# Anomalous aortic origin of coronary artery biomechanical modeling: Toward clinical application



Mauro Lo Rito, MD,[a] Rodrigo Maximiliano Romarowski, Eng PhD,[b] Antonio Rosato, Eng,[c] Silvia Pica, MD,[d] Francesco Secchi, MD, PhD,[e] Alessandro Giamberti, MD,[a] Ferdinando Auricchio, Eng PhD,[c] Alessandro Frigiola, MD,[a] and Michele Conti, Eng PhD[c]

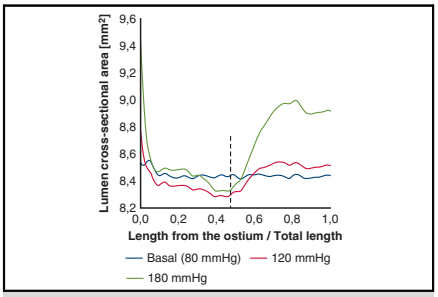
## ABSTRACT

**Objectives:** Anomalous aortic origin of the coronary artery can be associated with sudden cardiac death and ischemic events. Anatomic static characteristics mainly dictated surgical indications, although adverse events are usually related to dynamic physical effort. We developed a computational model able to simulate anomalous coronary behavior, and we aimed to assess its clinical applicability and to investigate coronary characteristics at increasing loading stress conditions.

**Methods:** We selected 5 patients with anomalous aortic origin of the coronary artery and 5 control subjects. For each of them, we construct a 3-dimensional model resembling the aortic root and coronary arteries based on 25 parameters obtained from computed tomography. Structural finite element analysis simulations were run to simulate pressure increasing in the aortic root during exercise (+40 mm Hg, +100 mm Hg with respect baseline condition, assumed at 80 mm Hg) and investigate coronary lumen characteristics.

**Results:** The 25 parameters were obtainable in all subjects with a consistent inter-observer agreement. In control subjects, the right coronary artery had a more significant lumen expansion at loading conditions compared with anomalous aortic origin of coronary artery (6%-19.2% vs 1.8%-8.1%, $P = .008$), which also showed an inability to expand within the intramural segment.

**Conclusions:** The proposed anomalous aortic origin of coronary artery model is able to represent the pathogenic disease mechanism after being populated with patient-specific data. It can assess the impaired expansion of anomalous right coronary at loading conditions, a process that cannot be quantified in any clinical set-up. This first clinical application showed promising results on quantifying pathological behavior, potentially helping in patient-specific risk stratification. (J Thorac Cardiovasc Surg 2021;161:191-201)




**Patient's AAOCA simulation at different pressure conditions.**

### CENTRAL MESSAGE

Computational simulations show that coronary lumen of anomalous aortic origin lack appropriate expansion during effort.

### PERSPECTIVE

Functional risk stratification in AAORCA is rarely possible because of frequent negative results at the stress test. The first clinical application of a patient-specific AAORCA model, populated with measurements from a coronary computed tomography, reliably predicts pathological behavior under stress conditions and potentially may be used to overcome current diagnostic limitations for risk stratification.

See Commentaries on pages 202, 203, and 204.

Anomalous aortic origin of the coronary artery (AAOCA) is a rare congenital disease in which the anomalous aortic origin of the left coronary artery (AAOLCA) or the anomalous aortic origin of the right coronary artery (AAORCA) originates from an ectopic site within the aorta. The prevalence in the general population has been estimated

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From the [a]Department of Congenital Cardiac Surgery, [b]3D and Computer Simulation Laboratory, [d]Multimodality Cardiac Imaging Section, and [e]Unit of Radiology, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy; and [c]Department of Civil Engineering and Architecture, University of Pavia, Pavia, Italy.

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Address for reprints: Mauro Lo Rito, MD, Department of Congenital Cardiac Surgery, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy (E-mail: mauro.lorito@gmail.com).

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CONG

**Abbreviations and Acronyms**

AAOCA = anomalous aortic origin of the coronary artery
AAOLCA = anomalous aortic origin of the left coronary artery
AAORCA = anomalous aortic origin of the right coronary artery
CCTA = coronary computed tomography angiography
FEA = finite element analysis
ICC = interclass coefficient correlation
IQR = interquartile range
IVUS = intravascular ultrasound
LCA = left coronary artery
RCA = right coronary artery
SCD = sudden cardiac death

to be 0.03% to 0.23% for AAOLCA and AAORCA, respectively.[1] Given the ectopic origin, the anomalous coronary artery may have a narrow lumen, a slit-like ostium, an intramural segment, and a course that can be interarterial, prepulmonic, subpulmonic, retroaortic, or retrocardiac,[1-3] Diagnostic imaging techniques, invasive assessment, and provocative stress tests have shown low sensitivity and specificity on detecting inducible ischemia and a multimodality assessment is then necessary.[1,4,5] Among the different subtypes, AAOLCA with intramural segment and interarterial course is considered at high risk for sudden cardiac death (SCD), and the indication to surgery is widely accepted.[6] Meanwhile, the indication to treat AAORCA remains debated because of the difficulties in defining the SCD risk. In AAORCA, high-risk morphologic features such as the intramural segment or the slit-like ostium are indications of surgical treatment. However, provocative functional tests often do not show inducible ischemia in such forms.

In the medical field, innovative tools have been developed using computer-based simulation, 3-dimensional reconstruction, machine learning, and artificial intelligence.[7] With the application of such new technologies, we aim to fill the gap of knowledge and the diagnostic limitation regarding the functional risk stratification for the majority of subjects with AAOCA. Patients' tailored simulation of the aortic root expansion and coronary arteries may allow visualization of the changes that occur during stress inside the coronary lumen. Therefore, we created a patient-specific computational model simulation framework[8] that can identify morphologic changes in the anomalous coronary artery lumen using structural finite element analysis (FEA). We designed this pilot study to understand if our computational model can be used in a clinical scenario by assessing (1) if all parameters are retrievable in a reproducible way from standard patient coronary computed tomography angiography (CCTA); and (2) if the model can reproduce anomalous coronary artery lumen behavior at different pressure loads when compared with healthy controls. To address these questions, we selected a group of patients with the diagnosis of AAORCA with similar anatomic characteristics and compared them with the coronary arteries of age- and sex-matched controls.

## MATERIALS AND METHODS

Two authors (M.L.R., R.M.R.), not involved in the imaging measurements process, retrospectively reviewed the institutional database (57 patients with AAOCA from 2003) to identify study candidates that underwent CCTA in the period 2015 to 2018 to ensure comparable image quality. Five patients with AAORCA with similar anatomic characteristics (RCA from the left sinus of Valsalva, presence of slit-like ostium, and intramural course) were enrolled. We selected a homogeneous population aiming to reduce the anatomic variation that could bias the interpretation of the results. We identified 5 age- and sex-matched control subjects with normal coronary anatomy and without other congenital cardiac anomalies that underwent CCTA. The presence of a myocardial bridge was not considered a contraindication to the study because it is distal to the coronary segment investigated with the simulation. The local ethical committee approved the study (registry number: 63/int/2019) and waived the requirement of informed consent.

