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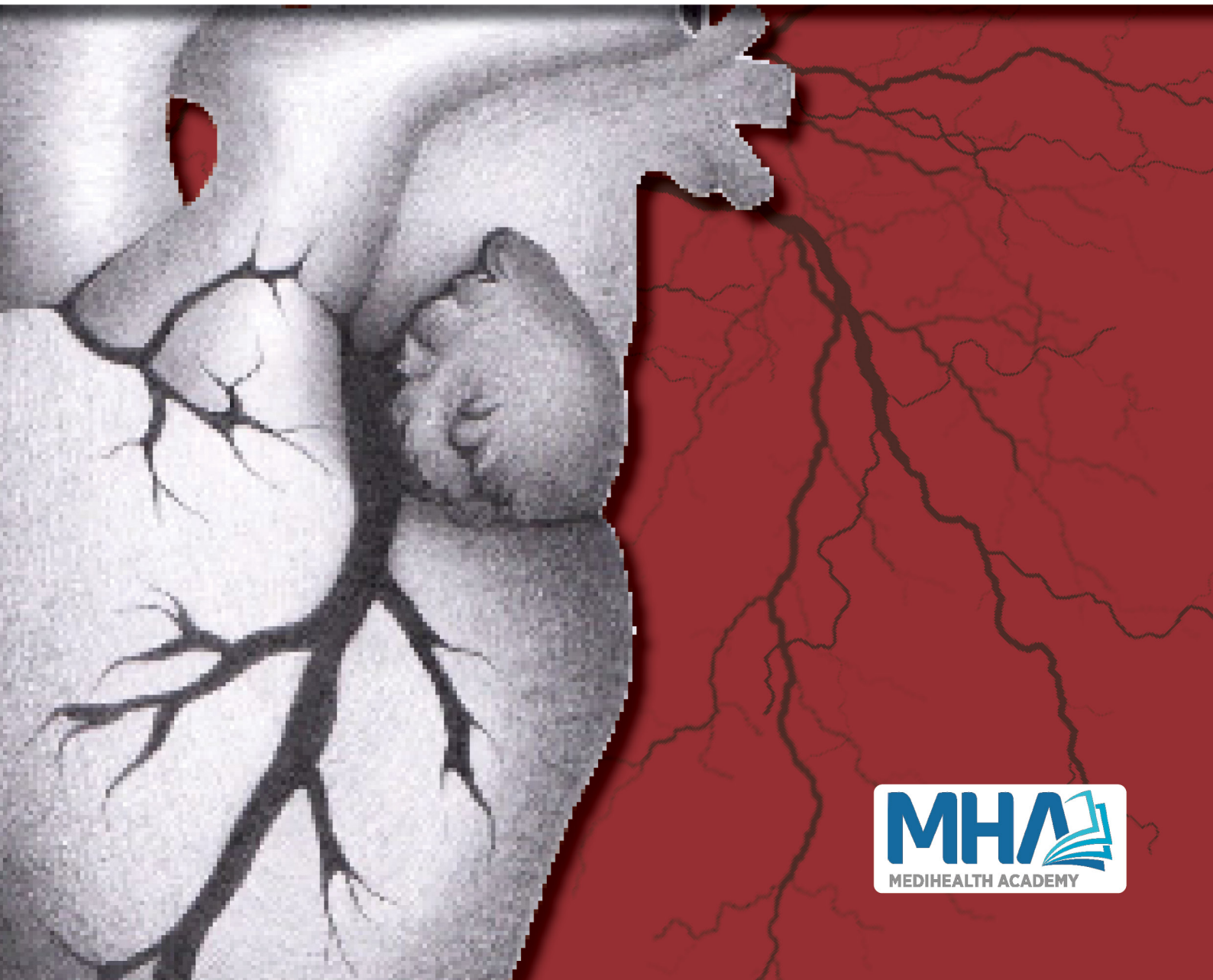

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Original Article

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The effect of hematological tests on fistula maturation in end-stage renal disease patients with radiocephalic arteriovenous fistula

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ABSTRACT

Aims: Arteriovenous fistula (AVF) is the most commonly used vascular access route for hemodialysis (HD) in patients with end-stage renal disease. The most significant cause of AVF dysfunction is stenosis and post-stenotic thrombosis. Fistula stenosis arises from neointimal hyperplasia and various inflammatory factors. Several inflammatory markers have been studied in relation to AVF loss. This study aims to provide a comprehensive perspective on this globally prevalent health issue by examining the association between the continuity of surgically created AVFs and the patients' clinical factors, inflammatory markers, and biochemical parameters.

Methods: A total of 146 patients were included in the study. All patients underwent preoperative examination of the upper extremity arterial and venous systems to confirm normal circulation. Patients with suitable arterial and venous structures underwent radiocephalic AVF creation at the wrist level. AVFs that achieved adequate flow and allowed for HD were considered matured.

Results: Of the patients, 83 were male and 63 were female. The mean age of the patient group was 58.9±11.41 years, with a minimum age of 30 and a maximum of 77 years. Male sex, low body-mass index (BMI), antiplatelet use, and low neutrophil-to-lymphocyte ratio (NLR) and red cell distribution width (RDW) values were positively associated with AVF maturation. However, age, smoking status, type of anesthesia, diabetes, hypertension, and other blood parameters were not significantly associated with AVF maturation.

Conclusion: Our study demonstrated that low maturation rates of AVFs were associated with high NLR and RDW values. In addition, antiplatelet use, male sex, and low BMI were found to be associated with AVF maturation.

Keywords: Arteriovenous fistula, fistula maturation, inflammation

INTRODUCTION

Due to declining birth rates and increased life expectancy, especially in developed societies, the elderly population and, consequently, the incidence of end-stage renal disease (ESRD) are rapidly increasing. The most commonly used treatment method for these patients is hemodialysis (HD) via an arteriovenous fistula (AVF).[1] The Brescia-Cimino AVF is considered the gold standard for primary vascular access.[2] Complications in vascular access represent a significant cause of prolonged hospitalization, morbidity, and mortality in HD patients. The most common cause of dysfunction in AVFs is thrombosis secondary to stenosis. Inflammation appears to be associated with AVF dysfunction and warrants investigation. AVF stenosis results from neointimal hyperplasia and a cascade of inflammatory factors. Various inflammatory parameters have been studied in relation to AVF failure.[3–5] Among these, the neutrophil-to-lymphocyte ratio (NLR) and red cell distribution width (RDW) are strong predictors of inflammation-associated stenosis, thus potentially playing a significant role in AVF stenosis. Due to their effectiveness, low cost, and ease of access, NLR and RDW continue to draw interest as useful markers.[6,7]

The aim of this study is to identify parameters associated with loss of AVF function in patients with ESRD who have undergone AVF creation. In doing so, strategies can be developed to ensure longer AVF patency, thereby reducing associated healthcare costs.

METHODS

Ethics

The study was conducted with the permission of the Erciyes University Clinical Researches Ethics Committee (Date: 04.07.2018, Decision No: 2018/343). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A prospective study was conducted between 2018 and 2019, involving 146 patients who underwent radiocephalic AVF creation (**Figure**). Only patients with successful radiocephalic AVF formation who did not require any further interventions were included in the study. Preoperative evaluations included the Allen test and detailed physical examination. Surgical success was confirmed by the presence of a palpable thrill. Patients were recalled at the 1st and 5th months postoperatively to assess AVF patency. AVF with HD blood flow rates of 350 ml/min or higher were considered mature. All surgical procedures were performed by two surgeons.

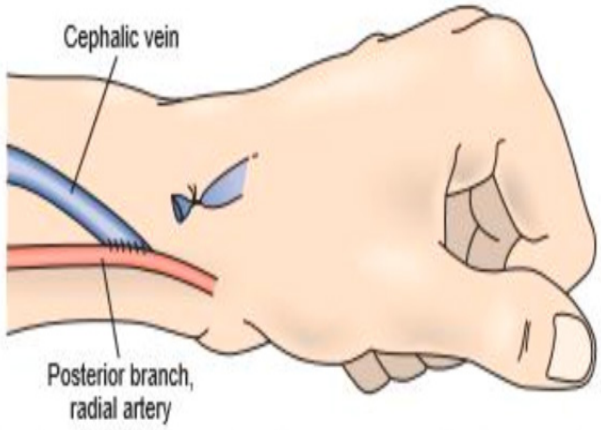

Figure. Autogenous posterior radial branch–cephalic vein (Snuffbox fistula) and autogenous radial-cephalic with direct access (Brescia-Cimino-Appel fistula)
(Reproduced from Silva MB, Hobson RW, Pappas PJ, et al. Vein transposition in the forearm for autogenous hemodialysis access. *J Vasc Surg.* 1997;26:981-988.)

Exclusion criteria were as follows: patients with chronic hepatobiliary and hematological diseases, chronic inflammatory diseases, malignancies, patients taking certain medications (steroids or nonsteroidal anti-inflammatory drugs), and those with acute infections.

Laboratory Analysis

Antecubital venous blood samples were collected from all patients in test tubes upon admission. All standard biochemical tests were performed on an autoanalyzer (Roche Diagnostic Modular Systems, Tokyo, Japan). An automated hematology analysis system (Sysmex K-1000 Hematology Analyzer, Guangdong, China) was used to measure hematological parameters. The NLR was obtained by dividing the neutrophil count by the lymphocyte count.

Statistical Analysis

SPSS 26.0 for Windows (IBM, Armonk, NY, USA) statistical software was used for data analysis. This study employed a case-control methodology. The Shapiro-Wilk test was used to assess the normality of the distribution of the results. Descriptive data were presented as mean or median with standard deviation (interquartile range, IQR), depending on the normality of the distribution. The Mann-Whitney U test was used to compare quantitative variables with non-normal distributions. The Chi-square test was used to compare groups. Group comparisons were performed using t-tests, and continuous variables were reported as mean and standard deviation. Correlations between continuous variables were measured using Pearson's correlation analysis. Multivariate logistic regression analysis was used to assess the association between NLR and AVF maturation. Additionally, 95% CI (confidence intervals) and OR (odds ratio) were calculated. The best cut-off values for NLR were found using receiver operating characteristic (ROC) analysis, which was used to assess the relationship between inflammatory markers and clinical outcome and prognosis prediction. P values less than 0.05 were considered significant.

RESULTS

Patients diagnosed with ESRD who were either scheduled to begin HD or were already undergoing HD treatment were included in our study. A total of 146 patients (83 males, 63 females) were enrolled. Of these, 56.8% were male and 43.2% were female (**Table 1**). The mean age of the patient group was 58.9±11.41 years (**Table 1**).

According to the results, 61.6% of the AVF created matured sufficiently for HD treatment, whereas 38.4% did not reach the level of maturation required for HD.

At the 1-month follow-up, a palpable thrill was detected in 71.2% of patients, while no thrill was detected in 28.8%. At the 3-month follow-up, thrill was present in 67.1% of patients and absent in 32.9% (**Table 1**).

Among male participants, AVF maturation was observed in 73.5%, while this rate was 46% among female participants (**Table 2**). These findings demonstrated a statistically significant relationship between AVF maturation and gender (p=0.001).

Similarly, at the 1st-month follow-up, a thrill was detected in 79.5% of male patients compared to 60.3% of female patients. The 1st-month thrill detection rate in male patients was statistically significantly higher (p=0.011) (**Table 3**).

At the 5th-month follow-up, a thrill was present in 75.9% of male patients and 55.6% of female patients. The thrill rate at 1 month in male patients was found to be statistically significantly higher (p=0.011) (**Table 4**).

Among the 146 patients included in the study, 47.3% had a body-mass index (BMI) below 25, and 52.7% had a BMI of 25 or above. The AVF maturation rate was 71% in patients with a BMI <25, while it was 41% in those with a BMI ≥25. A statistically significant association was found between BMI and AVF maturation (p=0.028) (**Table 2**). AVF maturation was significantly more common in patients with lower BMI.

The 1st-month thrill detection rate was 81.2% in patients with a BMI <25, compared to 62.3% in patients with a BMI ≥25. The 1st-month thrill presence in patients with lower BMI was statistically significantly higher (p=0.012) (**Table 3**).

Similarly, at the 5th-month follow-up, thrill was detected in 76.8% of patients with a BMI <25, and in 58.4% of patients with a BMI ≥25. The 1st-month thrill presence in patients with lower BMI was statistically significantly higher (p=0.012) (**Table 3**).

