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Long-term coronary artery outcome after arterial switch operation for transposition of the great arteries☆

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Abstract

Objective: To analyse the long-term patency of coronary arteries after neonatal arterial switch operation (ASO). **Methods:** A retrospective study of the operative reports, follow-up and postoperative catheterisation data of 119 patients, who underwent the great arteries (TGA) repair since 1991, has been carried out. **Patient population:** Among the 133 survivors of the 137 ASOs performed between 1991 and 2007, 119 patients have been studied by routine control cardiac catheterisation and form the study population. Median time between repair and the coronary angiography was 2.9 ± 1.9 years. A comparison between the eight patients (6.7% out of the entire study population), known to have postoperative coronary obstructions (group I) and the rest of the cohort with angiographic normal coronary vessels (group II) was performed by univariate analysis of variance and logistic regression models. One patient had surgical plasty of the left coronary main stem with subsequent percutaneous angioplasty, three patients had primary coronary stent implantation and four patients had no further intervention at all. In group I, all but one patient denied symptoms of chest pain and echocardiography failed to show any difference between the two groups in terms of left ventricular systolic function (ejection fraction group I $61 \pm 2\%$ vs $62 \pm 6\%$ of group II, $p = 1.0$). **Results:** The association of coronary obstruction with complex native coronary anatomy (Yacoub type B to E) was evident at both univariate (62% of group I vs 22% of group II, $p = 0.04$) and logistic regression ($p = 0.007$, odds ratio (OR) 8.1) models. The type of coronary reimplantation (i.e., coronary buttons on punch vs trap-door techniques) was similar between the two groups (punch reimplantation in 25% of patients of group I vs 31% of group II, $p = 0.1$) as was the relative position of the great vessels (aorta anterior in 100% of patients of group I vs 96% of group II; univariate, $p = 0.1$). **Conclusions:** The late outcome in terms of survival and functional status after ASO is excellent. Nevertheless, the risk of a clinically silent late coronary artery obstruction of the reimplanted coronary arteries warrants a prolonged follow-up protocol involving invasive angiographic assessment.
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Keywords: Transposition of the great arteries; Arterial switch operation; Coronary arteries

1. Introduction

As one of the most successful achievements in the history of congenital heart defects surgery, the anatomic repair of transposition of the great arteries (TGA) is rapidly becoming the standard procedure on which the performance of a paediatric cardiac surgery team is often evaluated. This is due to the outstanding results in terms of early mortality and morbidity, currently reported by most cardiac surgery institutions all over the world. However, during the past 10 years, some clouds have been gathering over the very long-term issues of neonatal arterial switch operation (ASO), especially about the problem of the neo-aortic valve [1,2], neo-aortic root enlargement [3] as well as the patency and function of the reimplanted coronary arteries [4–8].

The timely evaluation of these two last parameters to perform a timely treatment of any coronary stenosis is essential to assess the late success of this operative approach.

Hereby we describe our single-centre experience with a cohort of 119 patients operated on for TGA and who have been submitted to an invasive institutional protocol of cardiac catheterisation and angiography aimed to verify the patency of the reimplanted coronary arteries and to monitor potential prognostic factors by a retrospective review of clinical, echocardiographic and surgical data.

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2. Materials and methods

2.1. Data collection

A retrospective evaluation of all survivors of ASO for TGA between January 1991 and September 2007 and who had already been submitted to control cardiac catheterisation has been carried out.

All clinical, surgical and follow-up records have been analysed to collect data about the native cardiac and coronary anatomy as well as the surgical technique used for intracardiac repair and coronary translocation. Follow-up clinical, electrocardiographic and echocardiographic evaluation and, if available, exercise stress test data were studied for the detection of possible signs or symptoms related to myocardial ischaemia. The cardiac catheterisation and angiography sheets have been analysed with regard to evidence of coronary obstruction. Native coronary anatomy has been described according to the Yacoub and Radley–Smith Classification [9]. The parents of all children submitted to cardiac catheterisation gave written informed consent.

