Congenital Heart Disease

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REVIEW

Congenital Absence of Pericardium: The Largest Systematic Review in the Field on 247 Worldwide Cases (1977-Now)

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ABSTRACT

Background: Congenital absence of pericardium (CAP), also known as pericardial agenesis, represents an uncommon cardiac abnormality and mostly incidental finding. It can be subdivided into complete and partial (left or right-sided) forms. Because of its infrequency, just case reports and a few case series have been released so far. This paper represents the largest systematic review in the field. Nine features (age at diagnosis, type, gender, clinical presentation, electrocardiography, imaging (ultrasounds, CT/MRI), concomitant cardiac defects, and outcome) were analysed. **Methods:** The electronic database PubMed was investigated from its establishment up to July 15th, 2023. Just case reports and case series were included. Animal studies, papers that were not in English, Spanish, and Italian, and those manuscripts not reporting at least seven of the nine analysed features. were ruled out. The analysed data were reported mostly in terms of percentage. **Results:** One hundred eighty studies were included encompassing 247 patients. More than half of reviewed CAP cases were in males (63.2%). The mean age at diagnosis was 31.8 ± 19.3 years; a range of 32 weeks of gestation-81 years). 23.5% of the patients did not report any symptoms. The most common clinical presentations were chest pain (35.2%) and dyspnoea (29.2%). The most commonly seen ECG changes were right axis deviation (28.7%) and right bundle branch block (23.9%). CAP was suspected or diagnosed by echocardiography in 20.1% of cases. The diagnosis was made by CT and/or MRI in 61.9% of cases. CAP was left-sided in 71.2%, complete in 23.1%, and right-sided in 5.7%. A concomitant congenital heart defect was found in 22.7%, especially in the form of atrial septal defect (6.5%) and patency of ductus arteriosus (2.8%). The pericardial repair was required in 12.9% of the incomplete forms of the disease. Never did the complete form require surgical correction. The outcome appeared favourable in the vast majority of cases, with just 18 deaths (7.3%). **Discussion:** The main limitation of this systematic review is

that it is based just on case reports and case series, due to the lack of large studies on CAP. However, it represents the largest analysis in the field. Due to the rarity of CAP establishing an International Registry is recommended.

KEYWORDS

Congenital absence pericardium; pericardial agenesis; electrocardiography; echocardiography; computed tomography; cardiac magnetic resonance imaging

1 Introduction

Congenital absence of pericardium (CAP), which is also known as pericardial agenesis, is an extremely uncommon cardiac abnormality occurring in less than 1/10,000 [1–3]. The first report dates back to 1559 [4]. Regarding embryology, incomplete development of the pleuro-pericardial membranes, fusing at the midline, and separating the pericardial and pleural cavities, leads to complete or partial CAP. Partial pericardial agenesis is more common than complete agenesis [5]. Left-sided CAP occurs in approx.70% of cases, right-sided CAP in about 17%, and complete bilateral CAP just in 9% of cases [6]. CAP is sometimes linked with other congenital cardiac malformations [7]. CAP is at times suspected with echocardiography, but diagnosis needs to be refined with CT or cardiac MRI [8]. Clinical presentation is extremely variable: some patients are asymptomatic, whereas others report chest discomfort, shortness of breath, irregular heartbeats, and fainting episodes [9]. However, a few reports of sudden death have been published mostly in subjects with partial pericardial agenesis [10].

Because of its infrequency, just single case reports and small case series have been released in literature so far.

This paper aims to systematically review the available literature regarding CAP with associated characteristics and outcomes.

2 Methods: Search Strategy

The electronic database PubMed was investigated from its establishment up to July 15th 2023. The MeSH (Medical Subject Headings) search terms “case report” and/or “case series” and/or “absent pericardium” and/or “absence of pericardium” and/or “pericardial agenesis” were investigated. We ruled out animal studies, papers which were not in English, Spanish, and Italian, and those manuscripts not reporting at least seven of the nine analysed features (age, gender, symptoms, electrocardiographic characteristics, echocardiography, CT/MRI, partial or complete absence, association with other congenital heart disease, and outcome).

