Manuscript Details

Manuscript number	IJC_2018_977
Title	Anomalous Left Coronary Artery from the Pulmonary Artery (ALCAPA) diagnosed in adulthood: Varied Clinical Presentation, Therapeutic Approach and Outcome
Article type	Original article

Abstract

Introduction: The diagnosis of ALCAPA syndrome is sporadic in adulthood, of the limited cases in the literature most are incidental or without symptoms. There is a broad spectrum of clinical manifestations of ALCAPA syndrome however, including sudden cardiac death. Cases: We present herewith a series of 12 consecutive patients with ALCAPA, all diagnosed in adulthood (between 18 and 73 years of age). Five patients developed symptoms (breathlessness) after the fourth decade of life, 3 were undiagnosed despite a history of previous mitral valve repair, one presented with heart failure, one with resuscitated cardiac arrest, whereas two patients were asymptomatic. We review in this paper, the clinical history, diagnostic approach and therapeutic choices of ALCAPA syndrome. Conclusion: ALCAPA syndrome is not confined to childhood, late diagnosis in adulthood has a varied clinical presentation. ALCAPA syndrome should be particularly considered as a potential, albeit uncommon cause of mitral regurgitation and/ or dilated cardiomyopathy.

Keywords	ALCAPA; ischaemia; mitral regurgitation; adults
Taxonomy	Congenital Heart Disease
Manuscript category	Original clinical research studies, basic science/translational research papers
Manuscript region of origin	Europe

Corresponding Author	Maria Boutsikou
Order of Authors	Maria Boutsikou, Darryl Shore, Wei Li, michael rubens, Antonia Pijuan-Domenech, Michael Gatzoulis, Sonya Babu-Narayan

Submission Files Included in this PDF

File Name [File Type]

Boutsikou et al Cover letter.docx [Cover Letter]

Boutsikou et al Highlights.docx [Highlights]

Boutsikou et al, Title page.docx [Title Page (with Author Details)]

Boutsikou et al Manuscript.docx [Manuscript File]

Boutsikou et al. Figure 1.tif [Figure]

Boutsikou et al. Figure 2.tif [Figure]

Boutsikou et al. Figure 3.tif [Figure]

Boutsikou et al. Author Agreement Form.docx [Author Agreement]

Boutsikou et al Suppl material.tif [Supplementary Material]

To view all the submission files, including those not included in the PDF, click on the manuscript title on your EVISE Homepage, then click 'Download zip file'.

Maria Boutsikou, MD, PhD, MSc

Correspondence: Adult Congenital Heart Centre & National Centre for Pulmonary Hypertension, Royal Brompton Hospital, SW3 6NP, London, UK.

E-mail: M.Boutsikou@rbht.nhs.uk,

Boutsikoum@gmail.com

To the Editor of "International Journal of Cardiology"

London, 19th February 2018

Dear Editor,

Please find attached our MS entitled: "Anomalous Left Coronary Artery from the Pulmonary Artery (ALCAPA) diagnosed in adulthood: Varied Clinical Presentation, Therapeutic Approach and Outcome" for consideration and possible publication in the "International Journal of Cardiology".

The manuscript is being submitted only to the International Journal of Cardiology, it will not be submitted elsewhere while under consideration, it has not been published elsewhere, and should it be published in the International Journal of Cardiology, it will not be published elsewhere either in similar form or verbatim without permission of the editors. All authors are responsible for reported case, have been involved in the diagnostic management of the patients and contributed to the writing and revision of the manuscript. There are no financial conflicts of interest.

Yours sincerely,

Maria Boutsikou, MD, PhD, MSc for all authors

Highlights

- ALCAPA syndrome may present in late adulthood with a varied clinical presentation.
- Angina and shortness of breath are among the most common symptoms in adults with ALCAPA syndrome
- Mitral regurgitation and LV dilatation are common presentations of the syndrome and are frequently overlooked.
- Multimodality imaging is crucial for the initial diagnosis and follow up
- Patients with inducible ischaemia should be offered surgical repair as it provides symptomatic and prognostic benefit.

Anomalous Left Coronary Artery from the Pulmonary Artery (ALCAPA) diagnosed in adulthood: Varied Clinical Presentation, Therapeutic Approach and Outcome

Boutsikou M[1], Shore D[2], Li W[3], Rubens M[4], Pijuan A[5], Gatzoulis MA[6], Babu-Narayan S[7].

[1]Adult Congenital Heart Centre & National Centre for Pulmonary Hypertension, Royal Brompton Hospital, London, UK. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

[2]National Heart and Lung Institute, Imperial College School of Medicine, London, UK; Surgical Division of Adult Congenital Heart Disease Centre, Royal Brompton Hospital, London, UK. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

[3]Adult Congenital Heart Centre & National Centre for Pulmonary Hypertension, Royal Brompton Hospital, London, UK; National Heart and Lung Institute, Imperial College School of Medicine, London, UK. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

[4]Royal Brompton and Harefield NHS Foundation Trust, London, UK; National Heart and Lung Institute, Imperial College, London, United Kingdom. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

[5] Grown-Up Congenital Heart Disease Unit; Cardiology Department Vall d'Hebron Universitary Hospital, Barcelona, Spain. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

[6]Adult Congenital Heart Centre & National Centre for Pulmonary Hypertension, Royal Brompton Hospital, London, UK; National Heart and Lung Institute, Imperial College School of Medicine, London, UK. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

[7]Adult Congenital Heart Centre & National Centre for Pulmonary Hypertension, Royal Brompton Hospital, London, UK; National Heart and Lung Institute, Imperial College School of Medicine, London, UK. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Corresponding author: Dr Maria Boutsikou,
Adult Congenital Heart Centre & National Centre for Pulmonary Hypertension, Royal Brompton Hospital, SW3 6NP, London, UK.
Email: M.Boutsikou@rbht.nhs.uk
Boutsikoum@gmail.com

Funding: MAG has received support from the British Heart Foundation, London UK and Actelion, Allschwil, Switzerland.
SBN has received support from the British Heart Foundation, London UK

Conflicts of interest: none

Key words: ALCAPA, ischaemia, mitral regurgitation, adults

Abstract

Introduction: The diagnosis of ALCAPA syndrome is sporadic in adulthood, of the limited cases in the literature most are incidental or without symptoms. There is a broad spectrum of clinical manifestations of ALCAPA syndrome however, including sudden cardiac death.

