Turk Gogus Kalp Dama 2015;23(3):532-537
doi: 10.5606/tgkdc.dergisi.2015.10934

Original Article / *Özgün Makale*
Mini Series / *Mini Seri*

Clinical characteristics and outcomes in patients with endocardial fibroelastosis associated with critical aortic stenosis with biventricular circulation

Biventriküler dolaşımlı kritik aort darlığı ile ilişkili endokardiyal fibroelastozisli hastaların klinik özellikleri ve sonuçları

Vehbi Doğan,[1] Senem Özgür,[1] İlker Ertuğrul,[1] Tamer Yoldaş,[1] Utku Arman Orun,[1] Murat Koç,[2] Selmin Karademir[1]

Departments of [1]Pediatric Cardiology and [2]Cardiovascular Surgery
Dr. Sami Ulus Maternity and Children Research and Training Hospital, Ankara, Turkey

ABSTRACT

Background: This study aims to assess the characteristics, results and prognosis of patients with endocardial fibroelastosis secondary to critical aortic stenosis.

Methods: The study included 22 newborns (17 boys, 5 girls; mean age 7.5 days; range 0 to 28 days) having endocardial fibroelastosis associated with critical aortic stenosis between January 2008 and July 2014. Patients' demographic, echocardiographic and cardiac catheterization, and angiography findings were reviewed.

Results: Patients' mean weight at presentation was 3.3 kg (range 2 to 4.8 kg). Left ventricular systolic dysfunction with varying degrees (ejection fraction <55%) was present in 90% of the patients. Mean ejection fraction and fractional shortening were 34±13% and 17±6.5%, respectively. All patients were performed balloon aortic valvuloplasty. Peak-to-peak aortic valvular gradients before and after valvuloplasty were 56±23 and 22±15 mmHg, respectively. Early mortality rate was 31%.

Conclusion: Mortality rate is high in newborns with endocardial fibroelastosis associated with critical aortic stenosis. Identifying the patients whose chance of survival is higher with univentricular paliation rather than valvotomy or valvuloplasty may provide superior early results.

Keywords: Aortic valvuloplasty; critical aortic stenosis; endocardial fibroelastosis; newborn.

ÖZ

Amaç: Bu çalışmada kritik aort darlığına bağlı endokardiyal fibroelastozisi olan hastaların özellikleri, bulguları ve prognozu değerlendirildi.

Çalışma planı: Çalışmaya Ocak 2008 - Temmuz 2014 tarihleri arasında kritik aort darlığına eşlik eden endokardiyal fibroelastozisi olan 22 yenidoğan (17 erkek, 5 kız; ort. yaş 7.5 gün; dağılım 0-28 gün) dahil edildi. Hastaların demografik, ekokardiyografik ve kardiyak kateterizasyon ve anjiyografi bulguları incelendi.

Bulgular: Hastaların başvuru anındaki ortalama vücut ağırlıkları 3.3 kg (dağılım 2-4.8 kg) idi. Hastaların %90'ında değişik derecelerde sol ventrikül sistolik disfonksiyonu (ejeksiyon fraksiyonu <%55) vardı. Ortalama ejeksiyon fraksiyonu ve fraksiyonel kısalma sırasıyla %34±13 ve %17±6.5 idi. Tüm hastalara balon aortik valvüloplasti uygulandı. Valvüloplasti öncesi ve sonrası pikten pike sistolik gradiyent ortalaması sırasıyla 56±23 ve 22±15 mmHg idi. Erken mortalite oranı %31 idi.

Sonuç: Kritik aort darlığına eşlik eden endokardiyal fibroelastozisi olan yenidoğanlarda mortalite oranı yüksektir. Yaşam şansı daha yüksek olan hastaların valvotomi veya valvüloplasti yerine univentriküler palyasyonla belirlenmesi daha iyi erken sonuçlar sağlayabilir.

Anahtar sözcükler: Aortik valvüloplasti; kritik aort darlığı; endokardiyal fibroelastozis; yenidoğan.

