Violent coronary flow collision injuring the intima and starting atherosclerotic plaques: New evidences from the cardiac laboratories

The 16th Symposium of Atherosclerosis and Cardiovascular Intervention Research Institute Symposium

18:50-19-10 Thursday December 12th Busan Korea

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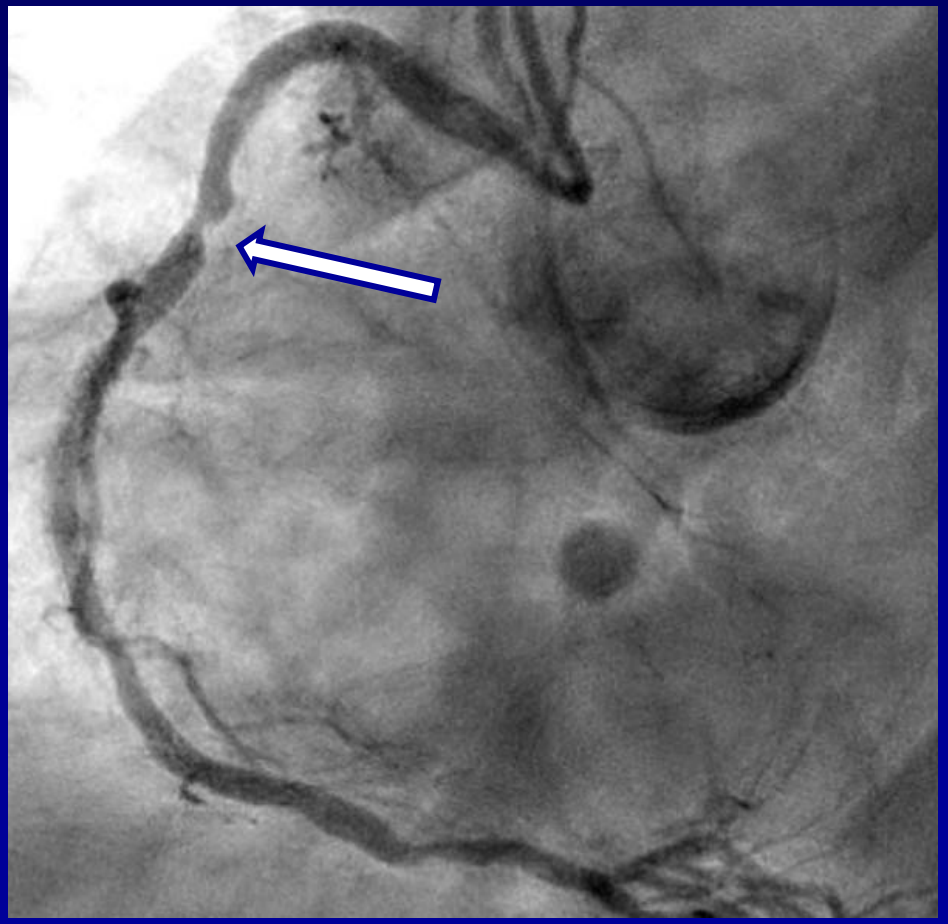
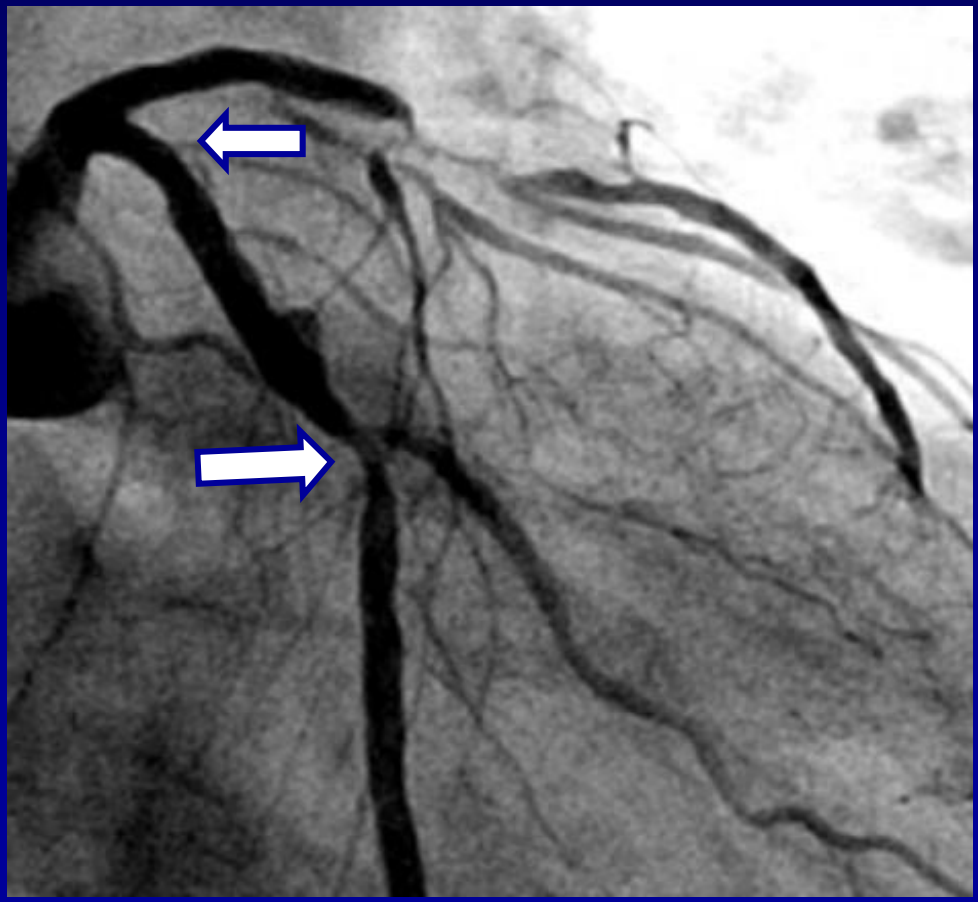
OUTLINE

1. What are the mechanisms of injury (non medical and medical)?
2. Where is the evidence of injury to the intima?
3. What is the role of LDL cholesterol and other conventional risk factors?
4. Applications and ongoing research

QUESTIONS: 1. Why do they appear?
2. Why at the mid segment?
3. Why the lesion in the mid LCX is more severe than the lesion at the ostium of LCX?





Background 1

How to create an animal model for atherosclerosis?

Male NZW rabbits

Atherogenic Diet

high fat (8.6%) and high cholesterol (1%) diet

ATHEROSCLEROTI C LESION DEVELOPMENT

Balloon injury at 1 week

2 Weeks

4 Weeks

Timeline

Aorta

Internal iliac

External iliac artery

Atherosclerotic Iliac artery

Uninjured Iliac artery

Background 1

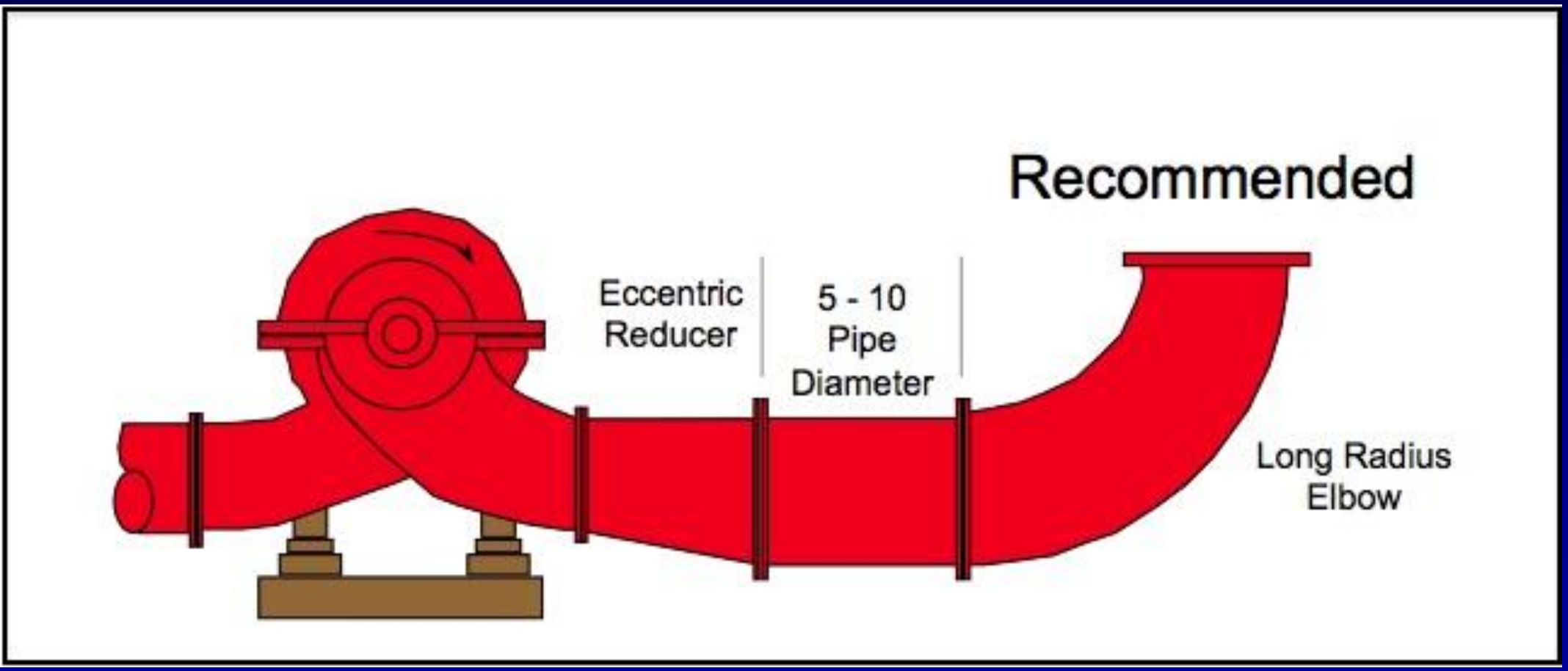
It starts with a mechanical injury or

1. Transplantation
2. Needle puncture,
3. Freezing,
4. Heat,
5. Exposure to electron radiation,
6. Induced hypertension, etc

