CYANOTIC CHILD WITH MURMUR
CRIANÇA CIANÓTICA COM SOPRO

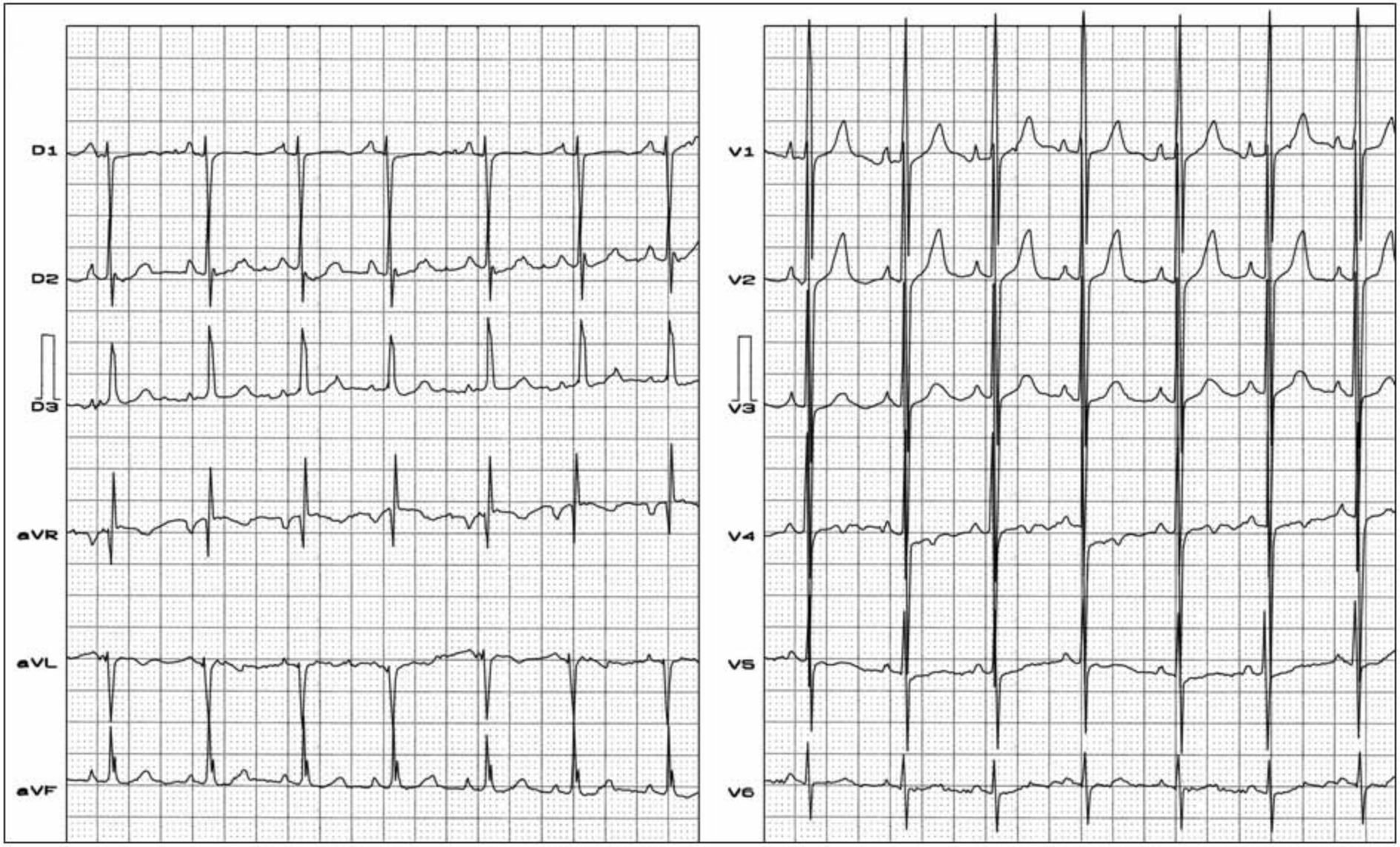
Andrés Ricardo Pérez Riera, MD
Chief of Electovectorcardiography Sector - Cardiology Discipline - ABC Faculty – ABC Foundation – Santo André – São Paulo – Brazil
riera@uol.com.br

