WHAT IS THE CULPRIT IN CORONARY ANOMALIES?

To the Editor:

I read with great interest and excitement the recent report by Bartoli and colleagues¹ concerning the mechanism of ischemia in anomalous origination of a coronary artery. Anomalous left coronary artery arising from the opposite sinus of Valsalva (called L-ACAOS when the involved artery has an intramural course²) is one of the most common causes of sudden cardiac death in the young, as observed in United States military recruits (mean age of 19 years).³

The true cause and individual case severity of anomalous coronary origination have been the elusive “holy grail” sought by many investigators. This search has been persistently marred by inadequate evidence and frustrating uncertainty on clinical grounds. The report of a calf with such an anomaly, studied by expert investigators with amazing means and dedication, is therefore a welcome event. Bartoli and colleagues¹ hypothesized that ischemia (at least during their experiments) was “present and caused by the course of this anomalous artery in the space between the aorta and pulmonary artery.” Aortography is not a proper method for studying the coronary course in this location, however, and ischemia was not well demonstrated by Bartoli and colleagues’ improvised protocol in the animal laboratory (aimed at

documenting the flow reserve but not ischemia). Electrocardiography is not an acceptable or quantifiable marker of ischemia (in Figure 1 of Bartoli and colleagues’ report,¹ the T wave seems to be negative in the 3 tracings, in the absence of ST-segment depression). Additionally, the current prevailing opinion is that the cause of ischemia in this type of coronary anomaly (L-ACAOS or the similar entity R-ACAOS) is best studied with intravascular ultrasonography, which can satisfactorily document in vivo the severity of obstruction at baseline or during exercise.^{4,5} Flow velocity is an interesting means of evaluation, but flow cannot be quantified unless accompanied by appropriate data concerning the variable baseline and exercise-induced cross-sectional area of stenosis.

Bartoli and colleagues¹ are to be congratulated for their admirable attempt at taking a new approach to this fascinating subject. It seems to me, however, that clarifying the pathology requires study of a large clinical population that has been properly evaluated for severity of obstruction—correlated with symptoms—and for empirical response to the elimination of intramural stenosis (by means of stent angioplasty or surgical correction).

My group at the Texas Heart Institute is completing a multiyear research study of a large case series (65 patients with R-ACAOS), and we hope that our findings will substantially advance current knowledge in this field.

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Reply to the Editor:

We thank Dr Angelini for his kind review of our work. We read his letter with great interest and welcome the opportunity to clarify a few methodological points. Each of his comments is addressed below.

Until now, the mechanism of myocardial ischemia with an anomalous coronary artery represented an important and elusive milestone in congenital cardiology. Our findings demonstrated in a calf that an ectopic left coronary artery that coursed from the right sinus of Valsalva between the aorta and the pulmonary trunk produced myocardial ischemia and ischemic myocardial remodeling.¹ As cardiac metabolic demands increased, compression between the great vessels increased coronary resistance and decreased coronary blood flow. These findings provide insight into a potential mechanism of myocardial ischemia when a coronary artery courses between the great vessels and raise additional questions. To further define the clinical implications, additional studies are needed.

We agree that aortography is an inappropriate technique to study coronary anomalies. Indeed, in our study the anomaly was surreptitiously identified via aortogram during a routine coronary microembolization procedure to create ischemic heart failure in a calf. The animal was not used

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for microembolization. Instead, we obtained institutional approval, and 2 weeks later we performed an open chest procedure to confirm the diagnosis of a coronary anomaly and directly measure myocardial and coronary blood flow in this unique experimental animal.

We agree that electrocardiography is not the best method to quantify myocardial ischemia. During the open chest experiment, electrocardiography was used to monitor the calf and as supplemental data, *not* to quantify myocardial ischemia. Ischemia was assessed by direct measurement of myocardial blood flow with 2 techniques: (1) We quantified and mapped regional myocardial blood flow with 15 μ m fluorescent-labeled microspheres.^{2,3} During each experimental condition, a calibrated blood flow sample was drawn to define absolute values of flow (milliliters/minute/gram of tissue). This well-established technique is a standard method to directly measure regional blood flow in an organ of interest.^{4,5} (2) We also quantified coronary blood flow with a transit-time ultrasonic flow probe placed around the distal left coronary trunk,⁶ which is a standard method to directly measure volumetric blood flow in an artery of interest.⁵ The probe was calibrated against known physical standards of flow to define absolute values of blood flow (milliliters/minute).

In Figure 1 of our article, we presented myocardial blood flow maps and cardiac cycle-dependent volumetric coronary blood flow. During a dobutamine stress test, classic signs of acute myocardial ischemia were observed. At baseline, the electrocardiogram demonstrated an inverted t-wave, as is typical in normal cattle.⁷ During the dobutamine challenge, t-wave depression, a large increase in the amplitude of the QRS complex, and moderate ST-segment depression worsened at higher heart rates. These findings suggested that increased

myocardial metabolic demands exacerbated myocardial ischemia with a dose-response relationship.

Specifically, flow-distribution maps generated with the microsphere technique demonstrated a large area of reduced myocardial blood flow in the left ventricular free wall and interventricular septum. During dobutamine challenge, myocardium supplied by the anomalous left coronary artery received 20% less blood flow than myocardium supplied by the normal right coronary artery. Likewise, during phenylephrine-induced hypertension, coronary blood flow measured with an ultrasonic flow probe decreased during systole and early diastole. In contrast, in normal animals, coronary blood flow increased throughout the cardiac cycle during hypertension. Overall, 3 independent findings (ischemic electrocardiographic changes, reduced regional myocardial blood flow, and reduced volumetric left coronary artery blood flow) documented myocardial ischemia and supported the hypothesis that an ischemic mechanism triggers sudden death in patients with this type of coronary anomaly.

