Impact of pulmonary regurgitation and age at surgical repair on textural and functional right ventricular myocardial properties in patients with tetralogy of Fallot

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Integrated backscatter; Pulmonary regurgitation; Tetralogy of Fallot.

Background. **The aim of this study was to identify non-invasively the potential impact of pulmonary regurgitation and age at surgical repair on the right ventricular (RV) textural and functional myocardial properties in patients operated on for tetralogy of Fallot (TOF).**

Methods. **We assessed the average intensity ($Int._{IB}$) and the cyclic variation (CV_{IB}) of the echocardiographic backscatter curve in 30 TOF patients (mean age 16.2 ± 8.3 years), who had undergone corrective surgery (mean age at repair 3.2 ± 2.6 years, range 0.2-11 years). They were divided into three age- and body surface area (BSA)-matched subgroups according to the results of the surgical repair: 12 patients had no significant postsurgical sequelae (group I), 12 patients had isolated moderate-severe pulmonary regurgitation (group II), and 6 patients had pulmonary regurgitation associated with significant (> 30 mmHg) RV outflow tract obstruction (group III). In addition, 30 age-, sex- and BSA-matched normal subjects were identified as the control group.**

Results. **In our study population, CV_{IB} was lower (7.86 ± 2.5 vs 10.6 ± 1.4 dB, p < 0.001) and $Int._{IB}$ higher (-18.6 ± 4.1 vs -21 ± 2.8 dB, p = 0.01) compared to the control group. Comparison between the control group and each subgroup of TOF patients showed: a) comparable values of CV_{IB} and $Int._{IB}$ in group I (10.6 ± 1.4 vs 9.4 ± 2.3 dB, p = 0.07; and -21 ± 2.8 vs -21.4 ± 2.3 dB, p = 0.7, respectively); b) $Int._{IB}$ was significantly different only in group III (-21 ± 2.8 vs -13.3 ± 4.6 dB, p < 0.0001), c) CV_{IB} was different either in group II or III (10.6 ± 1.4 vs 7.42 ± 2, p < 0.001; and 10.6 ± 1.4 vs 5.56 ± 1.8, p < 0.001, respectively). In addition, comparison of integrated backscatter indexes among the TOF subgroups revealed significant differences of CV_{IB} between group I and II (9.4 ± 2.4 vs 7.4 ± 2, p = 0.03) and between group I and III (9.4 ± 2.4 vs 5.56 ± 1.8, p = 0.004), and of $Int._{IB}$ between group I and III (-21.4 ± 2.3 vs -13.3 ± 4.66, p < 0.001) and between group II and III (-21.4 ± 2.3 vs -18.6 ± 2.8, p = 0.006). Group III patients, who had the most significant RV dilation, expressed as the ratio between RV and left ventricular end-diastolic diameter (0.55 ± 0.8) compared to group II (0.67 ± 0.11, p = 0.038) and group I (0.55 ± 0.87, p < 0.001), showed the lowest values of CV_{IB} (5.56 ± 1.8 dB) and the highest values of $Int._{IB}$ (-13.3 ± 4.6 dB). Finally, in our study population, both the degree of RV dilation and the age at surgical repair significantly correlated with $Int._{IB}$ (r = 0.49 and r = 0.4, p = 0.06 and p = 0.033, respectively) and inversely correlated with CV_{IB} (r = -0.55 and r = -0.53, p = 0.002 and p = 0.003, respectively).**

Conclusions. **In patients operated on for TOF: a) integrated backscatter analysis may identify patients with significant RV myocardial abnormalities related to postsurgical sequelae; b) residual pulmonary regurgitation, particularly if associated with pulmonary stenosis, appears to affect RV myocardial properties; c) an earlier repair of TOF may result in better preservation of myocardial characteristics.**

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Introduction

Although long-term survival after corrective surgery for tetralogy of Fallot (TOF) has become close to that of the general population[1,2], there is increasing evidence that both residual pulmonary regurgitation and age at surgical repair play a major role in determining postoperative right ventricular (RV) myocardial characteristics and function[3-6].