### Parameter Measurement Protocol and Observer Reproducibility

CCTA scan acquisitions were performed with a Siemens SOMATOM Definition AS scanner (Siemens, Erlangen, Germany) with the following characteristics: electrocardiogram-gated (retrospective or prospective according to patient heart rate), slice thickness 0.6 to 0.75 mm, reconstruction matrix 512 × 512, pixel spacing from 0.25 × 0.27 to 0.41 × 0.41 mm, 80 to 120 kV. All measurements and reconstructions were retrieved from the imaging stack at diastole. All CCTA were de-identified (M.L.R., R.M.R.) and provided to 3 independent observers blinded to the clinical history of the subjects. The observer group was formed by a cardiovascular radiologist (F.S.) with 10 years of experience, a cardiac imaging specialist (S.P.) expert with level 3 accreditation in cardiac magnetic resonance and 10 years of experience in the field, and a biomedical engineer (AR) with experience in analyzing cardiovascular images. They measured, in a given time of 30 days, for each subject, 25 parameters (Table E1) used to populate the simulation model (Figure 1). The simulation model reproduced the aortic root together with the initial segment of both coronary arteries, as described in the previous work of our group.[8] In particular, 13 of 25 parameters (Table E1) corresponded to the aortic root and 4 of 25 corresponded to the left coronary artery (LCA). For the right coronary artery (RCA), 4 parameters described the normal condition, whereas 4 more parameters described the anomalous characteristics of AAORCA. The pulmonary artery was excluded from the simulation because we believe it has a negligible contribution in the intramural segment compression. We believe it is unlikely that the pulmonary artery (lower pressure system) can compress the aortic root and coronaries (higher pressure system). We evaluate consistency and reproducibility among the 3 observers with interclass coefficient correlation (ICC), estimated using a 2-way random-effect model based on a single rating and absolute agreement.[9] For each of the 25 parameters, we calculated the ICC estimation with 95% confidence interval and *P* value. Consistency and reproducibility of the measurements were classified on ICC value as fair (ICC, 0.50-0.75), good (ICC, 0.75-0.90), and excellent (ICC, >0.90).[9]

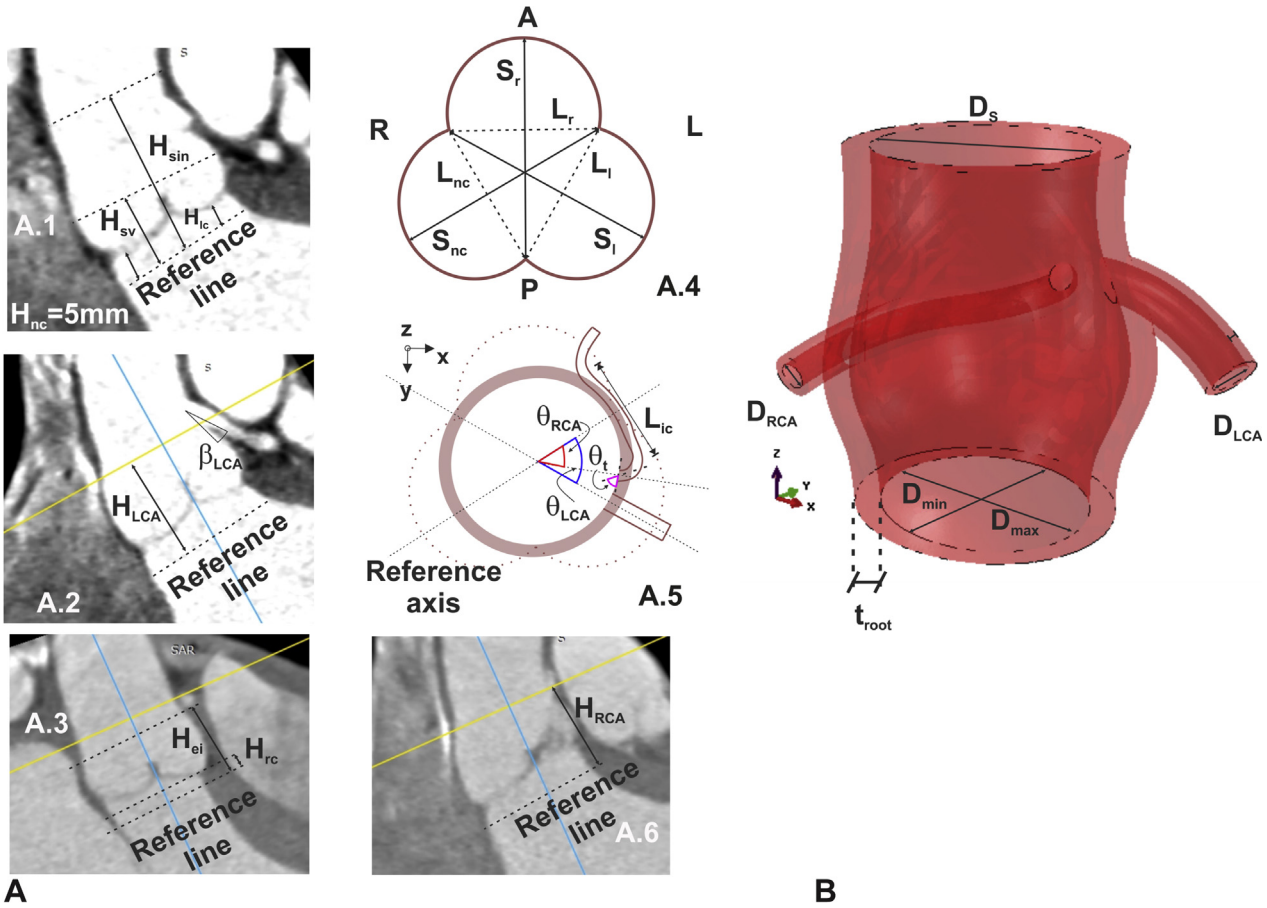


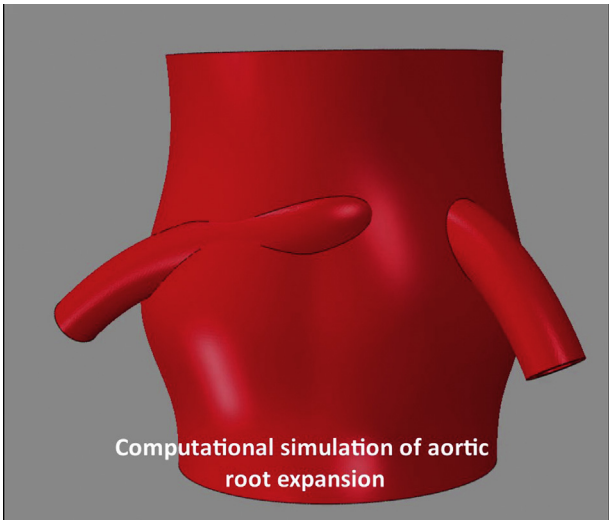

**FIGURE 1.** Geometric parameters measurement references (A) and 3-dimensional computer-aided design model (B). $H_{sin}$, Height of the sinotubular junction; $H_{sv}$, height of the maximum protrusion of the sinuses of Valsalva; $H_{lc}$, left cusp nadir height; $H_{rc}$, right cusp nadir height; $H_{LCA}$, height of the left coronary artery ostium; $\beta_{LCA}$, angle between the left coronary artery axis and aortic wall; $H_{ei}$, height at the end of the intramural course; *A*, anterior; *P*, posterior; *R*, right; *L*, left; $S_r$, protrusion of the right sinus; $S_l$, protrusion of the left sinus; $S_{nc}$, protrusion of the noncoronary sinus; $L_r$, distance between right sinus commissures; $L_l$, distance between left sinus commisures; $L_{nc}$, distance between noncoronary sinus commissures; $\theta_{RCA}$, angle between the right coronary artery and the aortic wall; $\theta_{LCA}$, angle between the left coronary artery and the reference line between the noncoronary sinus and tight-left aortic valve commissure; $\theta_t$, anomalous right coronary artery take-off angle; $L_{ic}$, length of the intramural course; $H_{RCA}$, height of the right coronary artery sinus; $D_s$, diameter of the sinotubular junction; $D_{min}$, minimum aortic annulus diameter; $D_{max}$, maximum aortic annulus diameter; $D_{RCA}$, internal diameter of the right coronary artery; $D_{LCA}$, internal diameter of the left coronary artery.

