ORIGINAL ARTICLE

Physiological and clinical relevance of anomalous right coronary artery originating from left sinus of Valsalva in adults

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ABSTRACT

Objective To examine physiological and clinical relevance of an anomalous right coronary artery originating from left sinus of Valsalva (right ACAOS) with interarterial course in adults.

Methods and results For physiological assessment, fractional flow reserve (FFR) during dobutamine challenge was measured in 37 consecutive adult patients with lone right ACAOS with interarterial course. At baseline, mean FFR was 0.91±0.06, declining to 0.89±0.06 upon dobutamine infusion (<p=0.001). Dobutamine stress FFR was significant (≤0.8) in three patients (8.1%), two of whom were surgically treated. Following surgery, dobutamine stress FFR rose from 0.76 to 0.94 and 0.76 to 0.98. Remodelling index (r=0.583, p=0.002), minimal lumen area (diastole: r=0.580, p=0.002; systole: r=0.0618, p=0.001) and per cent area stenosis (r=0.550, p=0.004) were measured by intravascular ultrasound, correlated with dobutamine stress FFR. To assess the clinical relevance, follow-up data of 119 patients with lone right ACAOS with interarterial course were analysed retrospectively. Two deaths occurred during a median follow-up period of 4 years, for a mortality rate of 0.34 per 100 person-year. No instances of myocardial infarction were recorded and one patient did undergo surgical revascularisation in the course follow-up.

Conclusions Most instances of lone right ACAOS with interarterial course discovered in adults were physiologically insignificant and ran benign clinical courses. Conservative management may thus suffice in this setting if no definitive signs of myocardial ischaemia are evident.

INTRODUCTION

Congenital coronary anomalies are common causes of sudden death in the young, and in these situations, an anomalous coronary artery originating from the opposing sinus of Valsalva (ACAOS) is the most likely contributor. Anomalous right coronary artery (RCA) arising from left sinus of Valsalva (right ACAOS) occurs more often than left coronary artery arising from right sinus of Valsalva (left ACAOS) and has been reported to be associated with myocardial ischaemia, myocardial infarction (MI) and sudden death. Coronary angiography, has boosted the discovery rate of right ACAOS in adults. These patients are more likely to undergo surgical intervention because current guidelines advise surgical correction if ischaemia is evident to prevent sudden cardiac death. However, the clinical significance of right ACAOS first detected in adults is subject to controversy.

Eckart et al found no instances of sudden cardiac death related to right ACAOS during the screening of 6.3 million military recruits in a 25-year period. Furthermore, the evidence of ischaemia is often tenuous in this setting. The imprecision involved in assessing coronary arterial morphology, symptoms and results of non-invasive functional tests does not ensure a valid basis for determining the presence of myocardial ischaemia and the risk of sudden cardiac death.

This study was devised to investigate the physiological aspects of right ACAOS in adults through the use of fractional flow reserve (FFR) and examine clinical outcomes of adult patients with right ACAOS.

METHODS

Physiological assessment of right ACAOS

Between June 2009 and September 2012, consecutive adult patients (≥18 years of age) with lone right ACAOS with interarterial course by coronary angiography were prospectively enrolled at Seoul National University Hospital, Bundang Seoul National University Hospital and Sejong General Hospital. The lone right ACAOS was defined as a right ACAOS not accompanied by significant stenosis in other coronary arteries or significant cardiovascular diseases requiring surgical intervention.
3 min intervals, for a maximal dose of 40 μg/kg/min. If the target heart rate (85% of maximal heart rate predicted for age, calculated as [220 – age]) could not be achieved at the maximal dose of dobutamine, atropine was administered. Lesions with an FFR ≤0.80, either at rest or after dobutamine stress, were considered functionally significant.19

Intravascular ultrasound

Intravascular ultrasound (IVUS) was performed in standard fashion using an automated motorised pullback system (0.5 mm/s) with commercially available imaging catheters (Boston Scientific/SCIIMED, Minneapolis, Minnesota, USA; or Volcano Corp, Rancho Cordova, California, USA). Quantitative IVUS analyses were performed using computerised planimetry software (echoPlaque; INDEC Systems, Santa Clara, California, USA) in an independent core laboratory blinded to FFR values and patient outcomes.