Among the study participants, 24.0% were on antiplatelet therapy, while 76.0% were not. AVF maturation occurred in 77.1% of patients receiving antiplatelet therapy, compared to 56.8% in those not receiving it. Fistula maturation was

Table 1. Analysis of the entire patient group

		Value
Age (year)		58.9±11.41
Gender (n,%)	Female	63 (43.2%)
	Male	83 (56.8%)
Fistula maturation (n,%)	No	56 (38.4%)
	Yes	90 (61.6%)
1. month thrill (n,%)	No	42 (28.8%)
	Yes	104 (71.2%)
2. month thrill (n,%)	No	48 (32.9%)
	Yes	98 (67.1%)
Body-mass index (kg/m²)	<18.5	15 (10.3%)
	18.5-24.9	54 (37.0)
	25-29.9	52 (35.6%)
	30-39.9	21 (14.4%)
	>40	4 (2.7%)
Smoking (n, %)	No smoking	103 (70.5%)
	<20 package/year	26 (17.8)
	≥20 package/year	17 (11.6)
Hypertension (n, %)	No	49 (33.6%)
	Yes	97 (66.4%)
Diabetes mellitus (n, %)	No	89 (61.0%)
	Yes	57 (39.0%)
Type of anesthesa (n, %)	Local	139 (95.2%)
	Regional	7 (4.8%)
Antiplatelet drugs (n, %)	No	111 (76.0%)
	Yes	35 (24.0%)
Hemoglobin (g/dl)		10.15±1.97
Platelet (10³/μL)		234.50±96.25
White blood cell (10³/μL)		7.95±2.05
Blood urea nitrogen (mg/dl)		52.82±34.72
Creatinine (mg/dl)		5.02±3.91
Glomerular filtration rate (ml/min/1.73m²)		29.35±32.51
Sodium (mmol/L)		134.87±11.73
Potassium (mmol/L)		4.53±0.87
Calcium (mg/dl)		8.45±1.15
Phosphorus (mg/dl)		4.45±1.84
Total protein (mg/dl)		6.38±0.92
Albumin (mg/dl)		3.37±0.65
Aspartate transaminase (U/L)		30.64±21.16
Alanine aminotransferase (U/L)		34.41±20.90
Neutrophil-lymphocyte ratio		2.98±1.80
Red blood cell distribution width (%)		14.84±1.94

significantly higher in patients on antiplatelet therapy (p=0.031) (**Table 2**).

At the 1st-month follow-up, thrill was present in 91.4% of patients on antiplatelet therapy, compared to 64.9% of those not on therapy. The effect of antiplatelet treatment on 1st-month AVF patency was statistically significant (p=0.002) (**Table 3**).

At the 5th-month follow-up, thrill was detected in 82.9% of patients on antiplatelet therapy and 62.2% of those not

Table 2. Association of fistula maturation with clinical parameters

		Maturation		p
		No n (%)	Yes n (%)	
Gender (n,%)	Male	22 (26.5%)	61 (73.5%)	0.001
	Female	34 (54.0%)	29 (46.0%)	
Body-mass index (kg/m²)	<25	20 (29.0%)	49 (71.0%)	0.028
	≥25	36 (46.8%)	41 (53.2%)	
Smoking (n,%)	No	38 (36.9%)	65 (63.1%)	0.574
	Yes	18 (41.9%)	25 (58.1%)	
Hypertension (n,%)	Yes	40 (41.2%)	57 (58.8%)	0.314
	No	16 (32.7%)	33 (67.3%)	
Diabetes mellitus (n,%)	Yes	26 (45.6%)	31 (54.4%)	0.149
	No	30 (33.7%)	59 (66.3%)	
Type of anesthesia (n,%)	Local	52 (37.4%)	87 (62.6%)	0.254
	Regional	4 (57.1%)	3 (42.9%)	
Antiplatelet drugs (n,%)	Yes	8 (22.9%)	17 (77.1%)	0.031
	No	48 (43.2%)	63 (56.8%)	

Table 3. Association of first-month thrill with clinical parameters

		First month thrill		p
		No n (%)	Yes n (%)	
Gender (n, %)	Male	17 (20.5%)	66 (79.5%)	0.011
	Female	25 (39.7%)	38 (60.3%)	
Body-mass index (kg/m²)	<25	13 (18.8%)	56 (81.2%)	0.012
	≥25	29 (37.7%)	48 (62.3%)	
Smoking (n, %)	No	26 (25.2%)	77 (74.8%)	0.145
	Yes	16 (37.2%)	27 (62.8%)	
Hypertension (n, %)	Yes	31 (32.0%)	66 (68.0%)	0.231
	No	11 (22.4%)	38 (77.6%)	
Diabetes mellitus (n, %)	Yes	21 (36.8%)	36 (63.2%)	0.085
	No	21 (23.6%)	68 (76.4%)	
Type of anesthesia (n, %)	Local	41 (29.5%)	98 (70.5%)	0.350
	Regional	1 (14.3%)	6 (85.7%)	
Antiplatelet usage (n, %)	Yes	3 (8.6%)	32 (91.4%)	0.002
	No	39 (35.1%)	72 (64.9%)	

Table 4. Association of fifth-month thrill with clinical parameters

		Fifth month thrill		p
		No n (%)	Yes n (%)	
Gender (n, %)	Male	20 (24.1%)	63 (75.9%)	0.010
	Female	28 (44.4%)	35 (55.6%)	
Body-mass index (kg/m²)	<25	16 (23.2%)	53 (76.8%)	0.018
	≥25	32 (41.6%)	45 (58.4%)	
Smoking (n, %)	No	32 (31.1%)	71 (68.9%)	0.471
	Yes	16 (37.2%)	27 (62.8%)	
Hypertension (n, %)	Yes	36 (37.1%)	61 (62.9%)	0.125
	No	12 (24.5%)	37 (75.5%)	
Diabetes mellitus (n, %)	Yes	22 (38.6%)	35 (61.4%)	0.239
	No	26 (29.2%)	63 (70.8%)	
Type of anesthesia (n, %)	Local	46 (33.1%)	93 (66.9%)	0.581
	Regional	2 (28.6%)	5 (71.4%)	
Antiplatelet drugs (n, %)	Yes	6 (17.1%)	29 (82.9%)	0.023
	No	42 (37.8%)	69 (62.2%)	

receiving therapy. The effect of antiplatelet therapy on 5th-month AVF patency was statistically significant (p=0.023) (Table 4).

The mean age of the patient group was 58.9±11.41 years. Non-parametric analysis using the Mann-Whitney U test revealed a statistically significant relationship between age and AVF maturation (p=0.011) (Table 5). No statistically significant associations were found between AVF maturation and the levels of hemoglobin, platelet count, WBC, BUN, creatinine, GFR, sodium, potassium, calcium, phosphorus, total protein, or albumin (Table 5).

Table 5. The relationship between continuous variables and fistula maturation

	Mean±standard deviation	p
Age (year)	58.9±11.41	0.011
Hemoglobin (g/dl)	10.15±1.97	0.127
Platelet (10^3/μL)	234.50±96.25	0.536
White blood cell (10^3/μL)	7.95±2.05	0.245
Neutrophil-lymphocyte ratio	2.98±1.80	0.014
Red blood cell distribution width (%)	14.84±1.94	0.001
Blood urea nitrogen (mg/dl)	52.82±34.72	0.781
Serum creatinine (mg/dl)	5.02±3.91	0.953
Glomerular filtration rate (ml/min/1.73m^2)	29.35±32.51	0.950
Sodium (mmol/L)	134.87±11.73	0.536
Potassium (mmol/L)	4.53±0.87	0.601
Calcium (mg/dl)	8.45±1.15	0.700
Phosporus (mg/dl)	4.45±1.84	0.726
Total protein (mg/dl)	6.38±0.92	0.459
Albumin (mg/dl)	3.37±0.65	0.810
Aspartate transaminase (U/L)	30.64±21.16	0.344
Alanine aminotransferase (U/L)	34.41±20.90	0.538

The mean NLR was 2.98±1.80. Evaluation of the relationship between NLR and AVF maturation using the Mann-Whitney U test revealed a statistically significant association (p=0.014) (Table 5). The RDW was 14.84±1.94, and its association with AVF maturation was found to be statistically significant (p=0.001) (Table 5).

Among the 146 patients included in the study, 63 (43.2%) were female and 83 (56.8%) were male. AVF maturation was observed in 73.5% of male participants and 46% of female participants (Table 2). These findings demonstrated a statistically significant relationship between AVF maturation and gender (p=0.001).

DISCUSSION

One of the important implications of this study is that NLR and RDW levels, which are considered inflammatory markers, can also be used to predict AVF maturation.

In patients with ESRD undergoing HD, establishing a vascular access with adequate blood flow for regular HD sessions is essential. AVFs are the most commonly used vascular access method for HD. However, AVF loss due to stenosis and thrombosis leads to frequent hospitalizations and significant healthcare costs.[4] Vascular anatomy and technical factors influence AVF maturation, requiring optimal coordination among multiple healthcare professionals, including surgeons, anesthesiologists, nurses, nephrologists, and dialysis unit staff.[8]

Although brachiocephalic AVFs demonstrate better patency rates than radiocephalic AVFs, higher complication rates make radiocephalic AVFs the preferred option.[9] This study focused on patients with radiocephalic AVFs using the most commonly used technique, an end-to-end anastomosis technique with the cephalic vein and radial artery.[10] Current literature reports a primary AVF failure rate ranging from 23% to 37% within the first year and patency rates ranging from 40% to 60%.[11,12] According to the Dialysis Outcomes Quality Initiative, the primary AVF failure rate is approximately 15% in the first year and 25% in the second year.[12] International Kidney Disease guidelines state a primary AVF success rate of 65%. A study by Irish and colleagues[13] observed obstruction and non-maturation rates ranging from 20% to 54%.

In this study, 61.6% of the AVFs created reached sufficient maturity for HD, while 38.4% did not. At 1-month follow-up, 71.2% of patients had a palpable thrill, while 28.8% did not. At 5-month follow-up, 67.1% of patients had a palpable thrill, while 32.9% did not. Advanced age, female gender, diabetes mellitus (DM), and small vessel diameter are known risk factors for AVF failure. Studies on the effect of age on arteriovenous access outcomes often yield conflicting results. However, given the shorter life expectancy in patients with ESRD, the question arises: Should proximal or prosthetic arteriovenous access be the initial approach in elderly patients? A meta-analysis by Lazarides et al.,[14] which included studies comparing elderly and non-elderly patients and forearm and upper arm accesses, found significantly higher AVF failure rates for radiocephalic AVFs at 1 and 2 years in elderly patients. Conversely, studies by Pisoni et al.[15] and others have shown that younger age favors AVF maturation.

A meta-analysis by Lazarides et al.[14] of 13 cohort studies revealed significantly higher radiocephalic AVF failure rates in elderly patients. However, studies by Lok et al.,[16] Swindlehurst et al.,[17] and Weale et al.[18] found no significant association between age and AVF failure. The likelihood of AVF failure appears to be higher in older individuals, which may be attributable to the increased prevalence of DM, hypertension, and peripheral vascular disease in this population. However, current evidence suggests that the relationship between age and AVF maturation is not definitive. In our study, we observed a statistically significantly higher AVF maturation rate in younger patients. This difference may be due to the increased incidence of comorbidities and atherosclerosis in older individuals.

Advanced age, female gender, DM, and small vein caliber are known risk factors for AVF maturation. Studies on the impact of age on arteriovenous access outcomes often yield conflicting results. In a study conducted by Pisoni et al.,[15] male gender was found to positively influence AVF maturation. In contrast, studies by Astor et al.[19] and Rooijens et al.[2] reported no significant difference between sexes. In our study, AVF maturation rates were significantly higher in male patients than in females. This may be explained by the generally larger and more superficial veins observed in males.

Most published reports consist of retrospective observational studies and suggest that DM adversely affects arteriovenous access patency. These reports demonstrate an increased incidence of arterial calcification and atherosclerosis in DM patients. To further evaluate the vascular effects of DM, Sedlacek et al.[20] compared preoperative non-invasive vascular mapping between DM and non-DM patients. While they found increased arterial calcification in DM patients, no significant differences were observed in arterial diameter or in the feasibility of placing autogenous arteriovenous access; however, long-term outcomes were not assessed in that study.[20]

When examining the long-term outcomes in DM patients, Konner et al.[21] reported an increased risk of thrombosis and arterial steal syndrome. Similarly, Kordzadeh et al.[22] found that DM negatively impacted AVF maturation. Pisoni et al.[15] also concluded that the absence of DM was a positive predictor of AVF maturation. Aronson et al.[23] demonstrated that DM-associated metabolic disturbances contribute to prothrombotic events, endothelial injury, dysregulation of growth factors, and extracellular matrix accumulation. These factors may trigger inflammation, which in turn promotes AVF stenosis and thrombosis.[24] In a study involving 31 AVF patients, DM was identified as a negative predictor of venous remodeling; however, the limited sample size may reduce the statistical power of that finding.[25]

Hemodynamic changes stimulate vascular remodeling, and the endothelium actively responds to these stimuli.[26] Previous studies have demonstrated that DM accelerates AVF failure through atherosclerotic mechanisms.[27] In our study, although AVF maturation appeared to be lower in DM patients than in non-DM ones, the difference was not statistically significant.