Cases: We present herewith a series of 12 consecutive patients with ALCAPA, all diagnosed in adulthood (between 18 and 73 years of age). Five patients developed symptoms (breathlessness) after the fourth decade of life, 3 were undiagnosed despite a history of previous mitral valve repair, one presented with heart failure, one with resuscitated cardiac arrest, whereas two patients were asymptomatic. We review in this paper, the clinical history, diagnostic approach and therapeutic choices of ALCAPA syndrome.

Conclusion: ALCAPA syndrome is not confined to childhood, late diagnosis in adulthood has a varied clinical presentation. ALCAPA syndrome should be particularly considered as a potential, albeit uncommon cause of mitral regurgitation and/ or dilated cardiomyopathy.

Abbreviations:

PA: pulmonary artery

LCA: left coronary artery

LAD: left anterior descending artery

RCA: right coronary artery

LM: left main stem

LIMA: left internal mammary artery

PDA: patent ductus arteriosus

LV: left ventricle

CXR: chest X-ray

CT: Cardiac Computed Tomography

CMR: Cardiovascular Magnetic Resonance

CRT-D: Cardiac Resynchronization Therapy Defibrillator

NYHA: New York Heart Association

MVR: mitral valve replacement

VT: ventricular tachycardia

VF: ventricular fibrillation

AHA: American Heart Association

CABG: Coronary Artery Bypass Grafting

AP window: aortopulmonary window

ICD: Implantable Cardioverter Defibrillator

Introduction

Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) is a rare but well described cardiac anomaly. It is present in 1 in 300,000 live births or 0.5% of children with congenital heart disease [1]. The first reports of anomalous origin of coronary artery from the PA were made by Krause and Brooks in 1865 and 1885 respectively [2-3], based on autopsy studies describing arteries originating from the PA and joining branches of the coronary artery tree. Konstantinowitch in 1906 and Abrikossoff in 1911 reported ALCAPA cases based on autopsies in a 2 day and a 5 month old infant. However, the first clinical pathologic correlation of ALCAPA syndrome was made by Garland, Bland and White in 1933 [4].

Embryologically, ALCAPA may result from abnormal separation of the conotruncus into the aorta and PA, or persistence of the pulmonary buds in conjunction with involution of the aortic buds, the former eventually forming the coronary arteries. Therefore, the LCA and left heart receive blood from the PA [5-7].

Two types of ALCAPA syndrome have been described. The classic presentation is with symptom onset in the first or second month of life when, PA pressure falls after closure of the ductus arteriosus [1]. The majority of patients with ALCAPA syndrome if not operated on, die within the first year of life from ischaemic cardiomyopathy and endocardial fibrosis due to decreasing oxygen supply in the LCA territory [8]. It has been suggested that without treatment, 15% of patients may survive to adulthood but approximately 90% of these die suddenly at a mean age of 35 years [1,9].

Diagnosis in living adults (versus autopsy series) is thought to be extremely rare with just a few cases reported in the literature [1,10]. Although angina is frequently described as common clinical presentation of ALCAPA in adulthood, patients may be asymptomatic with atypical symptoms at diagnosis. Surgical myocardial revascularization regardless of myocardial viability in adults diagnosed with ALCAPA has been suggested in American Heart Association for Adult Congenital Heart Disease treatment guidelines [11]. Rationalizing treatment options, however, remains challenging due to variety of clinical presentation, symptoms and degree of deterioration in

cardiac function. We describe herewith, the varied clinical presentation in 11 adults from our tertiary centre all with late diagnosis of ALCAPA syndrome, the diagnostic work up and our management strategy.

Methods

Study population

Twelve consecutive patients with a diagnosis of ALCAPA syndrome in adulthood followed in our institution were identified from our dedicated electronic database and retrospectively studied. Their demographic and clinical information was obtained from patients' records. In all patients the diagnosis of ALCAPA syndrome was established in adulthood. Medical history, previous symptomatology and initial clinical presentation were documented in all, as their diagnostic work up, therapeutic approach and follow up data.

Results

Patient characteristics- medical background

Age at ALCAPA syndrome diagnosis ranged from 18 to 73 years with a mean (SD) of 42(±16.8) years. Demographic, clinical, imaging and outcome data are presented in Table 1.

Ten of the 12 patients (83.3%) became symptomatic shortly before the diagnosis was made or the treatment was initiated. Symptoms included angina, shortness of breath and arrhythmia. One patient (8.3%) experienced cardiac arrest; subsequent investigations revealed ALCAPA syndrome associated with a genetically confirmed diagnosis of Long QT syndrome. Three patients from our series (25.0%) presented with mitral regurgitation and underwent surgical mitral valve repair or replacement prior to the diagnosis of ALCAPA syndrome being established. One patient (8.3%) was diagnosed at the age of 60 with signs and symptoms of decompensated left heart failure. Finally two patients (16.6%) with previous history of congenital heart disease and cardiac surgery in childhood had: A) repaired aortic coarctation and PDA (with three syncopal episodes in the past and developing symptomatic advanced heart failure) and B) bicuspid aortic valve who underwent ligation of PDA and was asymptomatic with incidental diagnosis of ALCAPA syndrome at routine follow up.