2.2. Study population

Between March 1991 and September 2007, 137 patients underwent ASO at our institution. Aortic arch obstruction was associated in nine cases (Table 1). Median age at ASO was 8 days (range, 3–565 days) and median weight was 3.3 kg (range, 2.0–8.1 kg).

Among the 133 early survivors, two patients (2.5%) were lost to follow-up and one died suddenly 8 months after the operation. Six patients were unavailable for the angiographic evaluation. Of the remaining 124 patients, three denied control cardiac catheterisation and were therefore excluded from the study population. Two patients (1.6%) are still awaiting the invasive control study.

A total of 119 patients constitute the study population.

Within the spectrum of the native coronary anatomy, 10 patients (8.4%) had a single coronary artery, arising from the posterior facing sinus in 7/10 patients (70%) and from the anterior facing sinus in three (30%). One of these had an intramural course. The other 18 patients had either inverted pattern or origin of the circumflex artery from the right coronary. Two patients had situs inversus with 'usual' coronary pattern.

To simplify the statistical inferences, a dichotomous variable was created for simple (situs solitus and type A) versus complex native coronary anatomy (all the others, including intramural course). In general, 90 patients had a simple coronary pattern versus 29 with a complex anatomy.

Table 1
Type of TGA.

Type of TGA	Number of patients	Associated aortic arch obstruction
TGA simple	84	1
TGA + VSD	51	8
TGA DORV	1	/
TGA criss-cross heart	1	/

TGA: transposition of the great arteries; VSD: ventricular septal defect; DORV: double outlet right ventricle.

The aorta was anterior in all but seven patients who had side-by-side relationship of the great vessels.

Mean time between repair and the cardiac catheterisation was 2.9 ± 1.9 years.

2.3. Coronary reimplantation technique

Coronary arteries transfer was performed using different techniques [9–11].

In all patients, the coronary artery ostia were excised with a generous U-shaped aortic cuff, dissected and diffusely mobilised. In some cases, small branches were sacrificed to avoid potential coronary distortion.

In 37 patients, a hole in the ascending aorta was prepared with a 2.7-mm punch after partial aortic anastomosis. In 82 patients, the coronary transfer was performed with a trap-door type technique. Since 2004, the myocardial protection has been achieved with crystalloid cardioplegia. A single dose (50 ml kg^{-1} min^{-1}) cardioplegia was injected in the ascending aorta leading to a prolonged safe time of myocardial protection, avoiding selective and repeated cannulation of the coronary arteries for infusion of cardioplegic solution.

2.4. Cardiac catheterisation and angiocardiography

It is the institutional policy of our centre to perform routine cardiac catheterisation and angiography between 18 months and 36 months after repair. Patients without complete angiographic evaluation have been excluded.

2.5. Non-invasive follow-up protocol

All patients have a scheduled follow-up programme with routine evaluation by clinical, electrocardiographic and echocardiographic investigations every 6 months before control cardiac catheterisation and every 12–24 months thereafter, in all patients without angiographic coronary abnormalities. If necessary, special investigations such as dobutamine stress echocardiography and/or exercise stress test were planned. Overall, left ventricular systolic function was determined by the calculation of the ejection fraction (measured using the Teicholz on M-mode recordings or the bullet and the area–length methods on bi-dimensional views).

The overall complete (clinical and echocardiographic) median follow-up time is 9.4 years (range, 2–22 years).

2.6. Statistical analysis

The data are expressed as mean ± standard deviation. The two-tailed Fisher exact test (for categorical variables) was used for the univariate analysis. A multivariate analysis (logistic regression) was used to assess the impact of independent variables.

Dichotomous values have been adopted to simplify the statistical evaluation: simple native coronary anatomy (Yacoub type A) versus complex (all others), reimplantation technique (punch technique vs trap-door technique).

The null-hypothesis is rejected for alpha $\leq$5% (p level less than 0.05).