Boy, with 5 years old. The mother refers cardiac murmur detected at the birth. Birth weight was low (2,200kg and 45cm). With five weeks of life, she noted a bluish color in his skin. She also noted shortness of breath during feeding or crying, and later with walking or exertion. One week ago, the boy had paroxysmal dyspnea episode associated with marked cyanosis of short duration, that repeated with a similar episode yesterday, but this time followed by fleeting syncope. The mother observed that the boy prefers lying one side hunched up like a fetus or in the "knee-chest position". Two episodes of hemoptysis was reported in the last year. Physical: Clear low development in relation to the age. Apical impulse not displaced with normal location, surface and amplitude. Single S_2 in the pulmonary area. A cardiac short systolic ejection murmur is ausculted with low intensity along the left sternal border in the third and fourth left interspaces. At palpation there are not systolic thrill but, a right ventricular predominance was noted. Insinuation of digital clubbing.

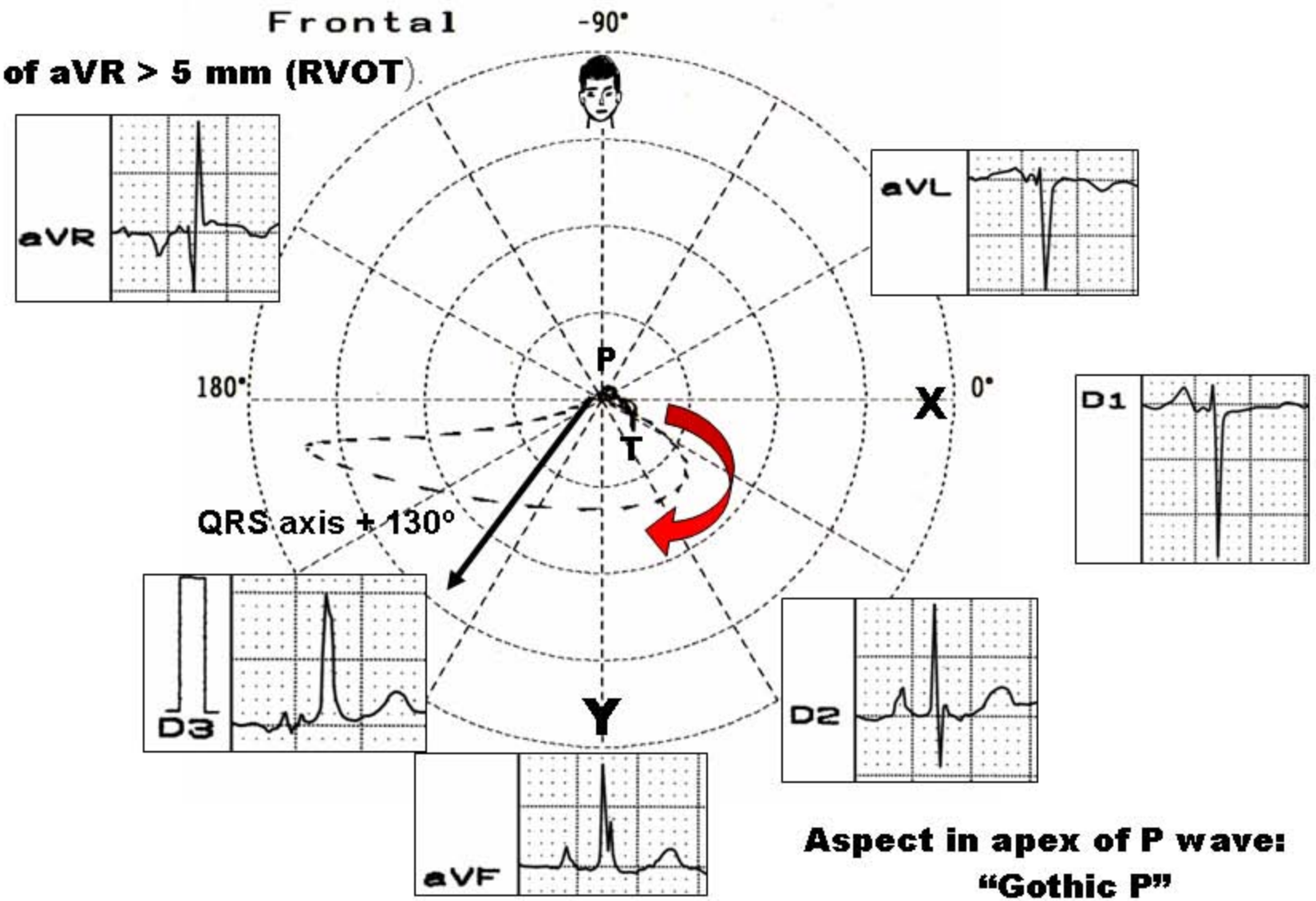
Menino, cinco anos de idade. A mão refere sopro cardíaco detectado ao nascimento. Baixo peso e altura ao nascimento (2,200kg e 45cm). Com cinco semanas de vida, a mãe notou uma cor azulada na pele. Ela também notou dispnea durante a amamentação ou choro, e mais tarde ao caminhar ou exercitar-se. Semana passada, apresentou episódio dispnea paroxistica com intensificação da cianose, de curta duração, que se repetiu com características similares ontem, desta vez seguido de síncope fugaz. A mãe observou que o garoto prefere deitar-se de lado em posição fetal, com os joelhos contra o peito. Dois episódios de hemoptise foram observados neste ultimo ano.

