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Original Article

Presence of reduced regional left ventricular function even in the absence of left ventricular wall scar tissue in the long term after repair of an anomalous left coronary artery from the pulmonary artery

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Abstract *Background:* We sought to assess left ventricular regional function in patients with and without left ventricular wall scar tissue in the long term after repair of an anomalous origin of the left coronary artery from the pulmonary artery. *Methods:* A total of 20 patients aged 12.8 ± 7.4 years were assessed 10 (0.5–17) years after the repair of an anomalous origin of the left coronary artery from the pulmonary artery; of them, 10 (50%) patients showed left ventricular wall scar tissue on current cardiac MRI. Left ventricular regional function was assessed by two-dimensional speckle-tracking echocardiography in 10 patients with scar tissue and 10 patients without scar tissue and in 10 age-matched controls. *Results:* In patients with scar tissue, MRI-derived left ventricular ejection fraction was significantly reduced compared with that in patients without scar tissue (51 versus 61%, $p < 0.05$), and echocardiography-derived longitudinal strain was significantly reduced in five of six left ventricular areas compared with that in healthy controls (average relative reduction, 46%; $p < 0.05$). In patients without scar tissue, longitudinal strain was significantly reduced in two of six left ventricular areas (average relative reduction, 23%; $p < 0.05$) and circumferential strain was reduced in one of six left ventricular areas (relative reduction, 56%; $p < 0.05$) compared with that in healthy controls. *Conclusions:* Regional left ventricular function is reduced even in patients without left ventricular wall scar tissue late after successful repair of an anomalous origin of the left coronary artery from the pulmonary artery. This highlights the need for meticulous lifelong follow-up in all patients with a repaired anomalous origin of the left coronary artery from the pulmonary artery.

Keywords: Regional wall motion; scar tissue; anomalous origin of the left coronary artery from the pulmonary artery

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Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) is a rare congenital anomaly that occurs in 1 in 300,000 live births.[1–3] Aberrant embryonic development leads to a left coronary artery that originates from the pulmonary artery instead of from the aorta. Subsequently, hypoxaemia and coronary hypoperfusion after birth are exerted onto the left ventricular myocardium, which can lead to myocardial damage[4] and clinical symptoms of heart failure. Patients typically present with infarct patterns on electrocardiography, reduced left ventricular ejection fraction, and mitral valve incompetence. Cardiac catheterisation was the traditional mode of diagnosis of ALCAPA, but recent publications have shown that echocardiography is a valid diagnostic tool for

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detecting the origin of an anomalous coronary artery from the pulmonary artery.[5] Without surgical treatment, patient mortality is >80%.[6]

Currently, the surgical technique of choice for anatomically repairing ALCAPA is the restoration of a two-vessel coronary system by direct aortic re-implantation of the left coronary artery.[7–9] With this technique, early postoperative mortality is low (~10%), which can be further improved by using postoperative mechanical circulatory support.[10,11] Short-, mid-, and long-term clinical outcome studies demonstrated restored global left ventricular function and a significant decrease in mitral valve incompetence;[10–15] however, left ventricular scar tissue and regional wall motion abnormalities have been described in the long term after successful repair of ALCAPA.[12,14,16]

In this study, we sought to assess left ventricular global function and left ventricular regional wall motion abnormalities using two-dimensional speckle-tracking echocardiography in relation to the presence of left ventricular wall scar tissue determined by late-enhancement studies on cardiac MRI late after successful surgical repair of ALCAPA.

Materials and methods

Patient population

A total of 20 patients aged 12.8 ± 7.4 years with ALCAPA were assessed at 10 (0.5–17) years after surgical repair with direct aortic re-implantation of the left coronary artery. The control subjects were 10 healthy volunteers aged 12.8 ± 6.1 years (Table 1). Permission to review the health records and follow-up data was obtained from the institutional review board committee. The need for individual or parental consent was waived.

The patients with ALCAPA underwent surgical repair at the Deutsches Herzzentrum Berlin between 1991 and 2007. At the time of surgical repair, seven patients (35%) required temporary postoperative mechanical circulatory support. Concomitant mitral valve annuloplasty was performed in four patients (20%) who had presented with severe mitral valve incompetence on echocardiography.

