Review



Sinus of Valsalva aneurysm in Africa: a literature review

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Abstract: Sinus of Valsalva aneurysm (SOVA) is a rare congenital anomaly. The incidence of SOVA is five times higher among Asians than among Western populations. Currently, there is a lack of information on the clinical presentations of this entity in Africans. This study aims to perform a comprehensive review of papers concerning SOVA in the African population. In this study, papers published from 1962 to April 2021 were collected by entering the keywords, "SOVA" and "The name of each African country", in the PubMed database, and a manual search was performed using citations from primary papers to retrieve any other reports not included in PubMed. As shown, 23 patients with SOVA were included in this review. There were 14 males (60.8%) and 9 females (39.1%), and their average age was 28.7 ± 13.9 years old. Their most frequent clinical presentation was dyspnea followed by palpitations. SOVA arose from the right sinus of Valsalva in 65.2% of cases, the dissection into interventricular septum (IVS) was the most frequent complication, accounting for 52.2% of cases, and the main cardiac anomalies associated with SOVA were other congenital cardiac aneurysms. In conclusion, in Africans, SOVA arises more often from the right sinus of Valsalva, the main complication of SOVA is their dissection into IVS, and the main cardiac anomalies associated with SOVA in the African population are other congenital cardiac aneurysms. These differences are important in the surgical planning of African patients.

Keywords: Sinus of Valsalva aneurysm, Echocardiography, Computed tomography, Magnetic resonance imaging, Africa

Introduction

Sinus of Valsalva aneurysm (SOVA) is considered a rare congenital anomaly. The pathognomonic histological finding lacks continuity in the aortic media and annulus fibrosis. The incidence of SOVA is five times higher among Asians than among Western populations [1-3]. Furthermore, among Asians, SOVA less commonly occurs among elderly individuals, more frequently originates from the right coronary sinus (RCS), more commonly ruptures into the right ventricle, has a higher incidence of associated supracristal ventricular septal defects (VSDs) and has a lower incidence of congenital cardiac anomalies

[1, 3].

Apart from a small case series [4] and a few isolated cases of SOVA reported in African patients, there is little information on the clinical presentations of this entity among Africans.

This study aims to perform a systematic review of SOVA in the African population.

Methods

Relevant papers published from 1962 to April 2021 were collected by entering the keywords, "SOVA" and

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Received: Dec.27,2021; Revised: Jan.31,2022; Accepted: Feb.22,2022; Published: Mar.7,2022

DOI: https://doi.org/10.55976/cds.120221471-10

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"The name of each African country", in the PubMed database. The review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. A manual search was performed using citations from primary papers to retrieve any other reports not included in PubMed.

One reviewer extracted data, with an independent review undertaken by another reviewer. A critical appraisal will depend on the nature of the included evidence. A narrative synthesis was collaboratively developed, with descriptive information presented in tables summarizing study characteristics and the thematic analysis of findings presented in the main text. This review only contained papers in which the diagnosis of SOVA was made using the diagnostic criteria exhaustively described in the literature or confirmed in surgery.

Eligibility criteria

Given that we aimed to scope a broad range of evidence, our study contained the published literature, including research articles, clinical cases and case series. Discussion papers, position papers, expert opinions, editorials and study protocols were excluded.

Our study included both primary (by using quantitative, qualitative and mixed methods) and secondary (e.g., review) level evidence. In view of our time and other resource constraints, we only considered literature written in English.

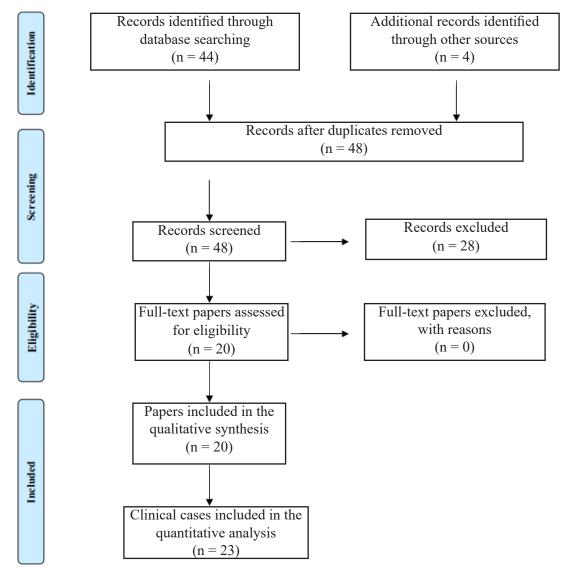


Figure 1. PRISMA Flow Diagram Records screened

Results

The literature retrieval process of this review is presented in Figure 1. A total of 48 papers were identified, of which 28 records not related to the theme were excluded. A total of 20 full-text papers representing 23 patients, children and adults included, were included in this review [4-23].