2.1 Study Selection

According to the PRISMA approach, each author checked the shortlisted abstracts and judged whether they were appropriate. Full-texts were read when all the involved reviewers thought that the abstract might fulfill the previously chosen inclusion criteria.

2.2 Data Taking Out

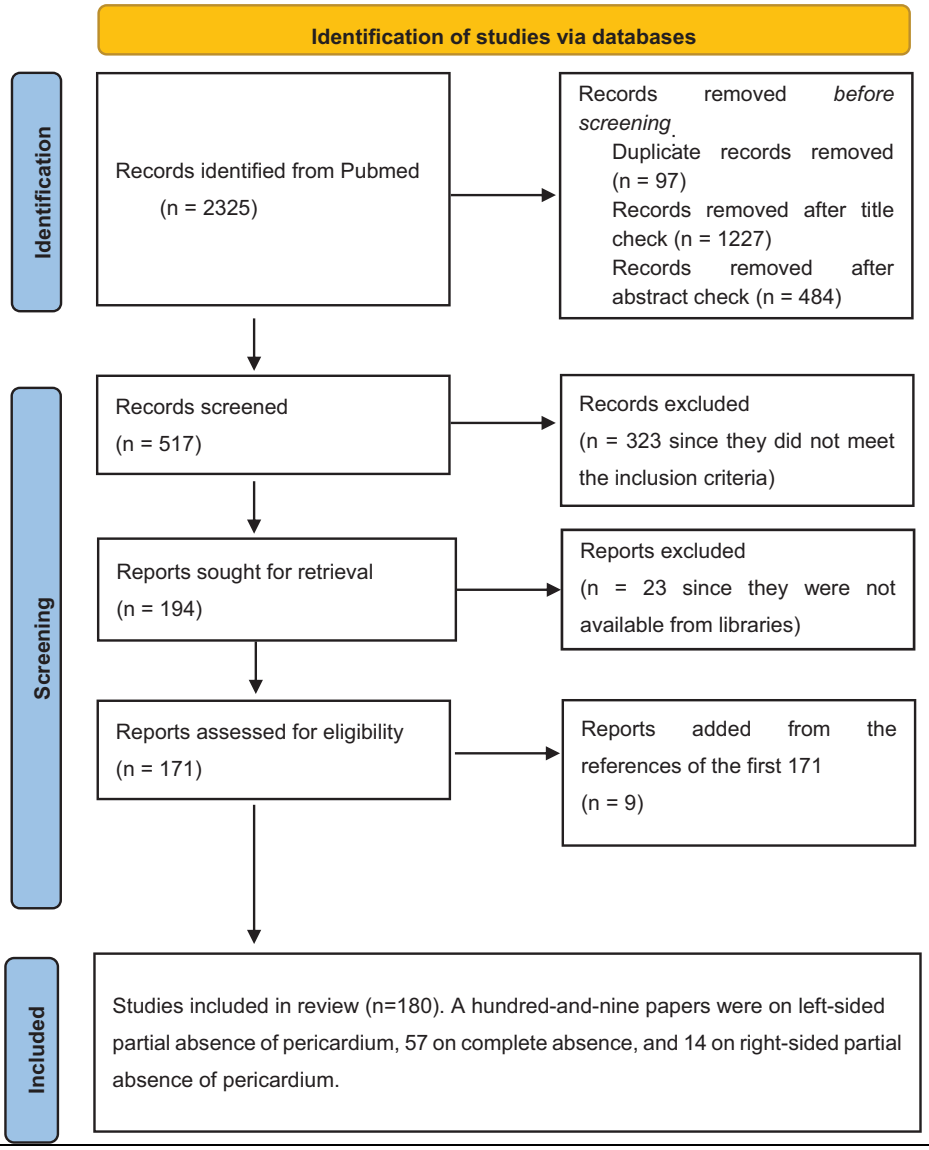
Data from the chosen single case reports and case series were extracted. The analysed features were: age at diagnosis, sex, clinical presentation, electrocardiography, imaging (echocardiography, CT scan and cardiac MRI), accompanying cardiac defects, and outcome.

