Cardiology in the Young

cambridge.org/cty

Original Article

Cite this article: Hanna BM, El-Mozy WE, and El-Saiedi SA (2022) Rheology of right ventricular outflow tract obstruction: sub-pulmonary membrane developing months after primary intervention to treat pulmonary atresia with intact interventricular septum. *Cardiology in the Young* **32**: 60–63. doi: 10.1017/S1047951121001591

Received: 18 January 2021
Revised: 26 March 2021
Accepted: 30 March 2021
First published online: 31 May 2021

Keywords:
Sub-pulmonary membrane; pulmonary atresia; radiofrequency perforation

Author for correspondence:
Baher Hanna, MD, Tel: +201222441732.
E-mail: baherhanna@gmail.com

Rheology of right ventricular outflow tract obstruction: sub-pulmonary membrane developing months after primary intervention to treat pulmonary atresia with intact interventricular septum

Baher M. Hanna[1], Wesam E. El-Mozy[2] and Sonia A. El-Saiedi[1]

[1]Division of Pediatric Cardiology, Department of Pediatrics, Cairo University, Cairo, Egypt and [2]Department of Radiology, Cairo University, Cairo, Egypt

Abstract

Isolated sub-pulmonary membrane is a rare condition, the origin of which has been debatable. Transcatheter treatment of pulmonary valve atresia with intact interventricular septum by radiofrequency perforation and balloon dilatation to restore biventricular circulation is gaining more popularity, with improving results over time. We report in our experience of 79 cases in 10 years the development of a sub-pulmonary membrane in 4 cases: causing significant obstruction requiring surgical excision in one case that revealed a fibrous membrane on pathology; causing mild right ventricular outflow tract obstruction in another and not yet causing obstruction in 2. On cardiac MRI, the right ventricular outflow tract and the right ventricular outflow tract/pulmonary atresia angle showed no morphological abnormalities.

Sub-pulmonary membrane is a rare disease and was described in relation to supracristal ventricular septal defects with or without aortic insufficiency,[1,2] with valvular pulmonary stenosis,[3] and as an isolated form causing critical neonatal sub-pulmonic stenosis.[4] Van Praagh believes that the fibrous membrane is a developmental condition related to the semilunar valve rather than the infundibulum, whereas the muscular membrane arises from the pulmonary infundibulum. Anderson states that this is an acquired condition produced by fibrous growth on top of a sub-pulmonary infundibular narrowing, also described in cases with Fallot's tetralogy.[5] Cases of sub-pulmonary membrane have also been described following correction of transposition of the great arteries and respond to percutaneous balloon pulmonary valvuloplasty.[6]

The conal septum and semilunar valves form embryologically from the conal septal cushions that fuse: the septal cushions become muscularised, while the valvular cushions remain fibrous.[7] Fibrous sub-aortic stenosis is well known to cause 8%–20% of left ventricular outflow tract obstructions.[8] Yet, to the best of our knowledge, the late development of sub-pulmonary membrane following successful intervention to relieve pulmonary atresia in cases with intact interventricular septum, atrio-ventricular and ventriculo-arterial concordance has not yet been described.

Description of cases

Out of our series of 79 cases of pulmonary atresia with intact interventricular septum that were treated during the period from 2009 to 2019 by radiofrequency perforation and balloon dilatation of the pulmonary valve with or without ductal stenting, we observed the development of a sub-pulmonary membrane in 4 cases on the long-term follow-up. Patients with pulmonary atresia with intact interventricular septum were attempted at radiofrequency perforation + balloon pulmonary valvuloplasty if the atresia was membranous with a preserved stem of main pulmonary artery, with a tripartite or bipartite right ventricle having a tricuspid annular Z-score not smaller than −4, and no evident coronary sinusoids indicating an right ventricle-dependent coronary circulation. In addition, Patent ductus arteriosus (PDA) stenting was attempted in cases with small right ventricles that were felt not enough to support the cardiac output. The degree of Tricuspid regurge (TR) or tricuspid dysplasia did not contraindicate the procedure. Table 1 provides a summary of the pre-operative findings in the cases, operative technique and outcome. In the first case, sub-pulmonary membrane caused significant obstruction that was resistant to balloon dilatation (Fig 1) and was sent for surgical excision: revealing a fibrous membrane on pathological examination (Fig 2). Another case had a right ventricular outflow tract gradient of 25 mmHg by echocardiography and is still following-up; the other 2 cases only demonstrate the sub-pulmonary membrane on