Background 2: Plumbing Repair at Home

Real Life Observations

Real Life Observations

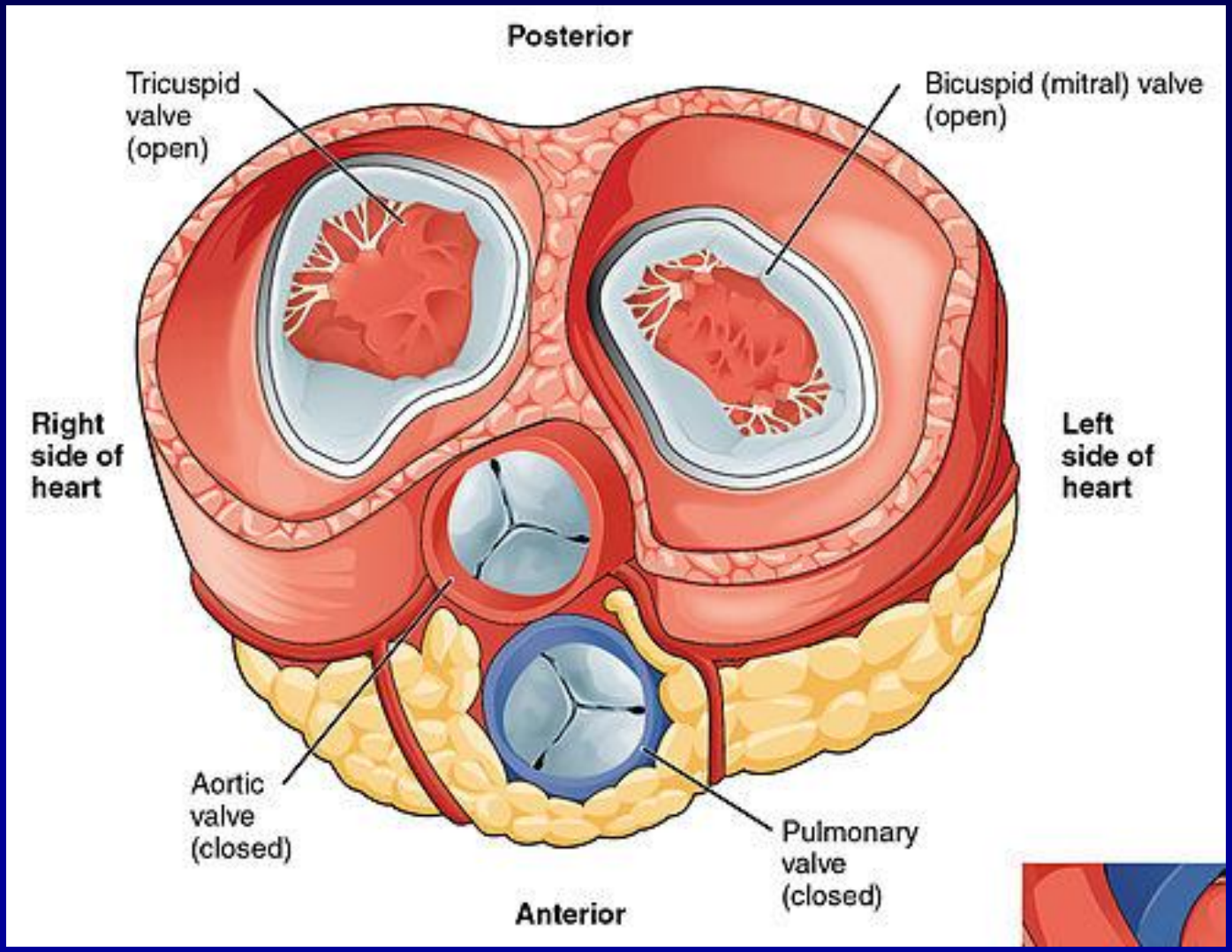


http://www.scielo.org.za/pdf/jsaice/v56n3/08.pdf

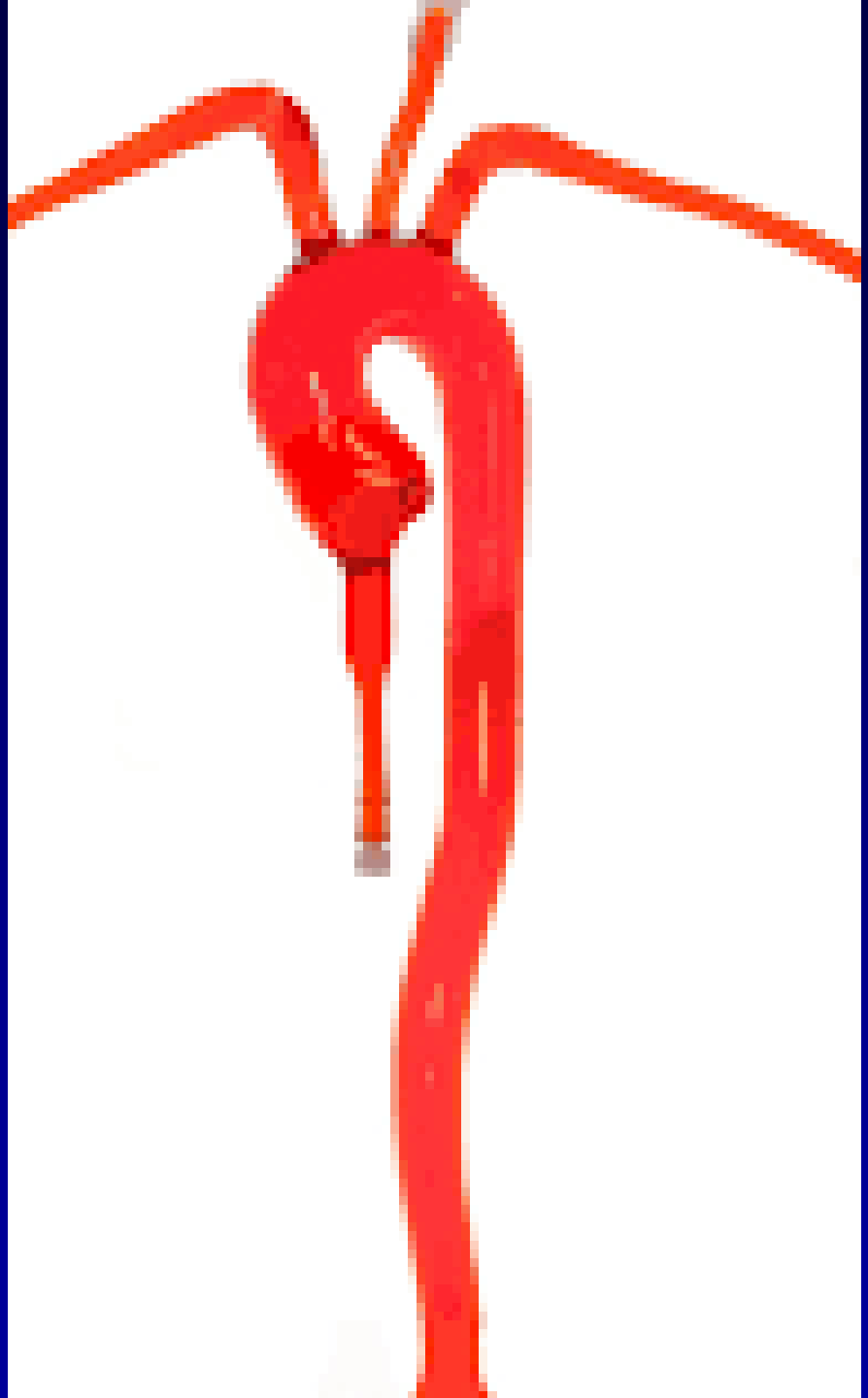

DR. NGUYEN
STUDENT

Challenging QUESTIONS

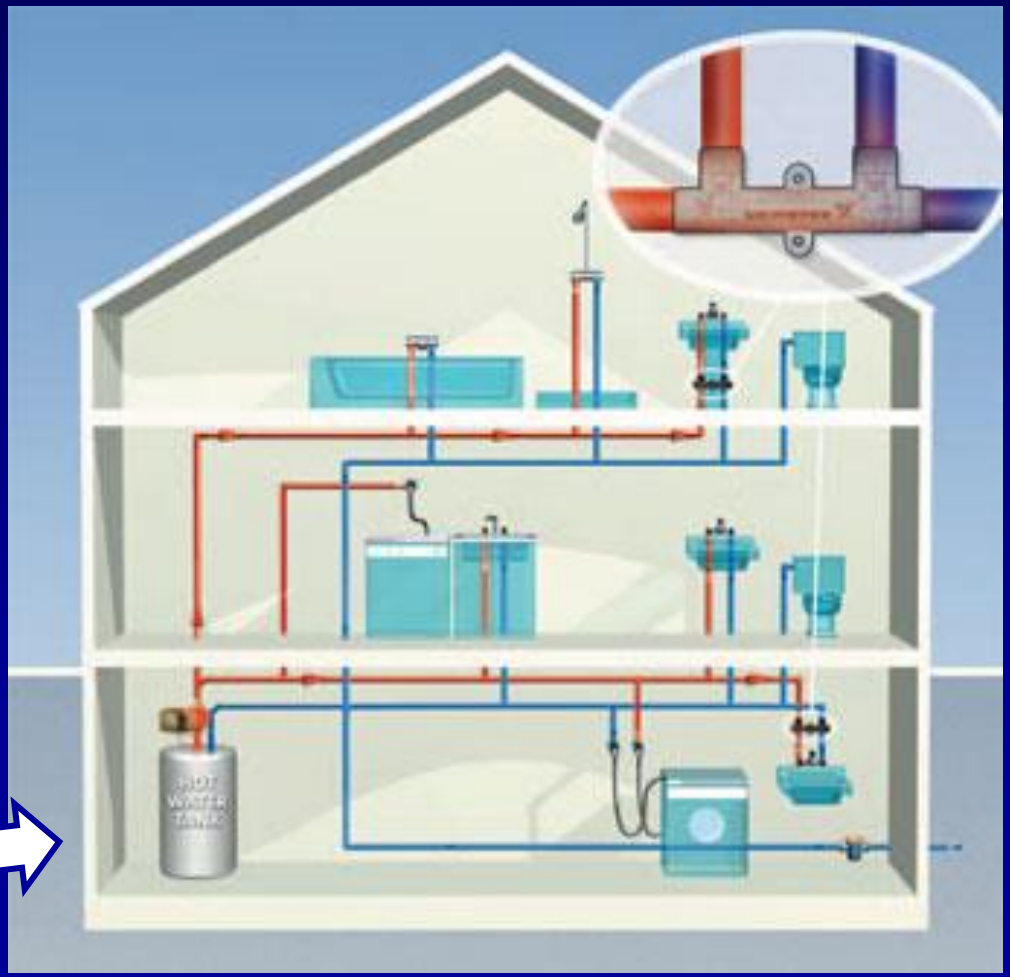
Why the Mitral Valve area (MVA) is larger than the Aortic Valve area (AVA)?