The response of the RV myocardium to pressure overload is age-dependent[7] and clinical follow-up of postoperative patients with TOF demonstrated the deleterious effects of pulmonary regurgitation on exercise performance and risk for arrhythmias[8,9]. Nevertheless, it remains unclear whether the textural and functional properties of the RV myocardium are related to the age at surgery and to the presence of significant pulmonary regurgitation.

Integrated backscatter (IB) analysis is a recent echocardiographic technique that allows a non-invasive characterization of the myocardium[10,11]. This technique has been used extensively to study the left ventricular (LV) myocardium in various diseases[12-15]. Recently, we have shown the ability of IB analysis to assess RV textural and functional properties, and to differentiate normal from pathological RV myocardium[16].

Thus, the aim of our study was to identify, by echocardiographic IB analysis, the potential impact of pulmonary regurgitation and age at surgical repair on the RV myocardium in patients operated on for TOF.

Methods

Our study population included 30 consecutive patients from January 2003 to September 2004 (mean age 16.2 ± 8.3 years), who had undergone corrective surgery for TOF (mean age at repair 3.2 ± 2.6 years, range 0.2-11 years), selected according to the following criteria: 1) transatrial approach for surgical repair, 2) no significant arrhythmias, 3) no relevant tricuspid regurgitation, 4) absence of isolated residual RV outflow tract obstruction and/or residual interventricular shunt, and 5) no symptoms and no cardiac medications.

They were divided into three age- and body surface area (BSA)-matched subgroups according to the results of the surgical repair: 12 patients had no significant postsurgical sequelae (group I), 12 patients had isolated moderate-severe pulmonary regurgitation (group II), and 6 patients had pulmonary regurgitation associated with significant (> 30 mmHg) RV outflow tract obstruction (group III). The three subgroups were comparable for the age at the operation and the length of the postsurgical follow-up.

Thirty age-, sex- and BSA-matched subjects without clinical and echocardiographic evidence of congenital or acquired heart disease were identified as the control group. All subjects were studied after informed consent was obtained.

Each patient underwent an echocardiographic evaluation (Sonos 5500, Agilent Technologies, Andover, MA, USA) using transducer frequencies appropriate for body size. In the normal subjects, a segmental approach was used to rule out congenital or acquired heart disease. In the TOF group, RV outflow tract obstruction was estimated by continuous wave Doppler from the peak velocity of the pulmonary stenosis jet using the simplified Bernoulli equation. Pulmonary regurgitation was quantified by Doppler evaluation as previously reported[17]. Measurements of the RV and LV internal dimensions were assessed at end-diastole according to methods established by the American Society of Echocardiography[18] and RV/LV end-diastolic diameter ratio was utilized as a measure of RV enlargement.

An Agilent Sonos 5500 echocardiograph with online acoustic densitometry software was utilized for two-dimensional IB image acquisition and analysis. All studies were performed with the broadband S 12 transducer (imaging bandwith ranging from 5 to 12 MHz) using the parasternal long-axis view. The methodological approach for IB analysis of the RV myocardium has been described previously[16].

From the time-intensity curve corrected with a smoothing (noise reduction) filter, we measured two IB parameters: the magnitude of cyclic variation of IB (CV_{IB}) and average myocardial IB intensity ($Int._{IB}$). The CV_{IB} was determined as the difference between peak and nadir IB values. The averaged myocardial $Int._{IB}$ of the pixels within the region of interest, obtained from the time-intensity curve, are represented as negative values after data normalization, that is, by subtracting the IB intensity of the adjacent pericardium from that of the RV myocardium.

All data are expressed as mean ± 1 SD. Comparisons of continuous variables were performed using a two-tailed Student's t-test. Multiple comparisons were performed using repeated analysis of variance measurements with *post-hoc* Bonferroni's test. The relation between the degree of RV dilation as well as the age at surgery and IB indexes were tested using linear regression analysis. A p value of < 0.05 indicated a significant relationship.

