Myocardial Perfusion, Scarring, and Function in Anomalous Left Coronary Artery From the Pulmonary Artery Syndrome: A Long-Term Analysis Using Magnetic Resonance Imaging

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Background. Anomalous left coronary artery from the pulmonary artery (ALCAPA) is a rare congenital heart defect. We aimed to examine the role of cardiac magnetic resonance imaging (MRI) in the long-term surveillance of repaired ALCAPA with regard to myocardial scarring, wall motion abnormalities, perfusion deficits, and myocardial function.

Methods. Twenty-one patients after direct reimplantation of ALCAPA (median age at operation, 2.8 years) were examined after a median 10.6 years by MRI at rest and under dobutamine stress conditions, echocardiography, and ergometry. Results were compared with preoperative, immediately postoperative (5 days), and intermediate-term (5.8 years) echocardiography.

Results. No early or late deaths occurred. Improvements in indexed left ventricular end-diastolic dimension, ejection fraction, and mitral valve function were observed in all patients. However, MRI at rest showed wall motion abnormalities in 67% and perfusion deficits in 28%. Myocardial scars were seen in 67%. Dobutamine stress MRI detected wall motion abnormalities in 19% and perfusion deficits in 14%, which were not seen on MRI at rest. Exercise testing did not reflect cardiac dysfunction.

Conclusions. Although long-term follow-up showed global left ventricular function had improved after ALCAPA repair, MRI showed left ventricular wall motion abnormalities, perfusion deficits, and myocardial scarring were seen in many patients. Dobutamine stress MRI identified deficits that were not evident on MRI at rest, and can therefore be considered a valuable surveillance tool. These results suggest the need for lifelong surveillance of repaired ALCAPA.


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A nomalous origin of the left coronary artery (LCA) from the pulmonary artery (ALCAPA) is a rare form of congenital heart disease (CHD) occurring in about 1:300,000 live births [1], comprising 1 in 2,000 children born with CHD. The mortality of untreated ALCAPA is estimated at 90% [2]. The treatment of choice is immediate surgical reimplantation of the LCA into the aorta [3, 4]. Although the mortality rate has decreased over the years [5], data regarding long-term follow-up are limited.

Preoperative myocardial ischemia manifests as reduced left ventricular (LV) ejection fraction (LVEF) and heart failure, mitral regurgitation (MR), and LV dilation [6, 7]. Despite improvement of myocardial function after correction, evidence of chronic myocardial injury, including wall motion abnormalities, perfusion deficits, and scarring, has been reported [4, 8, 9]. Development of collaterals for the prevention of myocardial infarction seems important [10, 11]. In patients with poor collateralization, myocardial ischemia and fibrosis appears to deteriorate the clinical course after corrective surgical intervention [9].

To evaluate for myocardial ischemia, stress echocardiography and single-photon emission computed tomography have been used with good results [12]. Furthermore, dobutamine stress magnetic resonance imaging (MRI) has demonstrated high diagnostic accuracy in the detection of wall motion abnormalities and nonviable myocardium, with superior spatial and temporal resolution [9, 13]. We sought to investigate the sequela of myocardial ischemia in the long-term after ALCAPA repair and to examine the additive benefit of dobutamine stress MRI for detection of wall motion and perfusion deficits.

Material and Methods

Study population

After obtaining written informed consent from all patients or their parents, clinical and imaging data were
evaluated in 21 patients (9 female, 12 male) with ALCAPA repaired between 1991 and 2007. All patients underwent direct reimplantation of the LCA into the aortic root. Median age at repair was 2.8 years (range, 0.1 to 10.5 years), median weight was 12.4 kg (range, 4 to 38 kg), and median body surface area (BSA) was 0.53 m² (range, 0.25 to 1.26 m²).

The preoperative evaluation and two postoperative assessments at a median interval of 5 days (short-term follow-up) and 5.8 years (intermediate-term follow-up) by clinical examination and echocardiography were retrospectively reviewed. The third postoperative assessment was conducted prospectively for this study 10.6 years after the repair (long-term follow-up). At long-term follow-up, all patients underwent a physical examination, echocardiography, cardiac MRI at rest and during dobutamine stress, and ergometry.