EF: Notável hipodesenvolvimento para a idade. Ictus não deslocado com características normais em sua localização, superfície e amplitude. Segunda bula única com foco pulmonar. Sopro sistólico ejetivo curto de baixa intensidade auscultado ao longo da borda esternal esquerda no terceiro e quarto espaço intercostal. A palpação, ausência de frêmito mas nota-se o latido do VD. Insinuação de baqueteamento digital.

Name: MPRS; **Age:** 5yo; **Gender:** Male; **Weight:** 12,4kg; **Height:** 94cm
Ethnic Group: Caucasian; **Date:** December, 14, 2010

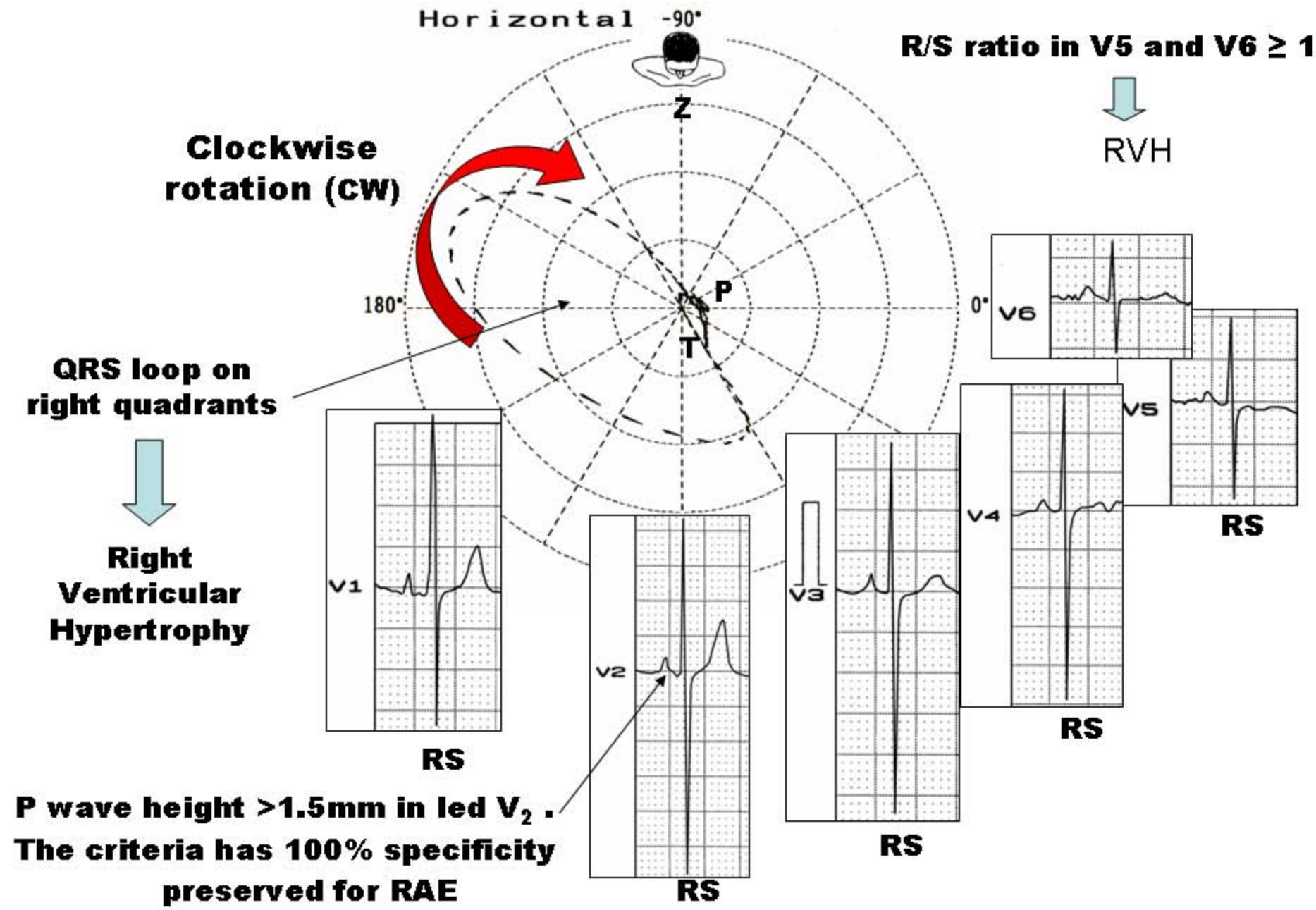


ECG/VCG CORRELATION FRONTAL PLANE



In Fallot´s tetralogy (TOF): only in 5% of cases there are criteria of RAE.

ECG/VCG CORRELATION HORIZONTAL PLANE



R/S ratio in V5 and V6 ≥ 1

RVH

Clockwise rotation (CW)

QRS loop on right quadrants

Right Ventricular Hypertrophy

P wave height >1.5mm in led V_2 .
The criteria has 100% specificity preserved for RAE

Clinical diagnosis: Fallot´s Tetralogy (TOF). This boys has several clinical element of suspect for TOF:

1)Low weight at birth

2)Cyanosis from developing in the first year of life.

3)Dyspnea upon exertion

4)Poor or retard in the development

5)Two episode of anoxic spells

6)Clubbing of fingers insinuation

7)Squatting equivalent: lying one side hunched up like a fetus or in the "knee-chest position".

8)Short systolic ejection murmur with low intensity along the left sternal border in the third and fourth left interspaces. In TOF This the murmur has it intensity inversely with the degree of RVOT obstruction. More cyanotic patients have greater obstruction and a softer murmur. An acyanotic patient with TOF (pink TOF) has a long, loud, systolic murmur with a thrill along the RVOT.

Pink-Fallot(mild)

Intense murmur, mild cyanosis, less evident RVH, late or absent cyanosis, O_2 saturation 90% to 100%.

Classical TOF (Moderate)

Systolic RVH of adaptation: R/S (R>S) in V_3R and V_1 with notch at the foot of the R wave and sudden transition from V_1 to V_2, i.e. predominantly positive QRS complexes in V_1 for rS type complexes in V_2. The sign is present in 50% of these cases.

TOF with pulmonary atresia, pseudo-truncus or extreme(Extreme)

Similar before situation + mild murmur + intense cyanosis

9) Right ventricular predominance was noted

Right atrial Enlargement: Aspect in apex of P wave: "Gothic P" P wave height >1.5mm in led V2.