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3. Results

3.1. Angiographic imaging

Among the 119 enrolled patients, eight (6.7%, Table 2) had angiographic signs of coronary stenosis or occlusion. Table 3 shows the affected group.

Usually, the angiographic picture of the affected coronaries was either a localised ostial stenosis (Fig. 1) or a more extensive hypoplasia or even complete occlusion of the coronary vessel with backward flow from the patent artery (Fig. 2).

3.2. Symptoms and signs of myocardial ischaemia

Before the angiographic evaluation, only one patient claimed mild occurrence of chest pain potentially due to exertional myocardial ischaemia. The echocardiographic evaluation of the left ventricular systolic function was normal in both groups (ejection fraction at rest in the affected patients was $61 \pm 2\%$ vs $62 \pm 6\%$ of patients with normal coronaries, $p = 1.0$), and no segmental wall motion anomaly was detected.

The basal rest electrocardiogram showed only a T-wave inversion in the aVL and aVF in one patient (FM, before the surgical repair of the main stem stenosis), while two more patients showed mild exertional electrocardiogram modifications at peak exercise (Fig. 3).

3.3. Statistical investigation

The results of the univariate analysis are shown in Table 4. Only the presence of a complex native coronary artery anatomy (i.e., a Yacoub type B to E) was associated with the occurrence of late coronary stenosis ($p = 0.04$), while the reimplantation technique had little to no impact on coronary prognosis ($p = 1.0$). Similarly, the less usual side-by-side relationship between the two great arteries was not

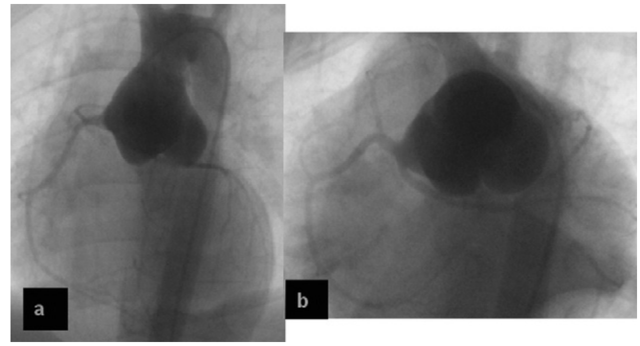

Fig. 1. A patient with single coronary orifice reimplanted into the right Valsalva sinus. Part (a) shows a typical left oblique view depicting the typical appearance of a 'trap-door' reimplantation. However, perfusion of the right coronary artery seems to be mildly impaired in respect to the aortic root. A 'laid-back' view (b) clearly shows how the main left coronary artery superimposing the aortic root may lead to a false positive of ostial obstruction.

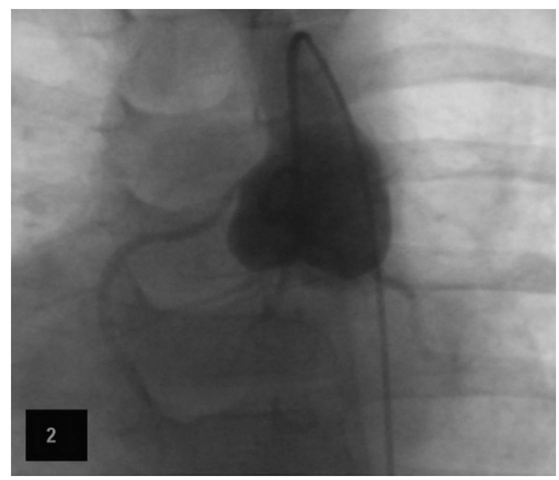

Fig. 2. Situs inversus transposition of the great arteries. The right coronary artery has been implanted high towards the sino-tubular ridge with an acute angle leading to ostial obstruction.

Table 2
Demographic data of the affected group.