Presurgical catheterization data and coronary angiograms were evaluated for the qualitative adequacy of collateral circulation between the left and right coronary artery. Collateral flow was “good” in 10 and “sparse” in 11 of the 21 patients. The surgeon made an assessment of collateral flow visually from the coronary angiograms obtained before the corrective operation.

Preoperative echocardiography included measurements of LVEF, LV fractional shortening (LVFS), LV end-diastolic diameter indexed to BSA (LVEDD/BSA), and grade of mitral insufficiency (MI). Preoperative median LVEF was 0.43 (range, 0.19 to 0.76), median LVFS was 21.7% (range, 7% to 50%), and median LVEDD/BSA was 9.7 cm/m² (range, 3.6 to 18.9 cm/m²). Of 14 patients with MR, there were 2 with grade I, 3 with grade II, 7 with grade III, and 2 with grade IV regurgitation. Reconstruction of the mitral valve was performed in 5 patients (4 with MR grade III, 1 with grade IV).

As described earlier for this cohort [3, 14], echocardiographic follow-up examinations revealed a decrease of MR in most of the patients and normalization of global LV function. Nevertheless, 5 of the 18 patients without MR after ALCAPA repair presented with MR grade I (n = 4) or II (n = 1) at the intermediate-term follow-up.

MRI Examinations
The cardiac MRI at long-term follow-up (1.5 Tesla Achieva 2.6, 5-channel cardiac coil; Philips Medical Systems, Best The Netherlands) was performed according to institutional guidelines. Children younger than 5 years underwent conscious sedation by midazolam (Dormicum [Roche, Basel, Switzerland], 0.1 mg/kg once) and propofol (Propofol-Lipuro 1% [B. Braun Medical, Melsungen, Germany]; 2.5 to 4.0 mg/kg/h). Breathing remained spontaneous. Continuous monitoring was ensured using electrocardiogram, peripheral pulse unit gating, and transcutaneous pulse oximetry. The MRI protocol consisted of the following sequences (Fig 1):

- Cardiac morphology and function, including wall motion, chamber dimensions, and volumes, were determined by 4-chamber, 3-chamber, 2-chamber, and short-axis cine MRI sequences at rest.
- For quantification of MR, LV inflow through the plane of the mitral valve was evaluated by velocity-encoded phase-contrast sequences (Fig 2).
- The contrast agent gadopentetate-dimeglumine (Magnevist; Bayer Pharma, AG, Berlin, Germany) was delivered at 0.1 mL/kg (0.05 mmol/kg) for a perfusion sequence applied at the apical, midventricular, and basal level for the detection of myocardial perfusion deficits at rest (Fig 3).
- A whole-heart 3-dimensional isotropic sequence was performed from the midventricular level up to the ascending aorta, yielding high spatial resolution images of the coronary arteries. This enabled assessment of the size of the LCA anastomosis at the reinsertion site and for diameter measurements of the proximal left and right coronary arteries (Fig 4).
- Dobutamine stress MRI for assessment of wall motion: Stress testing was terminated at a target heart rate calculated as [(220 – age in years) × 0.8]. This equation is still used in our institution, although it may underestimate maximal heart frequency in older individuals [15]. Dobutamine infusion was started at 10 µg/kg/min for 4 minutes. A short-axis stack and 4-chamber, 3-chamber, and 2-chamber cine images of the heart were obtained. Dobutamine was then increased to 20 µg/kg/min for another 4 minutes, followed by the same sequences as before. Dosing was increased every 4 minutes until the target heart rate, or the maximal dobutamine dose of 40 µg/kg/min, with a supportive maximum dose of 0.01 mg/kg atropine, was reached. After each increment of dobutamine, the images were screened for wall motion abnormalities.
- A stress perfusion sequence was used after cessation of the dobutamine infusion for detection of perfusion deficits, which may have remained unapparent at rest.
- Finally, an additional 0.2 mL/kg Magnevist was delivered, and after 10 minutes, a look locker sequence, followed by 4-chamber, 3-chamber, and 2-chamber late enhancement sequences of the LV was performed for assessment of myocardial viability.