Lumen diameter, lumen area (LA) and vessel area (VA) were measured at the site of minimal LA (MLA) and at a reference site. Per cent area stenosis was calculated as \(100 \times (\text{LA at } \text{MLA}/\text{reference LA})\); and plaque burden was calculated as \(100 \times (\text{VA at } \text{MLA}/\text{VA})\). Asymmetry index was defined as the ratio between minimal and maximal lumen diameters, remodelling index as [LA at MLA site/reference VA], and systolic compression index as [MLA at diastole – MLA at systole]/MLA at diastole].

Clinical outcomes of patients with right ACAOS

Between January 1992 and September 2012, patients with suspected right ACAOS interarterial course by conventional coronary angiography and at least 18 years old at time of diagnosis were selected from electronic medical records of Seoul National University Hospital, Bundang Seoul National University Hospital and Sejong General Hospital. Medical data and coronary angiograms were independently reviewed by two examiners blinded to patient outcomes. In the event of disagreement, a consensus was reached through reassessment.

Incidences of all-cause mortality, MI and surgical or percutaneous intervention for this condition were extracted from medical records. Outcomes of subjects whose follow-up data were electronically unavailable were ascertained by telephone contact, National Death Records and National Insurance Records. Unless the latter failed to list cause of death, all outcome data were otherwise complete.

Statistical analysis

Continuous variables were expressed as mean±SD except for the age, which was expressed as median (range). Categorical values were expressed as number and percentage. Shapiro–Wilk normality test in R program (V.3.2.1) was used to test for the normality of data. Resting FFR, dobutamine stress FFR, per cent area stenosis, MLA, reference LA, remodelling index, systolic compression index, asymmetric index at diastole, difference of LA between diastole and systole, difference of asymmetric index between diastole and systole at reference site followed a normal distribution. In contrast, the difference of FFR between resting and dobutamine stress, asymmetric index at systole, and the difference of asymmetric index between diastole and systole at MLA did not follow a normal distribution. The paired t-test was used to compare LA and asymmetry index at reference between diastole and systole. The Wilcoxon signed-rank test was performed to test for the difference of FFR between resting and dobutamine stress and the difference of asymmetry index at MLA between diastole and systole. Pearson’s correlation analysis was performed to evaluate the correlation between dobutamine stress FFR and IVUS data except for an asymmetric index at systole, which did not follow a normal distribution, and therefore, Spearman’s correlation analysis was used instead. Kaplan–Meier curves were generated for survival estimates. Statistical analyses were performed using SPSS (V.17; SPSS, Chicago, Illinois, USA), GraphPad Prism (V4.0; GraphPad Software, La Jolla, California, USA) and R program (V.3.2.1).

RESULTS

Baseline characteristics of prospective physiologic study cohort

Between June 2009 and September 2012, 42 consecutive adult patients with lone right ACAOS were enrolled in the prospective cohort. Clinical characteristics are summarised in table 1. Median age was 54 years (range 18–75 years), with men accounting for 69%. Most patients without symptom underwent invasive coronary angiography due to the coronary anomaly found by coronary CT angiography performed during a routine medical check-up. Three of the patients were treated surgically, seven patients received antiplatelet therapy, three received β-blockers, eight received calcium channel blockers and one patient received nicoaryl.

Physiological assessment of right ACAOS

Of 42 eligible subjects, 37 underwent physiological studies (figure 1). Two patients refused study enrolment, and one patient developed ostial dissection during diagnostic coronary angiography. In two patients, stable guiding catheter engagement was not possible. Physiological studies proceeded according to protocol in 36 of 37 patients, failing to reach the target heart rate in one patient due to dobutamine intolerance. Aside from the single instance of type B RCA ostial dissection, no other procedural complications resulted.