Patient	Weight (kg) at ASO	Age (days) at ASO	Associated aortic arch obstruction
AA	3.6	41	None
BE	3.2	5	None
TA	2.8	12	None
FG	3.7	24	None
MF	3.2	8	None
PC	2.4	10	None
TS	3	9	None
ZG	3.8	12	Interrupted aortic arch

Table 3
Cardiac anatomy, native coronaries, surgical technique and type of lesions in the affected group.

Patient	Type of TGA	Native coronary anatomy	Type of coronary reimplantation	Type of lesion	Position of the aortic valve	Procedure
AA	TGA + VSD	Type D	Punch	Complete occlusion of LAD	Anterior right	None
BE	Simple TGA	Type E	Trap-door	Stenosis of LAD	Anterior right	None
TA	Simple TGA	Type B single	Trap-door	Stenosis of the third proximal segment of RCA	Anterior right	None
FG	TGA + VSD	Type B single	Trap-door	1. Trivial stenosis of RCA 2. Moderate stenosis of RCA	Anterior right	Coronary stent
MF	TGA + VSD	Type A	Punch	Severe stenosis of LMCA	Anterior right	Surgery and subsequent coronary angioplasty
PC	Simple TGA	Type A	Trap-door	Complete occlusion of LMCA.	Anterior right	None
TS	TGA + VSD	Type A	Trap-door	Complete occlusion of LMCA	Anterior right	Coronary stent
ZG	TGA + VSD situs inversus	Type A	Trap-door	Severe stenosis of RCA	Anterior left	Coronary stent

TGA: transposition of the great arteries; VSD: ventricular septal defect; LAD: left anterior descending; LMCA: left main coronary artery; RCA: right coronary artery.

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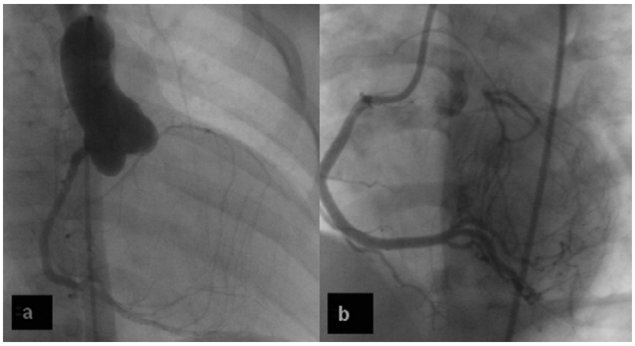

Fig. 3. Patient wit transposition and 'normal' coronary anatomy (Yacoub A). Aortic angiography (a) shows a dilated right coronary artery but no sign of the left main coronary vessel. Selective injection (b) into the right coronary artery confirms complete occlusion of the left main stem with retrograde filling from the right coronary artery until 4—5 mm from the aortic root.

associated with an unfavourable coronary prognosis ($p = 1.0$).

The logistic regression model computed for two variables (the native coronary anatomy and the reimplantation technique) confirms the coronary anatomy as the only predictive factor for late-occurring coronary stenosis ($p = 0.01$, OR = 6.3, CI 95% 1.37—29.3).

3.4. Outcome of patients with coronary abnormalities

Among the affected patients, two had complete occlusion of a main coronary branch (the left main stem in one and the left anterior descending (LAD) in another) with secondary severe vascular hypoplasia beyond any possible interventional and/or surgical treatment. Two patients had mild-to-moderate coronary stenoses for which the risk/benefit ratio of interventional treatment was considered as unfavourable, mainly due to the mismatch between the native vessel and the smallest available coronary stent without jeopardising the potential for further growth of the vessel over time. This subset of patients was followed for detection of myocardial ischaemia by routine treadmill stress test and (in one case) dobutamine echocardiography. Three patients, one presenting with exertional chest pain with electrocardiographic (ECG) signs of subendocardial ischaemia, have been treated by coronary stent implantation with one late complete stent thrombosis despite repeated angioplasty procedures.

One patient underwent surgery for relief from near-complete occlusion of the LAD 35 months after the ASO. An associated severe stenosis of the left pulmonary artery was diagnosed. In this patient, the native coronary anatomy was a Yacoub type A with a big conal branch arising from the first portion of the LAD, which, despite being diffusely mobilised, may have caused a kink of the LAD at the time of coronary transfer.