## Patient-Specific Model and Simulation

On the basis of the measurements acquired from CCTA, patient-specific computer-aided design representations were generated with Rhinoceros v5.0 software (McNeel and Associates, Seattle, Wash) integrated with the plug-in Grasshopper v0.9.0076. Once the computer-aided design surface of the aortic root and coronaries was ready, we used FEA to mimic their mechanical behavior. FEA virtually reproduces the deformation of a given body (in our case the aortic root and coronaries) at different loads considering the geometric and material characteristics to predict what the final spatial configuration could be (Video 1). FEA simulations were performed using Abaqus/Standard 2017 (Dassault Systemès, Providence, RI) by inflating the model at 2 incremental pressures from the basal value assumed to be at 80 mm Hg: (1) +40 mm Hg (120 mm Hg, ie, medium effort); +100 mm Hg (180 mm Hg, ie, exercise). The coronary arteries were considered as compressible hollow pipes originating from the aorta with different take-off angles and intramural segment characteristics. Total length (Lmax) of anomalous RCA was calculated as the sum of intramural segment length (Lic) and a fixed length nonintramural segment set at 15 mm. To simulate the mechanical behavior of the biological tissue, a linear elastic model (St Venant-Kirchhoff) was used for both the root and the coronaries with Young's modulus of 1 MPa and a Poisson ratio of 0.45. A constant thickness of 3 mm[10] and 0.9 mm[11] was used for the wall of the aortic root and coronary arteries, respectively. The lumen of the normal and anomalous coronary artery were postprocessed, and axial cross-sections of the vessel were defined every 0.5 mm at the considered pressure loads. The cross-sectional areas of these sections were calculated starting from the ostium along the total coronary length (Lmax) and used to study potential enlargement/narrowing. We normalize coronary length across the different subjects using the ratio between the lengths of the measured cross-sectional axial sections (L) to the total length (Lmax) of the coronary investigated.

## Statistical Methods for Group Comparison

Continuous variables were summarized as median and interquartile ranges (IQRs) and compared using the Mann–Whitney *U* test. RCA and LCA size comparisons were made to assess differences between AAORCA




**VIDEO 1.** Patient's specific simulation of aortic root with anomalous coronary artery parameter variation and aortic root pressure expansion. Video available at: https://www.jtcvs.org/article/S0022-5223(20)32430-2/fulltext.

cases and controls. We used Friedman test for paired samples to compare variations at the 3 different pressure conditions. All statistical analyses were performed with Stata Statistical Software (Release 12; StataCorp 2011; StataCorp LP, College Station, Tex).

## RESULTS

### Patient Demographics

The demographics of the 5 patients with AAORCA are summarized in Table 1. Patients' median age was 18 years (IQR, 8), similar to that of healthy controls (17 years; IQR, 4). In 3 patients, the diagnosis followed a chest pain event that occurred during competitive sports activity. Only 1 patient presented an ST elevation at the electrocardiogram with a peak of troponin (23 ng/mL). In the other 2 patients, the chest pain regressed with rest, and they were referred for cardiologic assessment lately after the event. Two patients were asymptomatic and reported unspecific pain event at rest that triggered the cardiologic assessment. The institutional diagnostic protocol includes a transthoracic echocardiogram, CCTA, cardiac magnetic resonance, and stress test. Three patients had invasive coronary angiography and intravascular ultrasound (IVUS) for risk profiling (the 2 asymptomatic cases) and evaluation of a myocardial bridge in 1 symptomatic subject. All the 3 symptomatic patients, in whom was documented a significant slit-like ostium and intramural segment, underwent surgical repair. The surgery consisted of the unroofing of the intramural segment (n = 3) and myocardial bridge resection (n = 1). The postoperative course was uneventful in all patients; they were all in good condition and without symptoms at their last follow-up conducted in 2018. The remaining 2 asymptomatic patients were judged to have a low-risk profile with negative inducible stress test and negative IVUS evaluation and were restricted from competitive sports activity and directed to follow-up without medications.

### Computed Tomography Parameter Measurements and Interobserver Agreement

All parameters were obtained from the 10 subjects and are listed in Table E1. ICC demonstrated agreement in 22 of 25 parameters (88%) with a good/excellent accuracy in 14 of them. The baseline parameters of the aortic root did not show any significant differences between AAORCA and controls (Table E1). Patients with AAORCA showed some significantly different LCA characteristics compared with controls at baseline. The LCA ostium of the AAORCA group seemed to locate closer to the left and right aortic cusp commissure compared with controls ($\Theta_{LCA}$: 68.9° vs 83.5°, $P = .008$) and with a more acute angle between coronary and aortic root ($\beta_{LCA}$: 30° vs 39.7°, $P = .01$). For the RCA, apart from the expected differences related to the anomalous origin from the opposite sinus, the subjects with AAORCA presented a smaller luminal diameter at the ostium compared with controls (2.8 vs 3.5 mm, $P = .026$).

### Computational Simulation Results

At basal conditions, the ostium median cross-sectional area was not different between AAORCA and controls in the LCA (13.09 vs 12.44 $mm^2$, $P = .690$) or in the RCA (6.10 vs 9.49 $mm^2$, $P = .222$) (Table 2).

In the AAORCA group, the loading pressure state determined an increase in the RCA ostium cross-sectional area.

**TABLE 1. Demographics of patients with anomalous aortic origin of the right coronary artery**

| Subject | Age | Intramural length (mm) | Slit-like ostium | Symptoms | Treatment |
|---|---|---|---|---|---|
| 1 | 18 | 10.5 | Yes | None | Observation + competitive sport restriction |
| 2 | 18 | 12.2 | Yes | Chest pain during effort | RCA unroofing |
| 3 | 24 | 13 | Yes | Chest pain during effort | RCA unroofing and debridging |
| 4 | 14 | 7.5 | No | None | Observation + competitive sport restriction |
| 5 | 12 | 10.5 | Yes | Chest pain at the stress test | RCA unroofing |

*RCA*, Right coronary artery.

**TABLE 2. Ostial cross-sectional areas in millimeters squared at incremental loading pressures**

| Vessel | Group | Basal (80 mm Hg) | +40 mm Hg | +100 mm Hg | *P* value* |
|---|---|---|---|---|---|
| RCA | AAORCA | 6.10 (2.99) | 6.21 (3.12) | 6.60 (3.43) | .007 |
| | Controls | 9.49 (8.59) | 10.09 (9.26) | 11.43 (10.72) | .007 |
| | *P* value† | .222 | .151 | .151 | |
| | % **Median increment from basal cross-sectional area** | | | | |
| | AAORCA | | 1.8% (1.0) | 8.1% (3.1) | |
| | Controls | | 6.0% (1.9) | 19.2% (5.8) | |
| | *P* value† | | .008 | .008 | |
| LCA | AAORCA | 13.09 (6.17) | 13.67 (6.53) | 15.21 (7.44) | .007 |
| | Controls | 12.44 (8.35) | 13.24 (8.88) | 15.04 (10.26) | .007 |
| | *P* value† | .690 | .690 | .690 | |
| | % **Median increment from basal cross-sectional area** | | | | |
| | AAORCA | | 4.6% (1.3) | 16.7% (2.9) | |
| | Controls | | 5.4% (1.4) | 18.2% (4.9) | |
| | *P* value† | | .421 | .548 | |

Cross-sectional areas ($mm^2$) values are reported as median and IQR. Proportional increment (%) at loading pressure from the basal cross-sectional area is calculated for each patient and then expressed as median and IQR for each group. *RCA,* Right coronary artery; *AAORCA,* anomalous aortic origin of the right coronary artery; *LCA,* left coronary artery. *Statistical significance of the difference between different loading conditions in the same group. †Statistical significance of the difference between AAORCA and controls for each loading condition.