Clinical examination and diagnostic work up

The most frequent finding on clinical examination was the presence of a pansystolic murmur at the left sternal border and the apex (in 10/12). Two patients had signs of heart failure with significant impairment of LV systolic function.

All patients underwent a series of tests examining coronary and cardiac anatomy and function and presence and degree of myocardial ischemia.

Cardiomegaly on CXR was present in 7 patients, all with impaired LV function. Q or inverted T waves in the lateral or precordial leads were present in 12lead ECGs in 9 patients .

Initial or suspected diagnosis was made by echocardiography in a high volume specialized centre. The main echocardiographic features included retrograde flow from the LAD into the PA with significant left to right shunting, presence of intramyocardial collateral vessels and dilatation of the RCA origin. LV dilatation with variable degree of LV systolic impairment was present in 8 cases. Moderate to severe mitral regurgitation with calcification of the mitral annulus and the papillary muscles was common (n=7, Figure 1).

Coronary angiography, CT or CMR confirmed the diagnosis in all cases and showed the presence of a single large RCA originating from the aorta and extensive collaterals arising from the LCA draining into the PA. Exercise test, stress echocardiogram, Thallium myocardial perfusion scan and perfusion CMR with gadolinium study were performed for assessing myocardial ischemia and/or viability (Figure 2). Nine out of the twelve patients (75%) had at least one of these investigations positive for ischemia.

Treatment management

Myocardial revascularization and restoration of dual coronary artery supply was attempted in eight patients (66.6%) who underwent surgical repair of the ALCAPA Three types of repair were performed in our study group. These included ligation of LM (n=1), ligation of LM and re-implantation of LAD to the aorta (n=3), ligation of anomalous LAD, implantation of vein graft or left

internal mammary artery (LIMA) to the LAD (n=3) and Takeuchi procedure (n=1) (Figure 4). Surgery was offered to two more patients who declined. Both were reluctant to undergo a surgical operation for prognostic reasons as they were asymptomatic; one of them had evidence of myocardial ischaemia.

A conservative approach was adopted in two patients presenting with heart failure at the time of diagnosis but no significant inducible ischemia, as surgery seemed unlikely to convey substantial prognostic benefits. Instead, optimization of medical therapy treatment and Cardiac CRT-D implantation were employed.

Follow up

Of the 12 patients studied, 10 were alive at a mean follow up of 5.3±4.2 years. One patient died two months after surgical repair, the post-operative period being complicated by lung sepsis and multi-organ failure. The remaining 7 patients (58.3%) who underwent surgical repair report no symptoms and remained stable on periodic follow up of 5.9±3.8 years; two (16.6%) developed atrial fibrillation which was controlled well medically. The 2 patients who declined surgery have remained stable at follow up (7.5±7.7 years). Finally, the last 2 patients who were managed conservatively and received a CRT-D device, both improved their functional status (now in NYHA II functional class) and remained stable on clinical follow up (3.5±0.7 years).

Discussion

We report herewith our experience with 12 consecutive patients presenting in adulthood with ALCAPA syndrome. Clinical presentation was varied, 6 patients had symptomatic relief after surgery, one died from sepsis; four patients are followed up medically. Six of our patients diagnosed after their 4th decade of life; six developed symptoms leading to diagnosis in the fifth decade of life or later; the older patient at the time of diagnosis was 73 years of age. ALCAPA syndrome typically presents in the first year of life.

Presentation in adulthood, particularly in late adulthood is thought to be extremely rare. In a previously published systematic review on ALCAPA syndrome based on reported cases from 1908 to 2008, the mean reported age at diagnosis was 41 years [1]; of the 151 adults identified, 48 were older than 50 years. There is an increase in cases of ALCAPA syndrome diagnosed in late adulthood, this was related to advances in noninvasive imaging, at least in part.

Three patients from our series had a previous history of MVR, due to congenital mitral stenosis, "childhood dilated cardiomyopathy" and/or mitral regurgitation in association with left ventricular systolic dysfunction. Mitral regurgitation is known to be common clinical finding in patients with ALCAPA syndrome, evident even early in the course of the disease with or without concomitant ventricular dysfunction [12]. It can be functional, secondary to a dilated left ventricle and annulus. [13] or the result of papillary muscle ischemia and fibrosis [1,14-16]. In the majority of pediatric patients reparative surgery for ALCAPA results in improvement of mitral regurgitation [13, 17]. Our data suggests that this combination of dilated cardiomyopathy and mitral regurgitation is also present in adults with ALCAPA syndrome and therefore should be considered in the differential diagnosis.

It has been suggested that the risk of sudden cardiac death with ALCAPA decreases with age [11]. Autopsy studies identifying adult cases with untreated ALCAPA showed an average age at death of 35 years [9,18-19]. Formation of scarred tissue due to myocardial ischemia and new ischemic episodes could trigger life threatening arrhythmias and death [1]. In our series, a 25 year old male, had ventricular fibrillation as his first clinical manifestation of ALCAPA syndrome. This patient was also diagnosed with long QT syndrome, thus it is somewhat unclear whether his ALCAPA related ventricular dysfunction and ischaemia/fibrosis or the Long QT syndrome was the triggering factor for this episode. He, nevertheless responded well to surgery and ICD implantation with no further VT/VF.

Although ALCAPA is generally an isolated defect, it can be associated with other cardiac congenital malformations like ventricular septal defect, PDA, tetralogy of Fallot and aortopulmonary window. In our series, two patients had a PDA ligated or bicuspid aortic valve (with coarctation of the aorta). PDA leads to volume overload, potentially with functional mitral regurgitation, thus the diagnosis of ALCAPA may be overlooked. ALCAPA syndrome with bicuspid aortic valve and/or coarctation of the aorta is rare [1,20].