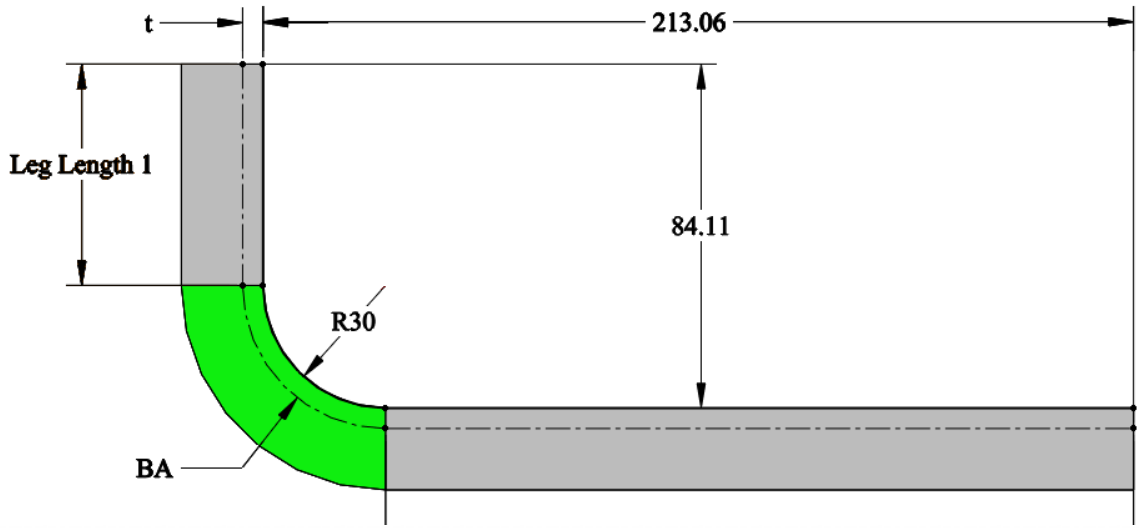
3 Questions

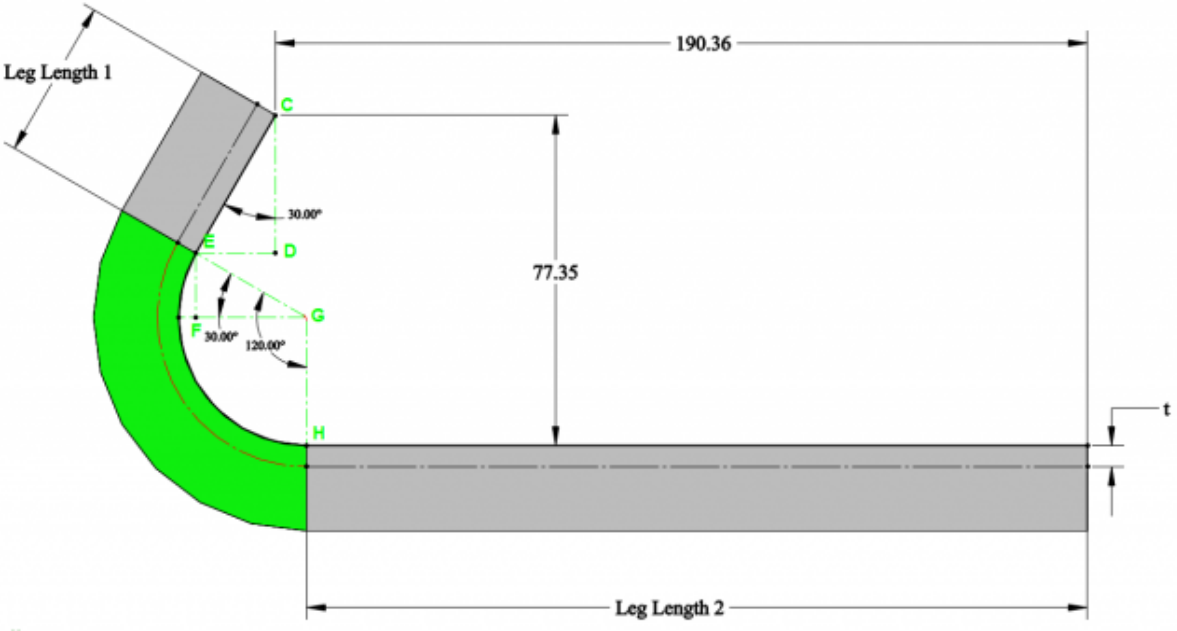


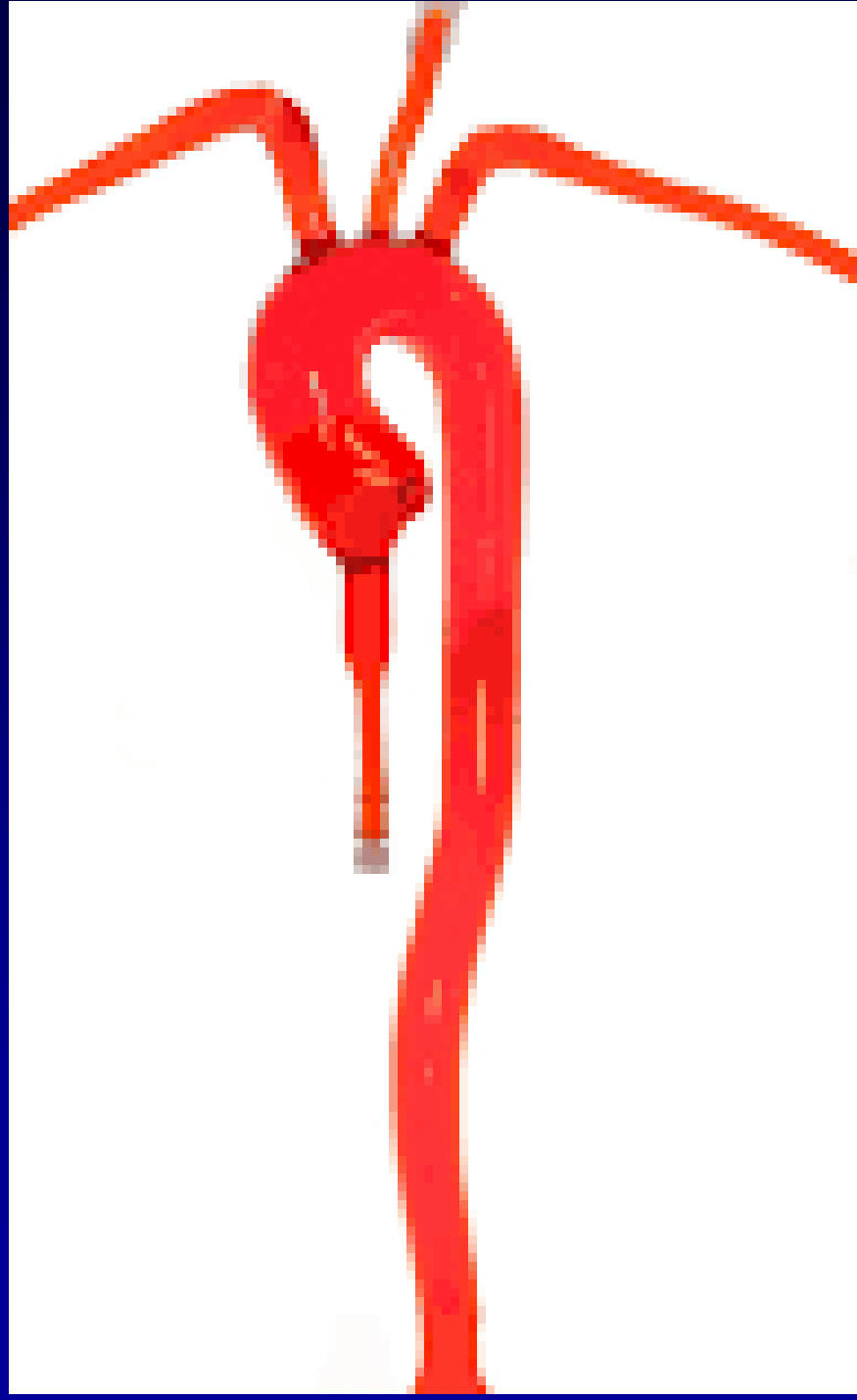
Location of water pump in a house



Angle of the aortic curvature

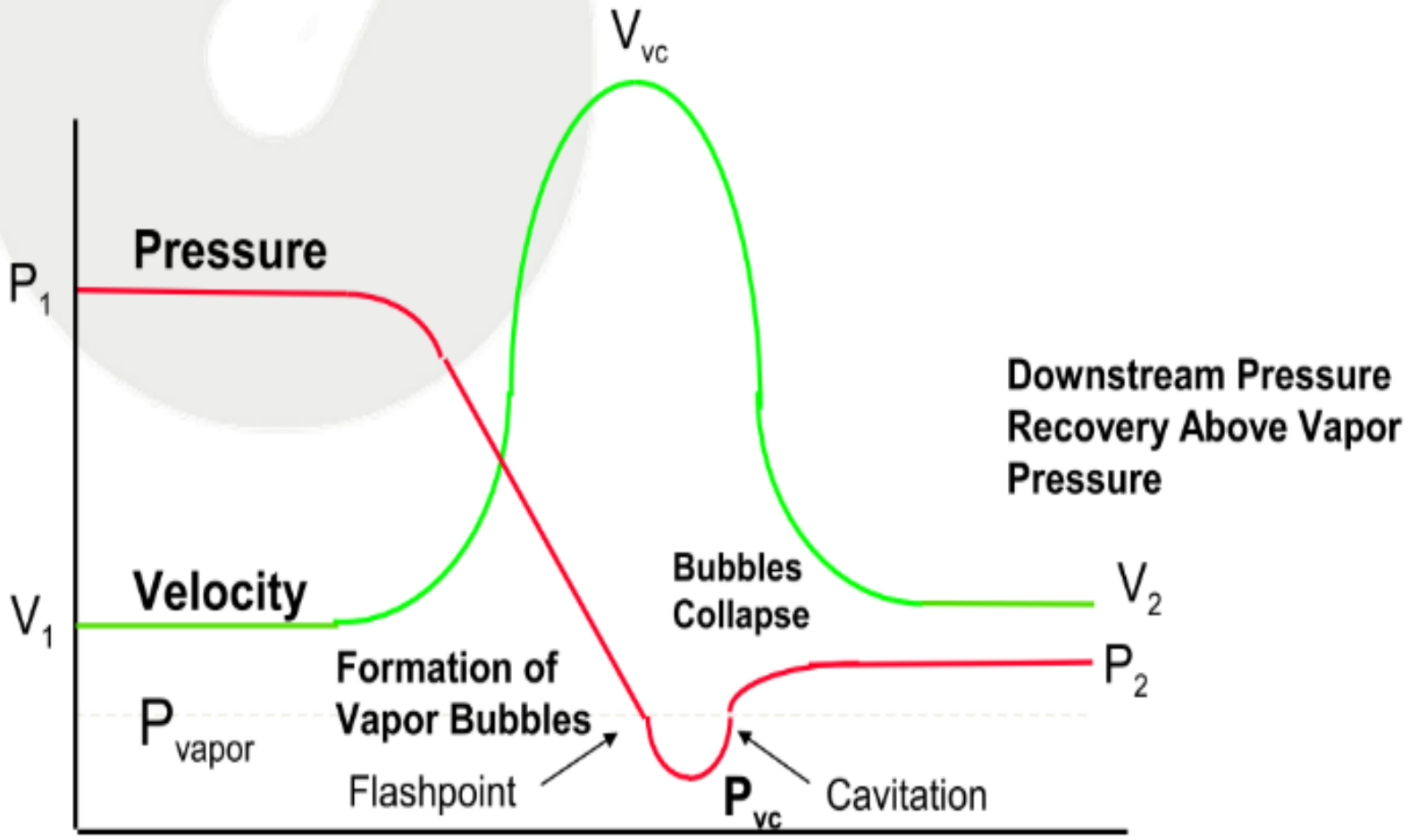






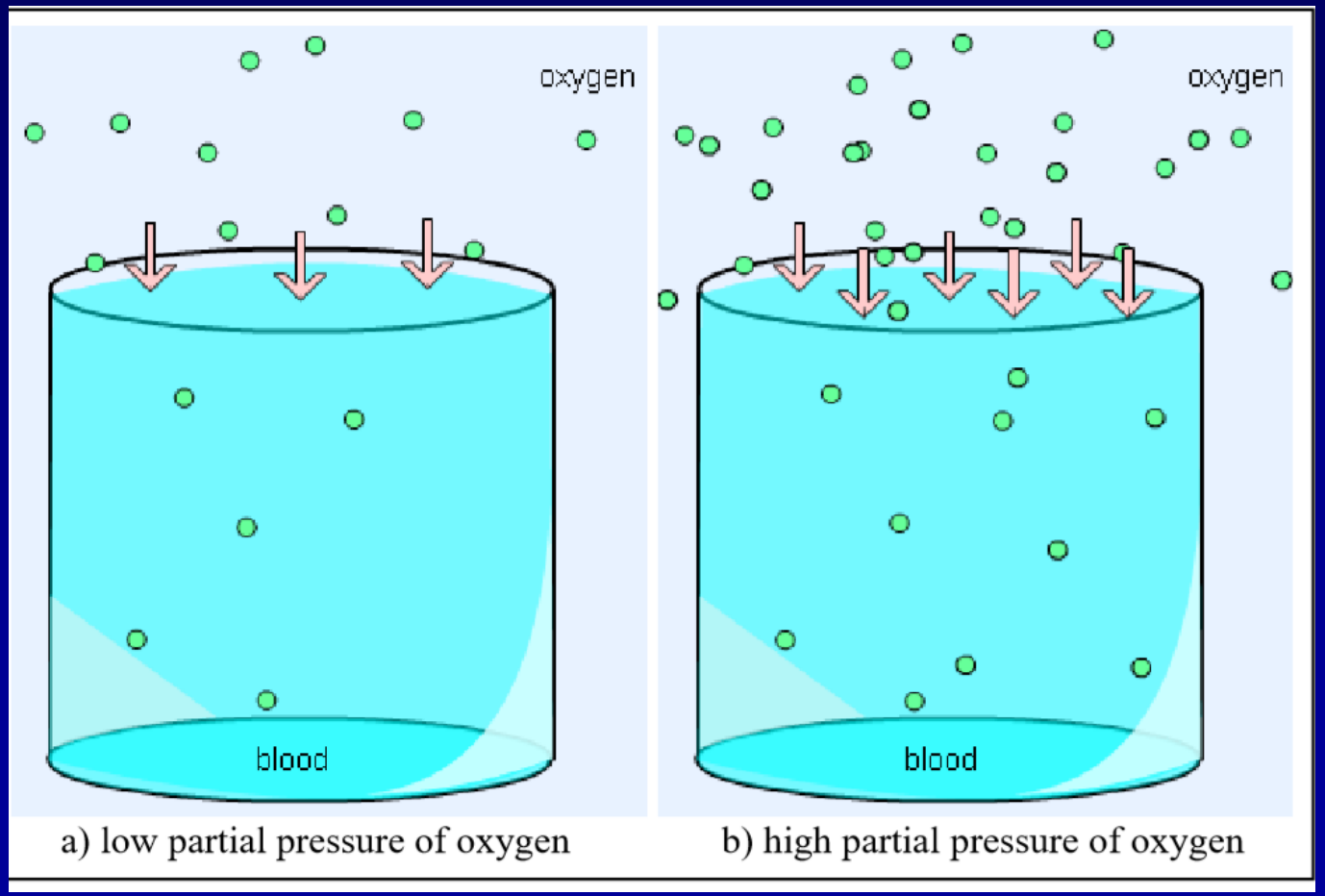
Real Life Observations : Damage of the copper pipe by air bubble rupture (cavitation)

Cavitation Phenomena



Henry's Law: Solubility of Air in Water

- The amount of air dissolved in a fluid is proportional to the pressure in the system