The increment was significant only between the basal condition and +100 mm Hg (6.10 vs 6.60 $mm^2$, $P = .005$). The RCA median cross-sectional area increase was 1.8% (IQR, 1.0%) at +40 mm Hg and 8.1% (IQR, 3.1%) at +100 mm Hg. In the control group, there was a significant enlargement of the RCA ostium cross-sectional area from a basal value of 9.49 to 11.43 $mm^2$ ($P = .005$) at +100 mm Hg. The RCA median increment was 6.0% (IQR, 1.9%) at +40 mm Hg and 19.2% (IQR, 5.8%) at +100 mm Hg. The patients with AAORCA showed a significantly reduced ostium enlargement compared with controls at +40 mm Hg (1.8% vs 6%, $P = .008$) and at +100 mm Hg (8.1% vs 19.2%, $P = .008$) (Figure 2). The LCA cross-sectional areas had comparable increments with pressures loads between AAORCA and controls (Table 2).

For each patient, we studied the entire length of the coronary artery at the 3 different loading conditions (Figure 3). The RCA of the AAORCA showed a localized ostial expansion, but the cross-sectional area remained at the basal value, or even below, for the intramural segment (Figure 3), followed by a return to ostial area values in the distal part. The absence of dilation in the intramural portion of the RCA in patients with AAORCA reproduces the anatomic substrate responsible for the reduction of coronary blood flow reserve.[12-14] Conversely, the RCA of the control group showed an evident enlargement in the ostium and a constant separation between the curves along the entire coronary length, suggesting a physiologic adaptation of the artery to different loading pressures (Figure 4).

## DISCUSSION

The AAOCA has become increasingly studied in the scientific community. The main controversies are on

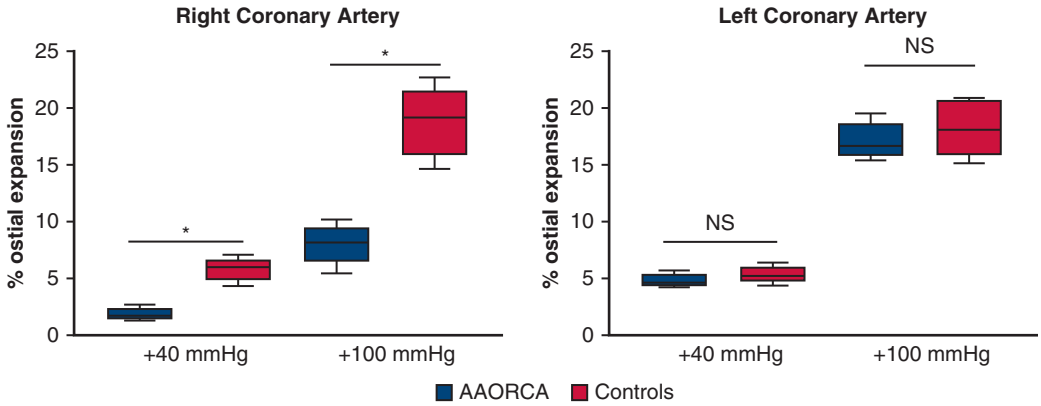



**FIGURE 2.** Increment from the basal cross-sectional area of the RCA and LCA in AAORCA and controls. The RCA of patients with AAORCA shows a significantly lower enlargement compared with controls both at +40 mm Hg (1.8% vs 6%, $P = .008$) and at +100 mm Hg (8.1% vs 19.2%, $P = .008$). *AAORCA*, Anomalous aortic origin of the right coronary artery; *NS*, not significant.

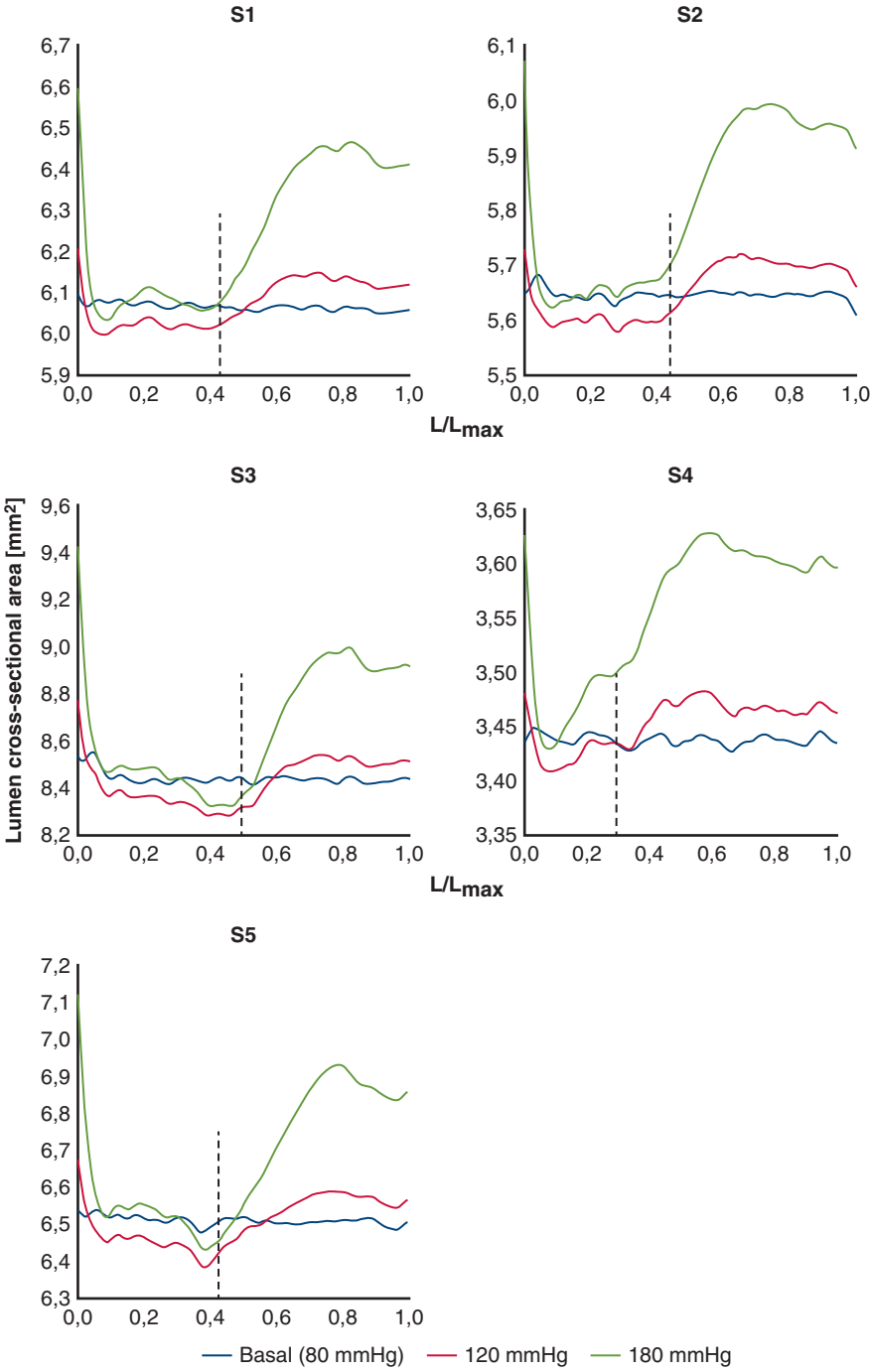



**FIGURE 3.** AAORCA patient-specific simulation of RCA cross-sectional area at different pressure loading conditions. Patients show a reduced expansion at incremental pressure loads along the initial intramural segment with a return to "normal" coronary cross-sectional area in the more distal sections. Cross-sectional area is expressed in $mm^2$ in the vertical axis. L/Lmax is the ratio between the length at each axial section (L) to the total length (*Lmax*). The reference vertical dashed line in the x-axis indicates the end of the intramural segment. The *blue line* depicts basal (80 mm Hg) condition, the *red line* +40 mm Hg pressure load condition, the *green line* +100 mm Hg pressure load condition. Each panel represents a different subject tagged from S1 to S5, demographics data of patients are cross-referenced in Table 1.