CAMBRIDGE UNIVERSITY PRESS

Table 1. Summary of cases

	Case 1	Case 2	Case 3	Case 4
Age at intervention	11 days	17 days	2 months	18 days
Weight at intervention	3 kg	2.8 kg	3.4 kg	2.8 kg
Echocardiographic details pre-procedural	Severe TR, non-restrictive PFO (RT-LT)	Ebsteinoid TV with RV hypertrophy, bidirectional ASD	TV & RV hypoplasia, severe TR, small non-restrictive PFO (RT-LT)	Severe TR, non-restrictive PFO (RT-LT)
Procedure	RF	RF	RF + PDA stent	RF
Follow-up period until the development of SPM	1 year	11 months	6 months	4 years
SpO_2	88%	85%	92%	
Echocardiography	Severe RVOTO (PG 85 mmHg), severe TR	Non-obstructive SPM	Non-obstructive SPM	Mild RVOTO (PG 25 mmHg), severe TR
Outcome	Trial for balloon dilatation then surgical excision	Following-up	Following-up	Following-up

PDA = Patent ductus arteriosus; RF = radiofrequency; SPM = sub-pulmonary membrane; TR = Tricuspid regurge.

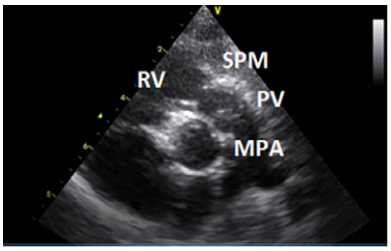

Figure 1. PS view showing the SPM. MPA = main pulmonary artery; PV = pulmonary valve; RV = right ventricle; SPM = sub-pulmonary membrane.

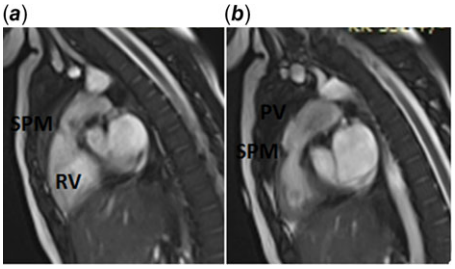

Figure 2. Sagittal cardiac MRI view showing the RVOT in (a) diastole and (b) systole. PV = pulmonary valve; RV = right ventricle; SPM = sub-pulmonary membrane.

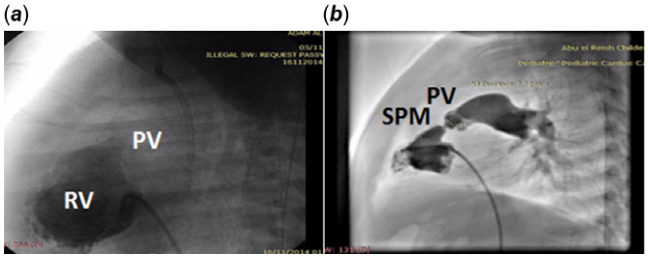

Figure 3. Lateral angiograms (a) prior to the perforation of pulmonary valve showing a blind RVOT; (b) after 1 year showing the SPM. PV = pulmonary valve; RV = right ventricle; SPM = sub-pulmonary membrane.