All patients included in this study had undergone a cardiac MRI examination during their follow-up visit to our institution in order to rule out the existence of postoperative scar tissue, at a median time of 10.1 ± 5.7 years after the repair of ALCAPA.[16] Cardiac MRI (1.5 Tesla Achieva 2.6, 5-channel cardiac coil; Philips Medical Systems, Best, The Netherlands) was performed according to institutional guidelines. On these MRI analyses, an open coronary anastomosis and non-obstructed coronary flow was found to be present in all patients; however, 10 patients (50%) showed positive late gadolinium enhancement, which suggested the presence of consolidated left ventricular wall scar tissue; six of these displayed transmural scars in the left ventricular apical and mid sections, and four of these patients showed endocardial scars at the anterior and mid sections of the left ventricle. The remaining 10 patients with ALCAPA (50%) showed no late gadolinium enhancement. The aim of our study was to compare left ventricular strain measurements between patients who showed postoperative left ventricular wall scar tissue and those who did not after ALCAPA repair.

In 15/20 patients, cardiopulmonary exercise testing had been performed at long-term follow-up on a bicycle ergometer with respiratory gas exchange analysis. Heart rate, blood pressure, and electrocardiographic changes were monitored during the test. The main variable studied was peak oxygen uptake (VO_{2max}) derived from respiratory gas analysis during maximal exercise testing.

Age at operation, years of follow-up, and M-mode-derived left ventricular ejection fraction measured preoperatively did not differ between patients with ALCAPA and left ventricular wall scar tissue and those without at long-term follow-up (Table 1). Infarct patterns in the electrocardiogram and the presence of good or poor coronary collaterals at preoperative angiography did not differ between patients with and those without left ventricular wall scar tissue at long-term follow-up (Table 1).

Echocardiography

Transthoracic two-dimensional echocardiography (VIVID 7; GE Medical Systems, Horten, Norway) was performed on the same day as the MRI for all 20 patients with ALCAPA and for 10 healthy volunteers as control subjects.

Left ventricular global function was assessed using monoplane modified Simpson's method. The degree of mitral valve incompetence was evaluated by means of colour flow jet analysis and subdivided into mild, moderate, and severe according to the length of the colour flow jet into the atrium.

For two-dimensional speckle tracking, two-dimensional Doppler myocardial data were recorded in the apical four-chamber and parasternal short-axis views at the level of the papillary muscles. For each patient, three separate apical four-chamber views and three separate parasternal short-axis views were acquired. Longitudinal, radial, and circumferential strain measurements were taken in each separate view and averaged. Offline analysis was performed in order to determine longitudinal, radial, and circumferential strain values using a customised software package (EchoPAC; General Electrics, Horten, Norway).

To assess left ventricular regional wall motion abnormalities, peak systolic longitudinal strain was measured in the lateral and septal left ventricular wall, which were additionally subdivided into basal, mid, and apical segments. Peak systolic radial and circumferential strains were assessed in six areas, namely septal, septal anterior, anterior, lateral, posterior, and inferior (Fig 1).

Statistics

Continuous variables are presented as means and standard deviations or as medians and ranges, as appropriate. Comparative univariable analyses were carried out using the t-test or the Mann–Whitney U-test, as appropriate. Binominal or ordinal data were expressed as percentages, and comparative univariable analyses were carried out using the χ^2 test, two-sided Fisher exact test, or binomial logistic regression. Statistical analysis was performed with one-way analysis of variance with post hoc Bonferroni correction to compare strain values of healthy controls with those of patients with ALCAPA with or without left ventricular wall scar tissue. A value of $p < 0.05$ was considered significant.

Results

Patient characteristics and global left ventricular function at long-term follow-up

Left ventricular ejection fraction derived from echocardiography was significantly reduced in patients with ALCAPA with or without left ventricular wall scar tissue compared with that in healthy volunteers (51 (45–69)%, 54 (46–66)%, 63 (54–71)%, $p > 0.05$); however, there was no significant difference between patients with and those without left ventricular wall scar tissue (51 (45–69)%, 54 (46–66)%, $p = 0.6$) (Table 1). Left ventricular ejection fraction derived from MRI measurements was significantly reduced in patients with left ventricular wall scar tissue compared with that in patients without left ventricular wall scar tissue (51 versus 61%, $p = 0.02$, Table 1). There was no significant correlation between left ventricular ejection fraction derived from echocardiography and that from MRI ($r = 0.4$, $p = 0.08$).

At long-term follow-up, the degree of mitral valve incompetence and cardiopulmonary exercise capacity were not significantly different between patients with left ventricular wall scar tissue and those without (Table 1).