the usefulness of extensive population screening, sudden death prevention, risk stratification, treatment indications, and long-term outcomes. Because of the low incidence of the disease, national and international multicenter studies[15,16] and large patients' databases[17,18] have been developed to answer several of the mentioned unsolved questions. International guidelines recommend surgical treatment in case of SCD events, high-risk

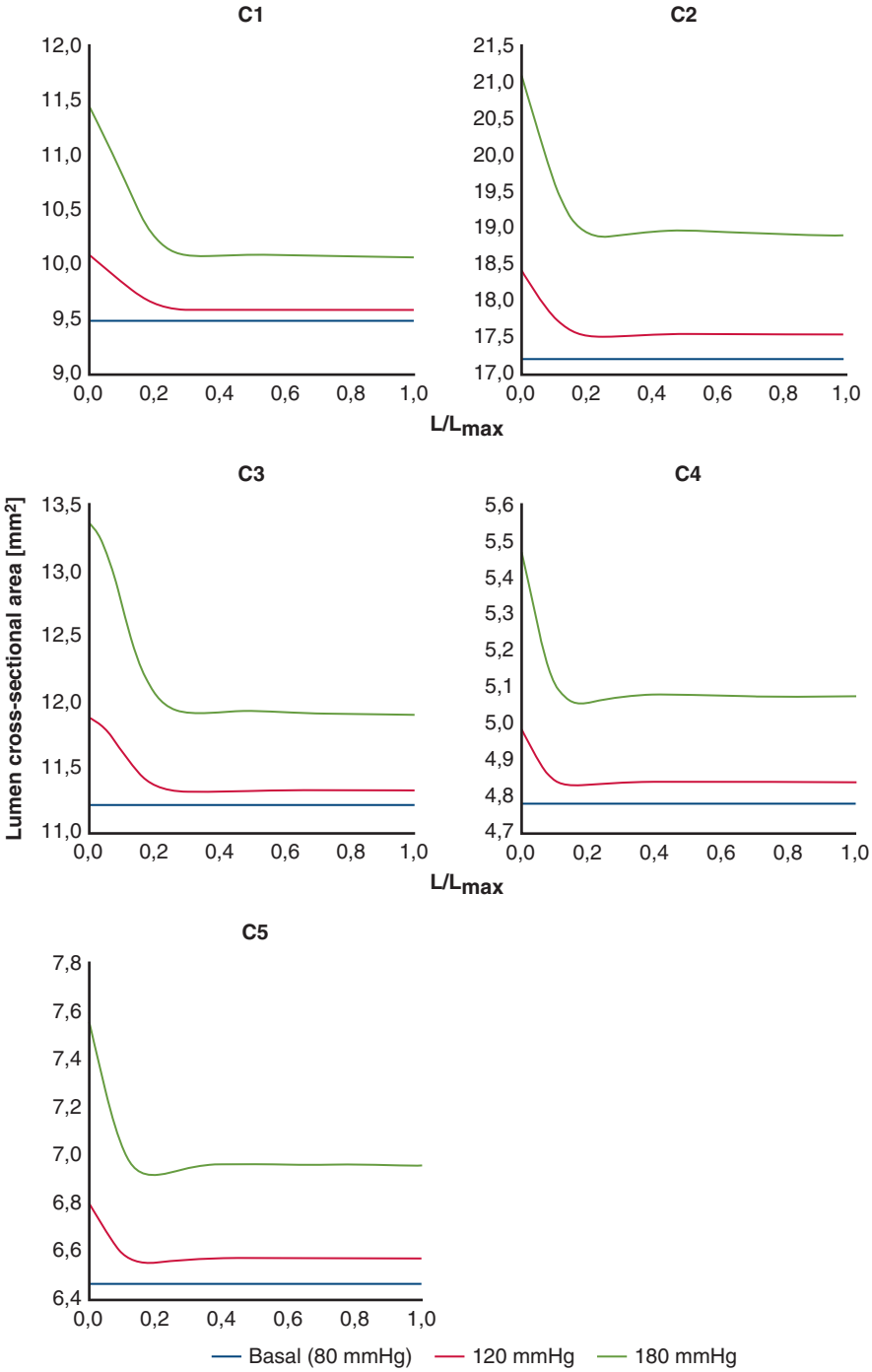



**FIGURE 4.** Control subjects' patient-specific simulation of RCA cross-sectional area at different pressure loading conditions. RCA shows an evident enlargement in the ostium that gradually decreases along the length of the coronary but with constant separation between curves above the basal level. Cross-sectional area is expressed in $mm^2$ in the vertical axis. L/Lmax is the ratio between the length at each axial section (L) to the total length (Lmax). The *blue line* depicts basal (80 mm Hg) condition, the *red line* +40 mm Hg pressure load condition, the *green line* +100 mm Hg pressure load condition. Each panel represents a different control subject tagged from C1 to C5.

forms (AAOLCA), meanwhile in low-risk forms (AAORCA) is necessary also a documented ischemia.[6] Unfortunately, 40% to 60% of cases in autopsy series did not present symptoms or signs before death,[1,19] revealing that the first presentation is often lethal. Surgical treatment has low operative mortality,[15,20] but it carries a significant risk of symptoms persistence, aortic insufficiency, and coronary stenosis.[21]