A case series with 4 patients and 19 clinical cases of SOVA were identified from reports published between 1962 and 2021 [4-23]. Overall, 23 patients with SOVA were identified, and there were 14 males (60.8%) and 9 females (39.1%) (male/female ratio: 1.6/1). SOVA occurred in all age groups, with the youngest patient being 7 years old (3), and the average age was 28.7 ± 13.9 years old.

Infective endocarditis was considered the cause of SOVA in one patient [5]. In the remaining 22 patients, SOVA was congenital in origin.

Information on the clinical presentations of previously described cases of SOVA in Africans is presented in Table 1. All patients were symptomatic. The most frequent clinical presentation was dyspnoea in 15 (65%) patients and palpitations in 7 (30%) patients, followed by chest pain in 6 (26%) patients and syncope in 4 (17.4%) patients.

In this review, a heart murmur was a common finding in 13 (56.2%) patients on the physical examination of patients with SOVA — 4 patients had a continuous murmur, 3 patients had a diastolic murmur of aortic regurgitation (AR), 2 patients had a systo-diastolic murmur in the aortic area, 2 patients had a systolic ejection murmur and another 2 patients had a diastolic murmur of AR along with a systolic murmur of mitral regurgitation.

The demographic data, the origin of the affected sinus of Valsalva, and complications and diagnostic methods of previously described cases of SOVA in Africa are presented in Table 2. The main differences among Asian, Western and African populations regarding the origin of SOVA, chambers into which SOVA ruptured and in associated congenital cardiac anomalies are presented in Table 3.

SOVA arose from RCS in 65.2% of cases, followed by left coronary sinus (LCS) (4/23) and noncoronary sinus (3/23). In 1 patient, SOVA arose from both RCS and LCS [17]. Dissection into the interventricular septum (IVS) with the formation offalse cavities from the base to the apex (Figure 2) was the most frequent complication, accounting for 52.2% of cases. Furthermore, in 2 other patients with IVS dissection, these new false cavities in the IVS ruptured into the left ventricle (LV) [10, 13]. The rupture into adjacent cavities occurred in only 30.4% of cases, most often into the right atrium. Information regarding AR detected by echocardiography was reported in 10 patients: severe in 20%, moderate in 30% and mild in 50%. Twelve (52.2%) patients were in NYHA class III

and IV heart failure.

Arrhythmias and conduction disturbances were reported in 3 (13%) and 7 (30.4%) patients (6 of whom had completed atrioventricular block), respectively.

The association of SOVA and other congenital aneurysms was found in 4 patients [6, 14, 16, 18]. SOVA was associated with left ventricular noncompaction (LVNC) in 2 patients [4, 10]. Furthermore, the coexistence of SOVA, submitral aneurysm (SMA) and LVNC was present in another patient [16]. We would like to emphasize that the coexistence of SOVA and VSD was found in only one patient [8].

All patients underwent two-dimensional transthoracic echocardiography (TTE), and 11 (47.8%) patients underwent transesophageal echocardiography (TEE). Contrast aortography was the diagnostic technique used in 5 patients. Multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) were performed in 10 (43.4%) and 3 (13.0%) patients, respectively. To better characterize the diagnosis, 19 (82.6%) patients underwent two or more imaging modalities.

The treatments, outcomes and follow-ups of previously described cases of SOVA in Africans are presented in Table 4. Surgical treatment is recommended for the 23 (100%) patients. Of this, 1 patient died of congestive heart failure refractory to treatment waiting for cardiac surgery [18], 1 patient with a high surgical risk was refused by the surgical team [13], and 3 patients refused surgery [15, 18, 20]. Fifteen patients underwent surgical treatment with no surgical mortality.

Follow-up time was reported in 11 patients, of whom 3 patients refused surgery and 8 patients underwent surgery. The follow-up time ranged between 3 and 36 months. The 3 patients who refused surgery died at 3 and 12 months after diagnosis, showing the poor prognosis of this pathology due to the lack of timely treatment [16, 19, 21]. Two of them died suddenly, and one patient died of refractory heart failure. Among the 8 operated patients, one patient with three months and another with 6 months, and five patients with one year and another with 3 years of follow-up remain asymptomatic, which reflects a good result in the short-medium term [4, 5, 7, 8, 15, 17, 23].