According to Kim et al.,[28] hypertension is not considered a major risk factor for AVF maturation. Their cohort study, which included 50 patients, also found no significant association between AVF maturation and DM or gender. However, the study may have been underpowered due to the small sample size. Cardiovascular comorbidities, including hypertension, appear to exert less influence on hemodynamic profiles and vascular morphology.[27] Nevertheless, in hypertension, endothelial function is impaired due to reduced vasodilation and increased inflammatory cell infiltration.[29]

Macrophages and T lymphocytes represent key pathological components in the development of atherosclerosis. Neovascularization is initiated at the sites of high shear stress in elastic arteries.[30] In our study, no statistically significant relationship was found between hypertension and AVF maturation.

Serum albumin has emerged in recent years as a prognostic factor for surgical outcomes and AVF patency.[31] However, its precise role in vascular surgery remains unclear. Serum albumin contributes to oncotic pressure and influences various pathophysiological mechanisms including dehydration, malnutrition, wound healing, and edema, all of which impact inflammation and AVF function.[32] Churchill et al.[33] found hypoalbuminemia to be significantly associated with AVF thrombosis, likely due to its role as an indicator of systemic inflammation. Chang et al.[34] observed that infiltration of macrophages and lymphocytes into the vessel wall exacerbates the inflammatory process, contributing to AVF stenosis. Several studies have also implicated thrombosis resulting from inflammation-induced neointimal hyperplasia as a major cause of AVF failure.[35]

Recent studies have identified several preoperative hematological and biochemical markers as prognostic indicators for surgical outcomes. While brachiocephalic AVFs demonstrate better patency rates than radiocephalic ones, their higher complication rates make radiocephalic AVFs the preferred choice. This study focused on patients with radiocephalic AVFs, utilizing the end-to-side anastomosis technique with the cephalic vein and radial artery, which is the most commonly employed method. Among inflammatory markers, RDW has been found to be significantly elevated in patients with AVF failure and is also associated with coronary artery disease and myocardial infarction.[36] The NLR, an indicator of neointimal hyperplasia, negatively affects AVF maturation.[7]

Endothelial dysfunction, commonly observed in renal impairment, results from the presence of uremic toxins in plasma, which disrupt critical endothelial processes such as proliferation, migration, and wound healing.[37] These abnormalities play a central role in vascular remodeling. In AVF creation, endothelial cells undergo rapid proliferation to restore barrier function, permeability, and biochemical regulation, which facilitates vascular repair, localized thrombosis, inflammation, and neointimal hyperplasia.[38] When uremia inhibits endothelial proliferation and migration, abnormal remodeling and neointimal hyperplasia may occur at the anastomosis site, resulting in AVF failure.[3]

Endothelial dysfunction contributes to atherosclerosis by impairing vasoregulation, promoting thrombogenesis, facilitating leukocyte infiltration and lipid accumulation in the intimal layer, and enhancing vascular smooth muscle cell proliferation and migration.[39–42] Atherosclerosis disrupts endothelial integrity, triggers platelet aggregation, and initiates the coagulation cascade, increasing the risk of vascular occlusion.[43] Studies suggest that RDW may be a superior inflammatory marker compared to CRP and WBC in this context.[35]

Establishing effective vascular access is fundamental to successful HD. Selecting the appropriate type and location is crucial to maximizing fistula success and minimizing the need for revisions. Unfortunately, there is no universal criterion for AVF creation. Despite the absence of consensus, autogenous AVFs are generally preferred over grafts, as grafts require 3.8 times more thrombectomy procedures and three times more interventions to maintain patency. Furthermore, AVFs typically require 1.5 to 3.3 additional interventions during their lifespan to maintain access functionality which leads to prolonged hospitalizations and increased healthcare costs.[44]

Therefore, there is a strong need for AVFs that are durable, rapidly maturing, and require fewer interventions. If an AVF functions well during the first six months, it can remain patent for up to 20 years.[45]

CONCLUSION

In our study, age and gender were found to be significantly associated with AVF maturation. Additionally, antiplatelet therapy was positively associated with AVF maturation, while elevated NLR and RDW levels were negatively correlated with successful AVF maturation.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Erciyes University Clinical Researches Ethics Committee (Date: 04.07.2018, Decision No: 2018/343).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Facilitating factors of venous risk among patients diagnosed with pulmonary thromboembolism followed in different clinical settings

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ABSTRACT

Aims: This study aims to analyze the risk factors contributing to the development of pulmonary thromboembolism (PTE) from a multidisciplinary perspective, focusing on clinical, demographic, and laboratory variables that may influence venous thrombosis pathogenesis. By elucidating the interrelationships among these factors, the study seeks to support preventive strategies and provide a scientific basis for diagnostic and management processes.

Methods: This study was conducted through a systematic evaluation of the diagnostic data—including clinical, laboratory, and imaging findings—of individuals aged 18 to 80 years who were followed for PTE between 2023 and 2025 at the Chest Diseases, Cardiovascular Surgery, and Internal Medicine Departments of Yozgat Bozok University Research and Training Hospital. Patients with uncertain diagnoses, individuals under 18 years of age, and those who received only prophylactic treatment were excluded. Imaging data (thoracic CT angiography (CTA), scintigraphy, abdominal CT, and venous Doppler ultrasound) were analyzed based on prior reports without performing any additional procedures. Clinical variables such as smoking status, comorbid conditions, surgical history, immobility, and hormonal factors in female patients, along with laboratory parameters including complete blood count, biochemistry, blood gas analysis, and D-dimer levels, were reviewed retrospectively.

Results: A total of 41 patients (25 female, 16 male) diagnosed with PTE were evaluated. The mean age of participants was 61.59±17.92 years. The average age was 62.56±17.93 years in women and 60.06±18.40 years in men. Among 11 patients with available data on body mass index (BMI), the mean BMI was 29.97±3.05. Of these, 5 were overweight, 5 had class 1 obesity, and 1 had class 2 obesity. The most common comorbidities included hypertension (n=24), diabetes mellitus (n=10), coronary artery disease (n=7), and hyperlipidemia (n=4). Among the 4 smokers, the average consumption was calculated as 21 pack-years. Surgical history was present in 17.1% of cases, and a history of immobilization was identified in 14.6%. Malignancy was observed in 2.4%, history of pregnancy in 4.9%, and oral contraceptive use in 2.4% of the patients. Genetic mutations related to hereditary thrombophilia were found in 19.5% of patients. Laboratory analyses revealed a mean hemoglobin (Hb) level of 13.25±2.12 g/dl, significantly lower than the reference range ($p=0.0225$). Blood urea nitrogen (BUN) was elevated, with a mean level of 27.16±10.43 mg/dl ($p=0.0004$). Arterial blood gas analysis showed a mean sO_2 of 74.92±12.35%, pO_2 of 52.21±10.87 mmHg, and pCO_2 of 30.26±6.14 mmHg, all significantly below normal reference values ($p<0.0001$). The mean D-dimer level was 3.31±2.36 µg/ml ($p<0.001$). According to CTA, bilateral embolism was observed in 15 patients, segmental/lobar embolism in 14, and multiple emboli in 12. Deep vein thrombosis (DVT) was detected in 4 patients via Doppler ultrasound, while 21 patients showed no evidence of DVT.

Conclusion: This study underscores the multifactorial etiopathogenesis of PTE and emphasizes the importance of a personalized and holistic evaluation approach in diagnosis and treatment. Risk factors such as age, obesity, comorbidities, surgical history, immobility, and genetic predisposition were shown to be significant contributors to PTE development. Low Hb levels and marked hypoxemia-hypocapnia reflected the systemic impact of the condition, while elevated D-dimer levels and CTA findings played a crucial role in early diagnosis. The findings highlight that integrating clinical, laboratory, and radiological data within a multidisciplinary framework can enhance risk stratification and improve patient outcomes.

Keywords: Pulmonary thromboembolism, venous thromboembolism, risk factors

INTRODUCTION

Pulmonary thromboembolism (PTE) represents one of the most serious and potentially fatal complications of venous thromboembolism (VTE). It is an acute-onset clinical condition that can pose an immediate threat to life. Often developing as a complication of deep vein thrombosis (DVT), PTE typically results from thrombi that form in the deep veins of the lower extremities and subsequently dislodge, obstructing the pulmonary arteries. This cascade disrupts pulmonary perfusion, imposes pressure overload on the right ventricle, induces hypoxemia, and—if left untreated—can lead to sudden death.[1,2]

According to the 2019 guidelines of the European Society of Cardiology, the annual incidence of PTE ranges from 39 to 115 per 100.000 individuals, varying significantly depending on demographic factors, healthcare infrastructure, and diagnostic/screening strategies across countries.[2] U.S.-based data report approximately 900.000 VTE events annually, of which an estimated 100.000 result in death.[10] PTE that develops during hospitalization is particularly significant, representing a leading cause of nosocomial morbidity and mortality.[3,4]

The pathophysiology of PTE is grounded in the interaction of three principal mechanisms known as Virchow's triad: venous stasis, endothelial injury, and hypercoagulability. One or more of these factors can substantially increase the risk of thrombosis in an individual.[12]

Major orthopedic procedures—such as hip and knee replacements—as well as abdominal and pelvic surgeries, elevate the risk of PTE five- to tenfold due to both direct vascular trauma and postoperative immobility.[3] Similarly, prolonged immobilization after trauma and restricted mobility due to neurological conditions increase thrombotic risk by promoting venous immobility.[3]

Cancer is a prominent predisposing factor for VTE, both through its intrinsic biological mechanisms and via treatment modalities such as chemotherapy. Cancer patients face a four- to sevenfold higher risk of developing VTE compared to the general population, with this risk influenced by tumor type and treatment regimen.[5]

Pregnancy and the postpartum period are physiologically prothrombotic due to hormonal shifts, increased coagulation potential, and mechanical limitations on venous return. The incidence of VTE is estimated to rise approximately fivefold during this time.[6]

Obesity contributes to thrombotic risk through both mechanical and inflammatory pathways. Increased intra-abdominal pressure impairs venous return, while chronic low-grade systemic inflammation and elevated procoagulant factors in obese individuals create a prothrombotic milieu.[7,9]

Hereditary thrombophilias—including Factor V Leiden mutation, Prothrombin G20210A mutation, protein C and S deficiencies, and antithrombin III deficiency—are associated with a markedly increased risk of VTE.[8,13,14] These genetic predispositions, when combined with environmental risk factors, can synergistically amplify the likelihood of thrombotic events.[15,16]

Cigarette smoking contributes to a prothrombotic state through endothelial dysfunction, systemic inflammation, and platelet activation. This effect is particularly concerning when combined with estrogen-containing oral contraceptives (OCP), where the thrombotic risk is further compounded in a synergistic manner.[9]

In light of this evidence, identifying and characterizing the risk factors that contribute to the development of PTE—and evaluating them through a multidisciplinary lens tailored to individual patients—are essential for both early diagnosis and the development of targeted preventive strategies. The aim of this study is to retrospectively analyze the facilitating factors that increase venous thrombotic risk in patients diagnosed with PTE across various clinical settings, thereby contributing to a region-specific risk profile based on national data.

METHODS

Ethics

The study protocol was reviewed and approved by the Non-interventional Clinical Researches Ethics Committee of Yozgat Bozok University (Date: 02.07.2025, Decision No: 2025-GOKAEK-2513_2025.07.02_530). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, informed consent from the participants was not required. All data were anonymized in accordance with the Personal Data Protection Law No. 6698, and no interventions or additional medical procedures were performed on any patient within the scope of the study.

Study Design and Participants

This retrospective study was conducted by reviewing the clinical data of patients who were followed with a diagnosis of PTE between January 1, 2023, and January 1, 2025, in the Departments of Chest Diseases, Cardiovascular Surgery, and Internal Medicine at Yozgat Bozok University Research and Training Hospital. Patients aged between 18 and 80 years with a confirmed diagnosis of PTE were included. Cases with an uncertain diagnosis, individuals under 18 years of age, and those who had received only prophylactic treatment were excluded from the analysis. The study did not involve a comparative control group.

Imaging Evaluation

All radiological examinations performed during the diagnostic process were retrospectively assessed through archived records. These included thoracic computed tomographic angiography (CTA), scintigraphy, abdominal computed tomography (CT), and venous Doppler ultrasonography (USG), which are standard imaging modalities used in diagnosing pulmonary embolism. The imaging data were obtained exclusively from pre-existing patient reports in medical records; no new imaging procedures were conducted specifically for the study.