Regional left ventricular function at long-term follow-up

Longitudinal strain. Patients with ALCAPA with left ventricular wall scar tissue at long-term follow-up showed a significant reduction in five of six areas in longitudinal strain measurements, namely the basal, mid, apical, septal-apical, and septal-mid areas of the left ventricle, compared with healthy controls (Table 2), and also showed significantly reduced strain values in the left ventricular mid area compared with patients with ALCAPA without left ventricular wall scar tissue (Table 2). In patients with ALCAPA without left ventricular wall scar tissue, left ventricular longitudinal strain was significantly reduced in two of six areas – mid and basal – compared with that in healthy controls (Table 2) (Fig 1a, c, and e).

Radial strain. Radial strain measurements showed no significant differences between patients with ALCAPA with left ventricular wall scar tissue and those without and in healthy volunteers (Table 3) (Fig 1b, d, and f).

Circumferential strain. Circumferential strain measurement in the posterior area was significantly reduced in patients without left ventricular wall scar tissue compared with that in healthy controls (Table 4). Patients with left ventricular wall scar tissue also showed reduced circumferential strain compared with that in healthy controls, but these measurements did not reach statistical significance (Table 4).

Discussion

The present study shows that reduction of left ventricular global and regional function can be related to the presence of left ventricular wall scar tissue late after successful repair of ALCAPA. Further, subtle changes in left ventricular regional function in certain left ventricular areas can be seen even in patients without left ventricular wall scar tissue. Left ventricular global function determined by MRI was significantly reduced in patients with left ventricular wall scar tissue compared with that in patients without left ventricular wall scar tissue, whereas standard echocardiographic measurements of global left ventricular function, mitral valve incompetence, and cardiopulmonary exercise capacity showed no statistical difference.

The left ventricular myocardium is composed of longitudinally, radially, and circumferentially oriented fibres,[17,18] which contribute to systolic and diastolic left ventricular function. Two-dimensional speckle-tracking echocardiography offers the opportunity for an isolated evaluation of longitudinal, radial, and circumferential regional deformation. Longitudinal shortening has been shown to be reduced in myocardial scar tissue,[19] but also to be impaired in patients with mild cardiovascular diseases like hypertension and left ventricular

Table 1. Patient characteristics.

	Controls (n = 10)	+ LV wall scar (n = 10)	–LV wall scar (n = 10)	p-value
Sex (F/M)	5/5	5/5	6/4	ns
Age (years)	12.8 ± 6.1	12.9 ± 9.3	12.8 ± 5.5	ns
Age at surgery (years)	na	1.4 (0.3–10.5)	0.4 (0.1–10.5)	ns
LVEF (%) pre by echo	na	41 ± 17	44 ± 19	ns
MVI (grade 0–4) pre (echo)	na	1.5 (0–4)	2.5 (0–3)	ns
Collaterals (poor/good) pre	na	5/5	6/4	ns
Q waves aVL pre (yes/no)	na	8/2	8/2	ns
MV reconstruction (n)	0	2	2	ns
MCS postoperative (n)	0	6*	1**	<0.01* <0.05**
Years of follow-up (years)	na	11.8 (0.5–15.8)	10.3 (2.5–17)	ns
LVEF (%) fu echo	63 (54–71)	51 (45–69)*	54 (46–66)*	<0.05*
LVEF (%) fu MRI	na	54 (32–66)	62 (37–74)**	<0.02**
MVI (grade 0–4) fu (echo)	0	1 (0–3)*	1 (0–3)*	<0.05*
Vo_{2max} (ml/minute/kg) fu	na	32 (22–36)	29 (22–36)	ns

F = female; fu = follow-up; LV = left ventricular; LVEF = left ventricular ejection fraction; M = male; MCS = mechanical circulatory support; MV = mitral valve; MVI = mitral valve incompetence; na = not applicable; ns = not significant; pre = preoperative

Data are presented as means and standard deviation (SD) or as medians and ranges, as appropriate

*Compared with controls

**Compared with + LV wall scar

Table 2. Longitudinal two-dimensional (2D) strain.