To reiterate, we directly measured volumetric coronary blood flow (milliliters/minute) and regional myocardial blood flow (milliliters/minute/gram of tissue) with 2 widely accepted techniques. We did not use flow velocity (centimeters/second), which is less accurate. This was a major strength of our study. Combined with high-fidelity aortic root blood pressure measurements, we calculated coronary arterial resistance throughout the cardiac cycle. In normal animals, hypertension decreased coronary resistance and increased coronary blood flow during systole and early diastole. However, in the animal with the ectopic coronary, the opposite occurred. Systolic and early diastolic expansion of the aortic root and pulmonary trunk compressed the segment of the left coronary artery that coursed between the great vessels

and produced a pathologic pattern of coronary blood flow.

Intravascular ultrasound (IVUS) will certainly assist in further documenting this phenomenon. With IVUS, it should be possible to quantify real-time changes in the coronary cross-sectional area as the anomalous coronary is compressed between the great vessels. However, IVUS cannot directly measure coronary or regional myocardial blood flow, cannot quantify ischemia, and may only be useful to visualize cardiac cycle-dependent changes in coronary lumen size.

Importantly, in our study we used multiple histologic and molecular techniques to confirm that prior ischemia produced chronic remodeling in myocardium supplied by the ectopic coronary. The classic pattern of patchy fibrosis and myocyte hypertrophy was observed. Increased capillary density and collateralization suggested ischemia-induced neovascularization. Abnormal numbers of apoptotic nuclei in the myocardium likely represented transient inflammatory cells. Taken together, these findings suggested that episodic ischemic injury produced chronic myocardial remodeling. Consequently, in patients with this anomaly, a remodeled and electrically unstable myocardial substrate that is predisposed to ventricular arrhythmia may trigger sudden death.

A large clinical study is needed to further investigate this phenomenon. Dr Angelini's contributions to the field of coronary anomalies are unsurpassed,⁸ and there is no investigator better suited to undertake this important task. We commend Dr Angelini and eagerly await the results of his study. We hope that our small contribution has complemented his efforts.

In summary, we are encouraged by Dr Angelini's enthusiasm and appreciate his interest in this project. Our study documented a pattern of abnormal coronary artery resistance and myocardial ischemia with an anomalous coronary artery from the right sinus of Valsalva. Multiple quantitative

measurements of coronary blood flow, regional myocardial blood flow, systemic hemodynamics, and electrocardiography during different physiologic conditions confirmed that coronary compression between the great vessels produced myocardial ischemia. A clinical study is urgently needed to replicate and clarify the implications of this finding and to generate standardized treatments for congenital coronary anomalies. Finally, we thank the editors of *The Journal of Thoracic and Cardiovascular Surgery* for the opportunity to comment on our work.

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AWAKE THORACIC SURGERY FOR SECONDARY SPONTANEOUS PNEUMOTHORAX: ANOTHER ADVANCEMENT

To the Editor:

With a great and renewed interest, we read the recent article by Noda and colleagues.¹ They advocated the usefulness of awake thoracoscopic surgery in treating patients with secondary spontaneous pneumothorax, listing various advantages in a total of 57 consecutive patients whom they treated. These advantages compel us to answer “yes” to the question in the title of their article, “Is there a benefit of awake thoracoscopic surgery in patients with secondary spontaneous pneumothorax?” Noda and colleagues¹

appropriately deserve credit for this growing experience in awake surgery.

In our own personal experience, the awake surgical treatment of secondary spontaneous pneumothorax has been one of the most critical challenges, first because of the severe and sometime lethal underlying lung disease and second because of the deteriorated general condition of the patients, which often makes them surgically untreatable.

In this setting, we have recently speculated on the biologic bases of these clinical advantages. Indeed, our preliminary observations have shown that awake procedures may attenuate the release of stress hormones (cortisol) and systemic inflammation biomarkers (interleukin 6) and preserve natural killer cell proportion from the early postoperative period onward (Table 1). The impairment of immune function may lead to several adverse effects, including postoperative infections, thus explaining better clinical results seen after awake surgery.

With attention to the particular medical needs of our patients, we offer awake surgery and follow the preference of the patient after adequate information about technical aspects of the procedure. Nowadays, we see favorable satisfaction with the procedure among both patients and referring physicians.

TABLE 1. Stress and immunologic response markers assessed at timed intervals from the procedure for spontaneous secondary pneumothorax in awake patients (n = 14) and nonawake controls (n = 17)

		Postoperative		
		12 h	24 h	48 h
Preoperative				
Cortisol (μg/dL)				
Awake	13 (8-17)	14 (9-18)	13 (8-18)	12 (9-15)
Control	14 (8-18)	23* (17-43)	21† (13-30)	18‡ (14-28)
P value	.4	.02	.01	.05
Interleukin 6 (pg/mL)				
Awake	3.5 (2.5-4.5)	80* (59-121)	61* (41-86)	10‡ (5-21)
Control	3.4 (2.4-3.8)	124* (82-177)	111* (88-153)	43* (22-91)
P value	.5	.03	.01	.001
Natural killer lymphocytes (%)				
Awake	11 (7-15)	10 (6-13)	10 (7-13)	11 (6-14)
Control	10 (5-15)	5* (2-7)	6† (3-9)	8‡ (4-10)
P value	.4	.01	.02	.06

Values represent medians and interquartile ranges of unpublished data. * $P \leq .001$ for intragroup significance versus baseline value. † $P \leq .01$ for intragroup significance versus baseline value. ‡ $P \leq .05$ for intragroup significance versus baseline value.