2.3 Study Selection Process

Overall, 2,325 potential single case reports or case series of CAP were detected on PubMed. Ninety-seven were identical. Other manuscripts were ruled out following abstract and title check. The remaining 517 papers were further assessed. After screening, 180 papers were included in the analysis of the patients' characteristics and illness outcome [11–190] (see Supplementary Table S1).

A flow chart of the study selection process is showed in Table 1.

Table 1: Prisma flow diagram of the study selection process



2.4 Statistical Analysis

Data were introduced in the form of mean ± standard deviation. Chi square and Mann-Whitney U tests were used to evaluate statistical significance when required. Statistical significance was set to $p < 0.05$. All statistical analysis was performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, Il, USA).

3 Results

More than a half of CAP cases were in males (63.2%; male-to-female ratio 1.7:1). Mean age at diagnosis was 31.8 ± 18.3 years; range 32 weeks-81 years). In males the mean age at diagnosis was 34.1 ± 20.0 years, whereas female patients were slightly younger (29.5 ± 16.6 years) at diagnosis. This difference was statistically significant ($p < 0.05$). Fifty-eight patients were asymptomatic (23.5%). The most usual clinical presentations were chest pain (35.2%) and dyspnoea (29.2%). No statistically significant differences were detected between genders as regard to symptoms (p = ns). See Table 2 for statistical significance.

Table 2: CAP patients subdivided into genders with statistical significance

	Males	Females	*p*
Mean age at diagnosis (years)	34.1 ± 20.0	29.5 ± 16.6	<0.05
Symptomatic patients (%)			
Chest pain	34.1	36.3	ns
Dyspnoea	28.7	29.7	ns

The most commonly detected ECG changes were right axis deviation (28.7%), (complete or incomplete) right bundle branch block (23.9%), and poor R wave progression in the precordial leads (12.5%). CAP was suspected or diagnosed by echocardiography in 20.1% of cases. Diagnosis was made by computed tomography and/or cardiac magnetic resonance imaging in 61.9% of cases. CAP was left-sided in 71.2%, complete in 23.1%, and right-sided in 5.7%. A concomitant congenital heart defect was detected in 22.7%, mostly in the form of atrial septal defect (6.5%) and patency of ductus arteriosus (2.8%). Pericardial repair was required in 12.9% of the incomplete forms of the disease. Never the complete form required surgical correction. The outcome was almost entirely favourable: just 18 deaths (7.3%) occurred. However, the majority of them were due to comorbidities rather than to CAP itself.

See Figs. 1–3 for a description of the diagnostic criteria.

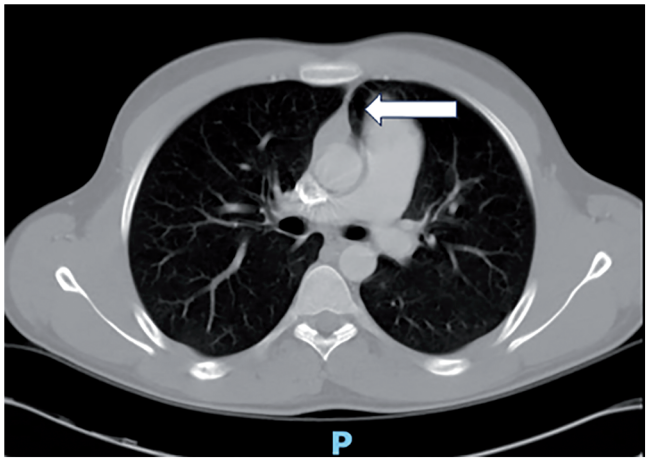


Figure 1: Computed tomography scan showing a tongue of lung tissue between the aorta and main pulmonary artery (white arrow). This is typical of CAP. The aortopulmonary window is usually bounded by pericardium and contains fat (previously unpublished image belonging to the authors)