Results

Comparison between tetralogy of Fallot patients and control group (Table I). Accordingly to the selected criteria, TOF patients and control group were comparable for age (p = 0.64) and BSA (p = 0.74). On the other hand, TOF patients had increased RV end-diastolic diameter (p < 0.001) and RV/LV end-diastolic diameter ratio (p < 0.001).

In addition, IB analysis showed in TOF patients lower CV_{IB} (7.86 ± 2.5 vs 10.6 ± 1.4 dB, p < 0.001) and higher $Int._{IB}$ (-18.6 ± 4.1 vs -21 ± 2.8 dB, p = 0.01).

Comparison among control group and tetralogy of Fallot subgroups (Table II). Comparison of IB values between control group and each subgroup of TOF patients showed: a) comparable values of CV_{IB} and $Int._{IB}$

Table I. Clinical and echocardiographic data: comparison between control group and total tetralogy of Fallot (TOF) patients.

	TOF patients (n=30)	Control group (n=30)	p
Age (years)	15.28 ± 7.9	16.24 ± 8.3	0.64
BSA (m^2)	1.42 ± 0.5	1.46 ± 0.45	0.74
RVEDD (mm)	29.58 ± 7.5	22 ± 3.7	< 0.001
RVEDD/LVEDD ratio	0.6 ± 0.17	0.34 ± 0.07	< 0.001

BSA = body surface area; LVEDD = left ventricular end-diastolic diameter; RVEDD = right ventricular end-diastolic diameter.

Table II. Integrated backscatter analysis: comparison between control group and different subgroups of tetralogy of Fallot (TOF) patients.

	Control group	TOF group I	TOF group II	TOF group III
CV (dB)	10.6 ± 1.4	9.4 ± 2.3^#	7.4 ± 2°	5.56 ± 1.8§
Int. (dB)	-21 ± 2.8	-21.4 ± 2.3#◊	-18.6 ± 2.3	-13.3 ± 4.6§

CV = cyclic variation; Int = average intensity. ^ TOF group I vs TOF group II, $p < 0.05$; # TOF group I vs TOF group III, $p < 0.05$; ° control group vs TOF group II, $p < 0.05$; § control group vs TOF group III, $p < 0.05$; ◊ TOF group II vs TOF group III, $p < 0.05$.

in group I (10.6 ± 1.4 vs 9.4 ± 2.3 dB, p = 0.07; and -21 ± 2.8 vs -21.4 ± 2.3 dB, p = 0.7, respectively); b) $Int._{IB}$ was significantly different only in group III (-21 ± 2.8 vs -13.3 ± 4.6 dB, p < 0.0001), c) CV_{IB} was different either in group II or III (10.6 ± 1.4 vs 7.4 ± 2, p < 0.001; and 10.6 ± 1.4 vs 5.56 ± 1.8, p < 0.001, respectively).

Comparison among tetralogy of Fallot subgroups. Comparison among the three subgroups of TOF patients showed: a) CV_{IB} differed between group I and II (9.4 ± 2.4 vs 7.4 ± 2, p = 0.03) and between group I and III (9.4 ± 2.4 vs 5.56 ± 1.8, p = 0.004). On the contrary, it was not significantly different between group II and III (p = 0.283); b) $Int._{IB}$ was significantly different between group I and III (-21.4 ± 2.3 vs -13.3 ± 4.66, p < 0.001) and between group II and III (-21.4 ± 2.3 vs -18.6 ± 2.8, p = 0.006). It was not significantly different between group I and II (p = 0.1) (Fig. 1).

In addition, group III showed the most significant RV dilation (RV/LV ratio 0.55 ± 0.8) compared to group II (0.67 ± 0.11, p = 0.038) and group I (0.55 ± 0.87, p < 0.001). Finally, the RV/LV end-diastolic diameter ratio significantly correlated directly with $Int._{IB}$ (r = 0.49, p = 0.006) and inversely with CV_{IB} (r = -0.55, p = 0.002) (Fig. 2).