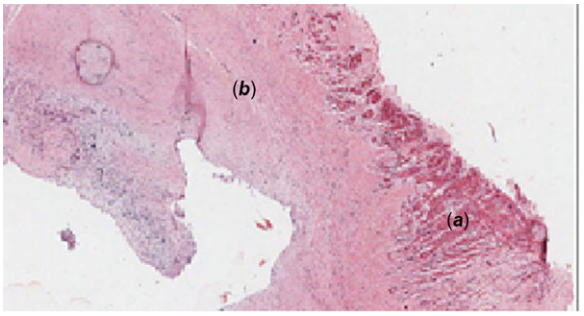

Figure 4. Pathological specimen of the excised fibrous membrane: (a) portion of myocardial muscle; fibrous membrane formed of hypocellular collagen entangling bland-looking fibroblasts with low vascularity.

echocardiography without significant gradient across the right ventricular outflow tract till the writing of this paper (Figs 3 and 4).

The four cases were assessed by cardiac MRI to evaluate the anatomy of the right ventricular outflow tract, the flow dynamics and the right ventricular outflow tract/main pulmonary artery angle analogous to that described for the aorto-septal angle in the sub-aortic membrane.[9] Comparing the shape and length of the right ventricular outflow tract infundibulum and the sub-pulmonary area to that of normal subjects showed right ventricular outflow tract narrowing in two cases with acceleration and turbulence of flow on one, and no anatomical narrowing in the other two including the post-operative case. The right ventricular outflow tract angle with the main pulmonary artery did not show obvious change. Three cases showed mild pulmonary regurge; one case had no pulmonary regurge. It is of note that the first case was imaged after the excision of the sub-pulmonary membrane. Cardiac MRI findings are listed in Table 2.

Discussion

The sequence of events that lead to semilunar valve atresia and ventricular hypoplasia needs better understanding, as to which is the primary pathology, and the mechanisms involved. More evidence is available for the left ventricle and outflow tracts; similar influences might be valid for the right ventricle and outflow tract.

https://doi.org/10.1017/S1047951121001591 Published online by Cambridge University Press

Table 2. Cardiac MRI findings in the patients

	Case 1	Case 2	Case 3	Case 4
LVEF (%)	67	76	68	57
LVEDV in ml (LVEDVI in ml/m^2)	49 (64)	24 (52)	34 (64)	51 (73)
LVESV in ml (LVESVI in ml/m^2)	16 (21)	6 (13)	11 (21)	22 (31)
LVSV in ml (LVSVI in ml/m^2)	33 (43)	18 (39)	23 (43)	29 (41)
RVEF (%)	76	72	82	74
RVEDV in ml (RVEDVI in ml/m^2)	59 (78)	25 (53)	26 (47)	77 (110)
RVESV in ml (RVESVI in ml/m^2)	14 (19)	7 (15)	5 (8)	20 (29)
RVSV in ml (RVSVI in ml/m^2)	45 (59)	18 (38)	21 (39)	56 (80)
PR (%)	17	33	12	0

LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVEDVI = indexed left ventricular end-diastolic volume; LVEDVI = indexed left ventricular end-systolic volume; LVESV = left ventricular end-systolic volume; PR = pulmonary regurgitation; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVEDVI = indexed right ventricular end-diastolic volume; RVEDVI = indexed right ventricular end-systolic volume; RVESV = right ventricular end-systolic volume.

Outflow obstruction results in complex secondary responses with disturbed flow dynamics and shear stresses, leading to impaired and disorganised ventricular growth and development. Genetic modifiers might impact subsequent remodelling, including intrinsic myocardial growth signalling pathways. Furthermore, during the latter stages of gestation, cardiomyocytes switch their myogenic capacities and become incapable of mitosis: ventricular hyperplasia cannot occur therefore, and remodelling becomes limited to ventricular hypertrophy.[10]