Different imaging modalities used for the diagnosis of the syndrome in our case series, revealed the presence of an extensive network of collateral arteries from the RCA to LCA and retrograde flow into the PA. The development of extensive collaterals from a dominant dilated RCA to LCA which supply oxygenated blood to the diaphragmatic portion of the left ventricle, part of the septum and the lateral wall, is the main protective mechanism from ischemia and infarction [9,14, 21-25]. Thus, adults may present with symptoms when reverse flow into the PA may lead to coronary steal syndrome and/or if stenosis of the collateral vessels develop compromise myocardial perfusion [26-28].

Resting ECG is usually abnormal in patients with ALCAPA syndrome with ST changes and Q waves mainly in the anterior and lateral leads. ECG abnormalities could also occur during exercise testing. Myocardial perfusion imaging may also be abnormal [1,16,29]. Eight of the eleven patients in our series had a leftward QRS axis, Q waves in anterior and lateral leads and ST changes in anterolateral leads. Cardiopulmonary exercise testing, stress echocardiography or myocardial stress perfusion imaging (CMR or Nuclear) was performed in all patients and documented ischaemia in 8 cases. Our findings are in agreement with previous studies showing stress ECG and stress imaging tests being positive for ischaemia in 85-87% [1].

Echocardiography set the primary diagnosis of ALCAPA in the vast majority of our cases. Dilatation of the proximal part of the RCA, retrograde flow from LCA into the PA and prominent septal flow were universal findings [30-31]. Notably, transthoracic echocardiography raised the

suspicion of the presence of ALCAPA in three asymptomatic patients with history of previously repaired cardiac lesions. Echocardiography is used in everyday clinical practice; its main limitations are poor image quality in patients with difficult echo windows and difficulties in visualizing the anomalous origin of the LCA. Compliment imaging such as CT and CMR permit the direct visualization of coronary vascular anatomy/ course with 3D reconstruction of the coronary arterial tree. Furthermore, CMR provides assessment of biventricular size and function, estimation of valvar abnormalities and shunts and, with pharmacological stress perfusion assessment of myocardial viability in the absence of ionizing radiation [32]. In most of our cases CT and/or CMR were the imaging techniques that confirmed the definitive diagnosis.

Cardiac catheterization and selective coronary angiography may demonstrate the presence and extent of collaterals, quantify the left to right shunt and provide end diastolic pressures.

According to the latest AHA treatment guidelines [11], surgery is the only definitive treatment of ALCAPA syndrome suggested even in asymptomatic patients due to the lifelong risk of ischaemia, ventricular arrhythmias and sudden cardiac death [1,8-9]. Different surgical techniques have been employed including ligation of LCA and CABG using a saphenous vein graft or LIMA, reimplantation of the left coronary artery to the aorta and the Tackeuchi procedure [1]. The latter is based on the formation of an AP window with intrapulmonary baffle to connect the origin of the anomalous LCA to the aorta (Figure 3) [33]. Early surgical treatment restores normal coronary circulation and adequate myocardial perfusion preventing long-term myocardial ischaemia and fibrosis. Four of our patients were not operated; two declined operation, whereas for the remaining two it was felt that a surgical repair would not be beneficial due to severe ventricular dysfunction at diagnosis and lack of significant inducible ischemia. Notably, in 151 cases of ALCAPA patients from a recent review, 37% of patients older than 50 years of age were managed medically [1]. The suggested lower risk of sudden cardiac death in older patients and the relative increase in surgical risk in older patients with other comorbidity may both have been contributing [1].

Conclusion

ALCAPA syndrome may present in late adulthood with a varied clinical presentation from asymptomatic to angina and sudden cardiac death. Mitral regurgitation with "dilated cardiomyopathy" seems also to be also a common and may have been overlooked. Echocardiographic features such as a large RCA and retrograde flow in the LCA should raise suspicion of ALCAPA which can be confirmed by CMR and/or CT. Patients with inducible ischaemia should be offered surgical repair, associated with symptomatic and probably prognostic benefit.

References

[1] J.M. Yau, R. Singh, E.J. Halpern, D. Fischman, Anomalous origin of the left coronary artery from the pulmonary artery in adults: a comprehensive review of 151 adult cases and a new diagnosis in a 53-year-old woman, Clin Cardiol 34 (2011) 204-210.

[2] W. Krause W, Cber den Ursprungeinerakzessorischen A. coronariaaus der A. pulmonalis, Ztschr rat Med. 24 (1865) 225–227.

[3] S.J. Brooks, Two cases of an abnormal coronary artery of the heart arising from the pulmonary artery: with some remarks upon the effect of this anomaly in producing cirsoid dilatation of the vessels, J Anat Physiol 20 (1886) 26–32.

[4] S. Menahemm, A.W. Venables, Anomalous left coronary artery from the pulmonary artery: a 15 year sample, Br Heart J 58 (1987) 78-84.

[5] L.F Lee, J.S. Chang, R.E. Hung, Y.L. Wu, Adult type anomalous origin of the left coronary artery from the main pulmonary artery: Report of one case. ActaPaedriat Taiwan 40 (1999) 112-5.

[6] M.L. Lee, I.S. Chiu, S.J. Chen, W.T. Chao, Imaging characteristics of anomalous left coronary artery from the pulmonary artery, J Thoracic Imaging 17 (2002) 96-100.

[7] H.B. Nielsen, M. Perko, J. Aldershvile, Saunamaki, Cardiac arrest during exercise: Anomalous left coronary artery form the pulmonary trunk, J ScandCardiovasc Surg 33(1999) 369-71.

[8] G. Wollenek, E. Domanig, U. Salzer-Mua, M. Havel, M. Wimmer, E. Wolner, Anomalous origin of the left coronary artery: a review of surgical management in 13 patients. J CardiovascSurg 34 (1993) 399- 405.