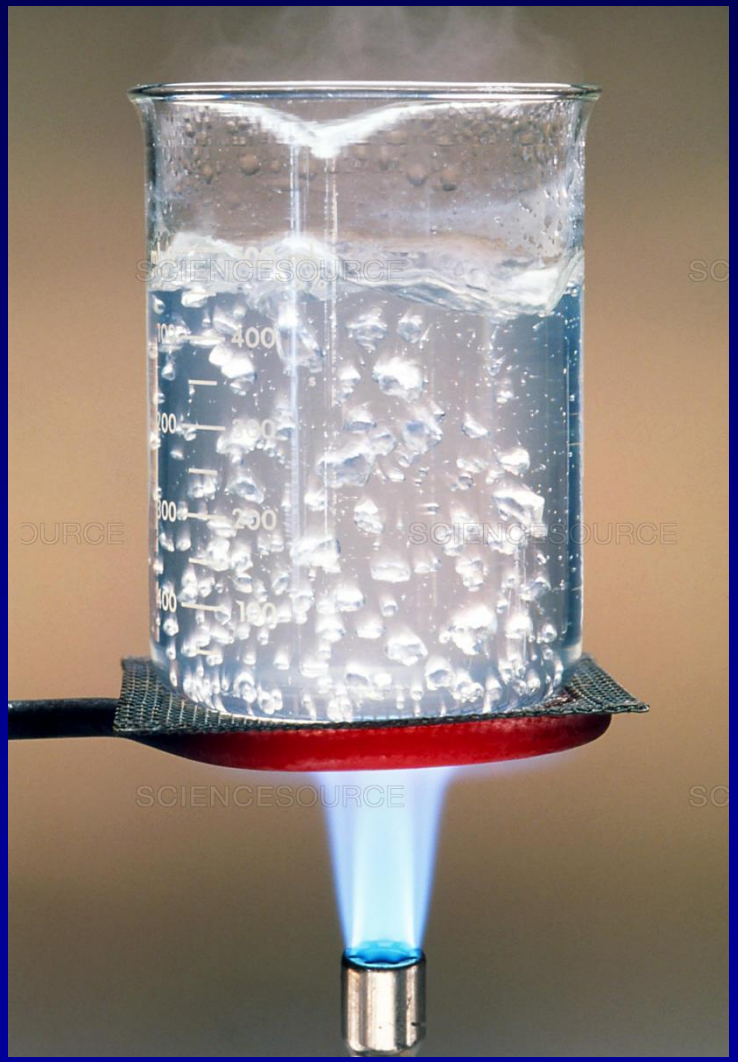
a) low partial pressure of oxygen

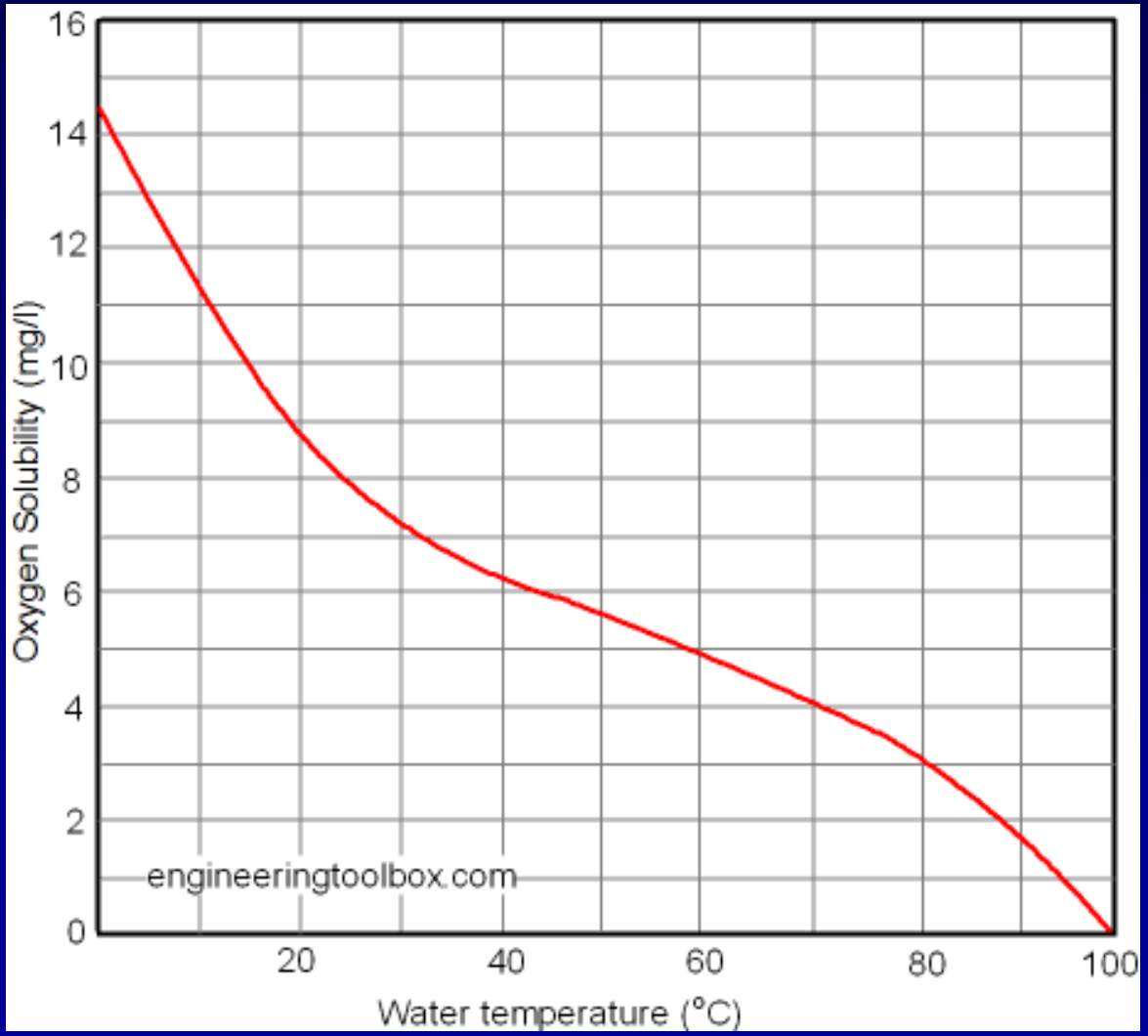
b) high partial pressure of oxygen

Real Life Observations

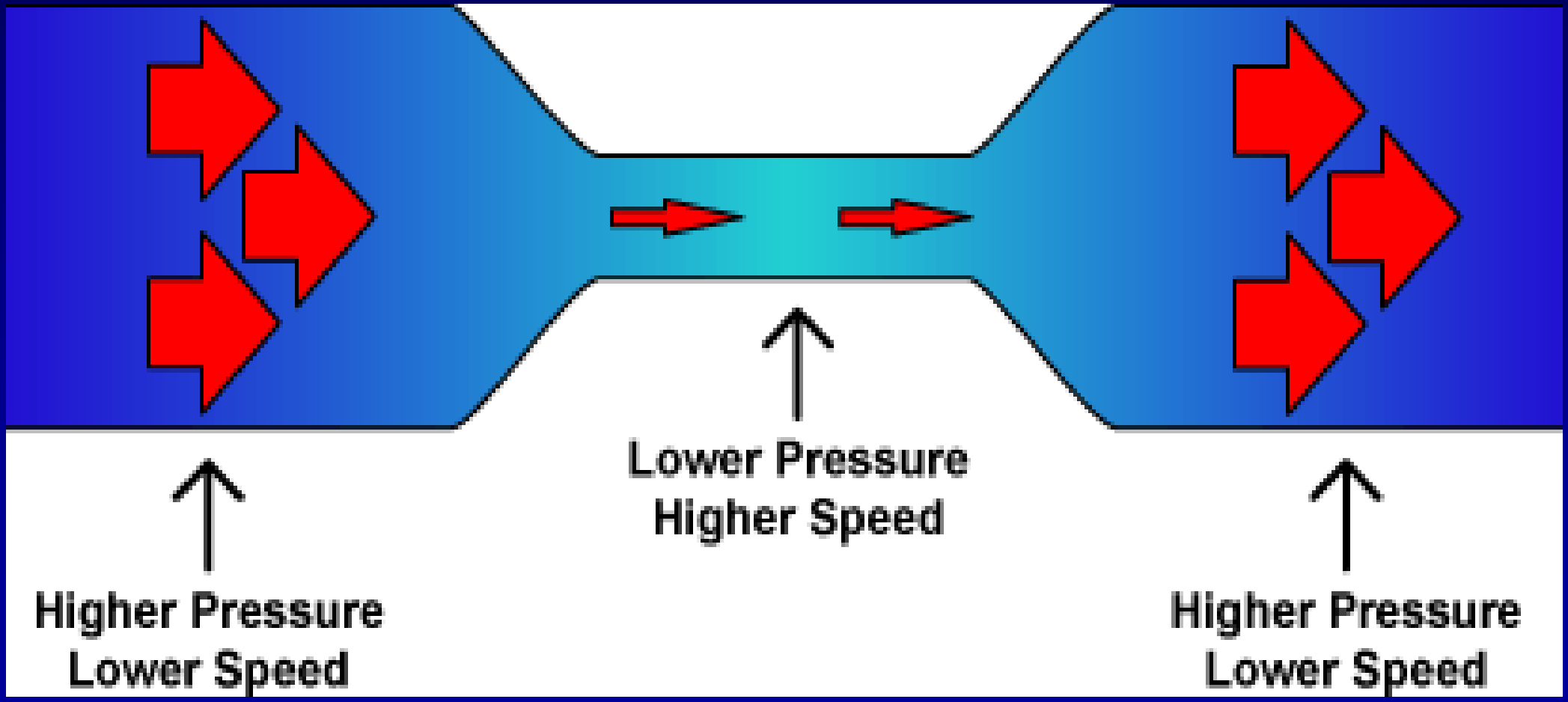
Patient on ventilator: Calculating the PO2

Boiling water



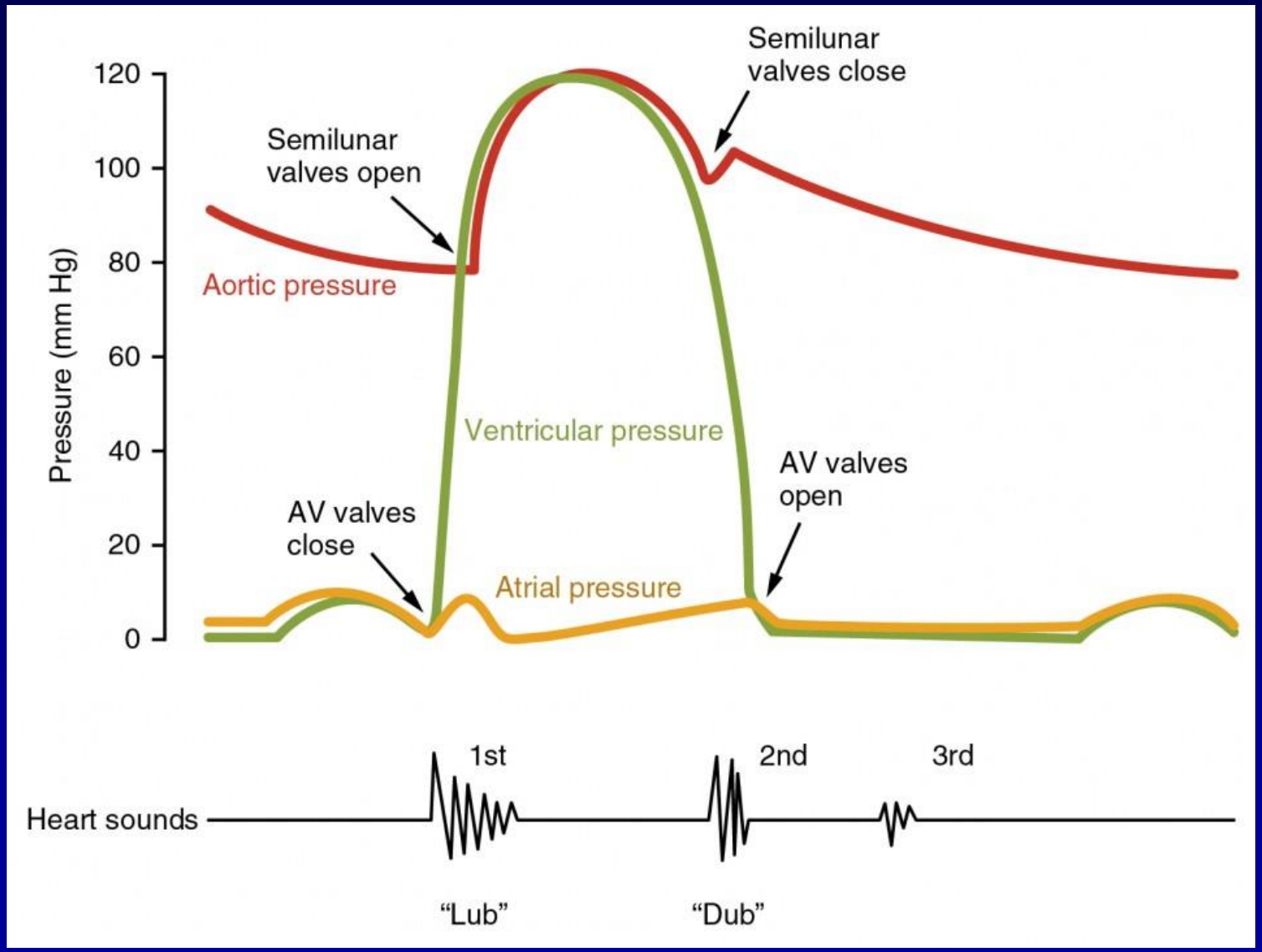


Correlation between Pressure and Speed according to the Conservation of Energy (Bernoulli's) Equation



Watering the lawn

Where can we find change in pressure?