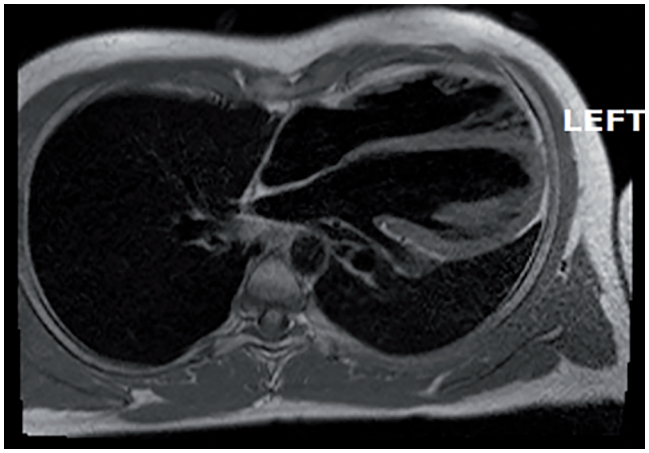


Figure 2: Cardiac magnetic resonance (axial view, T 1 weighed image) showing that the heart is rotated toward the left (previously unpublished image belonging to the authors)

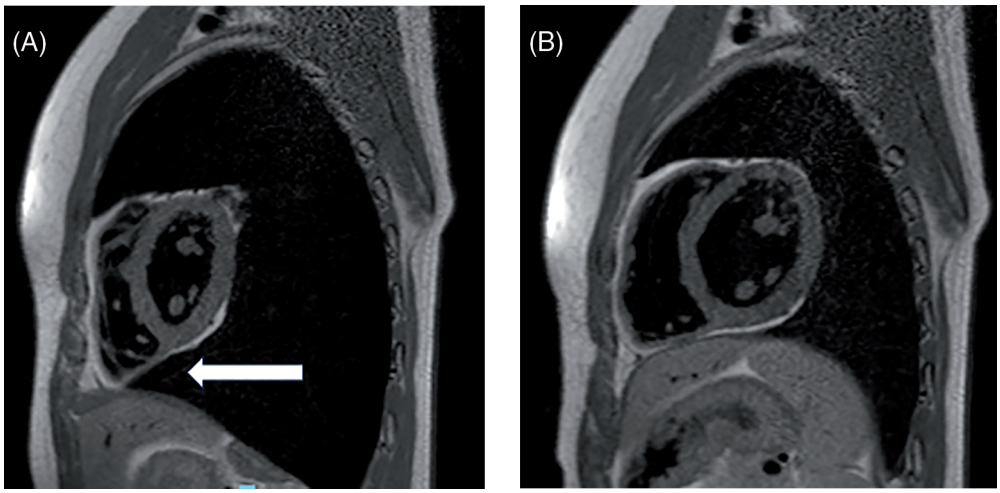


Figure 3: Cardiac magnetic resonance (sagittal views, T 1 weighed images) during inspiration (panel A) and expiration (panel B) displaying the lung interposing under the heart and extending between the cardiac inferior surface and the left diaphragm (see white arrow. Previously unpublished images belonging to the authors)

4 Discussion

CAP is a rare condition that as of 2023 has been reported in only approx. 500 cases. Its embryology is somewhat controversial. The most common forms of CAP are seen on the left side and are supposed to be due to the early atrophy of the left common cardinal vein or duct of Cuvier (5^{th}–6^{th} week of embryogenesis) [191], thus compromising the hematic supply to the left pleuro-pericardial fold [71]. Conversely, the right duct of Cuvier leads to the superior vena cava, which ensures that the developing right pleuro-pericardial membrane has a sufficient hematic supply [71]. This is the most widely accepted embryological theory. Other hypotheses are that CAP is caused by the heart enlarging before the fusion of the pleuro-pericardial membranes or by a tear induced by traction contributing to a defect in the pericardium [192,193].