Mean FFR at baseline (0.91±0.06) fell significantly upon dobutamine infusion (0.89±0.06; p<0.001) (figure 2). FFR was significant (FFR≤0.80) in only one patient before dobutamine infusion. After dobutamine infusion, 3 of 37 patients (8.1%) had significant FFR. Two of these patients were surgically treated, raising FFR from 0.76 to 0.94 and 0.76 to 0.98 after surgery. The other patient was treated medically, receiving a β-blocker. No deaths, MIs or revascularisations were registered during follow-up (median, 2 years) in this cohort.

IVUS findings versus dobutamine stress FFR

IVUS was performed in 26 patients (table 2). Intramural course was confirmed by IVUS in 24 out of 26 patients. MLA was 6.4 mm.
±2.3 mm² at diastole and 5.8±2.3 mm² at systole (p=0.001). Per cent area stenosis and remodelling index were 36.6% ±16.1% and 0.60±0.14, respectively. Asymmetry indices of MLA site were 0.59±0.16 at diastole and 0.50±0.15 at systole (p=0.002) and those of the reference site were 0.88±0.06 at diastole and 0.87±0.06 at systole (p=0.344). Dobutamine stress FFR correlated significantly with both diastolic and systolic MLA, per cent area stenosis and remodelling index, as determined by IVUS, but not with asymmetry or systolic compression indices (figure 3).

Clinical outcomes of patients with right ACAOS
Between January 1992 and September 2012, lone right ACAOS was detected in 145 patients by coronary angiography. After imaging review, 22 patients with anterior (not left coronary sinus) take-off of RCA, two patients with right ACAOS but diminutive RCA, and two patients lacking image documentation (diagnosed at other hospitals) were excluded, leaving 119 patients eligible for study. Seven of these patients (5.9%) initially received revascularisation for right ACAOS (surgery, six; percutaneous coronary intervention, one) and 112 patients were treated medically. Median age at diagnosis was 55 years, with male predominance (59%). During follow-up (median, 4 years), two deaths occurred (one at age 91 and the other at age 59) for a mortality rate of 0.34 per 100 person-year (figure 4). In the course of follow-up, one patient underwent surgical revascularisation for recurrent chest pain and positive result of dobutamine stress echocardiography. No instances of MI were recorded.

DISCUSSION
Through this study, addressing physiological and clinical aspects of lone right ACAOS in adults, we discovered the following: (1) physiologically significant right ACAOS was infrequent; (2) dobutamine stress FFR was feasible to assess the physiological significance of right ACAOS; and (3) most instances of lone right ACAOS found in adults were benign in nature. These results suggest that a conservative treatment strategy can be considered for lone right ACAOS in adults unless definitive signs of myocardial ischaemia are evident.

Physiological significance of right ACAOS
FFR is considered as the gold standard for determining functionally significant coronary stenosis during cardiac catheterisation. However, FFR measured at rest cannot accurately assess the presence of myocardial ischaemia in cases of dynamic obstruction such as myocardial bridging and right ACAOS. Therefore, FFR needs to be measured under the challenge of inotropic agents such as dobutamine to reflect the dynamic nature of a stenosis by right ACAOS, which depends on degree of extravascular compression, kinking and increased wall.
tension. In this study, dobutamine stress FFR was successfully performed in 36 of 37 patients without serious complications. Aside from a few prior case reports, this investigation represents the first attempt to systematically measure FFR at baseline and in an induced state of stress in patients with right ACAOS. In our study, mean FFR at baseline was 0.91±0.06 and it fell significantly upon dobutamine infusion to 0.89±0.06. According to a previous study, FFR in normal coronary arteries was 0.98±0.03, while it was 0.90±0.05 in our patients, even after excluding three patients whose FFR was ≤0.80. Furthermore, it was reported that FFR value did not significantly change after dobutamine infusion in fixed coronary lesions. However, functionally significant level (FFR ≤0.80) was found in <10% of our cohort. These results suggest that right ACAOS can dynamically decrease coronary flow to some extent, even though many of them do not cause significant myocardial ischaemia. Upon repeat dobutamine stress FFR in two patients after surgery, FFR levels improved significantly, rising from 0.76 each to 0.94 and 0.98, respectively. Hence, the specificity of this test in patients with right ACAOS is reinforced. This finding is important, considering that recurrent ischaemia is the presumptive mechanism of sudden death in patients with right ACAOS. In our study, no clinical events were manifested during a 2-year median follow-up period in medically treated patients with dobutamine stress FFR >0.80.