[9] V. Alexi-Meskishvili, F. Berger, Y. Weng, P.E. Lange, R. Hetzer, Anomalous origin of the left coronary artery from the pulmonary artery in adults, J Card Surg 10(1995) 309-315.10.

[10] T. Zhuang, F. Li-Gang, L. Yong-Tai, Z. Shu-yang, Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery Detected by Echocardiography in an Asymptomatic Adult, Intern Med 52 (2013) 233-236.

[11] C.A. Warnes, R.G. Williams, T.M. Bashore, et al, ACC/AHA 2008 Guidelines for the Management of Adults With Congenital Heart Disease: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Adults With Congenital Heart Disease) Circulation 118 (2008) 2395-2451

[12] A. Edmar, Case 5/2012 – Six-Year-Old Child with Anomalous Origin of Left Coronary Artery and Mitral Regurgitation, Arq Bras Cardiol 99(1) (2012) e105-e107

[13] E. Malec, A. Zajac, M. Mikuta. Surgical repair of anomalous origin of the coronary artery from the pulmonary artery in children, Cardiovasc Surg, 9(2002) 292-8.

[14] N. Kouchoukos, E. Blackstone, D. Doty, F. Hanley, R. Karp, Congenital anomalies of the coronary arteries, in Kirklin/Barratt-Boyes (Eds.), Cardiac Surgery: Morphology, Diagnostic Criteria, Natural History, Techniques, Results, and Indications, Churchill Livingstone, Philadelphia, Pa, USA, 3rd edition, 2003, pp. 945–969.

[15] M.H. Agustsson, B.M. Gasul, E.H. Fell, J.S. Graettinger, J.P. Bicoff, D.F. Waterman, Anomalous origin of left coronary artery from pulmonary artery, The journal of the American Medical Association 180(1962)15–21.

[16] A. Separham, P. Aliakbarzadeh, Anomalous left coronary artery from the pulmonary artery presenting with aborted sudden death in an octogenarian: a case report, J Med Case Rep 6(2012)12.

[17] J.W. Brown, M. Ruzmetov, J. J. Parent, M.D. Rodefeld, M.W. Turrentine, Does the degree of preoperative mitral regurgitation predict survival or the need for mitral valve repair or replacement in patients with anomalous origin of the left coronary artery from the pulmonary artery?, J Thorac Cardiovasc Surg 136(2008)743-8.

[18] A.J. Jurishica, Anomalous left coronary artery; adult type, Am Heart J, 54 (1957)429–436.

[19] D.S. Moodie, D. Fyfe, C.C. Gill et al. Anomalous origin of the left coronary artery from the pulmonary artery (Bland-White-Garland syndrome) in adult patients: long-term follow-up after surgery, Am Heart J,106(1983) 381–388.

[20] A.J.B. Clarke, D.J. Radford, H. Jalali, Anomalous Origin of the Left Anterior Descending Artery from the Pulmonary Artery Associated with Bicuspid Aortic Valve and Aortic Coarctation, Heart, Lung and Circulation 12(2003) 70-72.

[21] C. J. McMahon, D. J. DiBardino, A. Undar, C.D. Fraser Jr, Anomalous origin of left coronary artery from the right pulmonary artery in association with type III aortopulmonary window and interrupted aortic arch, Annals of Thoracic Surgery 74 (3) (2002) 919–921.

[22] A. Dodge-Khatami, C. Mavroudis, C.L, Backer, Anomalous origin of the left coronary artery from the pulmonary artery: collective review of surgical therapy, Annals of Thoracic Surgery 74(3) (2002) 946–955

[23] J.V. Richardson, D.B. Doty, N. P. Rossi, J.L. Ehrenhaft, The spectrum of anomalies of aortopulmonary septation, Journal of Thoracic and Cardiovascular Surgery 78(1)(1979) 21–27

[24] A. Smith, R. Arnold, R.H. Anderson et al, Anomalous origin of the left coronary artery fromthe pulmonary trunk. Anatomic findings in relation to pathophysiology and surgical repair, Journal of Thoracic and Cardiovascular Surgery 98(1) (1989)16–24.

[25] F. Berdjis, M. Takahashi, W. J. Wells, Q. R. Stiles, G. G. Lindesmith, Anomalous left coronary artery from the pulmonary artery: significance of intercoronary collaterals, Journal of Thoracic and Cardiovascular Surgery 108(1) (1994) 17–20.

[26] J.E. Edwards, The direction of blood flow in coronary arteries arising from the pulmonary trunk, Circulation 29(1964)163–166.

[27] C.L. Backer, M.J. Stout, V.R. Zales et al, Anomalous origin of the left coronary artery. A twenty-year review of surgical management, J Thorac Cardiovasc Surg 103(1992)1049–1057.

[28] A.E. Baue, S. Baum, W. S. Blakemore et al. A later stage of anomalous coronary circulation with origin of the left coronary artery from the pulmonary artery: coronary artery steal, Circulation 36(1967) 878–885.

[29] J. D. Keith, The anomalous origin of the left coronary artery from the pulmonary artery, British Heart Journal 21(2)(1959) 149–161.

[30] Y.L. Yang, N.C. Nanda, X.F. Wang, et al. Echocardiographic diagnosis of anomalous origin of the left coronary artery from the pulmonary artery, Echocardiography, 24(2007)405–411.

[31] M.A. Frommelt, E. Miller, J. Williamson et al, Detection of septal coronary collaterals by color flow Doppler mapping is a marker for anomalous origin of a coronary artery from the pulmonary artery, J Am Soc Echocardiogr 15(2002)259–263.

[32] E. Pena, E.T. Nguyen, N. Merchant, et al, ALCAPA syndrome: not just a pediatric disease. Radiographics, 29(2009)553–565.