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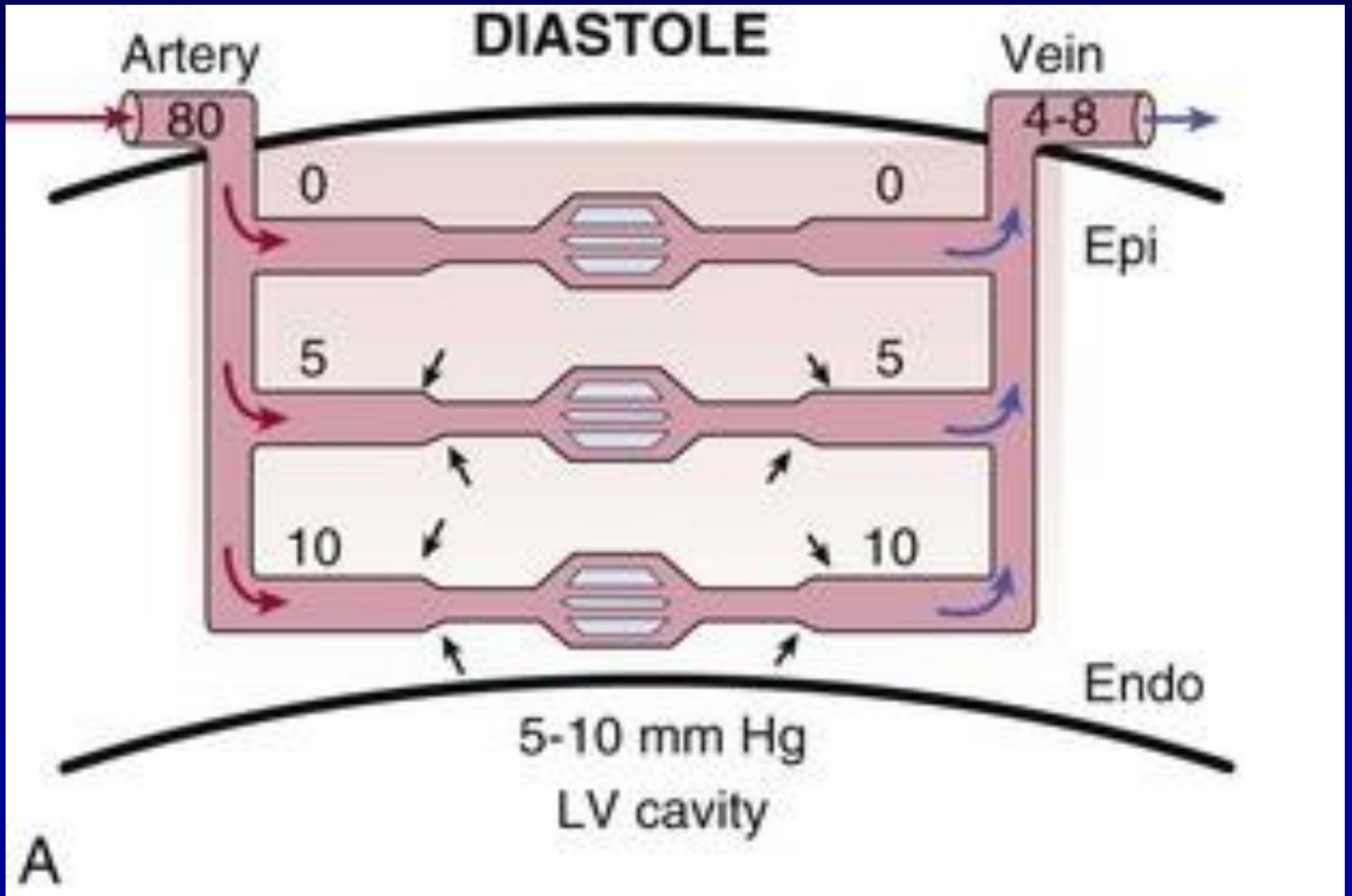
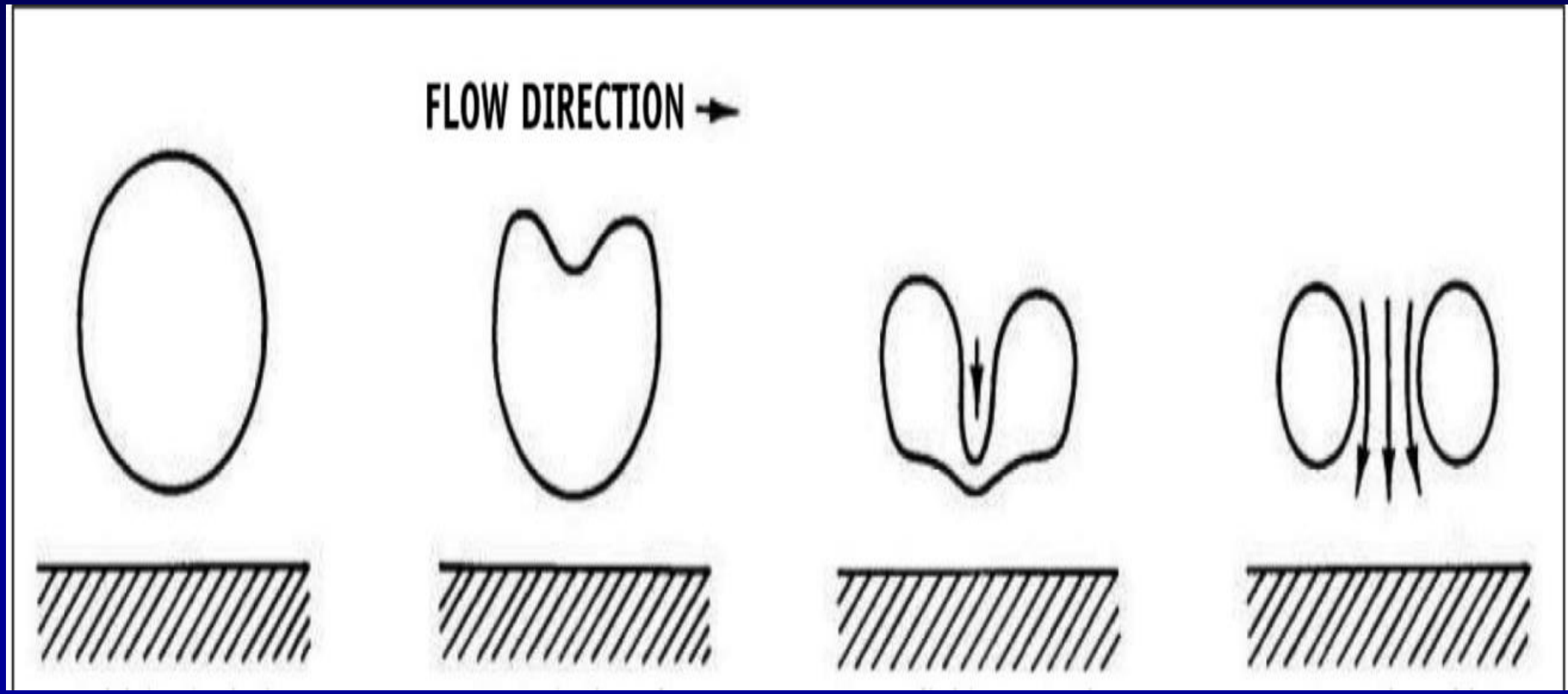


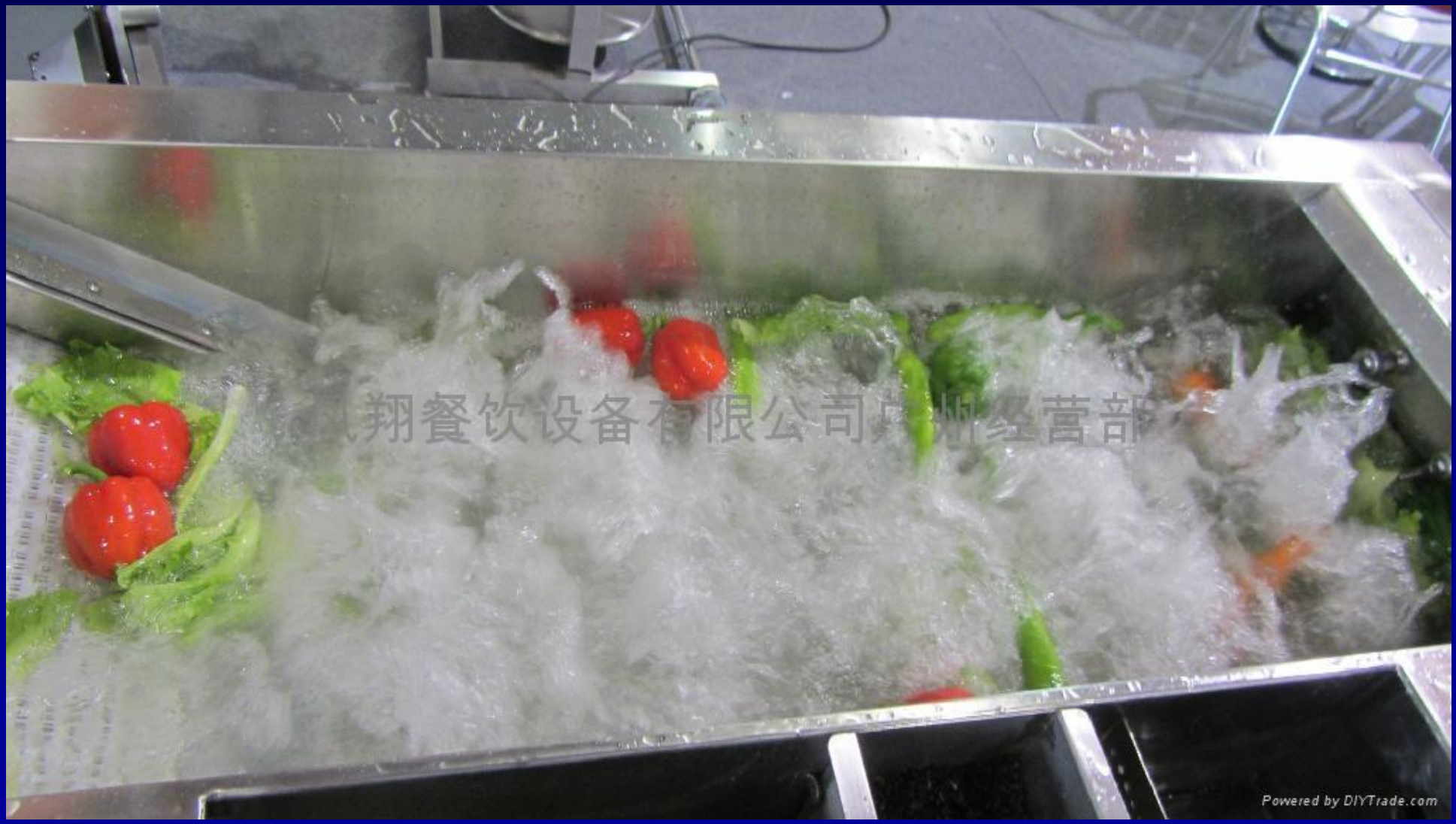
Bubble Ruptures Cause Microjet



Real Life Observations

How does the meat become tender?