Re-operation was performed at the age of 3.4 years by an autologous pericardial patch to enlarge the main stem of the coronary trunk and the proximal part of the LAD. The left pulmonary artery was enlarged using a heterologous pericardial patch.

Control coronary angiography 6 months after the re-operation showed a widely patent anastomosis. However, following the occurrence of exertional chest pain, a new coronary angiography was repeated and a recurrent mild LAD stenosis was balloon dilated with success.

4. Discussion

In the setting of ASO, the risks of tension, torsion or kinking of the coronary arteries, as well as the potential for growth of the coronary artery and aortic anastomosis and the incidence of coronary artery lesions, are some of the matters of debate on the late outcome of ASO [9,12,13].

In the present study, a complex native coronary artery anatomy was associated with the occurrence of late coronary stenosis, while the reimplantation technique had little-to-no impact on coronary prognosis. Complexity of the coronary pattern should not be regarded as the only important factor in determining the difficulty grade of coronary translocation. The relation between the great vessels and the proximal segment of the coronary arteries, as well as the course and the presence of important conal branches, may play a crucial role; but we do not have specific data to support this hypothesis. Indeed, abnormal vessel looping may cause tension, torsion or kinking of the coronary arteries at the time of their transfer, as we think may have happened in some of our patients.

As already documented, patients with even severe coronary lesions may not show any symptoms or instrumental evidence of myocardial ischaemia, so the ordinary non-invasive diagnostic tools seem completely inadequate. Despite being an invasive tool, coronary angiography, in our opinion, is best suited for routine evaluation of children after ASO, due to the low risk of complications (14) and the opportunity to perform simultaneous interventional treatment, if needed. Moreover, coronary spiral scans deliver a too-high radiation dosage, while optimal image acquisition requires cardiac rates, which are usually difficult to achieve in very young infants.

As reported by Legendre et al., by intracoronary ultrasound evaluation, on the basis of coronary artery lesions, there is a progressive proximal eccentric fibrocellular intimal thickening [8]. This process is not completely understood, but the complexity of coronary patterns and the surgical procedure of coronary transfer could be the cause for potential flow abnormalities leading to increased shear stress and progressive proximal eccentric fibrocellular intimal thickening [8,15].

Table 4
Univariate analysis.

Variable	Pts. with normal coronary arteries	Pts. with coronary artery disease	Univariate *p*
Complex native coronary anatomy	24/111 (22%)	5/8 (62%)	0.04
Punch reimplantation technique	34/111 (31%)	2/8 (25%)	1.0
Aorta anterior	106/111 (95%)	8/8 (100%)	1.0

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Table 5
Previous reports on coronary arteries after repair of transposition.

Authors (year of publication)	Pts. with angiography/total	Indications for angiographic study	Time between repair and catheterization	Coronary lesions
Legendre A. (2003)	324/1198	Symptoms or signs of ischaemia	7 years (10 days to 6.3 years)	22 (6.8%)
Tanel R. (1995)	366/575	Institutional	14.4 months (4.9 months to 4.8 years)	12 (3%)
Bonhoeffer P. (1997)	165/387	Symptoms or signs of ischaemia	3.7 ± 3.5 years	30 (18%)
Raisky O. (2007)	290/713	Institutional	33 ± 38 months (30 days to 10 years)	34 (12%)

During coronary transfer, we focus our attention to an accurate mobilisation of the vessels, even with the sacrifice of small conal branches if necessary. Avoiding repeated selective cardioplegic infusion into the coronary ostia may help in reducing damage to the arterial wall and potential induction of intimal thickening.

In our experience, patients who underwent ASO have been asymptomatic without any evidence of myocardial ischaemia even when a severe coronary lesion was present, thus making the angiographic control of the coronary arteries an important step of the follow-up during the early years after ASO.