Clinical and Demographic Data

In addition to demographic variables such as age, sex, and body-mass index (BMI), information on clinical risk factors was collected, including smoking status, comorbid conditions (e.g., hypertension, diabetes mellitus, malignancy), history of surgery, immobilization, and—for female patients—pregnancy and OCP use. Laboratory parameters, including complete blood count, biochemical analysis, arterial blood gas parameters (pH, pO_2, pCO_2, sO_2), and D-dimer levels, were also retrieved from archival records. All data were gathered retrospectively through hospital files and the hospital information management system.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean±standard deviation (SD), while categorical variables were expressed as frequencies and percentages (%). The Kolmogorov-Smirnov test was used to assess the normality of variable distribution. For comparisons between normally distributed groups, the Independent samples t-test was used; the Mann-Whitney U test was applied for non-normally distributed variables. Categorical data were analyzed using the Chi-square test. Correlation between chronic obstructive pulmonary disease (COPD), ascending aorta diameter, and cardiometabolic risk factors was evaluated using parametric (Pearson) or non-parametric (Spearman) correlation tests, as appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 41 patients diagnosed with PTE between 2023 and 2025 were included in the study. Of these, 25 were female and 16 were male. The mean age of the entire cohort was calculated as 61.59±17.92 years. When stratified by gender, the mean age of female patients was 62.56±17.93 years, while that of male patients was 60.06±18.40 years. These findings indicate that the study population encompassed a wide age range, and the mean ages of female and male patients were relatively comparable.

BMI data were available for only 11 patients. The mean BMI among these individuals was 29.97±3.05. According to the classification of obesity, 5 patients were overweight, 5 were categorized as having class 1 obesity, and 1 patient had class 2 obesity. No patients in the study group were underweight, of normal weight, or classified as having class 3 obesity.

A substantial proportion of the patient population had one or more chronic comorbidities. The most commonly observed comorbidity was hypertension, identified in 58.5% (n=24) of patients, followed by diabetes mellitus in 24.4% (n=10), coronary artery disease in 17.1% (n=7), and hyperlipidemia in 9.8% (n=4). In 21.9% of patients (n=9), no accompanying chronic disease was documented. Among the combinations of comorbidities, the coexistence of hypertension and diabetes mellitus was most prominent, occurring in 22% (n=9) of patients.

Analysis of smoking status revealed that 4 patients were active smokers—2 women and 2 men. The average smoking exposure among these individuals was 21 pack-years.

A history of surgical intervention was present in 17.1% (n=7) of patients, all of whom were female. Surgical procedures varied and included hysterectomy, thyroidectomy, tibial fracture repair, spinal surgery, hip arthroplasty, myomectomy, great saphenous vein (GSV) radiofrequency ablation, and coronary artery bypass grafting. Additionally, 14.6% (n=6) of patients had a history of prolonged immobility, predominantly among female patients (12.2%, n=5), with only one male case (2.4%). The remaining 85.4% (n=35) of the cohort had no reported history of immobilization.

Only one patient (2.4%) had a history of malignancy, specifically colon cancer. No other cases of active cancer were recorded. Among female patients, 4.9% (n=2) had a history of pregnancy, and 2.4% (n=1) had a recorded history of OCP use.

Hereditary thrombophilia was identified in 19.5% (n=8) of patients. The majority of these individuals were women, with only one male patient affected. The most common genetic abnormality was protein C resistance, found in 4.9% (n=2) of cases. Other inherited thrombophilic conditions—each observed in one patient (2.4%)—included Factor V Leiden mutation, heterozygous prothrombin gene mutation, various forms of MTHFR gene mutations, PAI-2 gene mutation with homozygous MTHFR mutation, and F13 homozygous mutation with MTHFR C and A variants.

Evaluation of basic laboratory parameters revealed that the mean hemoglobin (Hb) level was 13.25±1.83 g/dl. The mean platelet count (PLT) was 269.12±81.70x10^3/µL, AST level was 22.69±11.90 U/L, and ALT level was 30.15±35.68 U/L. Among renal function tests, the mean blood urea nitrogen (BUN) level was 27.16±18.18 mg/dl, while serum creatinine—available for a subset of patients—was calculated at 1.00±0.45 mg/dl.

When these laboratory findings were compared with standard reference ranges for the general adult population, several statistically significant differences were noted. The mean Hb level in patients with PTE was 13.25 g/dl, below the reference average of 14.0 g/dl, and this reduction was statistically significant (p=0.0225). Similarly, the BUN level was significantly elevated at 27.16 mg/dl compared to the reference average of 15.0 mg/dl (p=0.0004). Differences in platelet count, AST, ALT, and creatinine levels, however, were not statistically significant (p>0.05) (**Table 1**).

Table 1. Mean and standard deviation values of basic laboratory parameters in the patient group diagnosed with pulmonary thromboembolism (PTE)

Parameter (unit)	PTE mean	Reference mean	Difference	p-value
Hb (g/dl)	13.25	14.0	-0.75	0.0225
PLT (x10^3/µL)	269.12	250.0	19.12	0.1817
AST (U/L)	22.69	20.0	2.69	0.1958
ALT (U/L)	30.15	25.0	5.15	0.4058
BUN (mg/dl)	27.16	15.0	12.16	0.0004
sCr (mg/dl)	1.0	0.9	0.1	0.2287

Hb: Hemoglobin, PLT: Platelets, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, sCr: Serum creatinine

When the arterial blood gas parameters of patients diagnosed with PTE were compared with general clinical reference averages, several noteworthy findings emerged. The mean pH

value was 7.40, which was identical to the standard reference value (7.40), and no statistically significant difference was observed (p>0.05). However, the mean oxygen saturation (sO_2) in the PTE group was calculated as 74.92±16.27%, which is markedly below the reference average of 95%. This difference was found to be statistically significant (p<0.0001). Similarly, the mean partial oxygen pressure (pO_2) in PTE patients was 52.21 mmHg, significantly lower than the reference value of 75 mmHg (p<0.0001). The mean partial carbon dioxide pressure (pCO_2) was measured at 30.26 mmHg, which was also significantly lower than the reference value of 40 mmHg (p<0.0001) (**Table 2**).

Table 2. Mean values, differences, and p-values obtained by comparing arterial blood gas parameters of patients diagnosed with pulmonary thromboembolism (PTE) with clinically accepted reference averages

Parameter (unit)	PTE mean	Reference mean	Difference	p-value
pH	7.42	7.40	0.02	0.2558
pO_2 (mmHg)	46.52	75.0	-28.48	0.0000
pCO_2 (mmHg)	36.14	40.0	-3.86	0.0456
sO_2 (%)	71.56	95.0	-23.44	0.0000

pH: Acid-base balance of arterial blood, pO_2: Partial Pressure of oxygen, pCO_2: Partial pressure of carbon dioxide, sO_2: Oxygen saturation

In the study, D-dimer levels were found to have a mean value of 3.31±2.36 µg/ml. This level is markedly elevated when compared to the generally accepted upper reference limit of 0.5 µg/ml.

A one-sample t-test revealed a p-value of 0.00000947, indicating statistical significance at the p<0.001 level. This finding demonstrates that the D-dimer levels of the patients included in the study were significantly higher than the reference value.

When the pulmonary CT angiography (CTA) reports of the patients were reviewed, the most frequently observed radiological finding was bilateral pulmonary artery involvement. A total of 15 patients showed widespread evidence of PTE in both lungs, suggesting a more diffuse disease distribution.

Additionally, in 14 patients, PTE was localized to the lobar or segmental level, indicating a more limited pattern of involvement. In the remaining 12 patients, multiple thrombus foci were noted at various anatomical levels, as described in their CTA reports.

Analysis of the Doppler USG findings for all 41 patients revealed that 51.2% (n=21) had reports stating "no evidence of DVT." Positive findings indicating the presence of DVT were reported in 9.8% (n=4) of patients. The remaining 39.0% (n=16) had no available Doppler USG data on record.

DISCUSSION

The findings obtained from the evaluation of 41 patients diagnosed with PTE in this study, when compared with existing literature, suggest that several risk factors play a significant role in the development of PTE. The mean age of the study group was 61.59±17.92 years, with a higher proportion of female patients. This aligns closely with the large-scale study conducted by Konstantinides and colleagues,[2] as presented in the 2019 ESC Guidelines, which reported that PTE is more commonly seen in older adults and women.[1,2,10] Similarly, Chen and colleagues[36] provided a detailed evaluation of the impact of age and sex differences on the incidence and mortality of pulmonary embolism.

Among patients with available BMI data, the average BMI was 29.97, with most individuals classified as overweight or obese. Obesity has previously been identified by Stein and colleagues[7] as an independent risk factor for VTE. In their study, obesity was shown to promote changes in the coagulation cascade and reduce venous return, thereby facilitating thrombus formation.[7,9] In addition, Pastori and colleagues[34] reported that obesity, when combined with coagulation abnormalities, further increases the risk of thrombosis.

In terms of comorbidities, hypertension was the most common, followed by diabetes mellitus, coronary artery disease, and hyperlipidemia. Notably, the coexistence of hypertension and diabetes may contribute to endothelial dysfunction and create a prothrombotic environment. This interaction has also been highlighted in the studies by Cushman[11] and Anderson,[12] which emphasize the role of such comorbidities in the pathogenesis of VTE.[4,11,12]

Although the proportion of patients who smoked was low, the reported intensity of smoking was considerable. This finding parallels that of Pomp et al.,[9] who established a correlation between cigarette smoking and hypercoagulability. Moreover, the thrombotic risk may be further heightened when smoking is combined with hormonal factors.[9,14]

It is noteworthy that all patients with a history of surgical intervention were female. This may reflect the higher frequency of gynecological surgeries in women, as well as postoperative immobility contributing to increased PTE risk. Geerts and colleagues[3] have also emphasized surgery as a major risk factor for VTE development in their studies on postoperative thrombosis.[3,24] Hayssen and colleagues[35] also demonstrated that surgical patients are predominantly classified within high-risk categories according to Caprini score–derived risk stratification.

The predominance of women among patients with a history of immobilization may be attributable to factors such as osteoporotic fractures and prolonged postoperative recovery, particularly in elderly women. Clinical models developed by Spyropoulos[4] and Anderson[12] have also confirmed immobilization as an independent risk factor for VTE.

Although malignancy was identified in only one patient, this finding is consistent with the observations of Khorana et al.,[5] who demonstrated the thrombogenic impact of malignancies, particularly in the context of chemotherapy. Colorectal cancers, in particular, are frequently reported in the literature as having prothrombotic properties.[5,33]

The data related to pregnancy and OCP use support the understanding that both endogenous and exogenous estrogen can increase thrombotic risk through their effects on the coagulation system. Researchers such as Heit,[6] James,[26] and

Kalaitzopoulos[27] have explained this phenomenon in the context of increased venous stasis, changes in intravascular pressure, and hormonal fluctuations during pregnancy.[6,8,26,27]

Hereditary thrombophilic disorders were identified in a subset of patients. Conditions such as Factor V Leiden mutation, prothrombin gene mutation, and MTHFR polymorphisms are consistent with the findings of studies on inherited thrombophilia by Middeldorp,[13] Zöller,[16] and Franco.[15] These genetic factors are especially relevant in differential diagnosis, particularly in younger patients presenting with PTE.[13-16,28]

The laboratory findings of decreased Hb levels and elevated BUN suggest the systemic effects of PTE and the potential metabolic consequences of accompanying comorbidities. Similar observations were reported by Wada and colleagues[17] in their studies on post-traumatic hemostatic disorders, indicating that such hematological alterations may carry clinical significance.[17,20]

Arterial blood gas analyses in this study demonstrated the presence of hypoxemia (decreased sO_2 and pO_2) and hypocapnia (reduced pCO_2) in patients diagnosed with PTE. These findings are consistent with the pathophysiological mechanisms described by Carson[29] and Jaff,[31] who noted that acute PTE often leads to ventilation-perfusion mismatch, impairing oxygenation and triggering hyperventilation that results in excessive carbon dioxide elimination.[1,29,31] Moreover, Hasegawa and colleagues[37] reported that pulmonary embolism complicating sepsis and septic shock was associated with severe hypoxemia and increased mortality.

D-dimer levels in our study were substantially above the commonly accepted upper reference limit. In line with findings from the ADJUST-PE trial by Righini et al.[18] and Wells' study[19] on the role of D-dimer in DVT diagnosis, this biomarker is noted to have high sensitivity but limited specificity. In our cohort, D-dimer levels were significantly elevated, supporting its value as a diagnostic marker.[18,19,32]

CTA findings in this study illustrated the broad clinical spectrum of PTE, ranging from diffuse bilateral involvement to isolated segmental lesions. These findings are consistent with the work of Stein et al.,[23] who examined the diagnostic utility of multidetector CT in acute PTE. Imaging results obtained via CT have been shown to directly influence clinical decision-making.[22,30,33]

The relatively low number of patients with confirmed DVT on Doppler USG suggests that PTE can occasionally develop without obvious thrombotic events in the lower extremities. Nonetheless, as emphasized in the clinical guidelines by Ortel[21] and Barbar,[24] the presence of DVT increases clinical suspicion and serves as a valuable clue in establishing a diagnosis of PTE.[19,21,31]

Collectively, these findings reaffirm the critical importance of personalized evaluation strategies, interdisciplinary collaboration, and detailed risk factor assessment in improving clinical outcomes in the diagnosis and management of PTE.

Limitations

Nevertheless, the limited number of patients can be considered an inherent limitation of the study; conducting similar analyses in larger cohorts would enhance the generalizability of the findings and further increase the value of the results.