MRI Postprocessing
LVEF and LVFS were calculated from MRI cine end-diastolic and end-systolic images using the formula:

\[
\text{LVEF} = \frac{[(\text{LVEDV} - \text{LVESV})/\text{EDV}] 	imes 100}{\%} \quad (1)
\]

\[
\text{LVFS} = \frac{[(\text{LVEDD} - \text{LVESD})/\text{LVEDD}] 	imes 100}{\%} \quad (2)
\]

LVEDV and LVESV were obtained from volumetry on axial cine images [16]. LVEDD and LVESD were measured in MRI 4-chamber cine images at the mitral valve chordal level [17].

Exercise Testing
Respiratory variables were measured during an incremental exercise test [18] on a bicycle ergometer (n = 15), providing information on electrocardiographic changes,
arterial blood pressure, and endurance. The main variable studied was maximal oxygen consumption.

Statistical Analysis
Data on clinical course was analyzed by nonparametric Friedman test, and statistical differences determined using the Wilcoxon test. MRI results were compared using cross tables and the McNemar test for combined samples. Comparisons between tests were made using the Mann-Whitney U post hoc test. Differences were considered statistically significant at \( p < 0.05 \). Statistical analysis was performed using SPSS 12.0 software (SPSS Inc, Chicago, IL).

Results
LV Function
LV function significantly improved over the clinical course. Median LVEF by echocardiography enhanced from 0.429 preoperatively (range, 0.19 to 0.76) to 0.465 in the short-term follow-up (range, 0.34 to 0.77; \( p < 0.05 \)) to 0.66 at 5.8 years after repair (range, 0.44 to 0.80; \( p < 0.05 \) compared with preoperatively). MRI-derived LVEF at 10.6 years of follow-up was significantly higher than the preoperative value and was as high as the intermediate-term follow-up LVEF by echocardiography (median, 0.60; range, 0.39 to 0.66; \( p < 0.05 \); Fig 5A). LVEF values derived by MRI and echocardiography at 10.6 years were comparable.

The LVFS by echocardiography stayed nearly unchanged from a median of 22% (range, 7% to 50%) preoperatively to 23% (range, 16% to 44%) immediately postoperatively. At the intermediate-term follow-up, LVFS had increased to 36% (range, 21% to 46%; \( p < 0.05 \)). Similarly, there was improvement of LVFS assessed by MRI at 10.6 years of follow-up: 39.9% at baseline (range, 22.6% to 45.2%) and 41.1% with dobutamine (range, 23.6% to 63.8%; Fig 5B and Table 1).
Fig 2. Magnetic resonance imaging measurement across the mitral valve plane shows a competent valve closure (minimal regurgitation fraction of 3.2%) and normal E- and A-waves. (A) Graphical and (B) numerical display of the flow results measured within the region of interest (ROI). The ROI is marked in (B) anatomical view and (C) phase contrast view.

Fig 3. Myocardial perfusion displayed in a 3-level 6-segment model shows low perfusion of the left ventricular (LV) apex and anterior wall as typically seen in anomalous left coronary artery from the pulmonary artery.
The LVEDD/BSA decreased along the course from 10.4 cm/m² (range, 3.58 to 18.09 cm/m²) preoperatively to 8.38 cm/m² (range, 3.1 to 10.7 cm/m²; \( p < 0.05 \)) immediately postoperatively and to 4.28 cm/m² (range, 1.03 to 8.08; \( p < 0.05 \)) at 5.8 years. The LVEDD/BSA was 4 cm/m² (range, 2.2 to 8.5 cm/m²) at the baseline MRI and was 3.8 cm/m² (range, 2.0 to 7.2 cm/m²; Fig 5C) at the follow-up dobutamine stress MRI.

Mitral Valve Function

MR improved from preoperative median grade II to postoperative median grade I (\( p < 0.05 \)) and to median grade I (\( p < 0.05 \)) at the intermediate-term follow-up. On cardiac MRI, 6 of 21 patients showed MR (Table 1). Those 6 patients also tended to show perfusion deficits, wall motion abnormalities, and myocardial scarring (Fig 5D). A detailed description of the course of MR in each patient is shown in Figure 5E.