	Longitudinal 2D strain			
Area	Controls (n = 10)	+LV wall scar (n = 10)	–LV wall scar (n = 10)	p-value
Septal basal	−19 ± 2	−17 ± 2	−19 ± 3	ns
Septal mid	−21 ± 1	−18 ± 4*	−21 ± 3	<0.05*
Septal apical	−24 ± 5	−15 ± 7*	−20 ± 4	<0.01*
LV apical	−21 ± 5	−11 ± 6*	−16 ± 5	<0.01*
LV mid	−22 ± 3	−6 ± 7*	−13 ± 4*,**	<0.001* <0.05* <0.01**
LV basal	−23 ± 4	−10 ± 7*	−16 ± 5*	<0.001* <0.05*

LV = left ventricular; ns = not significant

Data are presented as means and standard deviations (SD)

*Compared with controls

**Compared with + LV wall scar tissue

hypertrophy with preserved left ventricular ejection fraction.[20,21] In our study, longitudinal shortening was reduced in two areas, left ventricular mid and basal, in surgically repaired patients with an ALCAPA artery without left ventricular wall scar tissue on MRI and with normal left ventricular ejection fraction measured using MRI at long-term follow-up. Anatomically repaired patients with ALCAPA with left ventricular wall scar tissue at long-term follow-up showed more pronounced findings, with reduction in longitudinal shortening in five of six left ventricular areas and reduced left ventricular ejection fraction on MRI. These patients with left ventricular wall scar tissue did not present with chest pain at rest or during exercise, nor with pathological changes on electrocardiography, suggesting that the existence of left ventricular wall scar tissue is not related to recent occlusion of the re-implanted left coronary artery but rather to preoperative hypoperfusion, leading to long-term damage of certain areas of the left ventricle.

The left ventricular wall scar tissue in our patients with ALCAPA identified with MRI was most often found within the left ventricular anterior free wall, which corresponds to the "mid segment" for longitudinal strain measurements and to the "anterior" and "lateral" segments for radial and circumferential strain measurements. In concordance with the MRI findings, strain measurements in the mid segment displayed the most significant reduction in

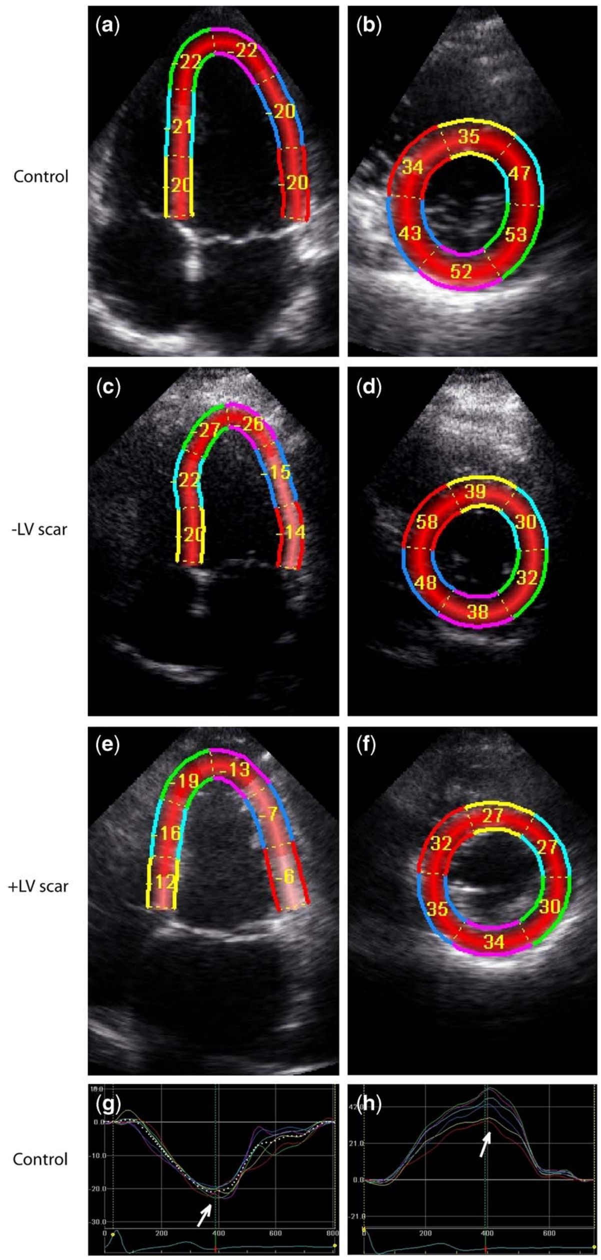

Figure 1.
*Longitudinal (**a**, **c**, **e**) and radial (**b**, **d**, **f**) strain measurements in a healthy control (**a** and **b**), in a patient with anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) without left ventricular wall scar tissue (– LV scar) (**c** and **d**), and in a patient with ALCAPA with left ventricular wall scar tissue (+ LV scar) (**e** and **f**). Curves of strain versus time are shown for longitudinal (**g**) and radial (**h**) strain in a healthy control. Arrows indicate peak strain measurements: for longitudinal strain, peak systolic strain values (peak S); for radial strain, peak radial strain (peak G).*