Available online at
www.tgkdc.dergisi.org
doi: 10.5606/tgkdc.dergisi.2015.10934
QR (Quick Response) Code

Received: September 19, 2014 *Accepted:* January 16, 2015

Correspondence: Vehbi Doğan, M.D. Dr. Sami Ulus Kadın Doğum, Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi Çocuk Kardiyoloji Kliniği, 06080 Altındağ, Ankara, Turkey.
Tel: +90 505 - 319 01 86 e-mail: vdogan86@yahoo.com

Endocardial fibroelastosis (EFE) is a rare disease that mainly involves the left ventricle, and it is characterized by the endomyocardial proliferation of collagen and elastic fibers, ventricular hypertrophy, and diffuse thickening of the endocardium.[1-3] The disease can be primary (i.e., not associated with any structural heart defect) or secondary to various congenital heart disease, with the latter being far more common. Secondary EFE occurs in association with underlying cardiovascular anomalies that lead to persistent, increased ventricular wall tension along with an inability to meet the increased myocardial oxygen demands. The secondary form most notably occurs as a frequent complication of congenital aortic stenosis, for example hypoplastic left heart syndrome (HLHS), coarctation of the aorta, congenital mitral stenosis, or coronary artery anomalies.[3] In addition, the presence of EFE in patients with congenital aortic stenosis is known to be associated with increased mortality and left ventricular dysfunction.[1,4,5] In this report, we describe the characteristics and results of our patients with EFE associated with neonatal critical aortic stenosis.

PATIENTS AND METHODS

Forty-six newborn patients [(17 boys, 5 girls; mean age 7.5 days; range 0 to 28 days); median weight at presentation 3.3 kg (range 2.0-4.8 kg)] who were diagnosed with EFE related to critical aortic stenosis and biventricular circulation and who underwent a neonatal balloon aortic valvuloplasty at our center between January 2008 and July 2014 were identified from the hospital medical records and cardiac catheterization database and included in this study. Those with HLHS and univentricular circulation were excluded. All of the patients underwent initial percutaneous transcatheter balloon dilation of the aortic valve using the technique previously described by Justo et al.[6] The patients' demographic characteristics, clinical status before the intervention and at the last follow-up, procedural characteristics and hemodynamic conditions, and outcomes were obtained from their records. Furthermore, the echocardiographic findings, such as the increased endocardial echo-brightness, poor contractility, and globular shape of the left ventricle, were suggestive of EFE.

Statistical analysis

Frequency, mean ± standard deviation (SD), or the median with minimum and maximum were used to present the data, as appropriate, and all analyses were carried out using the IBM SPSS Statistics for Windows, version 21.0 software program (IBM Corporation, Armonk, NY, USA).

RESULTS

Of the 46 patients in our study, 22 (48%) had varying degrees of EFE, and their demographic, clinical, and echocardiographic results along with their catheterization and angiographic findings are given in Table 1. All of the patients were at term, and a fetal diagnosis of the aortic stenosis was made in four (18.2%) of them. Of the 22 patients, 72% (n=16) presented with low cardiac output or heart failure symptoms, 31% (n=7) had multiorgan dysfunction, and 50% (n=11) were mechanically ventilated before and during the cardiac catheterization.

The most common site for EFE was the papillary muscles of the mitral valve (90%) while involvement of the left ventricular posterior wall and the interventricular septum were seen in 36% (n=8) and 27% (n=6) of the patients respectively (Figure 1). At admission, varying degrees of left ventricular systolic dysfunction [ejection fraction (EF) <55%] were present in 90% of the patients (n=20), and the mean EF and fractional shortening (FS) were 34±13% and 17±6.5% respectively. Echocardiography also revealed a systolic peak-to-peak aortic valvular gradient of 43.7±18.5 mmHg (range 20-75). In addition, all of the patients underwent a balloon valvuloplasty on a trial basis. During the cardiac catheterization and angiography, the mean left ventricular end-systolic and end-diastolic pressures were 114±33 and 8.6±6.4 respectively while the mean systolic peak-to-peak aortic valvular gradient by pullback was 56±23 mmHg. However, after the aortic balloon valvuloplasty, the mean gradient decreased to 22±15 mmHg.

Six of the 22 patients (27%) died during their initial hospital stays because of severe left heart dysfunction and heart failure, with five (23%) succumbing after the balloon aortic valvuloplasty and one (4.5%) during a valvotomy. Additionally, one (4.5%) died two months after being discharged because of aspiration pneumonia. Surgical intervention was performed on three (14%) patients. One of these underwent an aortic valvotomy while another developed an aortic intimal flap after being catheterized. The other pateint had an operation for an associated coarctation of the aorta. The mean follow-up time for the 15 survivors was 38±20 months. In addition, one patient also underwent a dilated cardiomyopathy (4.5%). The survivors also underwent a follow-up echocardiogram that showed

Table 1. The patients' demographic, clinical, echocardiographic, catheterization, and angiographic findings