Preoperative Data and Postoperative Outcome

Patients preoperatively diagnosed with negligible development of collateral flow between the right and left coronary artery showed lower LVEF and enlarged LVEDD/BSA (\( p < 0.05 \); Fig 6A). All of those patients displayed electrocardiographic signs of myocardial ischemia before the operation. Furthermore, there was a statistically significant association of limited preoperative collateralization and myocardial perfusion deficits on late follow-up MRI at rest and on dobutamine stress (\( p < 0.05 \); Figs 6B, 6C).

MRI Assessment of Cardiac Function

Wall Motion Abnormalities. Dobutamine stress MRI enabled the detection of myocardial wall abnormalities and perfusion deficits that were not manifested at rest. Arrhythmia or reaction to the contrast agent prevented 3 of the 21 patients from being investigated at stress. Of the remaining 18 patients, 12 showed wall motion abnormalities at rest (Table 2). Of these 12, 7 showed hypokinesia, 2 showed akinesia, and 3 patients showed dyskinesia. Wall motion abnormalities during dobutamine stress (hypokinesia) were revealed in an additional 4 patients (Fig 7A).

Myocardial Perfusion Deficit. Myocardial perfusion deficits were evident at rest in 5 of 17 patients. An additional 3 patients displayed perfusion deficits under dobutamine stress (Fig 7B). A statistically significant association of wall motion abnormalities and perfusion deficits occurred under rest (\( p < 0.05 \); Fig 8A) and stress conditions (\( p < 0.05 \); Fig 8B).

Myocardial Scar Assessment by MRI

Altogether, 13 of 20 patients demonstrated late myocardial contrast enhancement (1 patient was not examined due to adverse effects from the contrast media). The myocardial scarring occurred in conjunction with perfusion deficits (\( p < 0.05 \); Fig 8C) as well as with wall motion abnormalities (\( p < 0.05 \); Fig 8D). Delayed enhancement images were interpreted with the assumption that an alternate cause (infectious myocarditis or distinct myocardial fibrosis) was not responsible, and we considered no contrast enhancement as “no scarring” (grade 0); subendocardial late enhancement as grade 1, and transmural delayed enhancement was defined as grade 2, or as grade 3 when it extended.

Exercise Testing and Cardiac Function

Some patients showed good endurance during exercise testing performed within 2 weeks of MRI, even though LV function was reduced. Patients without myocardial scarring achieved similar exercise performance profiles as those who demonstrated evidence of scarring by late myocardial contrast enhancement (Fig 9A). Furthermore, exercise endurance was equivocal between groups with hypokinesia, akinesia, and dyskinesia (Fig 9B). Exercise capacity was not related to LVEF (Fig 9C) or MR. No significant arrhythmia occurred during exercise testing in any patient.

Comment

Main Findings

This study presents long term follow-up results from the largest single-center cohort of ALCAPA repaired with
direct reimplantation of the LCA by 1 surgeon [3]. In concordance with other studies [5, 6], LV recovery was excellent after surgical repair. Contrary to the observations made by Lange and colleagues [6] that a preoperative LVEF of less than 0.35 is an independent risk factor, we found good recovery of LVEF in all patients, even when the EF at presentation was as low as 0.19. LVEF and LVFS in these patients continued to improve during the entire clinical course. LVEDD/BSA decreased continuously, which we assume is related to the improvement of mitral valve function. In contrast to studies that observed a persistence or progression of MR after the operation, our data show amelioration of MR and improvement of mitral valve function in most patients.

Despite the improvement of LV function (even in those patients who had good collateral flow), sequelae of ischemic myocardial damage were detectable by cardiac MRI 10 years after repair. The perfusion deficits, wall motion abnormalities, and myocardial scarring observed would suggest incomplete recovery of LV function [4, 8, 19].