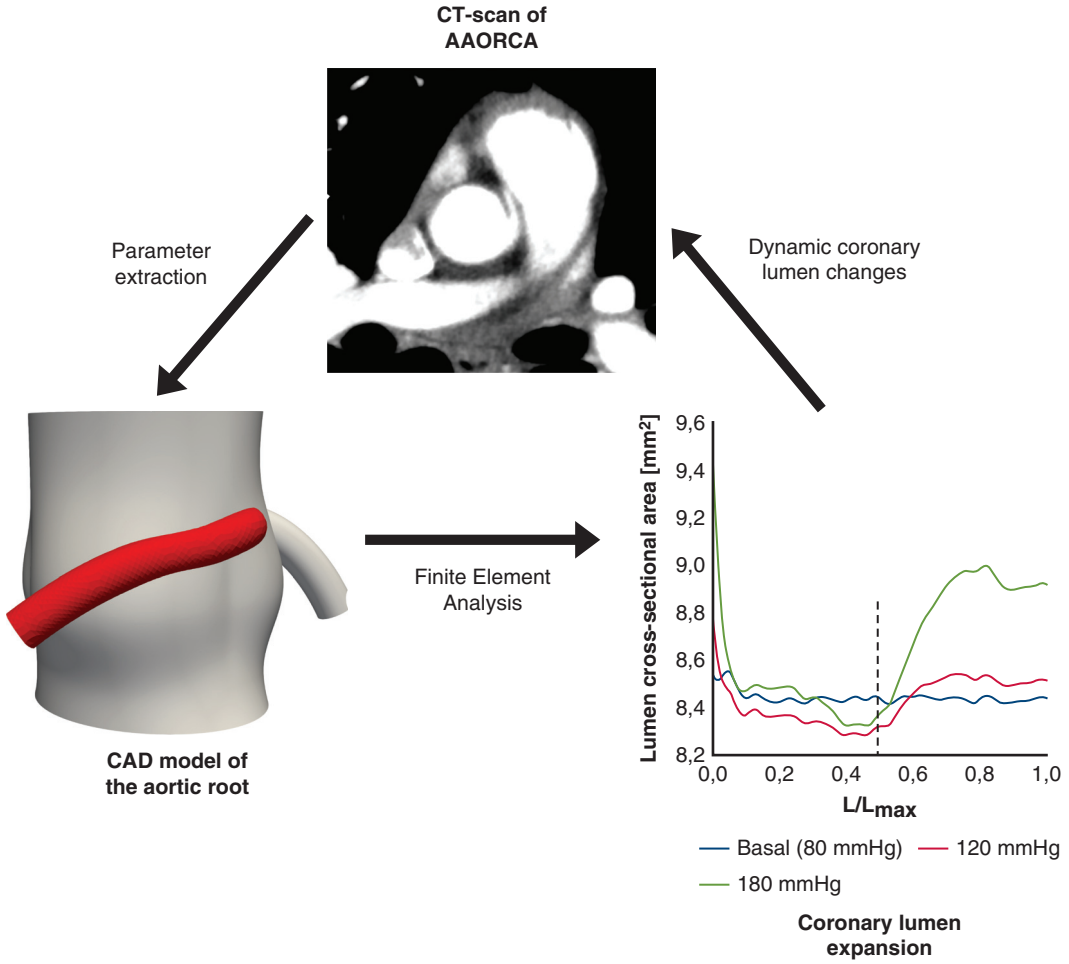



**FIGURE 5.** Computational simulation model pipeline. CCTA of patients with AAORCA is transformed into a 3-dimensional computational representation by extracting a set of 25 parameters. The model is pressurized to simulate a Physical effort condition, and through structural FEA, we estimate the luminal diameter changes along the vessel. The anomalous coronary artery shows an inability to expand the lumen under pressure loading conditions, mainly in the intramural segment. Evaluation of such impaired expansion using simulation may allow evaluating coronary changes during effort. *AAORCA*, Anomalous aortic origin of the right coronary artery; *CAD*, computer-aided design; *CT*, computed tomography.

Furthermore, indication for surgery is based only on few anatomic characteristics that fall short in making a functional stratification,[22] generating essential questions about whether the benefits of surgery outweigh the risks.[1,21,22] Functional assessment may improve the risk versus benefit evaluation of surgical treatment, especially on asymptomatic subjects, but exercise stress test fails to demonstrate myocardial ischemia in 6% to 30% of the patients.[19,23] Such failure may be related to the inability to reproduce the strenuous effort reach during competitive sport responsible for SCD in subjects with AAOCA.

To overcome all the limitations mentioned, we develop a computational simulation model[8] that can be populated with patient-specific data and evaluates the coronary behavior under different stress conditions (Figure 5). To the best of our knowledge, this is the first model able to simulate AAORCA and to assess coronary characteristics like diameters, cross-sectional areas, and ostial deformation under stress conditions, otherwise not measurable in a clinical environment.

The clinical applicability of a model lies on how easy, quick, and reproducible is the parameters retrieval from standard imaging set by different observers. In our study, the 3 observers demonstrate agreement on 88% (22/25) of the parameters measured on the CCTA. Our model reproducibility, also when used by different professionals, may allow an easy translation to the clinical environment. Currently, the retrieval of the parameters is too long because it requires between 30 and 40 minutes for each patient, but an automated algorithm[7,24] may accelerate the entire process.

The computational model populated with patient-specific parameters provides outputs that reliably resemble in vivo coronary behavior. In fact, we do not find any differences between the LCA in AAORCA and control subjects

at basal and loading conditions. Furthermore, simulated LCA shows a significant increase in the cross-sectional area uniformly along the coronary length under pressure loading, mimicking the physiologic adaptation to physical effort. In fact, during sports, the coronary arteries need to increase their lumen to guarantee adequate blood flow volumes maintaining stable pressures gradients.[25]

More important, for the anomalous RCA, the model well demonstrates the lack of dilatation in the intramural segment resembling functional stenosis at moderate/high pressure loads. We found an RCA basal median cross-sectional area of 6.1 $mm^2$ in line with the coronary dimensions measured with IVUS (6 $\pm$ 2.4 $mm^2$).[12] These findings support the accuracy of the model that provides dynamic outputs for AAORCA coronary size and behavior, starting from a static CCTA. Simulated outputs are in a range with what measured with IVUS, considered the dynamic examination with the greatest definition.[1,13] More important, in each patient, we quantified a different coronary behavior based on the individual anatomy for the entire segment.

Simulation data need to be introduced in a clinical scenario very carefully because simulation models tend to oversimplify complex natural processes introducing biases. There is a risk that we may be looking at what we want to see because we built the model in such way. For these reasons, we never used any of the simulation results to guide our clinical decision. Because our findings are preliminary, and all different forms of AAOCA have not been tested yet, we have to discourage the use of the model to make clinical decisions before a formal clinical validation. The initial findings are promising, suggesting that we may be able to develop a reliable personalized risk stratification tool for AAOCA patients using simulation models. We may be able soon to overcome current diagnostic limitations of functional stress-test evaluation.

### Study Limitations

The study has several limitations, mainly due to the early-stage nature and the small sample size. We admit that the findings are applicable only in AAORCA with the intramural segment and direct translation of the results to all forms is not possible. The coronary artery shape is simulated as a round pipe also for the intramural segment of the anomalous ones. Although it may seem a limitation, in reality, it is a conservative assumption because the intramural segment usually has an elliptic shape that is greatly affected by compression compared with the round shape. From an engineering perspective, the material model used to represent the biological tissue may be further improved by incorporating anisotropy, aortic wall thickness, and other anatomic details (ie, the rigidity of the aortic valve commissures) to better reproduce patient-specific conditions.

Moreover, we consider a stress-free configuration of both aortic root and coronaries as a starting point, disregarding the diastolic pressure; we apply an incremental systolic-diastolic pressure, assuming that the geometry is built resembling the anatomy of the aortic root and coronaries at the diastolic phase of the cardiac cycle. Our model tends to oversimplify "real-life" conditions but constitutes the "best-case scenario" of coronary compression. If we add more accurate modeling characteristics (ie, anisotropy, patient-specific wall thickness, commissure compliance), we expect an even greater inability of the vessel to expand. Finally, risk stratification and predictive value of our model have to be demonstrated against in vivo conditions.

## CONCLUSIONS

The proposed AAORCA model is able to represent the pathogenic disease mechanism after being populated with patient-specific data. The model demonstrates that anomalous RCA is unable to expand its lumen in the intramural segment at loading conditions. None of the functional outputs provided by this innovative model are measurable in a clinical set-up with standard diagnostic tools. More extensive validation studies are necessary before routine model adoption. However, the first clinical application showed promising results on quantifying the pathological behavior of AAORCA and potentially helping in patient-specific risk stratification.

### Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/19%20AM/Monday_May6/202BD/202BD/S90%20-%20Coronary%20artery%20anomalies%20in%20children/S90_6_webcast_054932071.mp4.


### Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

### References

1. Cheezum MK, Liberthson RR, Shah NR, Villines TC, O'Gara PT, Landzberg MJ, et al. Anomalous aortic origin of a coronary artery from the inappropriate sinus of Valsalva. *J Am Coll Cardiol*. 2017;69:1592-608.

2. Agrawal H, Mery CM, Krishnamurthy R, Molossi S. Anatomic types of anomalous aortic origin of a coronary artery: a pictorial summary. *Congenit Heart Dis*. 2017;12:603-6.
3. Brothers JA, Frommelt MA, Jaquiss RDB, Myerburg RJ, Fraser CD, Tweddell JS. Expert consensus guidelines: anomalous aortic origin of a coronary artery. *J Thorac Cardiovasc Surg*. 2017;153:1440-57.
4. Brothers JA. Multimodality imaging of anomalous aortic origin of a coronary artery. *World J Pediatr Congenit Heart Surg*. 2016;7:318-20.
5. Molossi S, Agrawal H. Clinical evaluation of the anomalous aortic origin of a coronary artery (AAOCA). *Congenit Heart Dis*. 2017;12:607-9.
6. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: executive summary. *J Am Coll Cardiol*. 2011;58:2584-614.
7. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med*. 2019;25:44-56.
8. Formato GM, Lo Rito M, Auricchio F, Frigiola A, Conti M. Aortic expansion induces lumen narrrowing in anomalous coronary arteries: a parametric structural finite element analysis. *J Biomech Eng*. 2018;140:111008-9.
9. Chen C-C, Barnhart HX. Assessing agreement with intraclass correlation coefficient and concordance correlation coefficient for data with repeated measures. *Comput Stat Data Anal*. 2013;60:132-45.
10. de Kerchove L, Jashari R, Boodhwani M, Duy KT, Lengelé B, Gianello P, et al. Surgical anatomy of the aortic root: implication for valve-sparing reimplantation and aortic valve annuloplasty. *J Thorac Cardiovasc Surg*. 2015;149:425-33.
11. Yoshitani H, Takeuchi M, Ogawa K, Otsuji Y. Comparison of usefulness of the wall thickness of the left anterior descending coronary artery, determined by transthoracic echocardiography, and carotid intima-media thickness in predicting multivessel coronary artery disease. *J Echocardiogr*. 2009;7:2-8.
12. Angelini P, Uribe C, Monge J, Tobis JM, Elayda MA, Willerson JT. Origin of the right coronary artery from the opposite sinus of Valsalva in adults: characterization by intravascular ultrasonography at baseline and after stent angioplasty. *Catheter Cardiovasc Interv*. 2015;86:199-208.
13. Angelini P, Uribe C. Anatomic spectrum of left coronary artery anomalies and associated mechanisms of coronary insufficiency. *Catheter Cardiovasc Interv*. 2018;92:313-21.
14. Brothers J, Gaynor JW, Paridon S, Lorber R, Jacobs M. Anomalous aortic origin of a coronary artery with an interarterial course: understanding current management strategies in children and young adults. *Pediatr Cardiol*. 2009;30:911-21.
15. Padalino MA, Franchetti N, Hazekamp M, Sojak V, Carrel T, Frigiola A, et al. Surgery for anomalous aortic origin of coronary arteries: a multicentre study from the European Congenital Heart Surgeons Association†. *Eur J Cardiothorac Surg*. 2019;55:823-8.
16. Padalino MA, Franchetti N, Sarris GE, Hazekamp M, Carrel T, Frigiola A, et al. Anomalous aortic origin of coronary arteries: early results on clinical management from an international multicenter study. *Int J Cardiol*. 2019;291:189-93.
17. Brothers JA, Gaynor JW, Jacobs JP, Caldarone C, Jegatheeswaran A, Jacobs ML, et al. The registry of anomalous aortic origin of the coronary artery of the Congenital Heart Surgeons' Society. *Cardiol Young*. 2010;20(Suppl 3):50-8.
18. Aubry P, du Fretay X, Dupouy P, Leurent G, Godin M, Belle L. Anomalous connections of the coronary arteries: a prospective observational cohort of 472 adults. The ANOCOR registry. *Eur Heart J*. 2015;36:1138.
19. Basso C, Maron BJ, Corrado D, Thiene G. Clinical profile of congenital coronary artery anomalies with origin from the wrong aortic sinus leading to sudden death in young competitive athletes. *J Am Coll Cardiol*. 2000;35:1493-501.
20. Brothers JA, Gaynor JW, Jacobs JP, Poynter JA, Jacobs ML. The Congenital Heart Surgeons' Society registry of anomalous aortic origin of a coronary artery: an update. *Cardiol Young*. 2015;25:1567-71.
21. Nees SN, Flyer JN, Chelliah A, Dayton JD, Touchette L, Kalfa D, et al. Patients with anomalous aortic origin of the coronary artery remain at risk after surgical repair. *J Thorac Cardiovasc Surg*. 2018;155:2554-64.
22. Balasubramanya S, Mongé MC, Eltayeb OM, Sarwark AE, Costello JM, Rigsby CK, et al. Anomalous aortic origin of a coronary artery: symptoms do not correlate with intramural length or ostial diameter. *World J Pediatr Congenit Heart Surg*. 2017;8:445-52.
23. Brothers JA, McBride MG, Seliem MA, Marino BS, Tomlinson RS, Pampaloni MH, et al. Evaluation of myocardial ischemia after surgical repair of anomalous aortic origin of a coronary artery in a series of pediatric patients. *J Am Coll Cardiol*. 2007;50:2078-82.
24. Brown M, Browning P, Wahi-Anwar MW, Murphy M, Delgado J, Greenspan H, et al. Integration of chest CT CAD into the clinical workflow and impact on radiologist efficiency. *Acad Radiol*. 2019;26:626-31.
25. Gorman MW, Feigl EO. Control of coronary blood flow during exercise. *Exerc Sport Sci Rev*. 2012;40:37-42.


**Key Words:** AAOCA, anomalous aortic origin of the coronary artery, computed tomography, congenital heart disease, ischemia, risk stratification, simulation, sudden cardiac death

## Discussion

### Presenter: Dr Mauro Lo Rito

**Dr Pirooz Eghtesady** *(St Louis, Mo).* As discussed by many of the presenters, we continue to struggle with knowing what parameters to use as a predictive measure for deciding on surgery or not for this population of patients. I understand your study has a small sample size, but I would like to push you a bit, if you will, to answer a few questions despite limited data. You show in your control group that the coronaries expand and contract, and in the anomalous right, they don't. I found it similarly a nice internal control that the LCA expanded in the patients with anomalous RCA and the anomalous coronary did not.

You had 5 patients, and I saw the aggregate data, but of these 5, 3 were symptomatic, and 2 had relief of symptoms with rest and 1 had release of troponin, ST changes, and so forth. Two were completely incidental findings. When you look at your data, did you see symptoms correlate with the degree of coronary expansibility, meaning less expansible were more symptomatic or anything along that paradigm?

**Dr Mauro Lo Rito** *(San Donato Milanese, Italy).* Yes, we may see them, but I did not want to comment on that because in such a small sample, we cannot draw any conclusion or correlation clinical decision or severity based on our model that is not entirely validated. Can we look back to a previous slide, please? I will show you the patient that we operated on, but we took the decision based on clinical evaluation of those who have the greatest compression.

These 3 patients on the first vertical column are those who have undergone operation. I don't want to draw any conclusions, but they have the lowest values of the cross-sectional area at stress. I want to draw your attention to these downward inflections. I thought initially there was a mistake in the model, but looking at the measurement and reconstruction, this is the point that corresponds to the aortic valve

commissure pillar that Dr Mery talked about. So the inflection correlates with the anatomy of the intraoperative findings. This region of major stiffness, see also at the simulation, may be a source of further compression. I don't want to draw any conclusion with these 5 patients, but we have promising results. We may be working in the right direction.