Patient No	Reference	Year	Age	Sex		Clin	Others	NYHA	Murmur					
					Asymptomat- ic	Dysp- nea	Chest pain	Palpita- tion	Syncope	Arrhyth- mia	Conduction defect	-	Class	
1	Morais et al. [4]	2007	7	F	-	-	-	Y	-	PSVT	-	-	-	-
2			26	F	-	Y	-	Y	-	AF	-	-	III	-
3			35	М	-	Y	-	Y	-	-	Complete AV block	dizziness	II	-
4			36	М		Y	-	-	-	-	1st Degree AV block	-	III	-
5	Abetti et al. [5]	2020	47	М	-	Y	Y	-	-	-	-	Fever	IV	Systo-diastolic (aortic area)
6	Afifi et al. [6]	2014	26	М	-	Y	-	-	-	-	-	Ortopnea	-	-
7	Amoah et al. [7]	2000	26	М	-	Y	-	-			-	Peripheral edema	-	Contimous
8	Charfeddine et al. [8]	2017	26	F	-	-	Y	-			-	-	-	Contimous
9	El Hattaoui et al. [9]	2008	48	F	-	-	-	-	Y		Complete AV block	-	-	Diastolic of AR
10	Fennich et al. [10]	2018	23	М	-	-	-	-	Y		Complete AV block	-	-	Systo-diastolic (aortic area)
11	Jesuorobo et al. [11]	2019	44	М	-	-	Y	-	Y		Complete AV block	Vertigo nausea	-	-
12	Matta et al. [12]	2020	35	F	-	Y	-	-	-				Ι	Systólic
13	Morais et al. [13]	2015	16	М	-	Y	Y	-	-		-	fatigue	III	Contimous
14	Morais et al. [14]	2016	9	F	-		Y	Y	-		-	-	-	-
15	Morais et al. [15]	2016	25	F	-	Y	-	Y	-		-	-	Ι	Contimous
16	Morais et al. [16]	2014	24	М	-	Y	-	-	-		-	Dyspnea at rest	IV	-
17	Morais et al. [17]	2020	25	F	-	Y	-	-	-		-	PND ortopnea peripheral edema	IV	Diastolic of AR
18	Manuel et al. [18]	2019	21	М	-	Y	-	-	-		-	PND cough ortopnea pe- ripheral edema	IV	Systolic
19	Okeahialam et al. [19]	2013	30	М	-	Y	-	Y	-		-	Dyspnea at rest PND or- topnea	IV	Diastolic AR Systolic MR
20	Przybojewski et al. [20]	1983	27	М	-	Y	-	-	-		-	PND ortopnea	IV	Diastolic AR
21	Talle et al. [21]	2018	70	F	-	Y	-	Y	-	WPM	-	Ortopnea peripheral ede- ma	III	Diastolic AR Systolic MR
22	Sebag et al. [22]	1981		М	-	-	-	-	Y	-	Complete AV block	-	-	-
23	Smedema et al. [23]	2011	14	М	-	-	Y	-	-	-	-	-	-	-

Table 1. Demographic and clinical presentations of previously described cases of sinus of Valsalva aneurysm in Africans

AF-Atrial fibrillation; AR-Aortic regurgitation; AV-Atrioventricular; NYHA-New York Heart Association; PND-Paroxysmal nocturnal dyspnea; PSVT Paroxysmal supraventricular tachycardia; Y-Yes; WPM-Wandering Pacemaker