In the literature, some reports may be found concerning the angiographic evaluation of coronary arteries after ASO (Table 5). However, most studies are on selected patient population without any clear strategy regarding the invasive follow-up of operated transposition patients. According to our experience, we believe that an early angiographic evaluation is mandatory in all patients, who underwent ASO, even those with usual coronary patterns and no reported symptoms, to predict coronary obstruction [14,16].

5. Conclusions

The long-term function of the coronary system is currently regarded as a possible cause of concern in patients with TGA, who have been operated for ASO.

Indeed, it is possible that endothelial dysfunction and intimal hyperplasia may play a role during adult life after an ASO. In this view, we opine that coronary function in such patients should be regarded as a lifelong issue and that every effort should be undertaken to prevent any kind of anatomic impairment to myocardial perfusion. Nevertheless, highly obstructive coronary disease may occur even during the early years after ASO, as repeatedly reported in the literature and by our group. Moreover, it must be emphasised that the common non-invasive follow-up protocols, relying on standard rest-ECG, bi-dimensional echocardiography and clinical observation, may easily fail in tracking the onset of progressive coronary obstruction. If caught too late, severe stenosis or complete occlusion of a coronary ostium may lead to progressive hypoplasia of the main vessel and hamper any further attempt of surgical/interventional revascularisation, with unforeseeable consequences for potential myocardial ischaemia during life. Indeed, two patients of our group showed complete occlusion of a coronary artery with corresponding vessel hypoplasia beyond any possible hope of repair.

For this reason, we endorse a policy of routine angiographic evaluation of the coronary arteries within the first 2–3 years after repair, to minimise impaired vessel growth due to a severe proximal stenosis, if present, and to maximise the potential for interventional procedures of revascularisation.

6. Limitations of the study

The limitations of this study are those inherent to retrospective studies where data have been collected in a clinical context. The surgical operating skill does surely have a deep impact on the delicate matter of translocation of neonatal coronary arteries. However, all the operations in our study have been performed by the same surgical team since 1991 and five out of eight patients with coronary lesions have been operated after the year 2000, thus making the topic concerning the learning curve a weak argument.

Another point of discussion may be the potential role of dimensional pulmonary-aortic mismatch, which may affect the ability to transfer the coronary arteries. While the presence of discordant aortic and pulmonary dimensions was always reported in the operating room records, nevertheless, precise measurements are sparse and unreliable, making a precise statistic evaluation practically impossible.

We are aware that, in our study, the subset of factors taken into account is very limited. This is partly due to the small amount of patients affected, which limits the number of variables amenable to a logistic regression test. Therefore, we preferred to perform our evaluation selecting the variables we think as theoretically the most attractive.

Furthermore, the decision to have the coronary anatomy split into a dichotomous variable (complex vs non-complex pattern) may cause patients with 'normal' coronary arteries, but carrying other risk factors such as very low body weight, to be incorrectly included into a low-complexity group. However, we felt this to be the only possible means to perform some kind of analysis with the low number of patients presenting with late coronary lesions.

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Appendix A. Conference discussion

Dr J. Comas (*Madrid, Spain*): I have three comments or three questions.

The idea that the coronary obstruction is independent of the original anatomy has already been published by different authors. However, you are introducing maybe a new concept, the influence of the final geometry between the great vessels and their diameter.

Is it possible that the silent fibrocellular intimal proliferation in the coronary lumen is mostly related to how the neoaorta and the proximal segments of the coronary artery are growing? What do you think?

Dr Angeli: I agree with you. This at the moment could simplify the coronary anatomy classification, but we don't have enough information to explain the complexity of the intimal proliferation. We believe that it is important to consider the discrepancy between the pulmonary artery and the aorta. And this can have an impact on the results and in the coronary artery stretching. So yes.

Dr Comas: My second question is related to other techniques less invasive than coronary angiography. Some reports have started to introduce multislice computed tomography. Do you have any experience with it? Are you planning to introduce it in certain cases?