**Dr Eghtesady.** The second question is related to the interesting observation you made on angulation of the left coronary, which you found was different in the subjects with anomalous coronary versus the controls. With the loading conditions you tested, did you see any changes in the angulation of the LCA beyond the 30/35 degrees that you mention? Was there any correlation with symptoms? It makes me wonder if we've ignored something important regarding the so-called normal coronary in these patients.

**Dr Lo Rito.** On that point, I have to talk honestly of course, because I do not want to give false findings regarding the model. I think it might be an issue related to the way we achieved the parameters on the CT. To measure that angle, we use the cross-sectional imaging of the aorta. We use as the first side of the angle a line between the half of the noncoronary sinus commissure and the commissure between the right and the left cusp. From there, in the left coronary sinus, we measure the angle of the left coronary ostium origin. Sometimes, the 2 coronary ostia may seem close because of a pouch in the aortic wall because the angle changes, so I don't want to comment on that in terms of anatomy definition.

**Dr Eghtesady.** Naturally, it would be interesting to see the results with more patients as well as in the anomalous left coronary, but it would be fascinating if you did this for patients postarterial switch and in hypoplasts and see how the coronaries change or respond to the same modeling techniques.

**Dr Lo Rito.** Thank you for the suggestion.

**Dr Pranava Sinha** *(Washington, DC).* Does your model take into account the abnormal compliance of the vessel wall as it is in the intramural course, and if so, what compliance indices did you use? Where did you get those?

**Dr Lo Rito.** As I said in the "Study Limitations," the aortic wall thickness in the model has been set up in a range value achieved by literature reference is not the thickness of the patient aortic wall aorta measured on CT. The same kind of assumptions we did for the compliance of the aorta that has been taken by reference values from different articles on aorta modeling, so there are no patient data in the model that allowed us to simulate the compliance of the aorta. That is a limitation. But you have to start from some point, so you have to make some assumptions and then from there, refine your model. Otherwise, if you have a too complicated model, you may introduce too many errors, and your output can be wrong or unreliable.

**TABLE E1. Model parameters retrieved from computed tomography scans**

| Parameter name | AAORCA (n = 5) | Controls (n = 5) | *P* value* | ICC | *P* value |
|---|---|---|---|---|---|
| $D_{max}$ | 26.9 (2.8) | 27.8 (2.8) | .098 | 0.674 | <.001 |
| $D_{min}$ | 19.9 (3.2) | 22.3 (5.0) | .081 | 0.748 | <.001 |
| $H_{rc}$ | 4.9 (0.9) | 4.4 (2.2) | .595 | 0.223 | .125 |
| $H_{lc}$ | 5.2 (1.1) | 6.1 (1.9) | .016 | 0.203 | .146 |
| $L_r$ | 19.9 (2.1) | 21.1 (4.1) | .050 | 0.821 | <.001 |
| $L_l$ | 19.5 (2.9) | 20.8 (3.5) | .116 | 0.692 | <.001 |
| $L_{nc}$ | 19.5 (2.8) | 19.8 (2.8) | .775 | 0.780 | <.001 |
| $S_r$ | 25.7 (3.1) | 26.2 (4.4) | .436 | 0.917 | <.001 |
| $S_l$ | 26.3 (3.0) | 26.2 (4.9) | .967 | 0.849 | <.001 |
| $S_{nc}$ | 27.0 (2.4) | 27.1 (5.4) | .806 | 0.912 | <.001 |
| $H_{sv}$ | 13.8 (1.8) | 13.7 (2.2) | .806 | 0.497 | .006 |
| $H_{sin}$ | 27.0 (3.1) | 25.4 (3.6) | .512 | 0.733 | <.001 |
| $D_s$ | 22.5 (2.4) | 22.3 (3.3) | .713 | 0.928 | <.001 |
| $H_{LCA}$ | 19.2 (6.1) | 19.4 (4.4) | .367 | 0.856 | <.001 |
| $\Theta_{LCA}$ | 68.9 (11.6) | 83.5 (21.2) | .008 | 0.815 | <.001 |
| $\beta_{LCA}$ | 30.0 (9.8) | 39.7 (11.0) | .011 | 0.753 | <.001 |
| $D_{LCA}$ | 4.3 (9.8) | 4.2 (1.4) | .436 | 0.642 | <.001 |
| $H_{RCA}$ | 21.5 (6.0) | 21.4 (4.6) | .902 | 0.770 | <.001 |
| $\Theta_{RCA}$ | 20.5 (10.4) | 274.9 (13.6) | <.001 | 0.827 | <.001 |
| $\beta_{RCA}$ | N/A | 69.9 (18.6) | N/A | 0.651 | .012 |
| $D_{RCA}$ | 2.8 (0.7) | 3.5 (1.4) | .026 | 0.654 | <.001 |
| $H_{ei}$ | 20.3 (4.5) | N/A | N/A | 0.597 | .021 |
| $L_{ic}$ | 10.6 (3.3) | N/A | N/A | 0.635 | .014 |
| $\Theta_t$ | 22.2 (5.8) | N/A | N/A | 0.811 | <.001 |
| Off | 2.8 (0.7) | N/A | N/A | 0.471 | .055 |

Values reported as median (IQR), differences between AAORCA and controls assessed with Mann–Whitney *U* test. *AAORCA,* Anomalous aortic origin of the right coronary artery; *ICC*, interclass coefficient correlation; *N/A,* not available. *For each parameter, agreement with the 3 observers was evaluated with ICC. Consistency was considered fair (ICC, 0.50-0.75), good (ICC, 0.75-0.90), and excellent (ICC > 0.90). Aortic root parameters: $D_{max}$, maximum aortic annulus diameter [mm]; $D_{min}$, minimum aortic annulus diameter [mm]; $H_{rc}$, right cusp nadir height [mm]; $H_{lc}$, left cusp nadir height [mm]; $L_r$, distance between right sinus commissures [mm]; $L_l$, distance between left sinus commissures [mm]; $L_{nc}$, distance between noncoronary sinus commissures [mm]; $S_r$, protrusion of right sinus [mm]; $S_l$, protrusion of left sinus [mm]; $S_{nc}$, protrusion of noncoronary sinus [mm]; $H_{sv}$, height of maximum protrusion of sinuses of Valsalva [mm]; $H_{sin}$, height of the sinotubular junction [mm]; $D_s$, diameter of the sinotubular junction [mm]; Left coronary artery parameters; $H_{LCA}$, height of LCA ostium [mm]; $\Theta_{LCA}$, angle between the LCA and reference line between noncoronary sinus and right-left aortic valve commissure [°]; $\beta_{LCA}$, angle between the LCA axis and the aortic wall [°]; $D_{LCA}$, internal diameter of the LCA [mm]; Right coronary artery parameters; $H_{RCA}$, height of the RCA ostium [mm]; $\Theta_{RCA}$, angle between the RCA and line between noncoronary sinus and right-left aortic valve commissure [°]; $\beta_{RCA}$, angle between the RCA axis and the aortic wall [°]; $D_{RCA}$, internal diameter of the RCA [mm]; Anomalous right coronary artery specific parameters; $H_{ei}$, height at the end of the intramural course [mm]; $L_{ic}$, length of the intramural course [mm]; $\Theta_t$, anomalous RCA take-off angle [°]; Off, *coronary offset* – distance between the inner aortic wall and the outer lumen of the RCA [mm].