[33] S. Takeuchi, H. Imamura, K. Katsumoto, et al, New surgical method for repair of anomalous left coronary artery from pulmonary artery, J Thorac Cardiovasc Surg 78(1979)7–11.

FIGURE LEGENDS

Figure 1. A1-2. 2D and color 2D on parasternal short axis view. White arrows show the dilated right coronary artery (RCA). **B1-2**. 2D and color 2D on parasternal short axis view. White arrows on color 2D show the increased flow in the intraventricular collateral vessels from the RCA to the left coronary artery (LCA). **C1-2.** 2D and color 2D on parasternal short axis view. White arrows on color 2D show the retrograde flow from the LCA into the pulmonary artery.

Figure 2. Advanced imaging of ALCAPA syndrome. A. Coronary angiography. Dilated RCA and extensive collaterals to the LCA. **B.** CT coronary angiogram- 3D reconstruction. LCA origin from the main pulmonary artery. **C.** Cardiac MRI ECG and respiratory navigator-gated 3D SSFP- axial plane **Ci**: dilated RCA originating normally from the right coronary sinus, **Cii**: anomalous origin of the LCA from the main pulmonary artery**-D.** Cardiac MRI- SSFP cine image 3chamber view: presence of extended collateral vessels in the septal wall. Arrows point the septal collateral vessels from RCA to the LCA. **E-F:** Cardiac MRI-late gadolinium images. Basal short axis (E) and four chamber view (F): Sub endocardial myocardial fibrosis at the lateral wall**.**

Figure 3. Types of surgical repair of ALCAPA syndrome. **A.** Anomalous origin of left coronary artery (LCA) from main Pulmonary artery (MPA). **B.** ligation of anomalous LCA, implantation of vein graft or left internal mammary artery (LIMA) to the LAD. **C** re-implantation of LCA to the aorta **D.** Takeuchi procedure establishing continuity between the aorta and the abnormal orifice of the LCA by creating an aortopulmonary window and an intrapulmonary tunnel or baffle.

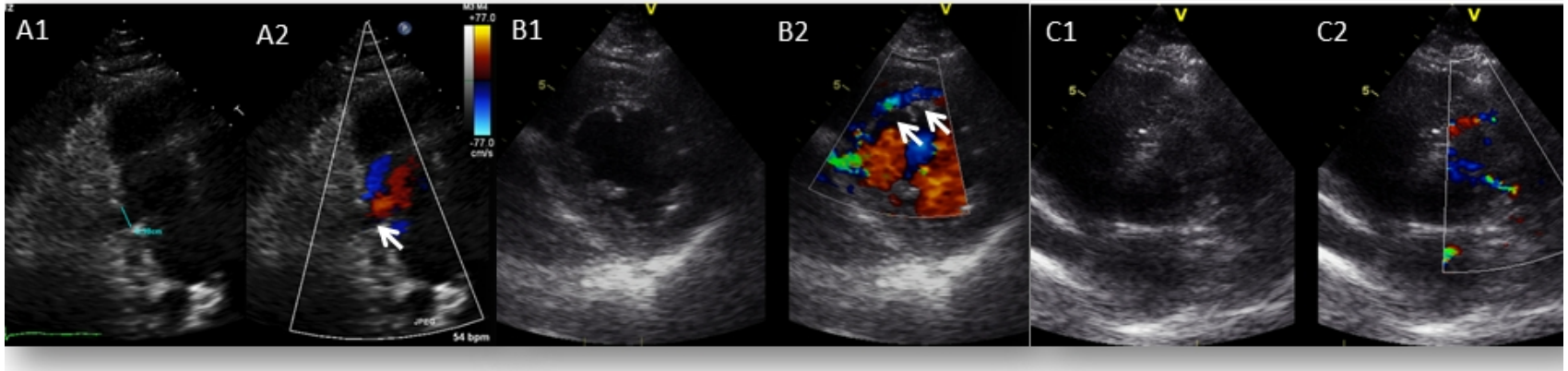
Table 1. ALCAPA syndrome diagnosed in adulthood: Demographics, clinical, imaging data and outcome data.