Patient	Reference	Year	Sinus of	Associated Congenital Cardiac Anomalies Complications											Diagnostic methods	
No			origin	AR	VSD	BAV	FSA	SMA	FMAA	CAA	LVNC	Rup- ture	Cavities	DIVS D	IVS & LV	-
1	Morais et al. [4]	2007	RCS	-	-	-	-	-	-	-	-	-	NA	Y	-	TTE
2			NCS	-	-	-	-	-	-	-	-	-	NA	-	-	TTE ETE
3			RCS	-	-	-	-	-	-	-	Υ	-	NA	Y	-	TTE ETE
4			LCS	Y	-	-	-	-	-	-	-	-	NA	Y	-	TTE ETE
5	Abetti et al. [5]	2020	RCS	-	-	-	-	-	-	-	-	Y	RA	-	-	TTE ETE CT
6	Afifi et al. [6]	2014	RCS	Y	-	-	Y	-	-	-	-	-	NA	Y	-	TTE CT
7	Amoah et al. [7]	2000	RCS	-	-	-	-	-	-	-	-	Y	RA	-	-	TTE
8	Charfeddine et al. [8]	2017	RCS	Y	Y	-	-	-	-	-	-	Y	RV	-	-	TTE CT Aortography
9	El Hattaoui et al. [9]	2008	LCS	Y	-	-	-	-	-	-	-	-	NA	Y	-	TTE ETE MRI
10	Fennich et al. [10]	2018	RCS	-	-	-	-	-	-	-	Y	-	NA	Y	Υ	TTE CT MRI Aorto and coronariography
11	Jesuorobo et al. [11]	2019	RCS	-	-	-	-	-	-	-	-	-	NA	Y	-	TTE CT Coronariography
12	Matta et al. [12]	2020	NCS	-	-	-	-	-	-	-	-	Y	RA	-	-	TTE ETE
13	Morais et al. [13]	2015	RCS	-	-	-	-	-	-	-	-	-	NA	Υ	Υ	TTE ETE
14	Morais et al. [14]	2016	RCS	-	-	-	-	-	-	Y	-	-	NA	Y	-	TTE CT
15	Morais et al. [15]	2016	RCS	Y	-	-	-	-	-	-	-	Y	RC	-	-	TTE ETE CT
16	Morais et al. [16]	2014	RCS	Y	-	-	-	Y	-	-	Υ	-	NA	Y	-	TTE CT
17	Morais et al. [17]	2020	RCS & LCS	Y	-	-	-	-	-	-	-	-	NA	-	-	TTE ETE CT
18	Manuel et al. [18]	2019	LCS	-	-	-	-	-	Y	-	-	-	NA	-	-	TTE ETE
19	Okeahialam et al. [19]	2013	RCS	Y	-	-	-	-	-	-	-	-	NA	Y	-	TTE
20	Przybojewski et al. [20]	. 1983	RCS	Y	-	-	-	-	-	-	-	Y	RC	-	-	TTE Aortography
21	Talle et al. [21]	2018	NCS	Y	-	-	-	-	-	-	-	Y	LA	-	-	TTE
22	Sebag et al. [22]	1981	RCS	-	-	-	-	-	-	-	-	-	NA	Y	-	TTE Aortography
23	Smedema et al. [23]	2011	LCS	-	-	-	-	-	-	-	-	-	NA	-	-	TTE ETE CT MRI Coro- nariography

Table 2. The sinus of origin, associated cardiac anomalies, complications and diagnostic methods of previously described cases of sinus of Valsalva aneurysm in Africans

AR-Aortic regurgitation; BAV-Bicuspid aortic valve; CAA-coronary artery aneurysm; CT-Computed tomography; DIVS-Dissection into interventricular septum; FMAA-Fibrosa mitral-aortic aneurysm; FSA-Fibrosous septum aneurysm; LCS-Left coronary sinus; MRI-Magnetic resonance imaging; NCS-Non-coronary sinus; LV-Left ventricle; LVNC-Left ventricular noncompaction; RC-Right cavities; RCS-Right coronary sinus; SMA-Submitral aneurysm; TTE-Transthoracic echocardiography; TEE-Transesophageal echocardiography; VSD-Ventricular septal defect.

Table 3. Differences between Asian, Western and African population in origin, chambers into which sinus of Valsalva aneurysm ruptured, and in associated congenital cardiac anomalies. Data referring to the Asian and Western population were compiled from the reference [3]

Population	Origin of SOVA	Chambers Into Which SOVA Ruptured					DIVS	No Rup- ture	Associate	Total Cases			
	RCS (%)	RV (%)	RA (%)	LV (%)	LA (%)	MC (%)	N (%)	N (%)	VSD (%)	AR (%)	BAV (%)	CCT (%)	Ν
Asian	561 (85.8)	474 (72.5)	160 (24.5)	2 (0.3)	2 (0.3)	4 (0.6)	2 (0.3)	10 (1.5)	343 (52.4)	220 (33.6)	4 (0.6)	0 (0)	654
Western	268 (67.8)	237 (60)	127 (32.2)	8 (2.0)	3 (0.8)	7 (1.8)	5 (1.3)	8 (2.0)	148 (37.5)	129 (32.7)	31 (7.8)	9 (0)	395
Africans	15 (65.2)	1 (4.3)	3 (13.9)	2(8.6)*	1(4.3)	2 (8.6)	12 (52.2)	3 (13.9)	1 (4.3)*	10 (43.5)	0 (0)	4 (27.4)	23