CONCLUSION

This study highlights the multifactorial nature of PTE, reflecting a complex clinical picture shaped by the interplay of individual and environmental risk factors. Advanced age, comorbidities, obesity, immobilization, history of surgery, hormonal factors, and genetic predisposition were identified as key contributors to thrombosis development.

Laboratory and imaging findings—particularly elevated D-dimer levels, hypoxemia, and widespread emboli on CT—emerged as strong diagnostic biomarkers. These results underscore the critical importance of early diagnosis and timely initiation of anticoagulant therapy in reducing mortality.

As a result, a multidisciplinary and personalized approach is essential in the management of PTE. Clinical decisions should not rely solely on laboratory results, but rather incorporate the patient's comprehensive medical history, comorbid conditions, and individual risk profile. This holistic strategy is a fundamental principle that directly influences both treatment success and patient quality of life.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was reviewed and approved by the Non-interventional Clinical Researches Ethics Committee of Yozgat Bozok University (Date: 02.07.2025, Decision No: 2025-GOKAEK-2513_2025.07.02_530).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Beyond glycemic control: SGLT2 inhibitors as foundational therapy in heart failure

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ABSTRACT

Heart failure affects over 64 million people worldwide and remains a leading cause of hospitalization, death, and health care costs. Despite advances with renin angiotensin aldosterone system inhibitors, beta blockers, and mineralocorticoid receptor antagonists, survival gains remain modest, and outcomes in preserved ejection fraction disease have historically been poor. This review examines how sodium glucose cotransporter 2 inhibitors, initially developed as glucose lowering agents, have redefined heart failure therapy. We synthesize mechanistic insights, pivotal trial data, and evolving guidelines to clarify their role as foundational treatment across the ejection fraction spectrum. Evidence was drawn from cardiovascular outcome studies, dedicated heart failure trials, mechanistic investigations, and international guidelines, with focus on physiologic mechanisms, efficacy, and safety. Sodium glucose cotransporter 2 inhibitors provide benefits that extend beyond glucose control. They promote sustained diuresis, improve myocardial energetics, reduce inflammation and fibrosis, and protect renal function. Landmark trials including DAPA HF, EMPEROR reduced, EMPEROR preserved, and DELIVER consistently reduced hospitalizations and cardiovascular death across reduced, mildly reduced, and preserved ejection fraction populations, regardless of diabetes status. Benefits emerge early, improve quality of life, and are supported by a favorable safety profile. These findings have rapidly reshaped international guidelines, positioning these drugs alongside renin angiotensin system inhibitors, beta blockers, and mineralocorticoid receptor antagonists as pillars of therapy.

Keywords: SGLT2 inhibitor, heart failure, mortality

INTRODUCTION

Heart failure (HF) affects more than 64 million people worldwide and remains a major driver of morbidity, mortality, and health care expenditures.[1-3] Despite decades of therapeutic innovation, ranging from renin–angiotensin–aldosterone system (RAAS) inhibition to β-blockade and mineralocorticoid receptor antagonism (MRA), survival gains have been modest, and hospitalization rates remain unacceptably high. The burden is particularly stark in heart failure with preserved ejection fraction (HFpEF), where traditional therapies have largely failed to improve outcomes.[3]

The epidemiologic backdrop underscores why emergent therapies are so urgently needed. HF is not only a disease of aging populations in high-income countries but a growing global challenge, affecting younger patients in low and middle income regions as well. The condition accounts for frequent hospital readmissions, reduced quality of life, and escalating healthcare costs.[2]

Against this backdrop, the discovery that sodium-glucose cotransporter-2 (SGLT2) inhibitors originally conceived as glucose-lowering agents for type 2 diabetes mellitus (T2DM) could dramatically reduce HF hospitalizations was nothing short of transformative.[4,5] What began as secondary findings in large cardiovascular outcomes trials (CVOTs) soon spurred dedicated investigations in HF populations, regardless of diabetes status. The arc from incidental observation to guideline-defining therapy has redefined the landscape of HF management. The aim of this mini review is to synthesize current mechanistic insights, pivotal clinical trial evidence, and evolving guideline recommendations to define the role of SGLT2 inhibitors as foundational therapy across the spectrum of HF.

MECHANISMS OF ACTION

The cardioprotective effects of SGLT2 inhibitors extend well beyond their modest glucose lowering properties. Their primary action blocking sodium and glucose reabsorption in the proximal renal tubule results in osmotic diuresis and natriuresis[6,7] (**Figure**). This dual effect reduces intravascular volume and blood pressure, thereby alleviating preload and afterload, two major drivers of HF progression. Unlike traditional loop diuretics, however, the volume reduction

induced by SGLT2 inhibitors is gentle, sustained, and not associated with neurohormonal activation, making them particularly attractive in the chronic HF setting.

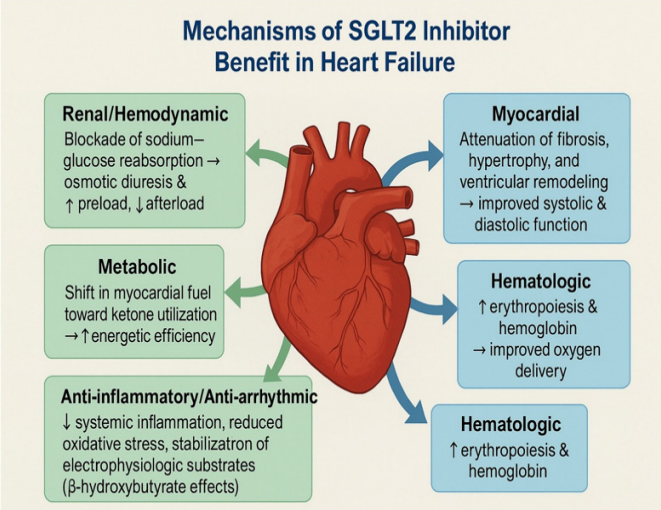

Figure. Mechanisms of SGLT2 inhibitor benefit in heart failure

Beyond volume management, SGLT2 inhibition reshapes cardiac metabolism. The failing myocardium is metabolically inflexible, often unable to efficiently utilize glucose or free fatty acids. By promoting mild ketosis, these agents shift myocardial substrate preference toward ketone bodies, which provide a more energy-efficient fuel for the stressed heart.[7] This "metabolic reprogramming" improves myocardial work efficiency and may explain the rapid symptomatic gains observed in clinical trials.

The pleiotropic effects extend to structural remodeling. Experimental studies suggest that SGLT2 inhibitors attenuate myocardial fibrosis, reduce oxidative stress, and downregulate pro-inflammatory cytokines. β-hydroxybutyrate, a ketone body elevated under SGLT2 inhibition, exerts direct anti-inflammatory and anti-arrhythmic effects, potentially reducing sudden cardiac death risk.[8]

Systemically, SGLT2 inhibitors enhance oxygen delivery by stimulating erythropoietin production, increasing hematocrit and hemoglobin levels.[9,10] This effect may mitigate anemia, a common comorbidity in HF, and further improve functional capacity. Renally, they lower intraglomerular pressure and prevent hyperfiltration, thus protecting against chronic kidney disease (CKD), a frequent companion of HF and an amplifier of poor prognosis.

Collectively, these multidimensional mechanisms establish SGLT2 inhibitors as comprehensive organ-protective therapies, simultaneously modulating hemodynamic, metabolic, renal, and hematologic pathways.

EVIDENCE IN HEART FAILURE WITH REDUCED EJECTION FRACTION (HFrEF)

The paradigm-shifting DAPA-HF trial, published in 2019, enrolled patients with symptomatic HFrEF (LVEF ≤40%), with and without diabetes, and showed that dapagliflozin reduced the composite of worsening HF or cardiovascular death by 26%.[11] Importantly, the benefit emerged early within weeks of initiation, underscoring a direct and rapid disease modifying effect. Subgroup analyses confirmed efficacy across diabetic and non-diabetic populations, cementing the notion that cardioprotection is independent of glycemic control.

The EMPEROR-Reduced trial extended these observations with empagliflozin, demonstrating reductions not only in HF hospitalizations but also in the rate of decline in renal function.[12] This renal protection is particularly relevant since CKD is both highly prevalent in HFrEF and a major driver of adverse outcomes.

Meta-analysis of DAPA-HF and EMPEROR-Reduced confirmed consistent reductions in cardiovascular mortality and HF hospitalizations.[13] The pooled data reinforce the robustness of benefit and highlight class effects rather than drug-specific actions.

Beyond hard clinical endpoints, trials also documented meaningful improvements in patient-centered outcomes. DEFINE-HF demonstrated improvements in health status and quality of life measures, reflecting symptomatic relief that translates into tangible patient benefit.[14] EMPA-TROPISM, a mechanistic study in non-diabetic HFrEF patients, provided structural evidence: empagliflozin induced reverse left ventricular remodeling, reduced volumes, and improved systolic function, thereby offering imaging correlates of clinical benefit.[8]

The cumulative evidence has firmly established SGLT2 inhibitors as one of the four foundational therapies for HFrEF, alongside ARNIs, β-blockers, and MRAs. Their inclusion represents not just an incremental advance but a leap forward in the comprehensive management of systolic HF.

EVIDENCE IN HF WITH PRESERVED AND MILDLY REDUCED EF (HFpEF, HFmrEF)

HFpEF has long been considered a therapeutic void, with numerous trials of RAAS inhibition, ARBs, and ARNIs failing to produce consistent outcome improvements. SGLT2 inhibitors have changed this narrative.

The EMPEROR-preserved trial demonstrated that empagliflozin significantly reduced the composite of cardiovascular death or HF hospitalization in patients with LVEF >40%, a Landmark achievement given decades of trial failures in this domain.[15] Importantly, the benefits were consistent across prespecified subgroups, including those without diabetes.

DELIVER, evaluating dapagliflozin in a similar population, not only confirmed reductions in HF hospitalizations but also demonstrated benefit in patients with mildly reduced EF (HFmrEF, LVEF 41–49%).[16] Together, EMPEROR-Preserved and DELIVER established that SGLT2 inhibitors deliver consistent clinical benefit across the entire EF spectrum.

Symptom-oriented trials such as DEFINE-Preserved and PRESERVED-HF further reinforced their role, showing improvements in patient-reported outcomes including quality of life and symptom burden.[17,18] While EMPERIAL-Preserved failed to demonstrate significant gains in six-minute walk distance, this likely reflects the heterogeneity

of HFpEF, where symptom improvement does not always translate to measurable functional capacity.[19]

A meta-analysis synthesizing these findings by Jaiswal et al.[20] confirmed that SGLT2 inhibitors reduce HF hospitalizations across HFpEF and HFmrEF, cementing them as the first truly effective pharmacologic class in this setting. The implication is profound as HFpEF is no longer a therapeutic void, but a condition with an evidence-based treatment option (**Table**).

GUIDELINE PERSPECTIVES

The rapid accumulation of evidence has translated into equally rapid changes in guideline recommendations. The 2021 European Society of Cardiology (ESC) guidelines awarded SGLT2 inhibitors a class I recommendation for HFrEF, but at the time refrained from extending this to HFpEF or HFmrEF given the lack of trial data.[21]

Just a year later, the 2022 AHA/ACC/HFSA guidelines incorporated results from EMPEROR-preserved and DELIVER, providing SGLT2 inhibitors with a class IIa recommendation for both HFmrEF and HFpEF.[22] This shift underscores how quickly clinical practice has been reshaped.

In 2024, the ACC Expert consensus placed further emphasis on the early initiation of SGLT2 inhibitors in HFrEF, advocating for rapid sequencing of all four pillars of therapy, informed by data from the STRONG-HF trial.[23,24] This reflects a broader cultural change in HF management: moving away from sequential uptitration toward aggressive, early, multidrug initiation to maximize survival gains.

SAFETY AND SPECIAL POPULATIONS

The tolerability of SGLT2 inhibitors has been key to their widespread uptake. Adverse events are generally mild and manageable. Genital mycotic infections are the most common but rarely necessitate discontinuation.[25] Volume-related effects, such as dizziness or hypotension, can occur but are usually mild.

Concerns about euglycemic diabetic ketoacidosis are limited to a small subset of insulin-dependent patients, where education and monitoring mitigate risk.[26] The CANVAS program's signal of increased amputations and fractures with canagliflozin has not been observed consistently across other agents.[5]

Importantly, renal function should not preclude use. Although SGLT2 inhibitors cause an early, modest dip in estimated glomerular filtration rate (eGFR), long-term effects are renoprotective. Clinical trials support their use down to eGFR thresholds of 20–25 mL/min/1.73 m^2. Elderly and frail populations, often underrepresented in clinical research, have not demonstrated excess harm, supporting generalizability.[27]

This safety profile allows SGLT2 inhibitors to be applied broadly across diverse HF populations, including those with advanced CKD, frailty, and polypharmacy.