Two hundred and forty-seven cases have been analysed in this systematic review as they are the only ones sharing the required features in terms of reporting age, gender, symptoms, imaging, an extension of the defect, and association with other congenital heart diseases, outcome, and language. CAP can be detected at any age ranging from premature newborns to elderly patients. However, it is often detected incidentally during postmortem [71]. Our findings are consistent with that already reported in the literature about the male prevalence of the disease [71,194]. Some patients-most often those with complete CAP-are asymptomatic, but especially those with partial CAP may suffer from vague atypical chest pain which is thought to be caused by cardiac mobility, torsion, or traction of cardiac structures [82]. In extremely rare cases, the chest pain is angina-like or other symptoms can occur such as arrhythmias or syncope [69]. Some CAP patients also report shortness of breath lying to one side—a phenomenon called trepopnoea that is uniquely linked to partial defects [195]. A few cases of serious potentially lethal complications, including cardiac herniation of the left atrial appendage or left ventricle with muscle strangulation, blockage of vena caval return, and squeezing of the coronary arteries, have been described [71].

As regards electrocardiography, in partial CAP, ECG usually displays right axis deviation, poor R wave progression owing to clockwise rotation in the horizontal plane, incomplete right bundle branch block, and sometimes T wave inversion [63]. Concerning imaging, chest X-ray may display a leftward shift of the cardiac silhouette (“snoopy sign”) and a tongue of lung tissue interposing between the pulmonary trunk and the aorta [196]. A few cases were diagnosed because of the heart displacement to the left in the course of an ultrasound scan [197]. As such, parasternal views are often detected at the apical window, and the apical view is found on the mid-axillary line. On the modified parasternal view, the dilated right ventricle is linked to paradoxical or flat systolic motion of the interventricular septum and teardrop aspect of the left ventricle (e.g., an elongated tubular left ventricle), whilst on the modified apical view, stretched atria are identified along with bulbous ventricles [198]. Currently, the best modality imaging to make or confirm the diagnosis are CT and cardiac MRI [199]. Initially, fluoroscopy and the creation of a diagnostic pneumothorax were used to diagnose CAP. The risk of pneumothorax is no longer needed, as more sensitive techniques have made this technique obsolete [200].

CAP is a very uncommon defect varying from partial to complete agenesis. Differentiating partial from complete CAP is crucial because of the different symptoms and prognosis. This systematic review confirms that right-sided and complete CAP are rare, the left-sided being by far the most commonly seen subtype of the disease.

CAP can be isolated or be a part of a syndrome (most of all the pentalogy of Cantrell). The most commonly seen associated congenital heart defects are atrial septal defect and patency of ductus arteriosus.

Even though the pericardium exerts some functions, its integrity is not mandatory, and the vast majority of cardiothoracic surgeons advise leaving incidental CAP untreated. The indication for surgery depends on symptoms, size, and location [131]. Partial CAP is more at risk of herniation thereby its closure reduces the risk. Conversely, complete CAP usually has a benign course and no intervention is required [82]. Symptomatic CAP can be surgically treated by means of many techniques. Many of them can be safely managed by enlarging the defect with a longitudinal pericardiotomy. Primary closure, patch closure (pericardioplasty) by porcine or bovine pericardium or goretex or polytetrafluoroethylene have also been done. Surgery may cause adhesions restricting heart mobility. The phrenic nerve should be carefully taken into account as its usual course can be modified in CAP [71,201].

5 Conclusion

The main limitation of this systematic review is that it is based just on case reports and case series, due to the lack of large studies on CAP. However, it represents the largest analysis in the field. Due to the rarity of CAP establishing an International Registry is recommended [202].

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