Demographic characteristics	n	%	Mean±SD
Gender			
Male	17		
Female	5		
Age in days			7.5±9.5
Weight in grams			3300±740
Clinical condition at admission			
Mechanical ventilation	11	50	
Multi-organ failure	10	45	
Prenatal diagnosis	4	18.2	
Echocardiographic findings at admission			
Maximum systolic gradient (mmHg)			43.7±18.5
Ejection fraction (%)			34±13
Fractional shortening			17±6.5
Cardiac catheterization and angiography			
Left ventricular end-systolic pressure (mmHg)			114±33
Left ventricular end-diastolic pressure (mmHg)			8.6±6.4
Gradient before valvuloplasty (mmHg)			56±23
Gradient after valvuloplasty (mmHg)			22±15
Clinical outcome			
Follow-up time in months			38±20
Second catheterization	2	9	
Operation	3	13	
Dilated cardiomyopathy	1	4.5	
Deaths	7	31	

SD: Standard deviation.

aortic valve insufficiency in the majority of the patients, with it being classified as moderate-to-severe in five (33.3%) of these.

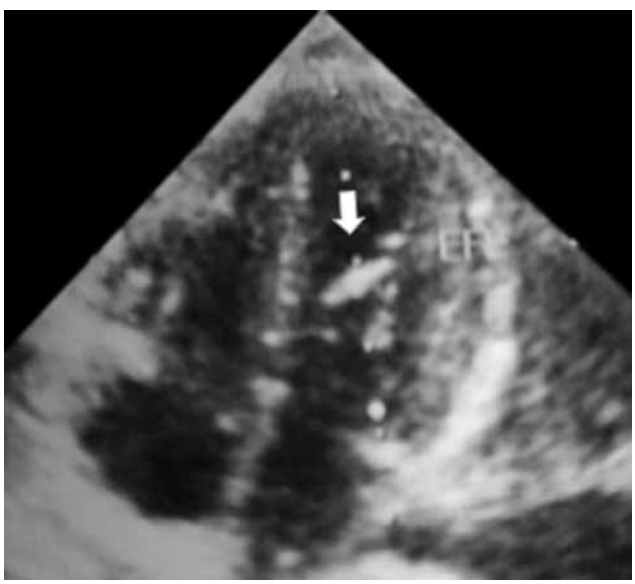

Figure 1. Parasternal four chamber echocardiographic view showing the endocardial fibroelastosis involving the papillary muscles of the mitral valve.

DISCUSSION

Critical neonatal aortic stenosis results in severe left ventricular hypertension (HT), left ventricular hypertrophy, and finally endothelial disruption represented as EFE. This disease is thought to occur as a result of high left ventricular pressure that leads to subendocardial ischemia. Then the endocardial smooth muscle cells proliferate and turn into fibroblasts, which produce collagen and elastine under myocardial stress. This fibroelastic reaction occurs mostly during the fetal period but it does continue to a lesser extent in the postnatal period through infancy.[2,7-9] Furthermore, smaller left ventricular size, progressive hypertrophy of the left ventricular wall, and greater hyperechogenicity of the endocardium can be seen as the gestational age increases, and the endocardial thickening gives rise to a decrease in left ventricular compliance, impaired diastolic function, and global hypokinesia.[5,10]

Endocardial fibroelastosis is characterized by an opaque, pearly-white thickening caused by the proliferation of collagen and elastic fibers. It occurs initially in the subendocardial region and rarely extends to the subepicardial region. A diagnosis

of EFE via echocardiography may be made on the basis of the increased echodensity of the endocardium and the poor contractility of the ventricle.[2,5,11] Sharland et al.[2] demonstrated the correlation between the echocardiographic diagnosis of EFE and the postmortem findings in patients with aortic valve anomalies. In addition, Stranzinger et al.[11] demonstrated that magnetic resonance imaging (MRI) that features perfusion and myocardial delayed enhancement can be useful for establishing the diagnosis. Moreover, the involvement of the myocardium can be diffuse or patchy, with the most common site being the papillary muscles.[3] This was also the preferred location in our patients.

In newborns with severe aortic stenosis, heart failure that is resistant to medical treatment creates a problem that usually necessitates an emergency valvuloplasty or a valvotomy. Furthermore, several studies have found an association between the higher mortality rates in these patients and the small size of the left ventricles as well as the presence of EFE.[1,5,10]

Aortic balloon valvuloplasties and surgical valvotomies offer similar short- and mid-term palliation. However, balloon valvuloplasty patients have higher reintervention rates but shorter hospital and ICU stays and reduced immediate morbidity. They also have less severe aortic regurgitation.[12-15] In our study, all of the patients initially underwent the balloon valvuloplasty procedure, which was deemed to be effective in 86.3% of the patients (n=19) with respect to the decreased pressure gradient. However, in two of the patients, a second valvuloplasty was required at the postprocedural first and second months respectively.