Washing vegetable with bubbles



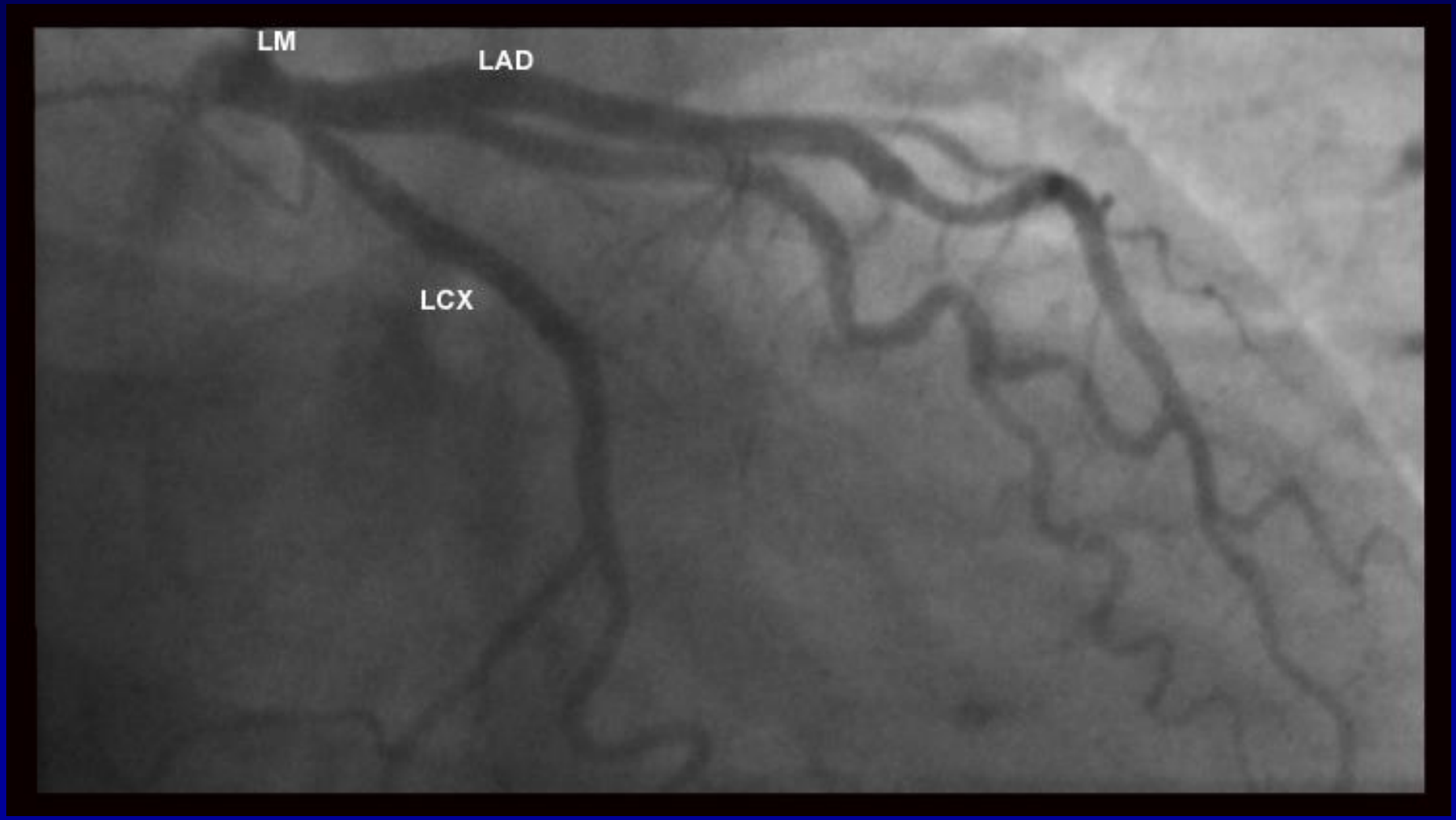
SUMMARY 1

1. Air is diluted in blood
2. Change of pressure, air forms bubbles
3. Bubbles rupture causes damage

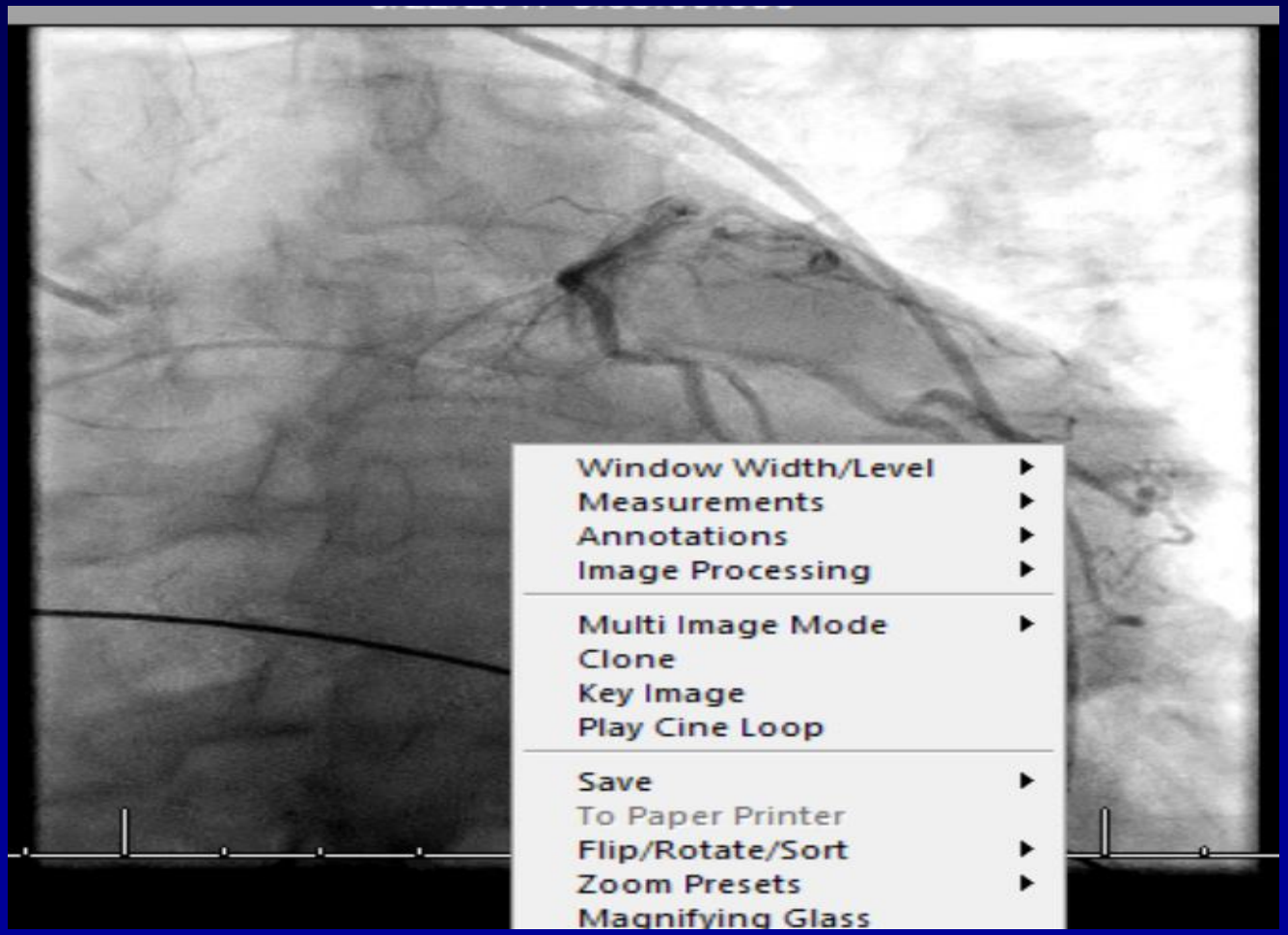
QUESTION 2

Where is the mechanical injury?

New Method of Recording Angigoram



Methods

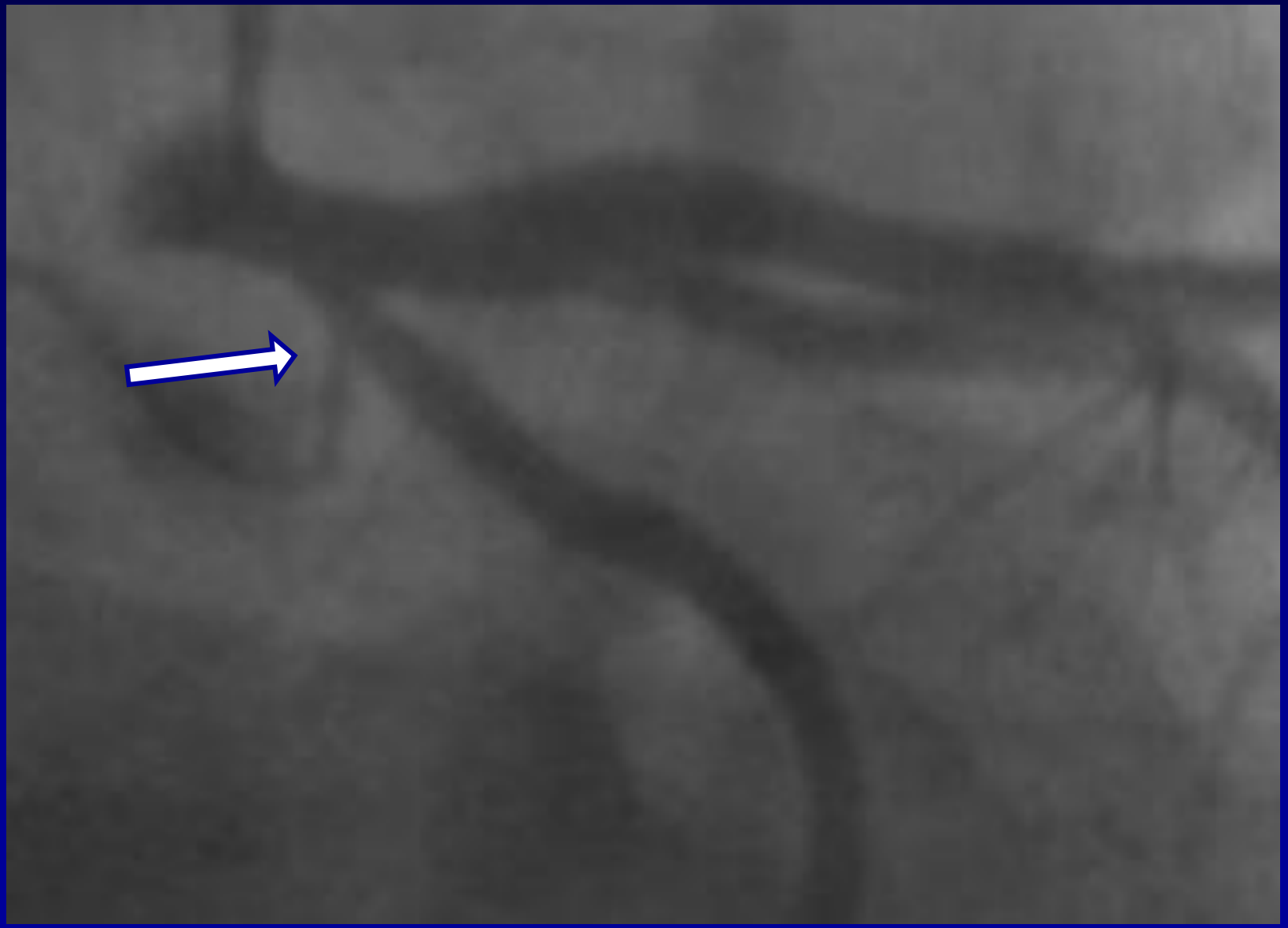


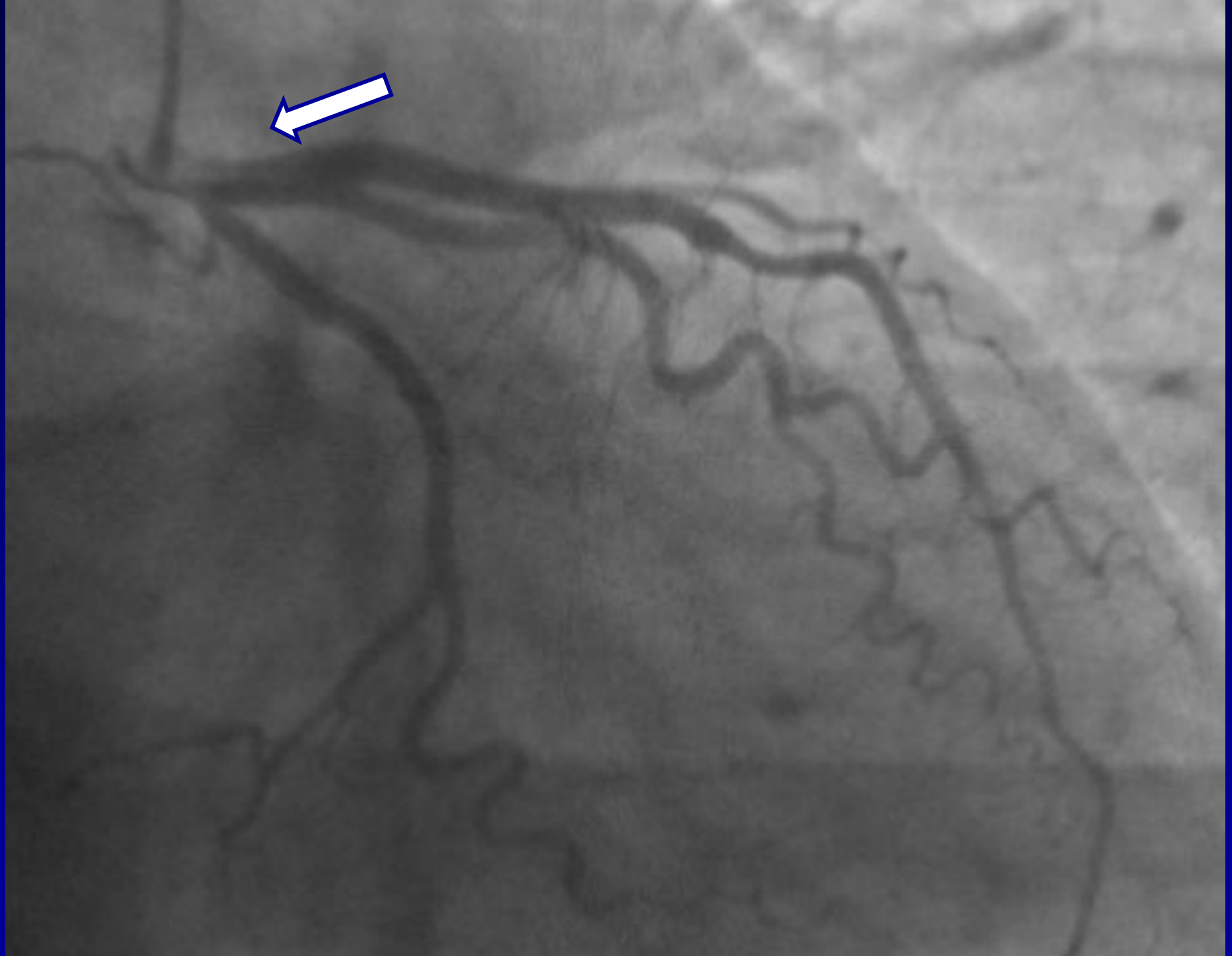
To review the coronary angiogram frame by frame