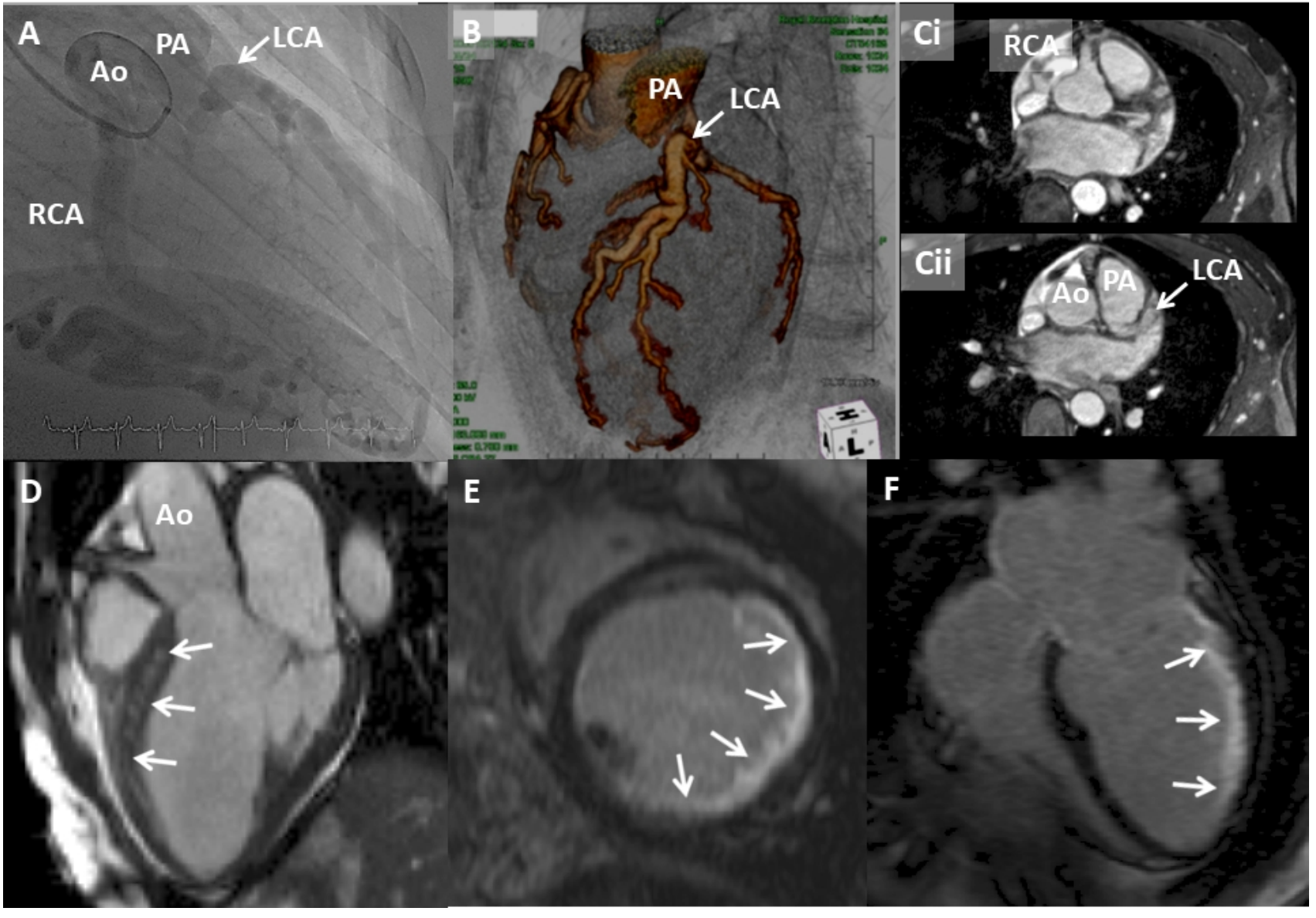
Case	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Gender	M	F	M	M	F	M	F	F	F	F	M	F
Age at clinical presentation (years)	18	21	25	25	37	45	46	48	49	52	60	73
Presenting symptoms	No	SOB	SOB/angina	VF	No	SOB	SOB	SOB	Angina	AF	SOB	Angina
NYHA Class	I	II-III	II	I	I	III	II	I	II	II	III	II
Heart Murmur	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Abnormal ECG	No	Yes	Yes	Yes	Yes	Paced	Yes	Yes	Yes	No	Yes	Yes
Abnormal	-	Yes	Yes	No	-	Yes	Yes	Yes	No	-	Yes	No

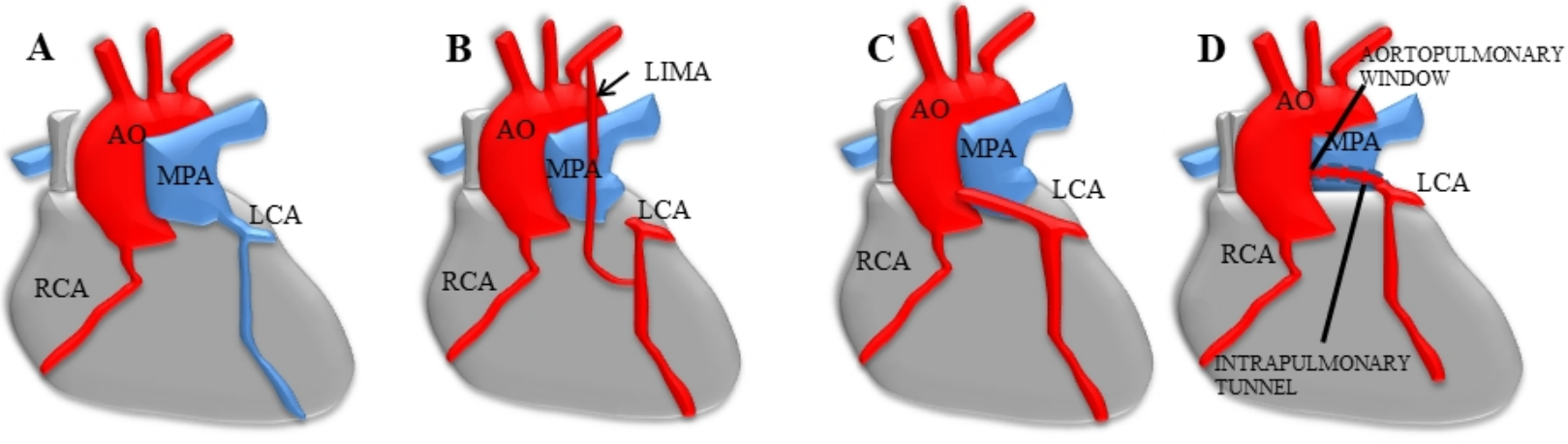
CXR												
Abnormal ETT/MPI	Yes	Yes	-	-	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-
MR grade at diagnosis	+3	+2	MS	+3	-	+/-1	+3	+2	+1	+2	+2	+1
Previous mitral intervention	MVR	MVR	MVR	No	No	No	No	Repair	No	No	No	No
LVEF, %	38	46	>60	46	60	20	51	43	58	64	34	55
Preoperative arrhythmia	No	No		Yes; VF arrest prior to repair	No	No	Yes; NSVT	No	No	No	No	No
Type of ALCAPA surgery	MVR/ LIMA to LAD	Takeuchi procedure	MVR, Ligation of LMS	Mitral repair/ reimplantation of LCA into the aorta and patch closure of the	N/A	N/A	MVR/ reimplantation of LCA into the aorta and patch closure	Ligation of LMS, SVG to LAD.	Reimplantation of LAD to the aorta	N/A	N/A	Ligation of LMS, LIMA to LAD.