Dr Angeli: Yes, we are planning to use it. But as you know in a CT scan, to evaluate the coronary artery, a 64-slice CT is necessary, and at the moment we don't have it.

So we know that this can be useful, even if we have some regret, because for the CT, X-ray exposure is nearly the same as for catheterization. And in both cases, the patient requires general anaesthesia because you saw that our group of patients is very young.

Dr Comas: And my final comment and question is related. Your mean age is quite low at 3 years old. Do you have any protocol for longest follow-up, for example, babies or boys 8 years, 10 years old?

Dr Angeli: Yes. Of course, it depends on the group of patients. If we have patients without any sign of a coronary lesion at the first angiography, we will perform echo dobutamine stress and exercise ECG stress routinely. It means every 2 years in the group of patients without a coronary lesion.

The situation is different in the group that has a coronary lesion like the data you saw in the presentation. There we believe that a controlled follow-up also with repeated angiographic evaluation is mandatory.

Dr P. Vouhe (*Paris, France*): Just a small question. Is there in your series any patient who had normal coronary arteries at the first evaluation and then developed coronary lesions, meaning that coronary lesions may appear despite a perfect initial transfer?

Dr Angeli: No, we don't have any patients. Of course, Professor, you know we evaluated them at the first analysis with angiography, but all the patients that in the follow-up of 9 years received an echo stress dobutamine exam or an ECG test were completely asymptomatic and the exam was negative.

Dr G. Stellin (*Padova, Italy*): Very nice study. However, coronary angiography is quite an invasive procedure. I wonder how you have convinced the parents of asymptomatic children to undertake a coronary angiography?

In our experience, we have performed myocardial scintigraphy at rest and under stress in order to select those patients who have a positive test for coronary angiography.

So how did you convince the parents of the children to undertake such an invasive test?

Dr Angeli: We explain to them that this is our protocol. This is what we do to all our patients, and that is important in our opinion to evaluate the coronary artery in this way. We say that we know that there are other ways to do it, so we explain well, we cover everything in the beginning.

And in 3 cases, I don't know if you saw the table, 3 patients refused the exam.

Dr Stellin: Okay. Thank you.

Dr Angeli: And we wait until they grow up. It was in the beginning. And then we did the CT scan and MRI. But we don't believe that it was enough, but they refused it.

Dr Stellin: Any problem during the coronary angiography?

Dr Angeli: No.

Dr Stellin: No problem?

Dr Angeli: Fortunately, no.

Dr H. Alsisi (*Cairo, Egypt*): My question is that you said you do the angio in the first 2 years. So, first, do you have an exact time, like, after 6 months to choose to do the angio?

And then on your comment about the angio, you said you do the angio to minimize the vessel end growth.

So my question is, what do you mean by 'to minimize the vessel end growth'?

Dr Angeli: The first part of the question is quite clear; the second not at all, but okay.

First, we decided to study all the patients between 18 and 36 months. We believe that this is a winning strategy, to see the disposition of the arteries and if they have any stretching.

And we believe that when you see this in the first 3 years, we can see the growth of the vessels and coronary artery disposition.

Second part, I didn't understand, but can you repeat please?

Dr Alsisi: Your comment about the angio. You said you do it to detect and to minimize the vessel end growth.

Dr Angeli: Yes.

Dr Alsisi: What do you mean by vessel end growth?

Dr Angeli: Oh, okay. You mean in the cases where we didn't perform any procedure?

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Well, we saw that in 2 patients, the anatomy of the coronary artery, the stenosis of the coronary artery, caused hypoplasia of the vessel that couldn't receive any procedure.

In the second 2 patients that didn't receive any procedure, it was because the benefit and the risk between the procedure or waiting, was in favour of waiting.

Of course, these patients are monitored with a follow-up, because at the moment — you see the patient I showed with the stent implantation — As you can see, in that patient we put a stent, the smallest that we have. And you saw in the image that there is a discrepancy between the native vessel and the stent. This is what we wanted to avoid.

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