AR-Aortic regurgitation; BAV-Bicuspid aortic valve; CCA-Congenital cardiac aneurysm; DIVS-Dissection into interventricular septum; LA-Left atrium; LV-Left ventricle; MC-Multiple cavities; RA-Right atrium; RCS-Right coronary sinus; RV-Right ventricle: SOVA-Sinus of Valsalva aneurysm; VSD-Ventricular septal defect. * These two patients had also DIVS



Figure 2. Two-dimensional transthoracic echocardiography, parasternal long-axis view showed a large aneurysm of the right sinus of Valsalva dissecting into the interventricular septum (asterisk). Ao-Aorta; LA-Left atrium; LV-Left ventricle

Patient	Reference	Year		Surger	у	Method of repair	Outcome	Follow-up	
No			Proposed	Refused	Underwent	-		(months)	findings
1	Morais et al. [4]	2007	Y		Y		Alive	36	Asymptomatic
2			Y						
3			Y		Y		Alive	12	NYHA Class I
4			Y						
5	Abetti et al. [5]	2020	Y		Y	The orifice was closed using a pericardial patch	Alive	3	Asymptomatic
6	Afifi et al. [6]	2014	Y		Y	Bentall procedure with size 29 mechanical valve	Alive		
7	Amoah et al. [7]	2000	Y		Y	The opening in the right aortic sinus was closed with interrupted $4/0$ ethibond suture, The sac of the aneurysm was plicated with $3/0$ prolenecontinuous sutures	Alive	12	Asymptomatic
8	Charfeddine et al. [8]	2017	Y		Y	The fistula and the VSD were closed with patches	Alive	12	Asymptomatic
9	El Hattaoui et al. [9]	2008	Y						
10	Fennich et al. [10]	2018	Y		Y	The fistula was closed using Dacron patch	Alive		
11	Jesuorobo et al. [11]	2019	Y		Υ	The right sinus of Valsalva aneurysm was repaired and aortic valve replaced	Alive		
12	Matta et al. [12]	2020	Y		Y	The fistulous tract was resected, and the aortic defect was closed involving a portion of the base of the aortic valve.	Alive		
13	Morais et al. [13]	2015	Y		Y		Alive		
14	Morais et al. [14]	2016	Y		Refused by surgical team				
15	Morais et al. [15]	2016	Y		Y	The fistula was closed	Alive	12	Asymptomatic
16	Morais et al. [16]	2014	Y Y	Y				12	Died
17	Morais et al. [17]	2020	Y		Y	Bentall-de Bono procedure with size 29 mechanical valve,	Alive	12	Asymptomatic
18	Manuel et al. [18]	2019	Y		Died waiting surgery				
19	Okeahialam et al. [19]	2013	Y	Y				Few	Died suddenly
20	Przybojewski et al. [20]	1983	Y			The fistulas were closed with interrupted Tycron sutures. The Aortic valve was replaced with a 23 mm Ionescu-Shiley bioprosthesis	Alive		
21	Talle et al. [21]	2018	Y	Υ				4	Died suddenly
22	Sebag et al. [22]	1981	Y				Alive		
23	Smedema et al. [23]	2011	Y			The fistula was closed with pericardial patch.	Alive	6	Asymptomatic

Table 4. Treatment and outcomes of previously described cases of sinus of Valsalva aneurysm in Africans

VSD-Ventricular septal defect

Discussion

The main findings of this review show that the RCS of Valsalva is the most affected in 65.2% of cases. These data are very similar to those found in Western populations but lower than those found in Asians [1, 3]. In two different reviews carried out by Chu et al. [1] and Wang et al. [3], which compare the findings of SOVA in Asians and Western populations, the authors find that in Western populations, the aneurysm arises from the right sinus of Valsalva in 63.6-67.8% of the cases, while in Asians, this happens in 85.8-87.9% [1, 3].

In the present review, in general, the main complaints and clinical presentations of SOVA are very similar to those described by other authors [1, 2, 24]. Dyspnea is the main complaint in this review, followed by chest pain and syncope. A cardiac murmur is a common finding in our study and present in more than half of the patients. The continuous murmur, together with a systolic-diastolic murmur, is the most frequent.

The results of our review show an average age of 28.7 ± 13.9 and a predominance of males (60.8%). These data are very similar to those reported in other series [1-3, 24].