				PA			of the PA					
Follow up to date (years)	11	6	8	9	13	3	0.5	5	2	2	4	Perioperative death
Postoperative arrhythmia	Yes (AF)	No	No	No	-	-	No	No	No	-	-	No
Device implantation	No	No	No	ICD	No	CRT-D	No	No	No	No	CRT-D	PPM preoperatively

F:female, M:male, SOB: shortness of breath, AF: atrial fibrillation, VF: ventricular fibrillation, NYHA; New York Heart Association Class, CXR; chest x-ray, ETT; exercise tolerance test, MPI; myocardial perfusion imaging, MR: +/-1: trivial, +1: mild, +2: moderate, +3: severe, MS: mitral stenosis, LAD: left anterior descending artery, LIMA: left internal mammary artery, SVG: saphenous vein graft, PA: pulmonary artery, AF: atrial fibrillation, CRT-D: cardiac resynchronization therapy- defibrillator, ICD: Implantable Cardioverter Defibrillator, PPM: permanent pacemaker, MVR: mitral valve replacement


A1
A2
+77.0
-77.0
cm/s
54 bpm
B1
B2
C1
C2


A
Ao
PA
LCA
RCA
B
PA
LCA
Ci
RCA
Cii
Ao
PA
LCA
D
Ao
E
F


A
AO
MPA
LCA
RCA
B
LIMA
AO
MPA
LCA
RCA
C
AO
MPA
LCA
RCA
D
AORTOPULMONARY WINDOW
AO
MPA
LCA
RCA
INTRAPULMONARY TUNNEL

Author Agreement Form – International Journal of Cardiology

Manuscript Title: **Anomalous Left Coronary Artery from the Pulmonary Artery (ALCAPA) diagnosed in adulthood: Varied Clinical Presentation, Therapeutic Approach and Outcome**

List of all Authors: Boutsikou M[1], Shore D[2], Li W[3], Rubens M[4], Pijuan A[5], Gatzoulis MA[6], Babu-Narayan S[7].

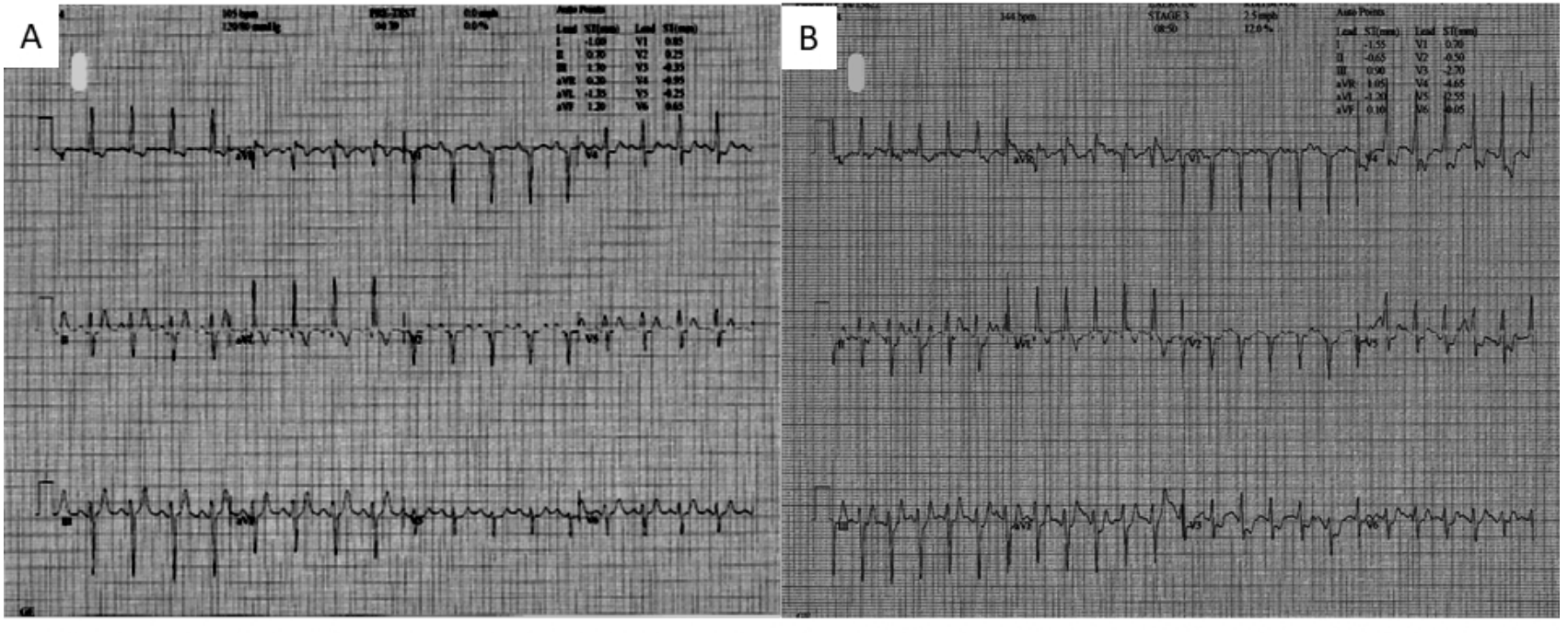
Corresponding Author: Maria Boutsikou

This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology.*

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: “The authors report no relationships that could be construed as a conflict of interest”.



ECG of a patient with ALCAPA syndrome. **A**. Rest ECG. Sinus rhythm with left axis deviation. Q waves and T wave inversion in V1 and V2 precordial leads. **B**. Stress ECG. ST wave depression in I and V3-V4 leads on peak exercise.