Our study included patients with critical aortic stenosis as well as biventricular circulation and varying degrees of EFE. Despite the high success rate associated with the valvuloplasties in our patients, the overall early mortality rate was 31% (n=7). However, it was only 8.3% (2/24) for those without EFE. Other studies have reported similar early mortality rates for surgical valvotomies and balloon valvuloplasties in patients with critical aortic stenosis, with rates ranging between 10 and 20%.[13-15]

In a study by McCrindle et al.,[13] the early mortality rates after surgical and transcatheter interventions for neonatal critical aortic stenosis with biventricular circulation were 18% and 11% respectively, and McElhinley et al.,[14] reported that the early mortality rate after an aortic balloon valvuloplasty was 14%. In this study, 11 of the patients underwent conversion to a functionally univentricular circulation, but five of these died in the early postoperative period.

Only four of the 22 patients in our study had a prenatal diagnosis of EFE and aortic stenosis, and these were referred to our hospital late in the pregnancy. Even though we performed an early postnatal aortic balloon valvuloplasty on our patients, six died during the neonatal period.

It has been shown that in utero left heart obstructive lesions are associated with the development or progression of left heart hypoplasia, which may in turn influence the postnatal outcome.[8,9] In several studies, the use of fetal aortic balloon valvuloplasties has been effective in preventing midgestational aortic stenosis from developing into HLHS and EFE in a subset of patients.[10,16-18] However, this procedure must be performed before significant left heart hypoplasia occurs and should not be carried out on fetuses with aortic stenosis that will not progress to HLHS. McElhinley et al.[5] reported that fetal EFE severity corresponded with some indices related to left heart size, geometry, and function as well as the probability of a postnatal biventricular outcome. In their study, they used a four-point grading system and found a significantly higher maximum instantaneous aortic stenosis gradient, an increase in left ventricular pressure with less globular left ventricular geometry, and a significantly higher time-indexed increase in the left ventricular end-diastolic volume from the pre-intervention stage to the late gestation period in patients with grade 1 EFE versus those with more severe EFE.

In a study by Mäkikallio et al.,[19] of the 23 patients diagnosed with aortic stenosis who had a normal left ventricular length at ≤ the 30th gestational week without fetal intervention, only six had biventricular circulation. In addition, they found that a retrograde flow in the transverse aortic arch, left-to-right shunting across the foramen ovale, a monophasic mitral inflow, and significant left ventricular dysfunction were risk factors for the progression to HLHS.

Patients who have biventricular circulation after a fetal valvuloplasty frequently have diastolic dysfunction.[1,10] In fact, Friedman et al.[10] determined that the more extensive the EFE in a patient, the worse the diastolic dysfunction.

Furthermore, Hickey et al.[20] analyzed the risk of reintervention in patients who underwent a biventricular repair to treat neonatal critical aortic stenosis along with the effects of this reintervention

on the survival of 139 neonates and found that 15 required reintervention within 30 days of the index biventricular procedure. Moreover, there was a 60% mortality rate associated with these patients versus a rate of 27% for those who underwent an index univentricular repair technique. Hence, they concluded that early intervention implies a poor prognosis and might reflect incorrect management decisions such as choosing the univentricular rather than the biventricular approach.

Our study had some limitations. Not only was it retrospective in nature, but it lacked some important echocardiographic indices, such as the z-scores of the left heart structures. However, we believe we still accomplished our goal, which was to emphasize the high mortality rate in cases with critical arotic stenosis and EFE in spite of technically successful interventions.