LIMITATIONS

Despite their transformative impact, several limitations of the current SGLT2 inhibitor evidence base must be acknowledged. First, most pivotal trials were designed with composite endpoints driven largely by reductions in HF hospitalizations, while the effect on all-cause mortality remains more modest. Although meta-analyses suggest a survival benefit, longer-term follow-up is needed to fully establish their impact on mortality.[13,20]

Second, patients enrolled in Landmark trials may not fully represent the broader HF population. Individuals with advanced HF (NYHA IV), those requiring inotropes, and patients with severe renal impairment were often underrepresented or excluded. Similarly, frail elderly patients and those with multiple comorbidities—who constitute a substantial proportion of real-world HF—require further study.

Third, while safety signals have been generally reassuring, questions remain. The risk of euglycemic diabetic ketoacidosis, though rare, is clinically significant in insulin-treated patients.[26] Observations of amputation risk in CANVAS[5] have not been replicated, but residual uncertainty persists, particularly in populations with peripheral arterial disease.

Fourth, mechanistic explanations, though compelling, are still incompletely understood. The relative contributions of hemodynamic unloading, metabolic remodeling, renal

Table. Landmark clinical trials of SGLT2 inhibitors in heart failure

Trial	Population (n)	EF range	Key outcome	Main findings
DAPA-HF (2019)[11]	4744	HFrEF (≤40%), ±DM	CV death or HF hospitalization	↓ risk by 26%; benefit irrespective of diabetes
EMPEROR-reduced (2020)[12]	3730	HFrEF (≤40%), ±DM	CV death or HF hospitalization	↓ risk by 25%; slower eGFR decline
DEFINE-HF (2019)[14]	263	HFrEF (≤40%), ±DM	KCCQ health status	Improved symptoms/quality of life
EMPA-TROPISM (2021)[15]	84 (non-DM)	HFrEF (≤40%)	LV remodeling	Reverse remodeling, improved LVEF
EMPEROR-preserved (2021)[16]	5988	HFpEF (≥50%)±HFmrEF	CV death or HF hospitalization	↓ risk by 21%, driven by ↓ HF hospitalization
DELIVER (2022)[17]	6263	HFpEF (≥40%), HFmrEF	CV death or HF hospitalization	↓ risk consistent across EF spectrum
PRESERVED-HF (2021)[19]	324	HFpEF (≥45%)	KCCQ health status	Improved QoL and functional status
DEFINE-preserved (2021)[18]	289	HFpEF (≥45%)	NT-proBNP & KCCQ	Symptom and biomarker improvement
EMPERIAL-preserved (2020)[20]	315	HFpEF (≥45%)	6MWT distance	Neutral; no improvement in exercise capacity

CV: Cardiovascular, HF: Heart failure, HFrEF: HF with reduced EF, HFmrEF: HF with mildly reduced EF, HFpEF: HF with preserved EF, KCCQ: Kansas City Cardiomyopathy Questionnaire, LVEF: Left ventricular ejection fraction, EF: Ejection fraction, eGFR: Estimated glomerular filtration rate

protection, and hematologic effects remain debated. Translational studies are needed to clarify how these pathways interact and to identify biomarkers predictive of response.

Finally, implementation challenges cannot be ignored. Cost, access disparities, and therapeutic inertia may limit uptake. In many regions, access to newer HF therapies is constrained by socioeconomic and health system factors, threatening to widen existing disparities in care.[29]

Addressing these limitations through dedicated research, registry data, and health policy initiatives will be essential to realizing the full promise of SGLT2 inhibitors in HF.

FUTURE DIRECTIONS

The therapeutic frontier continues to expand. The EMMY trial suggested that early post-myocardial infarction initiation of SGLT2 inhibitors improves biomarkers of remodeling, raising the possibility that these drugs may prevent HF onset after acute coronary events.[28] Ongoing large trials such as EMPACT-MI and DAPA-MI will test whether these early signals translate into reductions in clinical HF or recurrent ischemic events.

Other areas of interest include advanced HF requiring device therapy or inotropes, where the safety and efficacy of SGLT2 inhibitors remain under investigation. Their potential to modulate anemia and improve outcomes in cardiorenal syndromes is also under study.[9]

Beyond disease treatment, prevention is a tantalizing prospect. Given their efficacy across diabetic and non-diabetic populations, SGLT2 inhibitors could be deployed in high-risk individuals to forestall the development of overt HF. Cost-effectiveness analyses suggest that reduced hospitalizations offset drug costs, making widespread adoption both clinically and economically viable.[30]

The next decade will likely see integration of SGLT2 inhibitors into broader preventive and precision medicine strategies, guided by biomarkers, imaging phenotypes, and individualized risk profiles.

CONCLUSION

Few drug classes in modern medicine have transformed clinical practice as swiftly as SGLT2 inhibitors. Originally conceived as glucose lowering agents through the simple mechanism of inducing glucosuria, they have rapidly emerged as a cornerstone of HF therapy. Today, they sit at the very center of HF management, consistently reducing hospitalizations, mortality, and symptom burden, while simultaneously safeguarding renal function and improving systemic physiology across the entire ejection fraction spectrum.

Their ascent is more than the sum of trial outcomes. It is a story of serendipity meeting translational science, brought to life by rigorous clinical validation. What began as a metabolic therapy has become a paradigm shifting discovery that redefines the boundaries of cardiometabolic care. The task ahead is no longer to prove efficacy but to ensure these benefits reach all patients equitably, overcoming barriers to access, adoption, and the exploration of new indications.

Together with ARNIs, beta blockers, and MRAs, SGLT2 inhibitors now anchor the modern foundation of HF therapy. Yet their trajectory is far from complete. With expanding applications across the spectrum of cardiovascular and metabolic disease, they are poised to stand among the most influential therapeutic breakthroughs of the twenty first century, an exemplar of how science can reshape lives when opportunity, innovation, and persistence converge.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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Unusual complication: successful transcatheter extraction of an embolized coronary stent during percutaneous coronary intervention

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ABSTRACT

Despite advances in coronary angiography, systemic or coronary embolization of the stent remains a potentially lethal complication, although rarely seen. Stent embolization frequently happens following percutaneous coronary intervention in tortuous and calcified segments, with an incidence probability of 0.29% to 0.32%. It is linked to troublesome problems including complete loss of flow, stent thrombosis, coronary artery damage during retrieval procedures, and stent embolization into the systemic circulation. This uncommon consequence might induce significant stress for operators throughout the process. Numerous techniques exist for the extraction of embolized material, with operator expertise and laboratory equipment being the primary determinants of the selected method. We reviewed the techniques used to extract the stent that became loosened in the primary coronary.

Keywords: Coronary complication, embolized coronary stent, percutaneous coronary intervention

INTRODUCTION

Despite advances in coronary angiography, systemic or coronary embolization of the stent remains a potentially lethal complication, although rarely seen.[1] Stent embolization frequently happens following percutaneous coronary intervention in tortuous and calcified segments, with an incidence probability of 0.29% to 0.32%. It is linked to troublesome problems including complete loss of flow, stent thrombosis, coronary artery damage during retrieval procedures, and stent embolization into the systemic circulation.[2] This uncommon consequence might induce significant stress for operators throughout the process. Numerous techniques exist for the extraction of embolised material, with operator expertise and laboratory equipment being the primary determinants of the selected method. We reviewed the techniques used to extract the stent that became loosened in the primary coronary artery during percutaneous coronary intervention.

CASE

An 82-year-old male patient arrived to our outpatient clinic with an exacerbation of chest discomfort. The patient has a history of hypertension and had coronary stenting three years earlier. The patient was evaluated and determined to have a history of percutaneous coronary intervention (PCI) in the right coronary artery (RCA) and circumflex artery (CX) at a different facility three years before. He had third-degree anginal symptoms, classified by the Canadian Society of Cardiology (CCS-3), over the last month. Electrocardiography indicated left ventricular hypertrophy. Transthoracic echocardiography demonstrated a left ventricular ejection fraction of 50%, moderate hypokinesia in the anterior and apical walls, and grade 2 mitral regurgitation. Diagnostic coronary angiography was performed.

After administering local anesthesia, a 6F sheath was inserted into the left radial artery. Coronary angiography utilizing left and right Judkins® catheters revealed calcific 95% restenosis distal to the left main coronary artery (LMCA), extending to the left anterior descending artery (LAD), 95% restenosis proximal to the LAD, and 97% restenosis distal to the stent, extending from the circumflex (CX) ostium to the mid obtuse marginalis (OM). Diffuse restenosis was seen inside the stent extending from the proximal RCA to the distal crux, with repeated stenoses of 50-60% recorded (**Figure 1**).

A percutaneous transluminal coronary intervention (PTCA) was planned for a fragile patient with a SYNTAX Score of 35, targeting the LMCA, LAD, and OM artery.

The ad-hoc PCI continued to operate inside the same session. The LAD and CX crossed over with a floppy wire by planning a provisional approach. Progressive predilatations have been performed on the proximal LAD lesion using a 2.75x15 mm

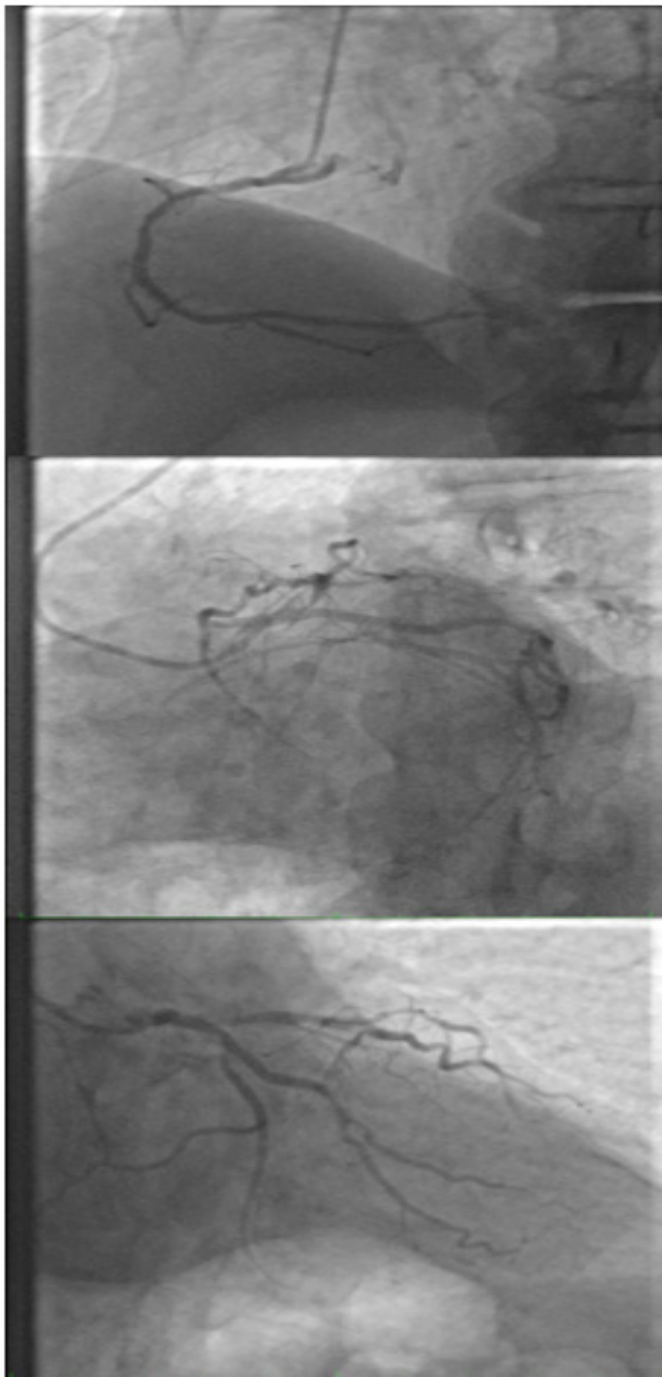

Figure 1. Coronary angiography

non-compliant (NC) balloon (CID® Fluydo, Alvimedica, Saluggia, Italy) and a 3mmx15mm scoring balloon (Wedge, Brosmed®, Guangdong, China). A 3mmx29mm drug-eluting stent (DES) (Firehawk, MicroPort® Shanghai,China), was implanted proximal to the LAD. A 3.5 mmx34 mm (Resolute, Onyx Trucor®, Medtronic, Minneapolis, MN, USA) DES was delivered into the LMCA-left anterior descending lesion, however the stent embolized inside the coronary artery by detaching from the balloon and extending from the LMCA into the aorta (**Figure 2**). The stent wire was secured while the stent balloon was removed. A 2 mmx15 mm semi-compliant balloon (Artimes, Brosmed®, Guangdong, China) was maneuvered across the wire to the distal segment of the stent. The balloon was inflated to a pressure of 4 atm at its distal end, and the embolized stent was extracted into the guiding catheter. A 2mmx15mm semi-compliant balloon (Artimes, Brosmed®, Guangdong, China) was inflated to a pressure of 10-12 atm inside the guiding catheter, after which the whole system was extracted from the coronary artery (**Figure 3**). The embolized stent was re-embolized proximal to the right radial artery during attempts to advance it into the right radial sheath under endoscopic guidance. A 1.5mmx15mm semi compliant (Artimes, Brosmed®, Guangdong, China) balloon (Artimes, Brosmed®, Guangdong, China) was attempted to be reinserted into the catheter through the stent wire, but it was not successful due to stent deformation. Afterwards, the stent was completely removed by manoeuvring with a micro snare (Amplatz, Medtronic®, Minneapolis, MN, USA) (**Figure 4**).