Regarding complications, in the present review, the dissection of SOVA to IVS was the most frequent complication (52.2% of cases) and followed by the rupture to adjacent cavities, which contrasts with the findings in other populations [1-3, 24]. In both the Asian and Western populations, the dissection into IVS is a rare complication, accounting for only 0.3% and 1.3% of cases, respectively [3]. The rupture into adjacent cavities is the main complication of SOVA in those populations [1-3, 24].

Regarding arrhythmias and conduction disturbances, in the present review, we found a high incidence of atrioventricular blocks, which was very likely related to the high incidence of interventricular septal dissection found in Africans. The mechanism for an atrioventricular block is easily explained by the extension of the sinus of Valsalva aneurysms to the vicinity of the conduction tissue [25].

Coexisting lesions are common in patients with congenital SOVAs. Unlike what occurs in both Asians and western populations, the ventricular septal defect (VSD) and the bicuspid aortic valve (BAV) are the most common cardiac anomalies associated with SOVAs, accounting for 37.5-52.4% and 0.6-7.8%, respectively [3]. In the present review, no cases of BAV were found, and VSD was found in only 4.3% of cases (one patient). In turn, SOVAs are associated with other congenital aneurysms, such as submitral aneurysms [16], fibrous mitral-aortic aneurysm [18], coronary artery aneurysm [14] and membranous septum [6]. This was a frequent finding in our review. The association of SOVAs with left ventricular noncompaction was also frequent in Africans [4, 10, 16]. On the other hand, the incidence of aortic regurgitation found in our review was slightly higher than that reported by Wang et al., with 33.6% in the Asian group and 32.7% in the Western group [3].

Imaging modalities such as echocardiography, computed tomography (CT), angiography, and magnetic resonance imaging (MRI) are essential in identifying and characterizing aneurysms as well as associated cardiac anomalies. However, there are no specific guidelines for the diagnosis and management of SOVAs [26].

TTE is performed in all patients reviewed herein, showing that it is the first-line diagnostic method for evaluating these patients due to its availability, portability and safety. TEE is especially important to guide surgical management. It provides important information about the location, size and morphology of sinus aneurysms. It also detects coexisting lesions, complications and hemodynamic sequelae [2, 4, 6, 26]. However, TTE is only used in less than half of the patients, which contrasts with the study conducted by Xu et al., where the use of TEE is high. According to these authors, the vast majority of TEE is performed as an intraoperative study [26]. Thus, the low percentage of TEE use found in our review can be explained by several reasons: 1) this technique is not widespread in African countries, 2) there is no routine for the use of TEE in the preoperative period, or 3) both.

CT can be of added value for the precise determination of size, extent, and anatomical relations [6, 26]. In line with those reported by Xu et al., the present review showed that MDCT was performed in 43.4% of patients, constituting the third imaging modality used [26]. Furthermore, in recent years, we have seen an increase in the use of 3 or more imaging modalities in the diagnosis of this pathology in the same patient [8-11, 15, 17, 26].

In countries with scarce resources, we consider that TTE and TEE allow the vast majority of cases to adequately characterize the SOVA. In cases where there are doubts regarding the location of the aneurysm and its complications, CT will be the second-line diagnostic test. MRI, due to its high costs and low availability in African countries, has rarely been used. In the present review, only 3 (13.0%) patients underwent MRI.

Aortography and coronary angiography should be used in patients with suspected coronary disease and in patients in whom percutaneous closure of the ruptured SOVA is planned [15].

Surgery is the traditional treatment of SOVA with excellent immediate and long-term results [3, 24]. More recently, percutaneous closure of ruptured SOVAs appears to be a promising treatment in selected patients [27]. In the present review, 65.2% of the cases underwent surgical treatment of the defect with zero surgical mortality and good results in the short-medium term, but none of the patients underwent percutaneous closure of ruptured SOVAs.

Conclusion

In Africans, SOVAs arise more often from the right sinus of Valsalva. Unlike other populations, the main complication of SOVAs is their dissection to IVS. The main cardiac anomalies associated with SOVAs in Africans are other congenital cardiac aneurysms and left ventricular noncompaction, withVSD being found very rarely. These differences are important in the surgical planning of our patients.

Author Contribution

Conceptualization: H.M.; Data collection: H.M. and H.S.F.; Formal Analysis: H.M. and H.S.F.; Methodology: H.M. and H.S.F.; Writing-Original draft: H.M.; Writingreview & editing: H.M. and H.S.F.; Approval of the final manuscript: H.M. and H.S.F.; Supervision: H.M.

Funding

Nothing to declare

Informed Consent Statement

Not applicable

Disclosure

There are no financial conflicts of interest to disclose.

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