longitudinal shortening in patients with left ventricular wall scar tissue. This myocardial area might be at risk for the development of scar tissue in patients with ALCAPA as it is not only the perfusion territory of the left anterior descending coronary artery, and partly of the left circumflex coronary artery, but also this myocardial area is the farthest from the perfusion territory of the right coronary artery and the possible collaterals originating from it.[22] At a microscopic level, the myocardium of patients with ALCAPA consists of chronically hypoperfused myocardium,[4] and fibrosis in the subendocardial longitudinally oriented layer may have selectively impaired long-axis function.[23]

Table 3. Radial two-dimensional (2D) strain.

	Radial 2D strain			
Area	Controls (n = 10)	+LV wall scar (n = 10)	–LV wall scar (n = 10)	p-value
Anterior-septal	39 ± 8	31 ± 16	44 ± 20	ns
Anterior	48 ± 15	37 ± 18	45 ± 21	ns
Lateral	59 ± 18	43 ± 16	47 ± 21	ns
Posterior	63 ± 20	45 ± 14	47 ± 19	ns
Inferior	56 ± 20	43 ± 11	45 ± 16	ns
Septal	46 ± 18	35 ± 11	44 ± 16	ns

LV = left ventricular; ns = not significant
Data are presented as means and standard deviations (SD)

Di Salvo et al[12] demonstrated reduced longitudinal left ventricular regional function in all six areas of the left ventricle late after repair of ALCAPA using Strain Doppler measurements in a study comparing patients with ALCAPA with healthy controls; however, no specification was provided concerning the existence of left ventricular wall scar tissue in these patients. In our study, patients with ALCAPA and left ventricular wall scar tissue showed left ventricular regional wall motion abnormalities in five of six areas on two-dimensional speckle tracking, and those without left ventricular wall scar tissue had reduced left ventricular regional function only in two of six areas compared with healthy controls, suggesting a high prevalence of left ventricular wall scar tissue in the patient population of Di Salvo.[12] Concordant with our findings, the lowest longitudinal strain measurements were also found in the left ventricular lateral wall, apical area, and in the mid segment of the patient cohort of Di Salvo et al. For assessing left ventricular global function, they used M-mode echocardiography in the parasternal long-axis view, which showed no significant difference between patients with ALCAPA and healthy controls. In our study, monoplane modified Simpson's method showed significantly reduced left ventricular ejection fraction in patients with ALCAPA with and without left ventricular wall scar tissue compared with healthy controls, but no difference was found between ALCAPA patients with and those without left ventricular scar tissue.

Table 4. Circumferential two-dimensional (2D) strain.

	Circumferential 2D strain			
Area	**Controls (n = 10)**	**+LV wall scar (n = 10)**	**–LV wall scar (n = 10)**	**p-value**
Anterior septal	−23 ± 5	−20 ± 11	−25 ± 4	ns
Anterior	−20 ± 6	−15 ± 7	−20 ± 6	ns
Lateral	−16 ± 5	−10 ± 5	−10 ± 7	ns
Posterior	−13 ± 8	−8 ± 4	−5 ± 4*	<0.05*
Inferior	−19 ± 8	−16 ± 4	−16 ± 3	ns
Septal	−25 ± 2	−24 ± 7	−24 ±6	ns

LV = left ventricular; ns = not significant

Data are presented as means and standard deviations (SD)

*Compared with controls

MRI-derived left ventricular ejection fraction has shown reduced left ventricular global function in patients with ALCAPA with left ventricular wall scar tissue compared with that in patients without left ventricular wall scar tissue, taking into account the whole three-dimensional volume of the left ventricle. This result also suggests that monoplane modified Simpson's method of echocardiography does not seem to be the appropriate method for the description of left ventricular ejection fraction in patients with surgically repaired ALCAPA.

