulmonary circulation was forgotten, until Sir William Harvey published it, seventy-five years later, in his work *De Motu Cordis* in 1628.[42] All of Servetus' works were entered into the index of books prohibited by the Holy Inquisition of 1559.[16]

Michael Servetus, a man of firm convictions and unwavering courage, was sentenced to death in Geneva in 1553 by the Calvinist Church for thinking differently from the scholastic theological dogmas of the time. The trial was an example of abuse of power and lack of justice. Calvin, who dominated the proceedings at the small Council of Geneva, used his influence to leave Servetus without a defense and presented questionable arguments.

The Sentence of the Minor Council of Geneva, read by Lord Syndic Darlod on October 27, 1553, read as follows: "…This detestable crime of heresy deserves a severe corporal punishment… condemning you, Michael Servetus, to be bound and led to the place of Champel, tied to a stake and burned alive, with the book written by your hand, which you printed, until your body is reduced to ashes; thus your days will end to give an example to others who would want to commit such an act".[43]

That same day, October 27, 1553, Servetus was taken to the square of Champel, where he was burned alive at the stake. His body was tied with a chain, his neck fixed with five turns of rope, and his head covered with a crown of straw dipped in sulfur. Surrounded by bundles of green firewood, Servetus suffered a slow and painful agony[43] *(Figure 5)*.

The sentence extended to "all" of the books written by Servetus, not just the confiscated edition of the *Christianismi Restitutio*. This is why it is of extreme significance that some copies of the original manuscript have survived to this day. Despite the tragedy surrounding his death, Servetus' legacy has endured. Although Calvin was outraged to read Servetus' work, he chose to preserve it, which allowed valuable copies of the work to be processed and have survived to this day. This copy had previously belonged to German Colladon, Calvin's right-hand man and one of the accusers against Servetus. Colladon underlined the passages he used to accuse Servetus, leaving a tangible mark of his role in the reformer's persecution. Several pages of this volume are charred and blackened by fire, a macabre reminder of the pyre on which Servetus and his work were burned together. The book was later owned by the English physician Richard Mead, who gave it to Boze, who sold it to the Royal Library in Paris for a considerable sum. From this manuscript, as we mentioned above, several copies were made in 1790, which allowed, ironically thanks to Calvin, that some of them have survived

Figure 5:

Monument to Miguel Servet, Square de l'Aspirant Dunand, Paris. (Monument à Miguel Servet, square de l'Aspirant Dunand, Paris).
Credit: Chabe01-Own work. Attribution-Share Alike 4.0 International license. Chabe01, CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0>, via Wikimedia Commons. work. https://commons.wikimedia.org/wiki/File:Monument_Miguel_Servet_Square_Aspirant_Dunand_-_Paris_XIV_(FR75)_-_2024-06-02_-_2.jpg

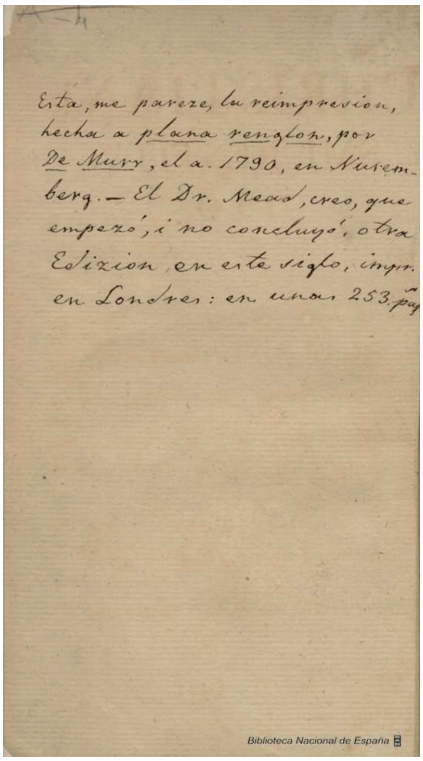

Figure 6:

Colophon of *Christianismi Restitutio* from the 1790 reissue in Nuremberg, with personal notes explaining the possible origin of the work. The reproduced work belongs to the collection of the National Library of Spain.

to this day, thus making known Servetus's masterpiece and the discovery of pulmonary circulation[41] *(Figure 6)*.

Michael Servetus died for thinking differently, for questioning the theological dogmas. As he himself said, he died "for reasons other than the truth".[44] Beyond his revolutionary discovery of pulmonary circulation, it is important to remember that Michael Servetus left us an immortal legacy. The monuments dedicated to Servetus in various cities such as Paris, Sijena, Geneva, Zaragoza, among others, are a lasting testimony to his influence and his commitment to tolerance and freedom of thought.

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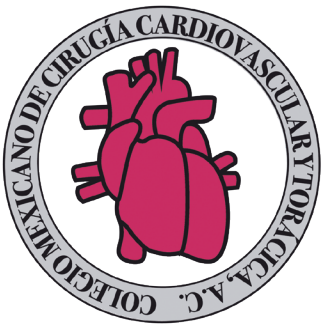

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