Sub-aortic membranes are well known to recur in a subset of patients after surgical removal; this proposes that an underlying pathology is present and not merely the anatomical condition restored by surgery. Gewillig and colleagues in 1992 studied patients with discrete sub-aortic membranes by echocardiography and showed abnormal flow patterns in these cases and suggested that these chronic flow disturbances trigger endothelial transformation and growth, leading to the development and recurrence of the anatomical stenosis.[11] It has also been reported that minor changes in the left ventricular outflow anatomy, including the aorto-septal angle,[9] can produce significant alterations in the dynamic forces and septal shear stress, and thus influencing the development and the progression of sub-aortic obstruction, which is much faster in infants than in older children.[12,13] These mechanical theories, however, could not explain the increased familial recurrence rate that is also well-identified in cases with sub-aortic membranes; an underlying genetic factors must therefore be co-existent.[8,14-16]

A theory that combines both the mechanical and the genetic hypothesis states that the disturbed flow dynamics might induce the expression of a number of genes responsible for endothelial and smooth muscle cell proliferation, similar to the mechanisms involved in atherosclerosis.[17] It is important to remember that discrete sub-aortic membrane can occur following a repair of underlying CHD. Irrespective of the gross appearance, the stenosing lesions exhibit five tissue layers beginning from the luminal aspect: endothelium, acid mucopolysaccharide-rich sub-endothelial layer, collagen-rich fibrous layer, fibro-elastotic layer and a smooth muscle layer.[18]

Fibrous sub-aortic or sub-pulmonary stenosis is in direct fibrous continuity with the overlying semilunar valve, indicating that this sub-valvar ring-like stenosis really is valvar, not infundibular or conal. If the obstruction becomes muscular, then most probably the origin is infundibular and not valvar.[4] Anderson thinks that this is not a "membrane" and appears to look more like a fibrous shelf, is almost certainly an acquired lesion and is a fibrous accretion exacerbating the narrowing at the mouth of the sub-pulmonary infundibulum. Anderson and colleagues have illustrated such fibrous accretions in their studies on tetralogy of Fallot, albeit not specifically commenting on the structure.[5]

In our statement, we are suggesting that the sub-pulmonary membrane that was not present before the first intervention might have developed later due to anatomical disturbance such as a long infundibulum forming the right ventricular outflow tract or due to malalignment of the septum in the right ventricular outflow tract reaching the sub-valvular area, either anatomic abnormality resulting in disturbed flow dynamics. Another postulation is that the sub-pulmonary membrane represents a response of the right ventricular outflow tract endothelium to the mechanical trauma during the initial intervention. This, however, does not explain fully the annular nature of the membrane but would have rather resulted in a shelf-like obstruction.

On echocardiography, it is important to differentiate this anomaly from valvar pulmonary stenosis with intact ventricular septum for the management plan. For valvar pulmonary stenosis, balloon pulmonary valvotomy is the treatment of choice with excellent results, while for sub-valvar pulmonary stenosis, surgery is the only option. We have excised the sub-pulmonary membrane in only one patient that had severe obstruction, another has mild right ventricular outflow tract obstruction and the other patients have no significant obstruction either by echocardiography or cardiac MRI. It is time and close follow-up that will show if the sub-pulmonary membrane will act in a similar manner as a sub-aortic membrane and progress into hemodynamic obstruction and recur after surgical excision or not. The rarity of the condition limits the extraction of sold conclusions; however, with the advancement and popularity of interventional treatment for pulmonary atresia with intact interventricular septum, the future might bare more insights.

Conclusion

We report the finding of newly developing sub-pulmonary membrane as a rare cause of right ventricular outflow tract obstruction after relieving pulmonary atresia with intact interventricular septum by radiofrequency perforation and balloon dilatation. Transthoracic echocardiography was helpful to delineate the lesion and was confirmed by cardiac MRI. Differentiating it from the usual valvar, pulmonary stenosis has guided us to formulate for each case a unique management plan. We believe that a careful serial follow-up echocardiography of all pulmonary atresia with intact interventricular septum and neonatal critical pulmonary valve stenosis post-intervention would enable us to learn more about this rare lesion.

Acknowledgements. None.

Compliance with ethical standards.