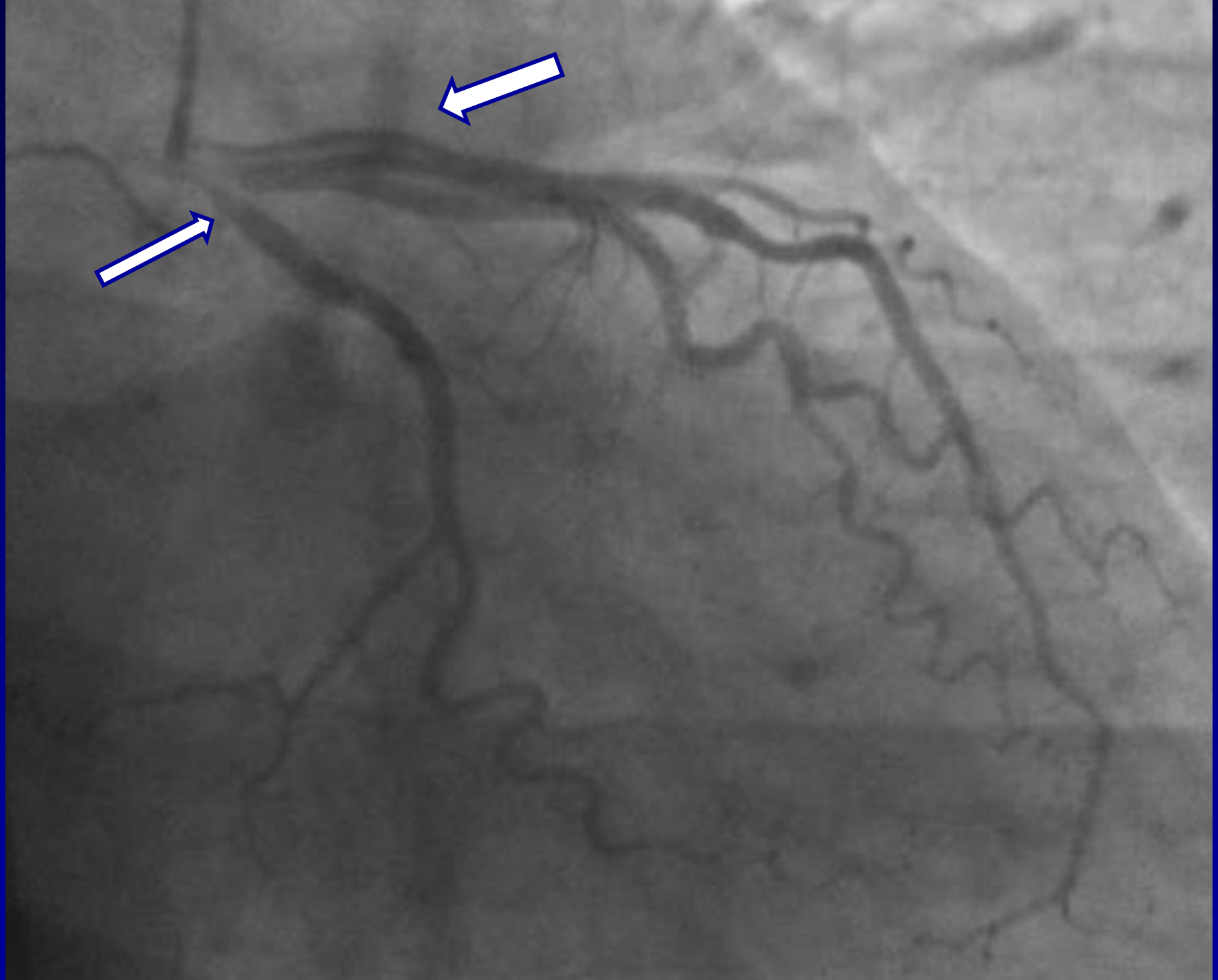
1. Right click
2. Select Key Image option,
3. Use the up and down arrows to move the picture, one at a time.