Benign clinical course of right ACAOS detected in adults

In the retrospective cohort, the mortality rate was 0.34 per 100 person-year despite a very low rate of initial revascularisation (5.9%). Moreover, one death occurred at age 91, which likely was unrelated to the coronary anomaly. Given an all-cause mortality rate of 1.26 per 100 person-year in another community-based cohort of Koreans (mean age, 58±10 years), our results indicate that most instances of lone right ACAOS detected in adults are clinically benign. This conclusion is also supported by an earlier retrospective study of 56 patients (age range, 32–85 years) where no deaths were attributable to anomalous origin of the coronary artery during a mean follow-up of 5.6 years. Similarly, our findings agreed with other cross-sectional studies based largely on autopsy documentation. Although autopsy reviews have linked right ACAOS with exercise-related sudden death, two large registries carefully monitoring sudden deaths in athletes over a 10-year to 20-year period recorded only one sudden death in association with right ACAOS. Eckart et al screened 6.3 million military recruits for sudden death over a 25-year period and reported that there was no case of sudden cardiac death related to right ACAOS. Furthermore,

| Table 2 Anatomic features of right ACAOS assessed by intravascular ultrasound (n=26) |
|---------------------------------|-----------------|-----------------|--------|
|                                 | Diastole        | Systole         | p Value |
| Reference site                  | Vessel area (mm²) | 13.6±3.3        |        |
|                                 | Lumen area (mm²) | 10.2±2.8        |        |
|                                 | Asymmetry index  | 0.88±0.06       | <0.001 |
|                                 | % Plaque burden  | 34.3±13.6       |        |
| MLA site                        | Vessel area (mm²) | 8.1±2.7         |        |
|                                 | Lumen area (mm²) | 6.4±2.3         |        |
|                                 | Asymmetry index  | 0.59±0.16       |        |
|                                 | % Plaque burden  | 27.8±12.8       |        |
|                                 | % Area stenosis  | 36.6±16.1       |        |
|                                 | Remodelling index| 0.60±0.14       |        |

*Wilcoxon signed rank test.
MLA, minimal lumen area; right ACAOS, anomalous right coronary artery originated from left coronary sinus.

Figure 3 Correlation between dobutamine stress FFR and IVUS parameters. FFR, fractional flow reserve; IVUS, intravascular ultrasound; MLA, minimal lumen area; r, Pearson’s correlation coefficient; ρ, Spearman’s correlation coefficient.
in medical studies published over the past 25 years, no patients with asymptomatic right ACAOS >30 years of age suffered sudden death.9

Clinical/anatomic characteristics and physiological significance of right ACAOS

To date, there is no reliable index of risk for adverse cardiac events among patients with ACAOS.12 13 Neither coronary arterial morphology nor clinical determinants (ie, the presence of premonitory symptoms and exercise stress testing) successfully predict the risk of serious cardiac events during follow-up.11 14 15 In accord with previous reports, we saw no significant association between patient symptoms and results of dobutamine stress FFR in our cohort, although the small number of patients was a limiting factor (table 3). On the other hand, all three patients with dobutamine stress FFR levels ≤0.80 showed RCA dominance and area stenosis >50% by IVUS. Hence, some anatomic characteristics of the anomalous RCA may help discriminate low-risk patients for conservative management.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Comparison between dobutamine stress FFR-positive and FFR-negative patients</th>
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<td>FFR &gt;0.80 (n=34)</td>
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<td>Cardiovascular risk factor</td>
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<td>Syncope</td>
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<td>RCA dominancy</td>
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<td>IVUS area stenosis &gt;50%</td>
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<td>21</td>
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FFR, fractional flow reserve; IVUS, intravascular ultrasound; RCA, right coronary artery.