We suggest that these findings should be monitored further, because their clinical relevance is not fully known. Cardiovascular MRI appears to be a suitable imaging modality for follow-up of these patients and capable of detecting even small areas of scarring, as has been suggested by others as well [2, 9, 13]. We note that there are disadvantages of performing MRI in children aged younger than 5 years due to the need for sedation [20].
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Table 1. Cardiac Dimensions by Magnetic Resonance Imaging

<table>
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<tr>
<th>Variables at Rest</th>
<th>Variables at Stress</th>
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<tbody>
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BSA = body surface area; LAD = left anterior descending artery; LCA = left coronary artery; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVFS = left ventricular fractional shortening; LVSV = left ventricular stroke volume; MI = mitral insufficiency; MRI = magnetic resonance imaging; N = no; Pt = patient; RCA = right coronary artery; Y = yes.
Mitral Valve

Mitral valve operations in patients with ALCAPA remain controversial. Some authors do not recommend a correction during coronary operations and anticipate improvement over time [6, 21], whereas others suggest repair of the valve at the time of coronary reimplantation [22, 23].

We speculate that valve function and preoperative collateral flow are interrelated in many patients: Poor collateralization with chronic ischemia leads to fibrosis and reduced ventricular function, thereby increasing the LVEDD/BSA ratio and resulting in annular dilation and MR (functional MR). In other patients, however, MR has a structural cause, such as papillary muscle infarction, so MR is unlikely to resolve after coronary reimplantation and improvement of LV function. These patients might need mitral valve repair at the time of the ALCAPA repair.

Collaterals

We agree with Sauer and colleagues [11] that collateral flow is an important factor in the development of myocardial ischemia. Patients in our population with poor collateralization showed significantly reduced preoperative LV function. Interestingly, scar tissue was found in 6 of 9 patients in our study with initially good collateral flow. These findings are in contrast to a study [24] that traced the absence of myocardial scarring to well-developed collateralization. Myocardial ischemia and, eventually, scarring, are less likely to develop in patients with good collateralization compared with patients with sparse collaterals. However, our findings suggest that even with good collateralization, the myocardium in ALCAPA is always at risk for ischemia.

In the current era of highly specialized preoperative care, including LV assist devices, children with ALCAPA and poor collateralization often survive until corrective operations. Future studies comparing this group with children who had good preoperative collateralization are necessary to precisely evaluate the role of collaterals with regard to chronic perfusion deficits, wall motion abnormalities, and scar formation.

Dobutamine Stress Testing

MRI at rest showed wall motion abnormalities in 12 of 18 patients and perfusion deficits in 5 of 17. Dobutamine stress testing unmasked wall motion abnormalities in an additional 4 patients and perfusion deficits in an additional 3. The changes in these patients were marginal, from subtle wall motion abnormality to hypokinesia; however, dobutamine stress testing correlated better with the presence and size of scar tissue than testing at rest. We therefore advocate dobutamine stress MRI as the method of choice to evaluate long-term myocardial abnormalities after ALCAPA repair [2, 5, 9]. Dobutamine stress offers the possibility to detect myocardial ischemic changes that are not obvious at rest, and in our opinion, is a key component of comprehensive MRI testing of myocardial performance in these patients.

Late Gadolinium Enhancement

Late myocardial scarring was documented in 65% of our patients, although all displayed good LV recovery. Because of the circumscribed localization and typical distribution pattern in our cohort, we interpreted late gadolinium enhancement (LGE) as scarring caused
Table 2. Variables of Cardiac Function by Magnetic Resonance Imaging

<table>
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<tr>
<th>Pt</th>
<th>Repair (y)</th>
<th>MRI (y)</th>
<th>BSA at MRI (m²)</th>
<th>Max Dobutamine Dose (µg/kg/min)</th>
<th>Absolute Atropine Dose (mg)</th>
<th>HF Start (L/min)</th>
<th>Max (L/min)</th>
<th>Perfusion Deficit</th>
<th>Wall Motion Abnormalities</th>
<th>Scar (grade)</th>
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</table>

*a* Summarizes the results of dobutamine stress magnetic resonance imaging compared with rest, and the scores of scar size. 