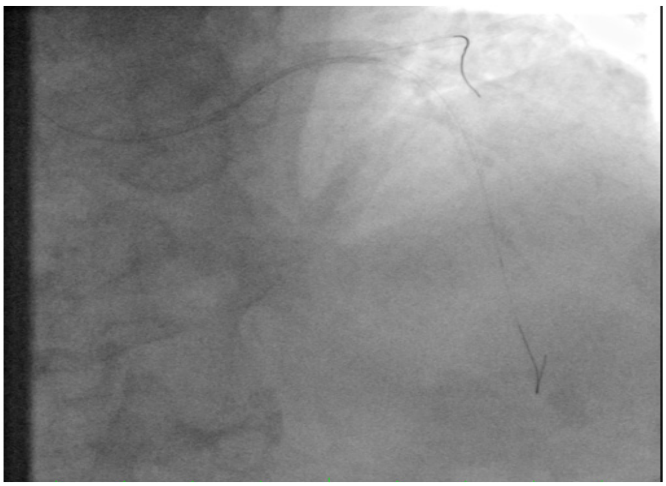

Figure 2. Angiographic visualization of a balloon-stripped embolized stent inside the coronary artery

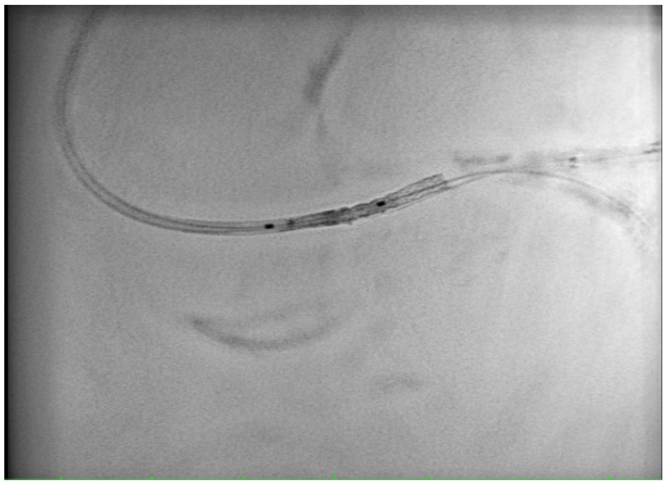

Figure 3. Extraction of the embolized stent into the catheter via a balloon

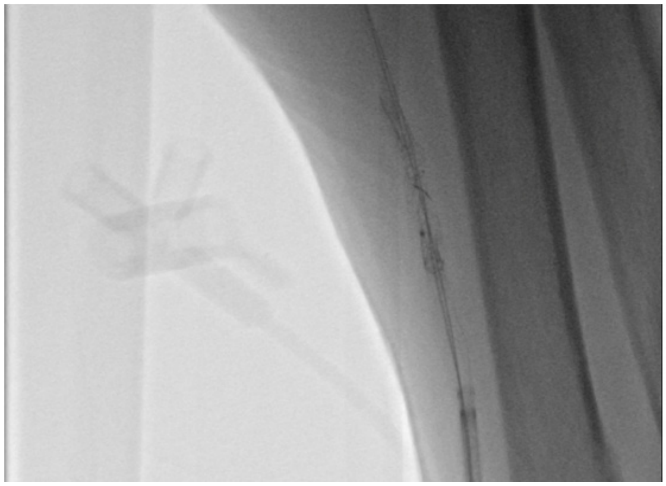

Figure 4. Extraction of the embolized stent from the sheath via a snare

Radial artery control imaging showed no complications (Removed stent material shown in **Figure 5**).

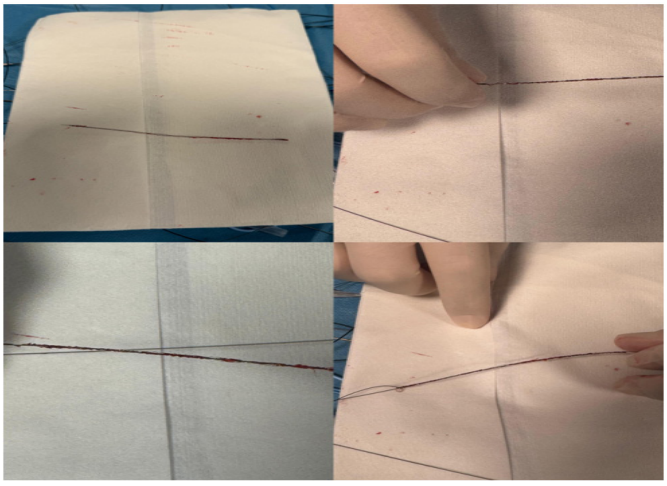

Figure 5. Removed stent material

Following to the puncture of the right femoral artery, the surgery proceeded via a 7F sheath inserted into the right femoral artery. The LMCA was cannulated with the assistance of a 7F EBU guiding catheter. Following the advancement of floppy wires to the LAD and CX, a 3.5mmx34mm (Resolute, Onyx Trucor®, Medtronic, Minneapolis, MN, USA) stent was deployed in the LMCA-LAD with the assistance of a guideliner (Terumo®, Minnesota, USA). Following proximal optimization (POT) with a 4mmx12mm NC (CID® Fluydo, Alvimedica, Saluggia, Italy) balloon, the CX was rewired. The strut at the Cx osteal was expanded using a 1.5mmx15mm semi-compliant balloon (Artimes, Brosmed®, Guangdong, China). 3.5 mmx15 mm NC (CID® Fluydo, Alvimedica, Saluggia, Italy) balloon were introduced to the LAD, and 3 mmx12 mm NC (CID® Fluydo, Alvimedica, Saluggia, Italy) balloon were introduced to the CX. Kissing dilatations were executed. Subsequently, a final POT was conducted using a 4.5mmx12mm NC (Fluydo, Alvimedica®, Saluggia, Italy) balloon, and the procedure was ended without complications.

Post-procedure, the patient was admitted to the coronary intensive care unit. Hydration initiated. On the third day of hospitalization, the patient, exhibiting excellent overall health, stable vital signs, no active cardiac complaints, and no abnormalities in routine assessments, was discharged with a medical treatment regimen.

DISCUSSION

Despite becoming less prevalent now due to advancements in the stent industry and increases in percutaneous coronary procedures, stent embolization remains particularly stressful for the operator and could result in lethal consequences for the patient.[3,4] To avoid this unfavorable situation, careful planning must occur before to the procedure, and the laboratory equipment should be carefully evaluated.

In cases of stent embolisation, a definitive protocol is lacking, consequently requiring the extraction of the embolised stent from the coronary circulation by multiple methods.

If the wire of the embolized stent remains maintained, the embolized material may be extracted via the catheter by inserting low-profile balloons over the wire and inflating them distal to the stent.[5]

Provided that the sizes of the embolized stent are suitable for the originating coronary artery and the wire within the stent remains intact, the stent may be positioned at the original site utilizing balloons of progressively increasing diameters, commencing with low-profile balloons and advancing to the appropriately sized balloon.

If the wire of the embolized stent is lost, the stent may be retrieved into the catheter using two wires that pass between the stent struts, advanced distally to the stent and creating a twisted wire configuration distally.

When these procedures fail, one approach is to grab the proximal end of the stent using a coronary snare and retrieve it into the catheter.[6]

One option involves compressing a balloon positioned on a wire next to the embolized stent and then deploying a stent in that region, however this approach is not widely favored.

CONCLUSION

The selection of approach is dependent upon the patient's clinic, the operator's expertise, and the laboratory's equipment. This case describes the sticking of a stent into a catheter using a distally inflated balloon and the subsequent removal of the stent from the radial area using a snare. Despite rotational atherectomy being a more suitable option in our case because of significant coronary calcification, we decided to scoring balloons due to their unavailability in our laboratory.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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Total anomalous pulmonary venous connection: mixed variation [2 (1/2)+1 (1/2)] type: bizarre pattern: a case report

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ABSTRACT

Among all variants of total anomalous pulmonary venous connection, mixed variety is a rare congenital anomaly. It comprises 3 different patterns including 2+2, 3+1, bizarre variations. These Bizarre variations are uncommon findings in mixed variety. In this particular case, we report surgical correction of such rare variation comprising [2 (1/2) cardiac+1 (1/2) supracardiac] type of pulmonary venous drainage. These variations impose the importance of preoperative delineation of heterogeneous venous drainage and subsequent planning for surgical repair.

Keywords: Mixed total anomalous pulmonary venous connection, total anomalous pulmonary venous connection, TAPVC

INTRODUCTION

The initial description of total anomalous pulmonary venous connection (TAPVC) was given by Wilson in 1798.[1] This particular cardiac malformation is characterized by absence of direct connection of any pulmonary vein to left atrium. Therefore, the presence of atrial septal defect (ASD) is essential with TAPVC for post natal survival.

In 1959, Darling and associates[2] classified TAPVC variants into 4 types based on pulmonary venous drainage:

- Supra cardiac (45-50%)
- Cardiac (25-30%)
- Infracardiac (25-20%)
- Mixed (5-10%)

Mixed variety though uncommon, demonstrates a wide spectrum of anatomical presentation. In 2007, Chowdhury and colleagues[3] have categorized this wide assortment of mixed TAPVC into three general groups based on heterogeneous of pulmonary venous drainage.

- 2+2 pattern,
- 3+1 pattern, and
- Bizarre pattern.

We hereby report, a rare case of mixed TAPVC with bizarre pattern, with [2 (1/2) cardiac+1 (1/2) supracardiac] pulmonary venous drainage type, being operated for total correction.

CASE

A 2-year-old male child presented with complaints of recurrent respiratory tract infections since 2 months of age. On examination, patient had minimal cyanosis with grade 2 clubbing, and ejection systolic murmur. His vitals were unremarkable. X-ray chest revealed cardiomegaly with pulmonary plethora. The echocardiography revealed pulmonary veins opening into coronary sinus and brachiocephalic vein via the vertical vein. For further delineation of the pulmonary vasculature CT cardiac angiography was performed, which depicted left superior pulmonary vein (LSPV) and a branch from left inferior pulmonary vein (LIPV) draining commonly into brachiocephalic vein via the vertical vein, whereas right superior pulmoner verin (RSPV) and right inferior pulmonary vein (RIPV) along with a branch from left inferior pulmonary vein were found to be draining into coronary sinus (CS) (**Figure 1**).

Surgical Procedure

Standard midline sternotomy was performed. Vertical vein was identified, well mobilized and looped. Pericardium was opened. After standard aortic bicaval cannulation, cardiopulmonary bypass (CPB) was commenced. Aorta was cross clamped and heart arrested using delnido cardioplegia and moderate hypothermia was attained. Right atriotomy was contemplated. Coronary sinus unroofing was performed. Right superior and right inferior pulmonary vein along with a branch from left inferior pulmonary vein was found

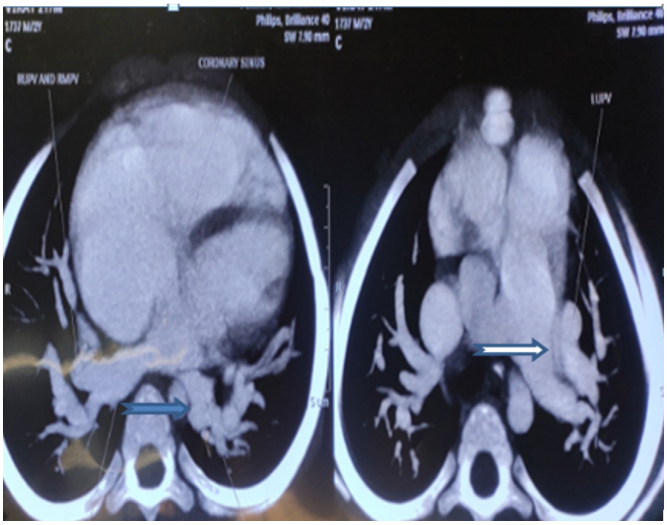

Figure 1. Computed tomography (CT) scan of the patient wherein, the blue arrow indicates drainage of left lower pulmonary venous drainage into cardiac chamber and vertical vein and white arrow indicates formation of vertical vein from left upper and branch of left lower pulmonary vein.

draining into coronary sinus through a common chamber underneath (**Figure 2**). Left vertical vein was divided just near to brachiocephalic vein and mobilized followed by rerouting of vertical vein was done to left atrial appendage. A pericardial patch closure of common chamber along unroofed coronary sinus directed to left atrium was done. Right atriotomy was closed. Patient was weaned off form CPB without any event. Total cardiopulmonary bypass time was 124 minutes and cross clamp time was 98 minutes. The patient was extubated after 8 hours postoperatively and maintained 100% saturation. The postoperative period was uneventful and the patient discharged on post-operative day 5th. Patient was being followed up for 12 months on regular intervals without any significant postoperative problems.