No differences in radial strain measurements were detected between healthy controls and patients with ALCAPA with or without left ventricular wall scar tissue. Consistent with this finding, Di Salvo et al[12] described normal radial function in the long term after repair of ALCAPA in his patient population. In contrast to those of Di Salvo, our radial strain measurements were taken not only in the posterior segment, usually perfused by the right coronary artery, but also in the anterior-septal, anterior, septal, inferior, and lateral segments in the parasternal short axis. Our study could further describe in detail that even in the presence of left ventricular wall scar tissue on cardiac MRI, radial function is not significantly impaired in the long term after repair of ALCAPA in perfusion territories of the left and right coronary arteries, although our data suggest a tendency towards lower radial strain in patients with ALCAPA with left ventricular wall scar tissue. In 40% of patients with ALCAPA with left ventricular wall scar tissue in the long term after surgical repair, only the subendocardial layer was affected, which might partly explain an unimpaired radial function. Further, radial strain measurements have been shown to be inferior in identifying myocardial scar tissue compared with longitudinal and circumferential strain measurements.[24]

In contrast to former studies, we also compared circumferential strain measurements between patients with ALCAPA and healthy controls. Mizuguchi et al[21] described reduced circumferential strain measurements in patients with concentric left ventricular hypertrophy and preserved left ventricular pump function. In patients with cardiovascular risk factors and preserved left ventricular pump function, circumferential strain was described to have a compensatory function in the presence of reduced longitudinal shortening in order to preserve global left ventricular function.[20] In our study, circumferential strain measurements in the posterior area, which belongs to the perfusion territory of the right coronary artery, was reduced in patients with ALCAPA compared with those in healthy controls. In patients with ALCAPA and left ventricular wall scar tissue, circumferential strain measurements were reduced, but only in patients without left ventricular wall scar tissue was circumferential strain significantly lower than that in healthy controls. One could speculate that patients with ALCAPA without left ventricular wall scar tissue might have had a better collateral system between the right and left coronary arteries that had helped to protect from developing left ventricular wall scar tissue but in turn might have led to a mild reduction in the perfusion of right coronary artery territories. In addition, patients with ALCAPA and left ventricular wall scar tissue showed significantly reduced longitudinal strain compared with patients with ALCAPA without left ventricular wall scar tissue, and this might be partly compensated for by higher circumferential strain measurements in order to maintain normal global left ventricular function.

Overall, our patients with successfully repaired ALCAPA showed normal global left ventricular function, no significant mitral valve incompetence, and only fairly reduced exercise capacity. This is in agreement with other studies[11,25,26] that describe the favourable long-term clinical outcome in patients with ALCAPA. When looking closer at the level of regional wall motion patterns, however, the detection of left ventricular wall scar tissue in 50% of our patients with an ALCAPA and the presence of reduced regional myocardial function – even in patients with ALCAPA without left ventricular wall scar tissue – implicate that re-implantation of the left coronary artery is not yet a curative procedure. In our study, ALCAPA patients without left ventricular wall scar tissue showed a trend towards a younger age at surgery compared with ALCAPA patients with left ventricular wall scar tissue, although this difference was not statistically significant. This finding could imply that a prolonged time of relative myocardial hypoxaemia might have an impact on the subsequent development of scar tissue. The non-invasive method of two-dimensional speckle-tracking echocardiography might be useful for the detection of residually damaged myocardial areas and, thus, for the detection of patients with a possibly higher risk for adverse events after surgical repair of ALCAPA – that is, left ventricular dysfunction and arrhythmias.

Limitations

In this single-centre study, not all patients with ALCAPA who were operated upon by direct aortic re-implantation of the left coronary artery in the German Heart Institute, Berlin were included. In total, 26 patients were operated upon using this technique between 1991 and 2007; four patients were lost to follow-up, and two patients had refused the intravenous application of the contrast agent during cardiac MRI. Thus, we included 20 patients in this study. Another limitation of the present study is that strain measurements were not performed in all regions of the left ventricle; however, scar tissue was mainly present in the left ventricular free wall, which was assessed using the four-chamber view. Further prospective multicentre studies are warranted for a better description of the long-term outcome of patients with ALCAPA who undergo surgical repair.

Conclusions

Despite a very good long-term outcome after surgical repair of ALCAPA, meticulous lifelong serial follow-up investigations of every patient is needed. The non-invasive method of two-dimensional speckle-tracking echocardiography might be a useful tool for the detection of residually damaged myocardial areas and, thus, for the depiction of patients with a possible higher risk for adverse events after surgical repair of ALCAPA.

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Conflicts of Interest

None.

Ethical Standards

This study complies the Helsinki Declaration and was approved by the local Institutional Review Board.

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