Financial support. This study received no external funding.

https://doi.org/10.1017/S1047951121001591 Published online by Cambridge University Press

Conflicts of interest. All authors declare no conflicts of interest.

Ethical standards. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent. Informed consent was obtained from all the caregivers of the individual participants included in the study.

References

1. Duggal B, Bajaj M, Bansal NO Subpulmonic membrane associated with a supracristal VSD: a rare cause of right ventricular outflow obstruction. Echocardiography 2011; 28: E89–E90.
2. Raff GW, Gaynor JW, Weinberg PM, Spray TL, Gleason M Membranous subpulmonic stenosis associated with ventricular septal defect and aortic insufficiency. J Am Soc Echocardiogr 2000; 13: 58–60.
3. Tefera E, Bermudez-Canete R, Rubio L Discrete subpulmonic membrane in association with isolated severe pulmonary valvar stenosis. BMC Cardiovasc Disord 2013; 13: 43.
4. Tomar M, Radhakrishnan S, Sharma R Isolated subpulmonary membrane causing critical neonatal pulmonary stenosis with concordant atrioventricular and ventriculoarterial connections. Ped Cardiol 2009; 11: 5–9.
5. Anderson RH, Jacobs ML The anatomy of tetralogy of Fallot with pulmonary stenosis. Cardiol Young 2008; 18 (Suppl 3): 12–21.
6. Vasec Jl, Goetz KK Balloon valvuloplasty of a subpulmonic membrane. Am Heart J 1990; 119: 1419–1421.
7. Spicer D, Bridgeman J, Brown N, Mohun T, Anderson R The anatomy and development of the cardiac valves. Cardiol Young 2014; 24: 1008–1022.
8. Foker JE Outcomes and questions about discrete subaortic stenosis. Circulation 2013; 127: 1447–1450.
9. Shar JA, Brown KN, Keswani SG, Grande-Allen J, Sucosky P Impact of aortoseptal angle abnormalities and discrete subaortic stenosis on left-ventricular outflow tract hemodynamics: Preliminary computational assessment. Front Bioeng Biotechnol 2020; 8: 114.
10. Hickey EJ, Caldarone CA, McCrindle BW Left Ventricular Hypoplasia, a spectrum of disease involving the left ventricular outflow tract, aortic valve, and aorta. JACC 2012; 59: S43–S54.
11. Gewillig M, Daenen W, Dumoulin M, et al. Rheologic genesis of discrete subvalvular aortic stenosis: a Doppler echocardiographic study. J Am Coll Cardiol 1992; 19: 818–824.
12. Mohan JC, Shukla M, Mohan V, Sethi A Acquired discrete subaortic stenosis late after mitral valve replacement. Indian Heart J 2016; 68: 105–109.
13. Silbiger JJ, Lee S, Christia P, Perk G Mechanisms, pathophysiology, and diagnostic imaging of left ventricular outflow tract obstruction following mitral valve surgery and transcatheter mitral valve replacement. Echocardiography 2019; 36: 1165–1172.
14. Gale AW, Cartmill TB, Bernstein L Familial subaortic membranous stenosis. Aust N Z J Med 1974; 4: 576–581.
15. Schmidt MA, Ensing GJ, Michels VV, Carter GA, Hagler DJ, Feldt RH Autosomal dominant supravalvular aortic stenosis: large three-generation family. Am J Med Genet 1989; 32: 384–389.
16. Richardson ME, Menahem S, Wilkinson JL Familial fixed subaortic stenosis. Int J Cardiol 1991; 30: 351–353.
17. Chiu JJ, Chien S Effects of disturbed flow on vascular endothelium: pathophysiological basis and clinical perspectives. Physiol Rev 2011; 91: 1–73.
18. Butany J, Vaideeswar P, David TE Discrete subaortic membranes in adults-a clinicopathological analysis. Cardiovasc Pathol 2009; 18: 236–242.

https://doi.org/10.1017/S1047951121001591 Published online by Cambridge University Press