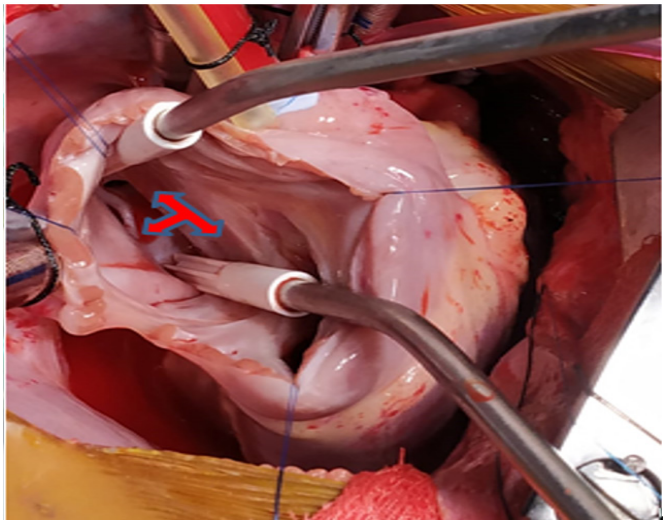

Figure 2. Surgical figure depicting the peculiar anatomy wherein, it indicates formation of vertical vein from left upper and branch of left lower pulmonary vein and the red arrow indicates opening of right upper and lower and branch of left lower pulmonary vein draining into coronary sinus through a chamber.

DISCUSSION

TAPVC is a rare congenital anomaly. Within the spectrum of TAPVC, mixed type variants comprise less than 5-10%.[2] Further as classified by Chowdhury et al.,[3] these mixed variants comprises of three different patterns including 3+1, 2+2 and bizarre with multiple variations of pulmonary venous drainage to heart. Preoperative diagnosis and anatomic delineation remains to be the mainstay for planning surgical treatment of such patients.[5] Echocardiography is a primary choice for diagnosis; however cardiac catheterization provides better results. In non-obstructing pulmonary veins, cardiac catheterization is less likely required, as echocardiography is considered sufficient when three veins are well visualised.[6] Magnetic resonance imaging, CT angiography, and trans-oesophageal echocardiography provides better anatomic delineation of pulmonary venous drainage.[7] Various surgical techniques have been recommended to patients with mixed TAPVC, with individualised approach to variations of 2+2, 3+1, or bizarre pattern.[8-10]

In this case, combined approach for surgical correction were considered, wherein mixed TAPVC with bizarre pattern [2 (1/2)+1 (1/2)] type, having dual LIPV drainage of left inferior lobe as supracardiac and cardiac component were rerouted to drain all the pulmonary venous drainage to left atrium using 'van paragh or mee technique' for (RSPV & RIPV & branch LIPV) and 'posterior approach' for (LSPV& branch LIPV). Surgery carries a high risk of mortality and morbidity, especially in repair of mixed form of TAPVC, having bizarre pattern.

CONCLUSION

A sound characterization of pulmonary venous drainage pattern, preoperative planning and individualization of optimal surgical approach ensures good outcomes.

ETHICAL DECLARATIONS

Informed Consent

The patient's parents have signed the informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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Anomalous circumflex artery originating from the right coronary sinus as the culprit in acute inferior myocardial infarction*

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ABSTRACT

Coronary artery anomalies are rare congenital conditions that are usually detected incidentally during coronary angiography or post-mortem examinations. Although many variants are clinically asymptomatic, they can be fatal in some cases. In this article, we present a 35-year-old male patient who presented with acute inferior myocardial infarction causing complete atrio-ventricular block. Angiography revealed a rare coronary anomaly, the left circumflex artery originating from the right sinus of Valsalva. The lesion, caused by severe stenosis in the proximal segment of this anomalous vessel, was successfully treated with primary percutaneous coronary intervention. This case highlights the diagnostic and therapeutic challenges of such anatomic variations in the setting of acute coronary syndrome and reviews the current literature on interventional strategies.

Keywords: Coronary artery anomalies, myocardial infarction, percutaneous coronary intervention, circumflex artery, cardiac syncope

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INTRODUCTION

Coronary artery anomaly (CAA) is a rare condition that is detected during coronary angiography or during autopsy. Most of the cases with CAA's are asymptomatic, but anomalies such as left coronary artery, which is ectopic and between the aorta and pulmonary artery, may cause syncope, arrhythmias, myocardial ischemia and sudden cardiac death.[1] The majority of these variations follow a benign clinical course and remain quiescent throughout a patient's life. However, certain "malignant" anomalies, particularly those with an interarterial course between the aorta and pulmonary artery, are implicated in myocardial ischemia, life-threatening arrhythmias, and sudden cardiac death.

Among the CAAs, the anomalous origin of the left circumflex artery (LCx) from the right coronary sinus (RCS) or directly from the right coronary artery (RCA) is one of the more frequently encountered variants. Its prevalence is estimated to be between 0.3% and 0.7%.[2,3] Typically, the anomalous LCx follows a retroaortic path to reach the left atrioventricular groove. This posterior course is generally considered a "benign" variation, as it is not susceptible to dynamic compression during physical exertion. Despite this, the vessel itself remains vulnerable to atherosclerotic disease. When an acute coronary syndrome (ACS) develops in such a vessel, its anomalous origin can pose substantial diagnostic and therapeutic challenges for the interventional cardiologist.

In this article, we present a case of acute inferior myocardial infarction accompanied by A-V block originating from the Cx artery originating from the right sinus of Valsalva.

CASE

A 35-year-old male, with a notable history of smoking, was brougt to the emergency department with chest pain and syncope. Upon initial assessment, the patient was in cardiogenic shock. His vital signs were: blood pressure was 70/40 mm Hg, heart rate was 35 beats per minute with regular rhythm, respiratory rate was 20 breaths/min and body temperature was 36.8°C. A 12-lead electrocardiogram (ECG) revealed a 3 mm ST-segment elevation in the inferior leads and 2 mm ST-segment elevation in the lateral leads, consistent with an inferolateral myocardial infarction. The ECG also demonstrated a complete atrioventricular (A-V) block. An emergent bedside transthoracic echocardiogram was performed. This revealed severe hypokinesia of the inferolateral wall with a moderately reduced left ventricular ejection fraction.

Atropine 1 mg intravenously was administered for bradycardia, but no increase in heart rate was observed. Additionally, 300 mg aspirin and 600 mg clopidogrel peroral, intravenous 10.000 U unfractionated heparin

were administered. Given the diagnosis of ST-segment elevation myocardial infarction (STEMI) with high-risk features, the patient was immediately transferred to the cardiac catheterization laboratory for primary percutaneous coronary intervention (PCI).

The patient underwent diagnostic coronary angiography via the femoral approach and revealed normal left main coronary artery from the left aortic sinus and RCA from right aortic sinus. However, the Cx artery could not be visualized originating from its usual location (**Figure 1**). Subsequently, selective cannulation of the right coronary sinus demonstrated a diminitive RCA and also showed the anomalous origin of a dominant Cx artery from a separate ostium within the same sinus. The culprit of acute inferior MI was determined to be the anomalous Cx artery. And than using an Amplatz Right 2 (AR-1) guiding catheter, coaxial engagement was achieved. The lesion was crossed with a floppy-tipped guidewire, and primary PCI was performed. A 3.5x24 mm drug eluting stent (B Braun, Melsungen, Germany) was deployed at the stenotic site and post-dilated at 10 atmospheres, leading to the restoration of TIMI grade 3 flow (**Figure 2**). Post-stent implantation the patient's hemodynamic status improved dramatically post-procedure, and the A-V block resolved. He was monitored in the coronary care unit and was discharged two days later in stable condition. His discharge medication regimen included dual antiplatelet therapy with Aspirin 100 mg daily and Clopidogrel 75 mg daily, prescribed for a minimum of one year, along with high-intensity statin therapy.

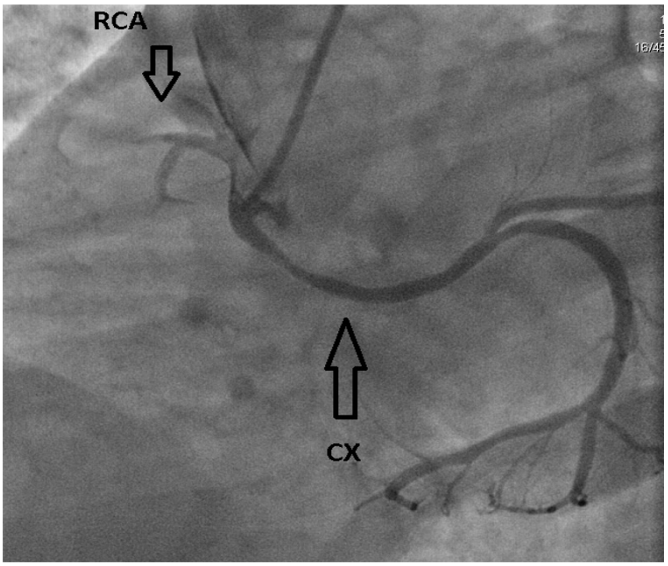

Figure 1. Selective angiogram of the right coronary sinus demonstrating the anomalous origin of the left circumflex artery (culprit vessel, pre-intervention with stenosis indicated by arrow)
RCA: Right coronary artery, Cx: Circumflex

DISCUSSION

This case highlights the successful management of a life-threatening STEMI occurring in a patient with a rare, generally benign, coronary anomaly.[4] The anomalous origin of the LCx from the RCS does not inherently predispose the artery to a higher incidence of atherosclerosis.[5] However, its presence make diagnosis and intervention difficult during STEMI. The primary diagnostic challenge arises when the

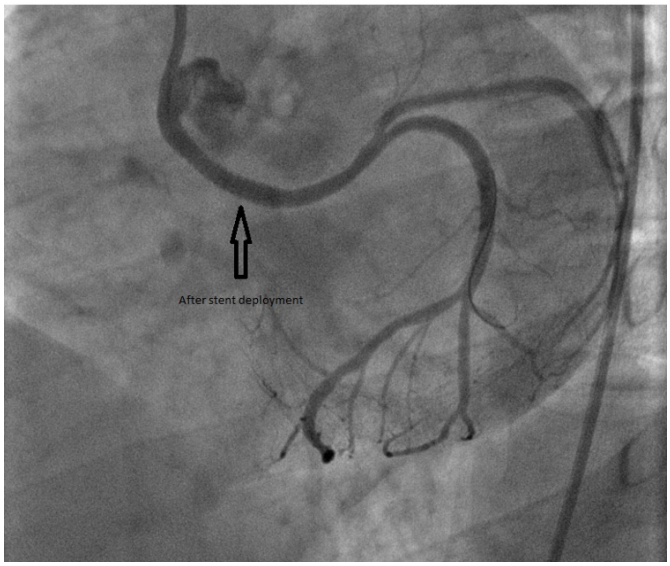

Figure 2. The successful post-stent deployment result with restored blood flow

LCx is not seen during left coronary system angiography. In the emergent setting of a STEMI, this can lead to confusion and delays. The angiographic finding of an "empty" circumflex sulcus, coupled with ECG evidence of lateral wall ischemia, should immediately raise the suspicion of an anomalous origin from the right sinus or RCA. Prompt and systematic interrogation of the RCS is therefore crucial to identify the vessel and the culprit lesion.

From a therapeutic standpoint, PCI of anomalous coronary arteries is fraught with technical difficulties. The abnormal osteal orientation of the vessel often prevent coaxial alignment of standard guiding catheters, which is essential for backup support.[6] The retroaortic course can also create unusual tortuosity, complicating the advancement of guidewires, balloons, and stent delivery systems.[7] The selection of an appropriate guiding catheter is paramount. While Judkins right catheters may be attempted, catheters with alternative shapes, such as the Amplatz or multipurpose configurations, are often required to successfully engage the anomalous ostium, as was demonstrated in our case. The favorable outcome in our patient underscores that despite these formidable technical challenges, primary PCI remains the gold-standard reperfusion strategy for STEMI, even in the complex coronary anatomy. In case of the anomaly, coupled with a versatile inventory of catheters and an experienced operator's skill, is essential for procedural success.

CONCLUSION

As a result, while the anomalous LCx from the RCS is a hemodynamically benign variant, its potential to develop atherosclerosis makes it a critical consideration in patients with ACS. Interventional cardiologists must be cognizant of this anatomical variation and prepared to adapt their angiographic and interventional techniques to ensure timely and effective coronary revascularization.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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