A recent article by Angelini et al 28 described that all of the 67 patients who received IVUS study had intramural proximal coronary course. Sixty-seven patients had significant symptoms, such as typical chest pain, dyspnoea and syncope, and 73% had a positive stress test. In our patients, intramural course was also observed in most patients who received IVUS study. The difference in enrolment criteria such as diagnostic methods (by IVUS in Angelini’s cohort vs by coronary angiography in ours), age and exclusion of those accompanied by significant lesions in other coronary arteries or by other significant cardiovascular diseases might have influenced the apparent difference in patients populations and symptoms between the two studies.

Evaluation of right ACAOS by IVUS

A recent case series focusing on ACAOS suggested that IVUS is useful in assessing severity and pathophysiological mechanisms of this condition.25 29 Three IVUS features reputed to objectively define related severity on an individual basis are as follows10; (1) extent of hypoplasia in intramural segment relative to distal vessel, measured by remodelling index, MLA and per cent area stenosis; (2) amount of lateral compression, quantified by asymmetry index or systolic compression index; and (3) degree of further lateral compression after pharmacological challenge. Our comparison of anatomic parameters with dobutamine stress FFR revealed that remodelling index, MLA and per cent area stenosis all correlated with dobutamine stress FFR values, whereas asymmetry index or systolic compression index did not. In addition, the anomalous segments were almost free of atherosclerotic disease, as previously reported.29 This observation underscores that extent of hypoplasia and consequent luminal narrowing may be the most important index of pathophysiology in this condition, corresponding with the development myocardial ischaemia in patients with right ACAOS.

Study limitations

First, the number of patients included in this study was unavoidably small due to the typically low incidence of this condition. However, this study includes the first prospective analysis of a cohort with right ACAOS, as well as the largest cohort with lone right ACAOS to be retrospectively assessed. Furthermore, this was the first use of FFR or IVUS to prospectively evaluate patients with right ACAOS. Second, the treatment decisions herein were determined by physicians in charge and were not dictated solely by FFR level. Thus, although our findings support the feasibility of dobutamine stress FFR testing in right ACAOS, it cannot support that dobutamine stress FFR can be used to predict adverse clinical outcomes in patients. Third, we only included lone right ACAOS and excluded those lesions that influenced the clinical decision or patient outcomes to evaluate the clinical, anatomical and physiological relevance of right ACAOS itself, and this might limit the application of our observations to the general population with right ACAOS in adults who occasionally have serious cardiac problems requiring surgery or significant stenosis in other coronary arteries. Fourth, we did not perform IVUS under dobutamine infusion and were unable to evaluate dynamic conformational changes of right ACAOS. Finally, we used dobutamine as an alternative to exercise, which may not necessarily be equivalent to upright exercise.

CONCLUSIONS

In this study, most instances of lone right ACAOS found in adults were physiologically insignificant and ran benign clinical
courses. Therefore, a conservative strategy can be instituted for adults with lone right ACAOS when there is no definite evidence of myocardial ischaemia.

**Key messages**

**What is already known on this subject?**
Anomalous right coronary artery arising from left sinus of Valsalva (right ACAOS) is a congenital anomaly that is associated with sudden death and myocardial ischaemia. Current guidelines advise surgical correction if ischaemia is evident, while the clinical significance of right ACAOS first found in adults is unclear and its treatment strategy is still under debate.

**What might this study add?**
This study revealed that most lone right ACAOSs have a benign clinical course when found in adults and that although they can cause myocardial ischaemia the incidence is low.

**How might this impact on clinical practice?**
These results suggest that a more conservative treatment strategy can be considered for lone right ACAOSs in adults unless definitive signs of myocardial ischaemia are evident.

**Contributors**
SEL and CWY contributed equally to the article. SEL, CWY and B-KK contributed to study design; acquisition, analysis and interpretation of data; and writing of the report. KP contributed to study design and acquisition of data. KWP, J-WS, Y-SC, T-JY, I-HC, D-JC, J-SP, S-HN, H-SK and K-BK all contributed to acquisition, analysis and interpretation of data.

**Competing interests**
B-KK received institutional research grants from St Jude medical.

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**REFERENCES**