Conclusion

The presence of EFE is known to be related with an increase in mortality and morbidity in patients with critical aortic stenosis, and we observed this to be true in our study. Thus, identifying those patients with a better chance of survival after receiving univentricular palliation versus undergoing a valvotomy or valvuloplasty could lead to better early results.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Mocellin R, Sauer U, Simon B, Comazzi M, Sebening F, Bühlmeyer K. Reduced left ventricular size and endocardial fibroelastosis as correlates of mortality in newborns and young infants with severe aortic valve stenosis. Pediatr Cardiol 1983;4:265-72.
2. Sharland GK, Chita SK, Fagg NL, Anderson RH, Tynan M, Cook AC, et al. Left ventricular dysfunction in the fetus: relation to aortic valve anomalies and endocardial fibroelastosis. Br Heart J 1991;66:419-24.
3. Saffitz JE. The heart. In: Rubin R, Strayer DS, Rubin E, editors. Rubin's Pathology: Clinicopathologic Foundations of Medicine. Baltimore: Lipincott Williams & Wilkins; 2012. p. 479-97.
4. Han RK, Gurofsky RC, Lee KJ, Dipchand AI, Williams WG, Smallhorn JF, et al. Outcome and growth potential of left heart structures after neonatal intervention for aortic valve stenosis. J Am Coll Cardiol 2007;50:2406-14.
5. McElhinney DB, Vogel M, Benson CB, Marshall AC, Wilkins-Haug LE, Silva V, et al. Assessment of left ventricular endocardial fibroelastosis in fetuses with aortic stenosis and evolving hypoplastic left heart syndrome. Am J Cardiol 2010;106:1792-7.
6. Justo RN, McCrindle BW, Benson LN, Williams WG, Freedom RM, Smalhorn JF. Aortic valve regurgitation after surgical versus percutaneous balloon valvotomy for congenital aortic valve stenosis. Am J Cardiol 1996;77:1332-8.
7. Allan LD, Sharland G, Tynan MJ. The natural history of the hypoplastic left heart syndrome. Int J Cardiol 1989;25:341-3.
8. Hornberger LK, Sanders SP, Rein AJ, Spevak PJ, Parness IA, Colan SD. Left heart obstructive lesions and left ventricular growth in the midtrimester fetus. A longitudinal study. Circulation 1995;92:1531-8.
9. Simpson JM, Sharland GK. Natural history and outcome of aortic stenosis diagnosed prenatally. Heart 1997;77:205-10.
10. Friedman KG, Schidlow D, Freud L, Escobar-Diaz M, Tworetzky W. Left ventricular diastolic function and characteristics in fetal aortic stenosis. Am J Cardiol 2014;114:122-7.
11. Stranzinger E, Ensing GJ, Hernandez RJ. MR findings of endocardial fibroelastosis in children. Pediatr Radiol 2008;38:292-6.
12. Tokel K, Ekici E, Kutsal A, İkizler C. Konjenital aort dalıklarında balon valvuloplasti: erken ve orta dönemli sonuçlar. Türk Kardiyol Dern Arş 1997;25:108-13.
13. McCrindle BW, Blackstone EH, Williams WG, Sittiwangkul R, Spray TL, Azakie A, et al. Are outcomes of surgical versus transcatheter balloon valvotomy equivalent in neonatal critical aortic stenosis? Circulation 2001;104:152-8.
14. McElhinney DB, Lock JE, Keane JF, Moran AM, Colan SD. Left heart growth, function, and reintervention after balloon aortic valvuloplasty for neonatal aortic stenosis. Circulation 2005;111:451-8.
15. Zain Z, Zadinello M, Menahem S, Brizard C. Neonatal isolated critical aortic valve stenosis: balloon valvuloplasty or surgical valvotomy. Heart Lung Circ 2006;15:18-23.
16. Tworetzky W, Wilkins-Haug L, Jennings RW, van der Velde ME, Marshall AC, Marx GR, et al. Balloon dilation of severe aortic stenosis in the fetus: potential for prevention of hypoplastic left heart syndrome: candidate selection, technique, and results of successful intervention. Circulation 2004;110:2125-31.
17. McElhinney DB, Marshall AC, Wilkins-Haug LE, Brown DW, Benson CB, Silva V, et al. Predictors of technical success and postnatal biventricular outcome after in utero aortic valvuloplasty for aortic stenosis with evolving hypoplastic left heart syndrome. Circulation 2009;120:1482-90.
18. Arzt W, Wertaschnigg D, Veit I, Klement F, Gitter R, Tulzer G. Intrauterine aortic valvuloplasty in fetuses with critical aortic stenosis: experience and results of 24 procedures. Ultrasound Obstet Gynecol 2011;37:689-95.

19. Mäkikallio K, McElhinney DB, Levine JC, Marx GR, Colan SD, Marshall AC, et al. Fetal aortic valve stenosis and the evolution of hypoplastic left heart syndrome: patient selection for fetal intervention. Circulation 2006;113:1401-5.

20. Hickey EJ, Caldarone CA, Blackstone EH, Williams WG, Yeh T Jr, Pizarro C, et al. Biventricular strategies for neonatal critical aortic stenosis: high mortality associated with early reintervention. J Thorac Cardiovasc Surg 2012;144:409-17.