Integrated backscatter analysis and age at surgical repair. In our study population the age at surgical repair correlated directly with $Int._{IB}$ (r = 0.40, p = 0.033) and inversely with CV_{IB} (r = -0.53, p = 0.003) (Fig. 3).

Discussion

This study confirms that, compared to the control group, patients unsuccessfully operated on for TOF have significantly higher values of $Int._{IB}$ and lower values of CV_{IB}[16]. Experimental evidences show a linear relation between collagen deposition and IB magnitude[10]; in addition, CV_{IB} is dependent on active contraction (i.e. changes in size and configuration of myofilaments from systole to diastole) and thus is a highly sensitive parameter of intrinsic myocardial function[11]. As a consequence, our IB data are consistent with the increase in fibrosis and impairment of myocardial contractility described in overloaded RV myocardium[19].

Significantly, although invasive studies showed that after corrective surgery of TOF, despite regression of RV myocardial hypertrophy, cell diameter and collagen content remain abnormal even in absence of postoperative clinical sequelae[20], IB analysis in our study popu-

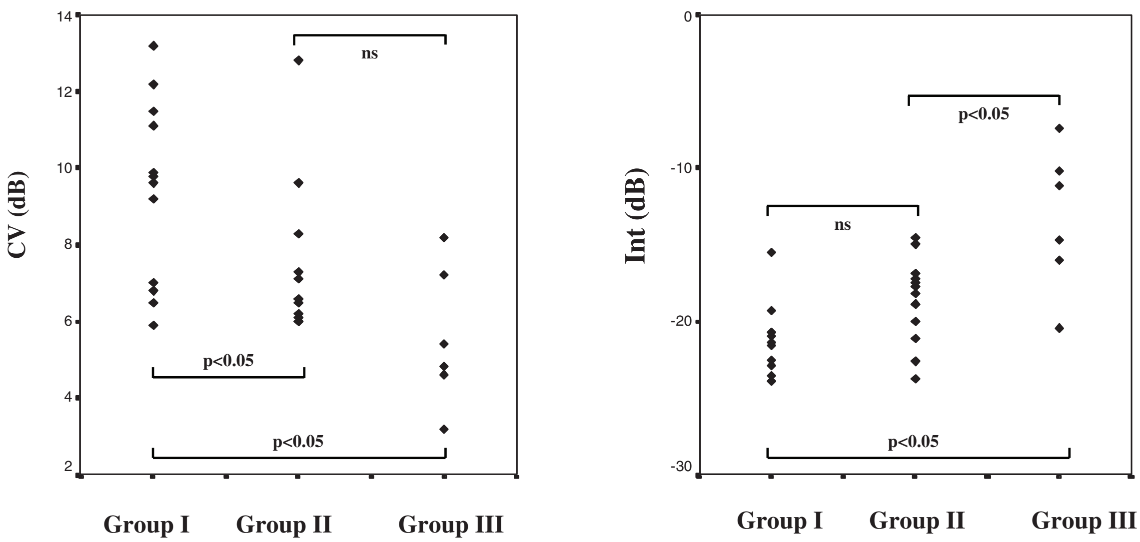

Figure 1. *Comparison by integrated backscatter analysis of cyclic variation (CV)* (left panel) *and average intensity (Int)* (right panel) *among the three subgroups of patients operated on for tetralogy of Fallot: group III shows the lowest values of CV and the highest values of Int.*