*b* Perfusion deficit: N = not existent; Y = existent.

*c* Wall motion abnormalities: 0 = not existent; 1 = hypokinesia; 2 = akinesia; 3 = dyskinesia.

*d* Scar grade: 0 = no scar; 1 = subendocardial; 2 = transmural; 3 = extended transmural.

BSA = body surface area; HF = heart frequency; MRI = magnetic resonance imaging; N = No; Y = Yes.
by ischemia. We could not evaluate for LGE before the ALCAPA repair, so we are unable to comment on the early incidence or progression of LGE. Myocardial ischemia from ALCAPA syndrome or perioperative myocardial injury from cardiopulmonary bypass are potential causes for LGE. Although all patients in our cohort underwent cardiopulmonary bypass for ALCAPA repair, some patients had no signs of LGE.

Similar to our results, a recent study reported half of all patients in that series remained without LGE on follow-up after cardiopulmonary bypass [25]. This suggests that cardiopulmonary bypass does not necessarily lead to...

Fig 7. Flow chart shows detection of new (A) myocardial wall motion abnormalities (WMA) and (B) perfusion deficits (PD) by cardiac magnetic resonance imaging (MRI) dobutamine stress testing.

Fig 8. Comparison of (A) wall motion abnormalities (WMA) vs perfusion deficit at rest, (B) WMA vs perfusion deficit at stress, (C) WMA at rest vs late gadolinium enhancement, and (D) late gadolinium enhancement vs perfusion deficit at stress. Data are expressed as median ± range. *p < 0.05.
alterations of the myocardium detectable by LGE. Browne and colleagues [8] showed a satisfactory correlation between the spatial distribution of LGE on MRI and the histologic prevalence of subendocardial fibrosis.

**Ergometry**

Importantly, evaluation of exercise stress testing by bicycle ergometry showed no relationship between cardiopulmonary performance and myocardial viability. One patient (displayed by the vertical split point in Fig 9C) reached suboptimal results in exercise testing despite good LVEF (0.64). This patient showed no physical impairment or elevated body mass index and did not cancel the examination. However, wall motion deficits and myocardial perfusion deficits occurred during MRI testing in this patient. Another patient (displayed by the horizontal split point in Fig 9C) had a low LVEF (0.32), but had normal exercise performance compared with the age-specific norms. Interestingly, severe wall motion abnormalities, perfusion deficits, and areas of distinct LGE were found during MRI in this patient. Moreover, patients with normal wall motion, hypokinesia, akinesia, or dyskinesia offered almost identical physical examination findings. Similar results in exercise testing were also seen in patients with none, mild, or high-grade myocardial scarring. These findings demonstrate that myocardial deficiencies were unrelated to the general physical performance in our patients.

In conclusion, cardiac MRI offers a safe and reliable method to detect residual myocardial injury in patients after ALCAPA repair. Although LV function was excellent in the clinical course, numerous patients showed sequelae of myocardial damage. The presence of myocardial scarring was related to wall motion abnormalities and perfusion deficits. The relevance of these findings for the future clinical course, however, remains unclear.

Our patients did not report symptoms or recent changes in effort tolerance or complain of a decline in their quality of life. Our results showed no correlation between MRI findings and performance on ergometry. On the basis of our results, we propose cardiac MRI as a means of follow-up for these patients. The combination of myocardial viability, stress perfusion, wall motion, and ventricular volume analysis makes MRI a powerful tool for predicting freedom from cardiac adverse events in patients at risk for coronary stenosis and myocardial ischemia [26].

At the present time, we can only speculate whether sequelae of myocardial damage in nonadult growing hearts (15 of our patients were younger than 18 years at MRI) will evolve and whether LGE findings will change over time. Further long-term MRI surveillance might help us gain insight into the course of myocardial remodeling. Studies with larger numbers of patients, ideally in a prospective multicenter setting [2], should be conducted to further elucidate and prognosticate outcomes in this disease.

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**References**

2. Secinaro A, Ntsinjana H, Tann O, et al. Cardiovascular magnetic resonance findings in repaired anomalous left