Right ventricular hypertrophy on ECG: Right axis deviation, R/S ratio in V1 >1, R wave of V1 and V2 , > 7 mm, *RS pattern in left leads V5-V6,* positive T wave in V1 after 3 days of life and up to 6 years of age, when the R/S ratio in this lead is > 1

RVH type A vectorcardiographyc on horizontal plane (QRS loop with clock wise rotation and located on right quadrants. It indicates severe RVH, QRS loop of clockwise rotation in the horizontal plane and of location predominant in right anterior quadrant. The Initial forces are preserved but without convexity to the right and to the front. They are directed to front and leftward.

In TPF systolic RVH of adaptation: the RV adapts to a regimen of systemic pressure: RV pressure = the right intraventricular pressure does not exceed the systemic one. Selective lateral-posterior-basal growth of the RV.

Atypical ECG/VCG features

1. Presence of Right Atrial Enlargement (RAE) criteria: In Fallot´s tetralogy (TOF): only in 5% of cases there are criteria of RAE[1]: apiculate aspect of P wave in inferior leads without reaching a voltage of 2.5 mm Aspect in apex of P wave: "Gothic P" + P wave height >1.5mm in led V_2 . The criteria has 100% specificity preserved for RAE.

2. The great voltage or wide isodyphasim of QRS complexes on intermediate precordial leads (In this case RS pattern from V_1-V_6). This signal is suggestive of biventricular overload: Katz-Walchtel`s signal[2] or Katz-Walchtel phenomenon.

1. **Pileggi F, Bocanegra J, Tranchesi J, Macruz R, Borges S, Portugal O, Villarinho MG, Barbato E, Decourt LV. The electrocardiogram in tetralogy of Fallot: a study of 142 cases. Am Heart J. 1960 May; 59: 667-680.**
2. **Katz LN, Wachtel H. The Diphasic QRS type of electrocardiogram in congenital heat disease. Am Heart J 1937;13:202.**

ELECTROCARDIOGRAM IN TOF

1. **P wave:** evidence of right atrial enlargement (RAE) is uncommon. Even in older children the incidence of RAE is 1:10[1]. In adults RAE is observed in 65% of cases. In older patients was observed in 20% to 30% of cases[2].
2. **QRS axis:** moderate to marked right-axix deviation between +120º to 210º is always observed, except in cases with increased pulmonary flow. In such circumstances the axis is +60° to 90°.In rare cases of Fallot´s pentalogy and the Noonan syndrome left axis deviation is observed.
3. **QRS:** Singnificative QRS prolongation, before or after pulmonary valve replacement (PVR), and the absence of a reduction in QRS duration after PVR, are major determinants of adverse outcome during long-term follow-up of patients with TOF[3]. PVR for severe pulmonary regurgitation after TOF repair is a safe procedure. However, the indications for such an operation in asymptomatic patients remain controversial. Further studies are required to better delineate the timing of PVR in this patient group. PVR may be beneficial for refractory arrhythmias, even in TOF patients with a with a severely dilated -RV, but it is difficult to completely normalize the hemodynamics and resolve the arrhythmogenicity[4].

1. Donzelot E, Metianu C, Durand M, Chrechi A, Vlad P. Electrocardiogram in tetralogy of Fallot; study of 100 cases. Arch Mal Coeur Vaiss. 1951 Feb;44:97-118.
2. Folli G, Capretti G, Joly F. Importance of hemodynamic factor in formation of electrocardiographic picture of right ventricular hypertrophy in congenital heart diseases.Cuore Circ. 1953 Oct;37:257-270.
3. Scherptong RW, Hazekamp MG, Mulder BJ, Wijers O, Swenne CA, van der Wall EE, Follow-up after pulmonary valve replacement in adults with tetralogy of Fallot: association between QRS duration and outcome. J Am Coll Cardiol. 2010 Oct 26;56:1486-1492.
4. Miyazaki A, Yamamoto M, Sakaguchi H, Tsukano S, Kagisaki K, Suyama K, et al. Pulmonary valve replacement in adult patients with a severely dilated right ventricle and refractory arrhythmias after repair of tetralogy of fallot.Circ J. 2009 Nov;73:2135-2142.