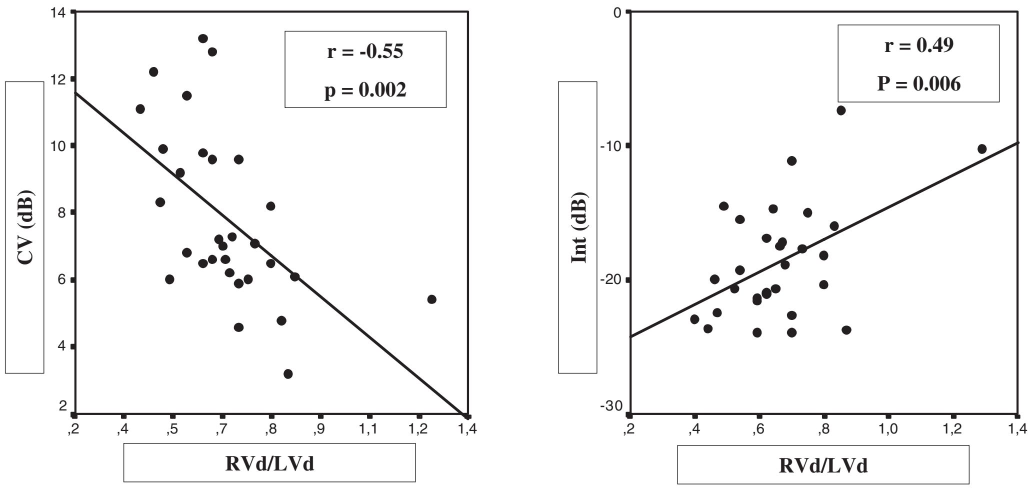

Figure 2. *The degree of right ventricular dilation (expressed as the ratio between right ventricular and left ventricular end-diastolic diameter [RVd/LVd]) correlates inversely with cyclic variation (CV)* (left panel) *and directly with average intensity (Int)* (right panel).

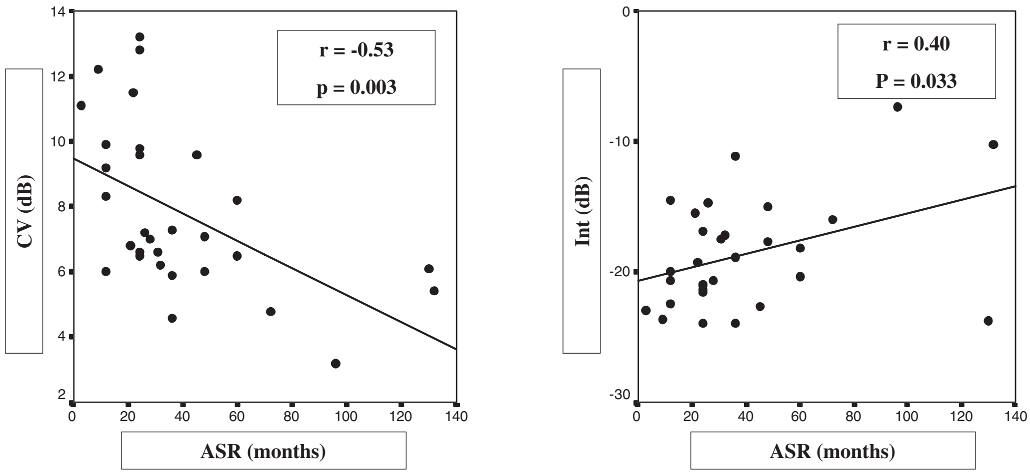

Figure 3. *Age at surgical repair (ASR) correlates inversely with cyclic variation (CV)* (left panel) *and directly with average intensity (Int)* (right panel).

lation was not able to differentiate successful repaired patients from normal controls. The inability of this technique to unmask subtle functional and textural myocardial abnormalities probably reflects its low frame rate (20-30 MHz) and thus low temporal resolution[21].

The main findings of our study are that both the older age at surgical repair and RV dilation usually due to chronic pulmonary regurgitation are strongly associated with RV myocardial textural and functional abnormalities.