QRSd in postoperative TOF patients reflects mainly abnormalities of the RVOT rather than the RV body itself. Thus, prevention and treatment of mechanical asynchrony and malignant arrhythmia should focus on the RVOT. Indications for cardiac resynchronization therapy after TOF repair warrant further investigation[1].

They are a common in children and adolescents after surgical repair of TOF; however, they are infrequent and benign in most of the cases. There is an association of ventricular arrhythmia with moderate and severe RVH, as well as with right ventricle-to-pulmonary artery gradient (RV/PA) > 45 mmHg. The logistic regression analysis showed that increased RV/PA gradient is an independent strong predictor of ventricular arrhythmia[2]. Dyssynchronous RV-septal wall mechanics occurs early after TFO repair. The magnitude of dyssynchrony appears to interact synergistically with pulmonary regurgitation to influence RV dimension and early outcome[3]. The Brugada and Vereckei algorithms have lower diagnostic accuracy in the pediatric population and in patients with congenital heart disease than in the adult population. Left superior axis deviation and a notch in the QRS downstroke were more commonly associated with VT, whereas a positive QRS deflection in V_1 was more commonly associated with SVT in this population[4]. Additionally, fQRS is an arrhytmogenic marker in TOF[5].

1. Uebing A, Gibson DG, Babu-Narayan SV, Diller GP, Dimopoulos K, Goktekin O, et al. Right ventricular mechanics and QRS duration in patients with repaired tetralogy of Fallot: implications of infundibular disease. Circulation. 2007 Oct 2;116:1532-1339.
2. Pfeiffer ME, Andrea EM, Serra SM, Assumpção CR, Herdy GV. Late clinical and functional assessment of arrhythmias in children after repair of Tetralogy of Fallot. Arq Bras Cardiol. 2010 Sep;95:295-302.
3. Peng EW, Lilley S, Knight B, Sinclair J, Lyall F, Macarthur K, et al. Synergistic interaction between right ventricular mechanical dyssynchrony and pulmonary regurgitation determines early outcome following tetralogy of Fallot repair. Eur J Cardiothorac Surg. 2009 Oct;36:694-702.
4. Ceresnak SR, Liberman L, Avasarala K, Tanel R, Motonaga KS, Dubin AM. Are wide complex tachycardia algorithms applicable in children and patients with congenital heart disease? J Electrocardiol. 2010 Nov-Dec;43:694-700.
5. Jacob S, Agarwal K, Afonso L. QRS fragmentation in patients with repaired tetralogy of Fallot. Am J Cardiol. 2009 Sep 1;104:740-741.

TOF includes four anatomical abnormalities:

1. Right ventricular outflow tract obstruction: Stenosis of the outflow tract of the right ventricle (infundibulum).
2. Ventricular Septal Defect (VSD) or Defect in the interventricular septum(VSD)
3. Dextroposition of the aorta and consequently overriding aorta
4. Secondary Right ventricular hypertrophy/ enlargement/ (RVH/RVE)

OTHERS DENOMINATIONS: Fallot's syndrome, Fallot's tetrad and Steno-Fallot tetralogy

The deformation of the heart known as the tetralogy of Fallot was first described in 1671 by the Danish physician, natural scientist, bishop – and later Saint –Niels Stensen (Nicolaus Stenonius). At least some forty case descriptions precluded that of Fallot. His delineation from 1888 was based on details of the pathological features of two persons with the condition, together with a survey of some 50 previous observations. Fallot considered the deformity as an entity and as such the most common cause of cardiac cyanosis. By his contemporaries Fallot's observations were considered to be solely of theoretical or curious interest. Congenital heart malformations attracted little attention, as there was still no therapy available. Fallot's work first received serious attention when Paul Dudley White (1886-1973) in 1931 discussed the malformation and translated Fallot's works.

1. **Stensen N. :*Embryo monsto affinis Parisiis dissectur.* Acta Medica & Philosophica Hafniensia, 1671-72, 1: 202-203.**
2. **Fallot E. L. A. :*Contribution à l'anatomie pathologique de la maladie bleue (cyanose cardiaque).* Marseille médical, 1888, 25: 77-93, 138-158, 207-223, 341-354, 370-386, 403-420.**

EPIDEMIOLOGIC DATES: TOF is the most frequent cyanotic congenital heart disease after 1 year of age, and it is associated with a wide range of intra- and extracardiac phenotypes. TOF occurs in 3 of every 10,000 live births, and accounts for 7-10% of all congenital cardiac malformations. TOF is the most frequent one is cyanotic congenital heart disease after 1 year. The etiology is multifactorial, but reported associations include untreated maternal diabetes, phenylketonuria, and intake of retinoic acid. Associated chromosomal anomalies can include trisomies 21, 18, and 13, but recent experience points to the much more frequent association of microdeletions of chromosome 22. Specific genetic associations include: JAG1[2]; NKX2-5[3]ZFPM2[4]; VEGF[5] . TOF is common in individuals with hemizygous deletions of chromosome 22q11.2 that remove the cardiac transcription factor TBX1[1]. 22q11.2 deletion represents the most common known cause of TOF, and that the associated cardiac phenotype is distinct for obstruction of the proximal pulmonary artery, hypoplastic central pulmonary arteries and subclavian artery anomalies. Atrioventricular septal defect associated with TOF is very suggestive of trisomy 21 and almost excludes 22q11.2 deletion. TOF cause is thought to be due to environmental or genetic factors or a combination.

1. Griffin HR, Töpf A, Glen E, Zweier C, Stuart AG, Parsons J, et al. Systematic survey of variants in TBX1 in non-syndromic tetralogy of Fallot identifies a novel 57 base pair deletion that reduces transcriptional activity but finds no evidence for association with common variants. Heart. 2010 Oct;96:1651-1655.
2. Eldadah ZA, Hamosh A, Biery NJ, Montgomery RA, Duke M, Elkins R, et al. Familial Tetralogy of Fallot caused by mutation in the jagged1 gene. Hum Mol Genet. 2001 Jan 15;10:163-169.
3. Goldmuntz E, Geiger E, Benson DW. NKX2.5 mutations in patients with tetralogy of fallot. Circulation. 2001 Nov 20;104:2565-2568.
4. Pizzuti A, Sarkozy A, Newton AL, Conti E, Flex E, Digilio MC, et al. Mutations of ZFPM2/FOG2 gene in sporadic cases of tetralogy of Fallot. Hum Mutat. 2003 Nov;22:372-377.
5. Lambrechts D, Devriendt K, Driscoll DA, Goldmuntz E, Gewillig M, Vlietinck R, et al. Low expression VEGF haplotype increases the risk for tetralogy of Fallot: a family based association study. J Med Genet. 2005 Jun;42:519.
6. Rauch R, Hofbeck M, Zweier C, Koch A, Zink S, Trautmann U, Comprehensive genotype-phenotype analysis in 230 patients with tetralogy of Fallot. J Med Genet. 2010 May;47:321-331

Gender: It occurs slightly more often in males than in females.
The risk of recurrence in families is 3%. Useful diagnostic tests are the chest radiograph, ECG, and echocardiogram. The echocardiogram establishes the definitive diagnosis, and usually provides sufficient information for planning of treatment, which is surgical. Approximately half of patients are now diagnosed antenatally.

Differential diagnosis includes primary pulmonary causes of cyanosis, along with other cyanotic heart lesions, such as critical pulmonary stenosis and transposed arterial trunks.

Management
Neonates who present with ductal-dependent flow to the lungs will receive prostaglandins to maintain ductal patency until surgical intervention is performed.

Initial intervention may be palliative, such as surgical creation of a systemic-to-pulmonary arterial shunt, but the trend in centres of excellence is increasingly towards neonatal complete repair.

Centres that undertake neonatal palliation will perform the complete repair at the age of 4 to 6 months.

Follow-up in patients born 30 years ago shows a rate of survival greater than 85%. Chronic issues that now face such adults include pulmonary regurgitation, recurrence of pulmonary stenosis, and ventricular arrhythmias.

As the strategies for surgical and medical management have progressed, the morbidity and mortality of those born with TOF in the current era is expected to be significantly improved.