Indeed, in our study population, the age at surgical repair significantly correlated with both $Int._{IB}$ ($r = 0.5$; $p = 0.005$) and CV_{IB} ($r = -0.66$, $p = 0.001$). Our non-invasive data suggest that an earlier repair of TOF, with the consequent decrease in RV myocardial wall stress, results in better preservation of RV myocardial properties. These findings are consistent with histopathological studies demonstrating in patients with TOF a significant correlation between RV myocardial abnormalities (hypertrophy, interstitial fibrosis and degenerative changes) and the age at surgical repair[3]. Experiments regarding the cellular basis of wall remodeling in long-term pressure overload-induced RV hypertrophy in 2-month-old rats show a significant increase in myocyte diameter and number, both of which tend to decrease the magnitude of systolic and diastolic stresses and thus improve the myocardial response to a prolonged and sustained mechanical load[22]. Nevertheless, the analysis on the effects of age on RV hypertrophic response to pressure-overload in rats aged 2, 7 and 18 months, shows an age-associated decrease and delay in hypertrophic response, thus favoring a progressive mechanical impairment[23].

These evidences associated with the excellent results after repair of TOF in the first year of life[24,25] seem to strengthen the attitude to an earlier timing of the total correction of TOF.

Recently, Parry et al.[26] have reported that complete repair of TOF can be performed also in early infancy with low requirement of transannular patching and thus low incidence of significant residual pulmonary insufficiency. This is crucial because of the deleterious impact of pulmonary regurgitation on long-term outcome in patients operated on for TOF[8,9].

Recently, Weidemann et al.[22] found abnormal regional function of the RV free wall in 30 patients with residual pulmonary regurgitation after surgical repair of TOF. Accordingly, in our TOF population with isolated chronic pulmonary regurgitation a significant reduction of CV_{IB} was seen compared to TOF patients without surgical sequelae ($p = 0.04$), thus confirming its significant impact on postoperative RV myocardial function. Our data are consistent with several clinical studies, showing that in postoperative TOF patients, RV volume overload (usually caused by pulmonary regurgitation) may play a major role in the reduction of exercise capacity[8]. Significantly, in these patients restoration of the pulmonary valve reduces RV volume overload and allows symptomatic improvement[27].

On the other hand, $Int._{IB}$ in our TOF patients with residual isolated pulmonary regurgitation (group II) was not significantly different compared to both the normal controls and TOF patients without postoperative sequelae (group I). This is consistent with data reported in patients with systemic hypertension, in whom only CV_{IB} but no $Int._{IB}$ was able to distinguish subgroups of patients with different degrees of LV hypertrophy[28,29].

Of interest, the lowest values of CV_{IB} and the highest values of $Int._{IB}$ were found in our patients operated on for TOF with both pulmonary regurgitation and RV outflow tract obstruction. This is in accordance with clinical studies showing that the combination of RV hypertension and volume overload exaggerates the deleterious effects of pulmonary insufficiency on the right ventricle after TOF repair[30]. Accordingly, Wessel et al.[31] demonstrated significant impairment in exercise performance in patients with a combination of pulmonary stenosis and regurgitation.

In addition, our TOF patients with concomitant pulmonary regurgitation and stenosis had also the most significant increase in RV size. Probably this reflects the inability of a dilated and abnormal RV myocardium to work against an increased afterload ("afterload mismatch"), with consequent further dilation and reduced pump function.

Some limitations of this study should be mentioned. First of all, we performed IB analysis only in one region of the RV free wall (usually in the center of its midportion) and thus we might only infere global RV functional and textural abnormalities. Nevertheless, previous studies in patients after surgical repair of TOF have found a homogeneous reduction of the functional properties within the RV free wall compared to age-matched normal subjects[26].

Secondly, in our study we utilized only non-invasive evaluations and thus no histological analysis or invasive functional measures were available. Indeed, myocardial biopsy or invasive functional studies would not have been justified in our patients for evident ethical reasons.

In conclusion, in patients operated on for tetralogy of Fallot: a) IB analysis may identify myocardial abnormalities in patients already known to have surgical sequelae; b) residual pulmonary regurgitation, particularly if associated with pulmonary stenosis, appears to affect textural and functional RV myocardial properties; c) an earlier repair of tetralogy of Fallot may result in better preservation of myocardial characteristics.

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