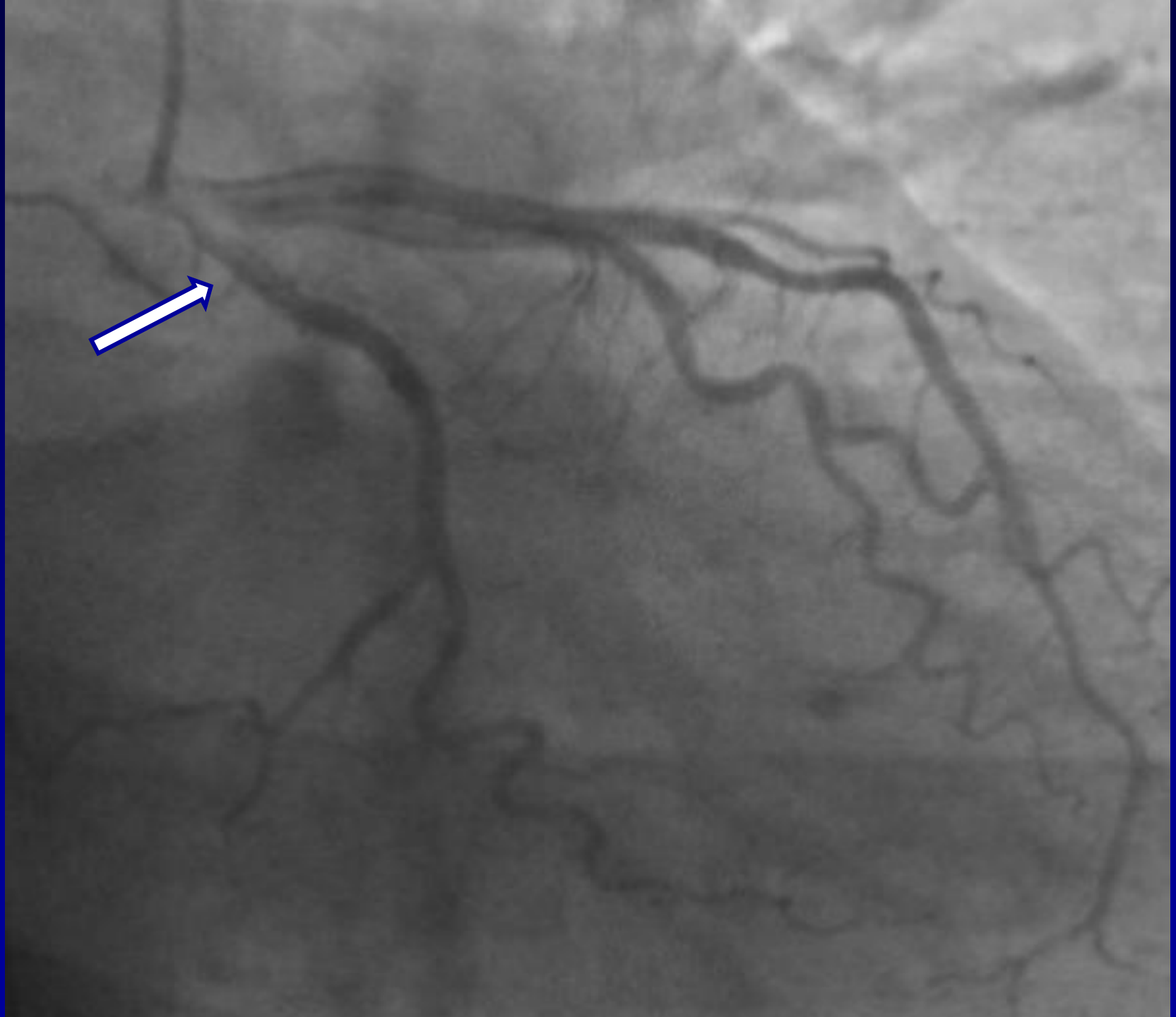
New way of reading angiogram

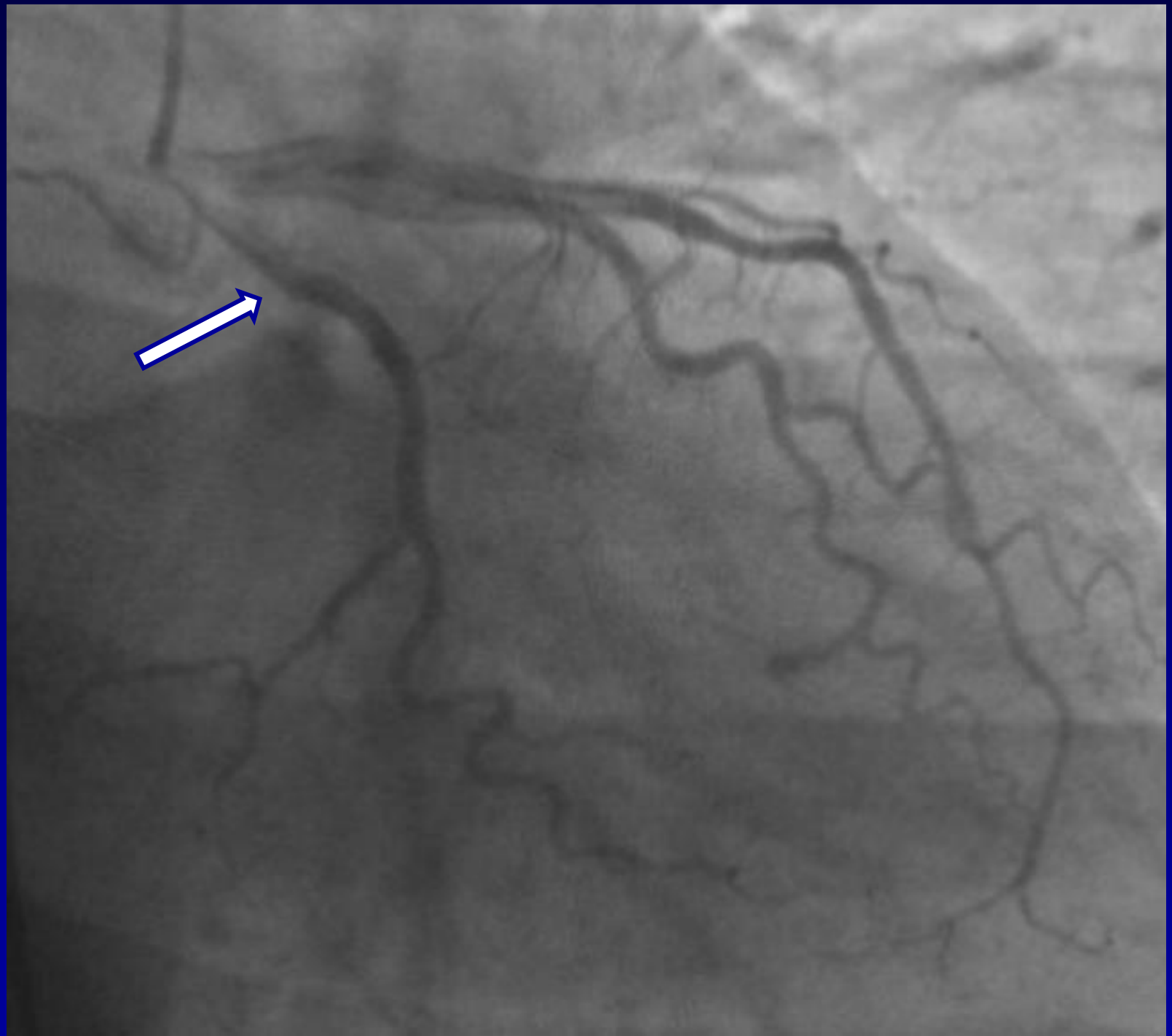
There is a lesion at the ostium LCX

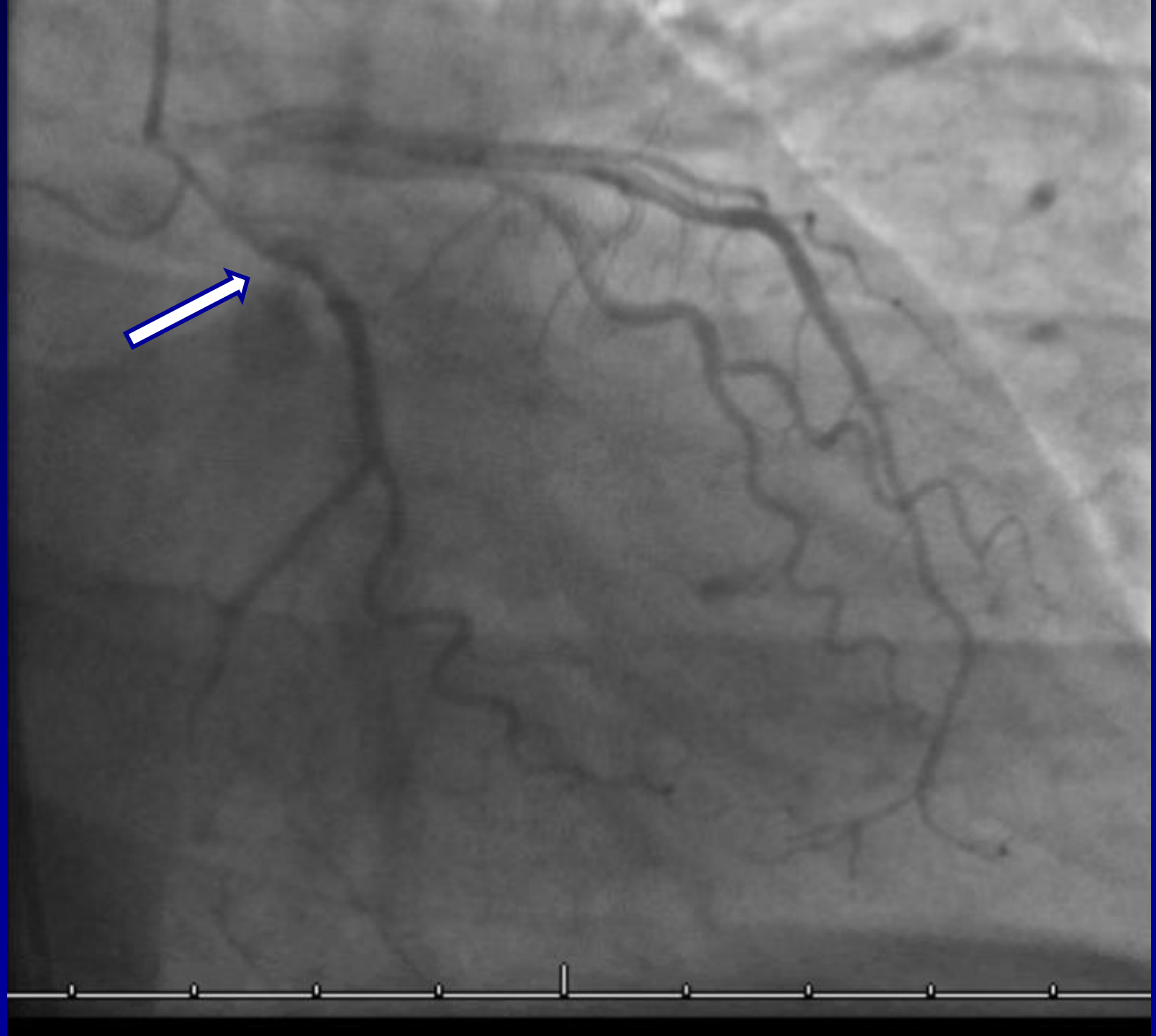


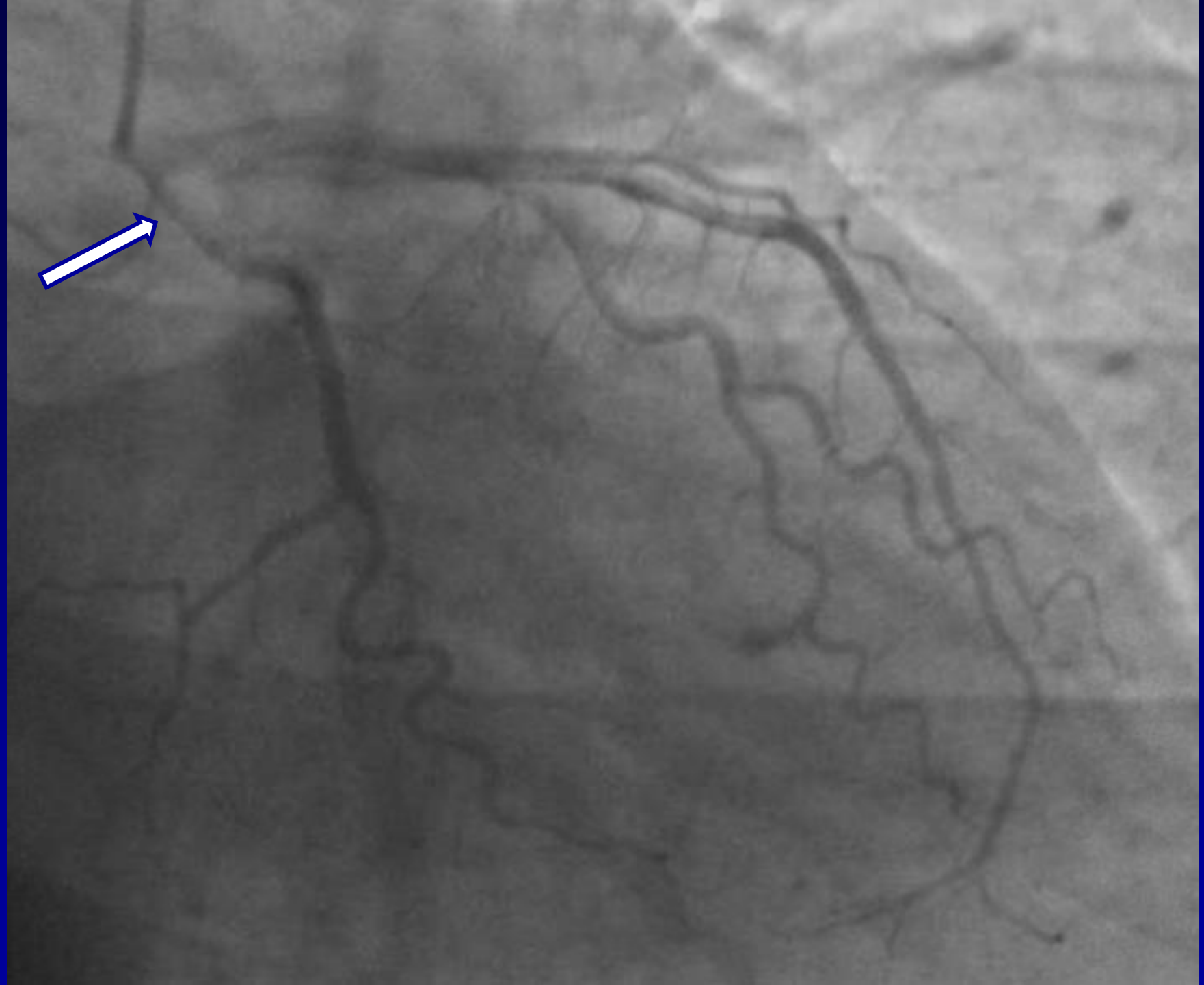


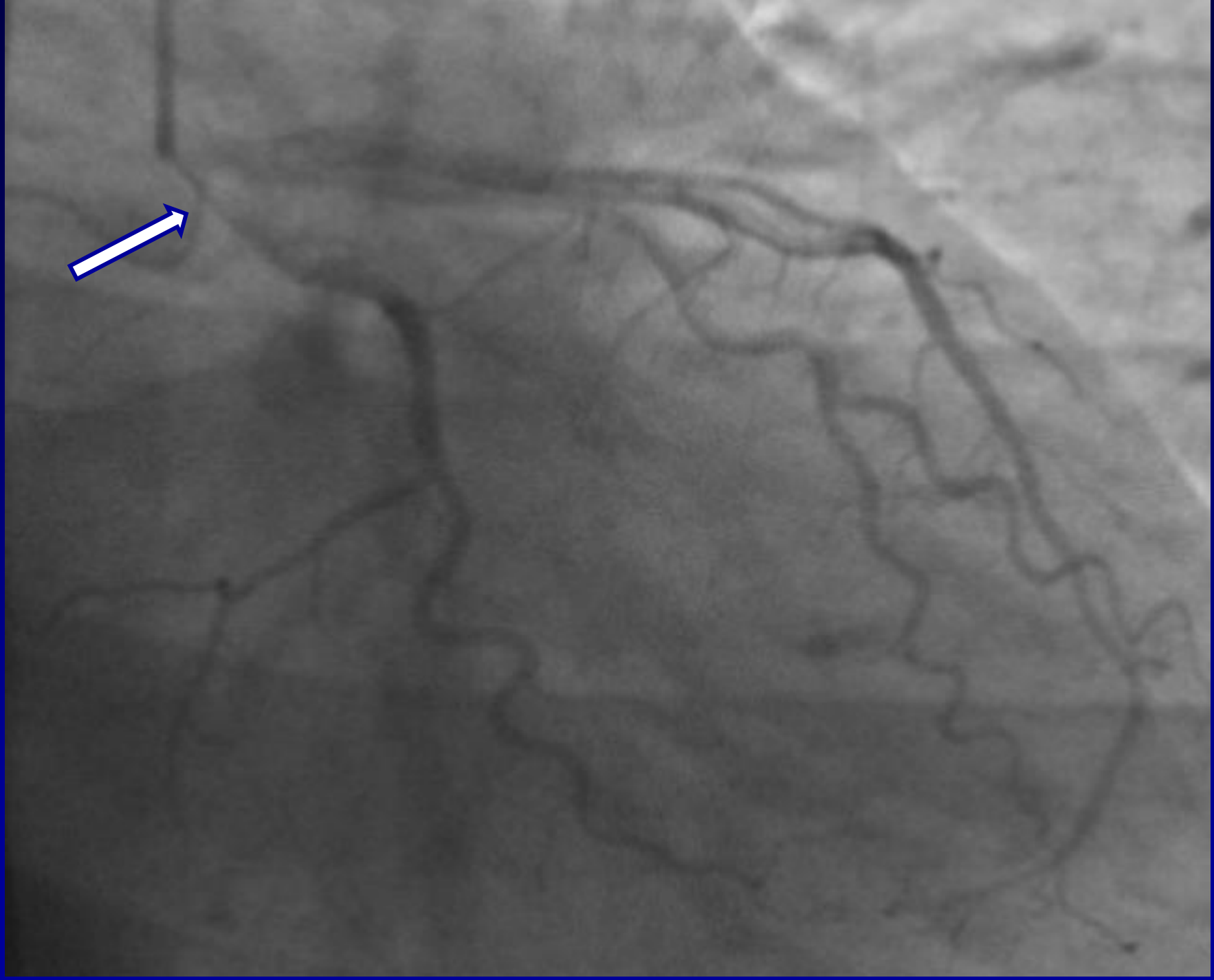


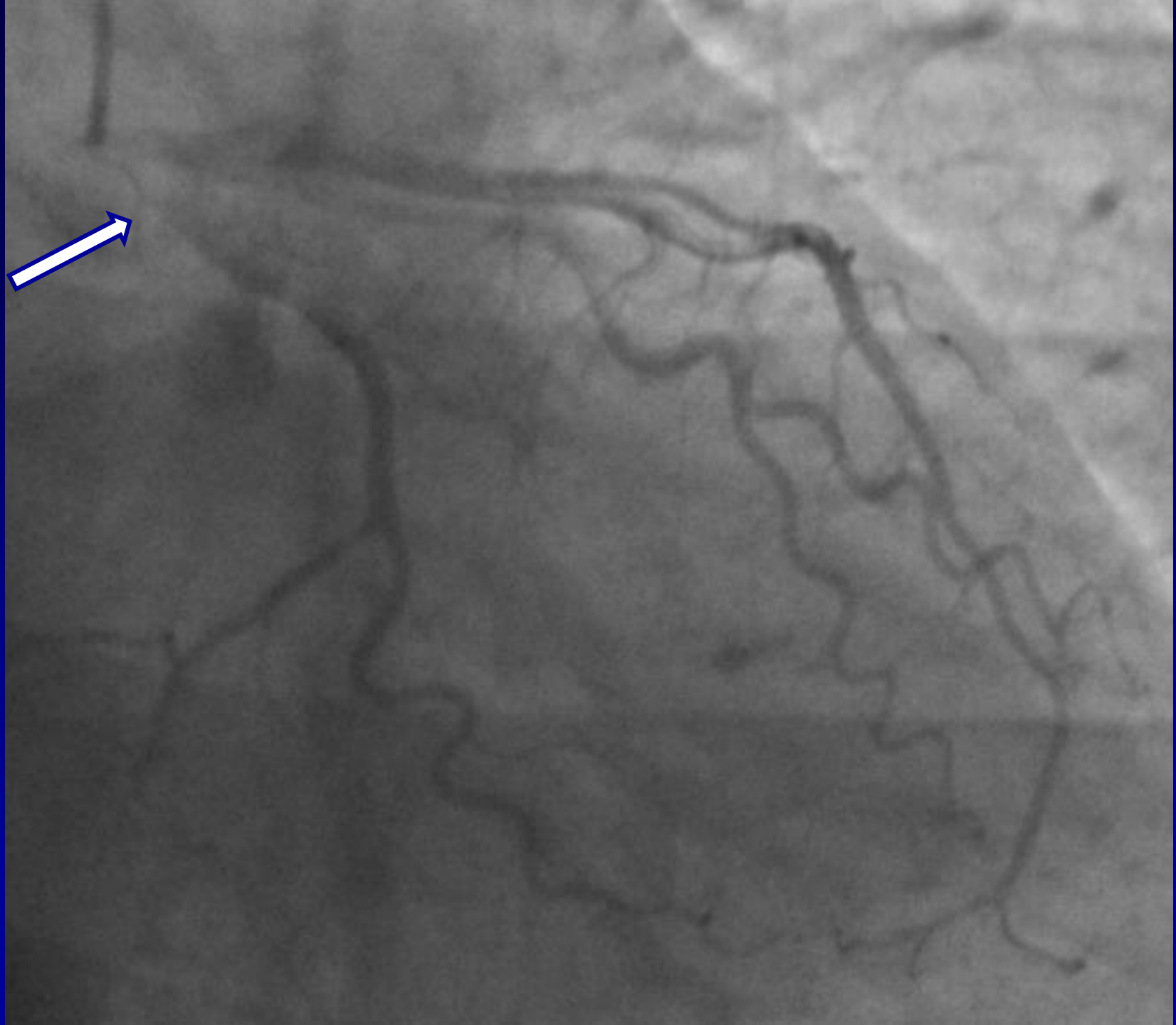


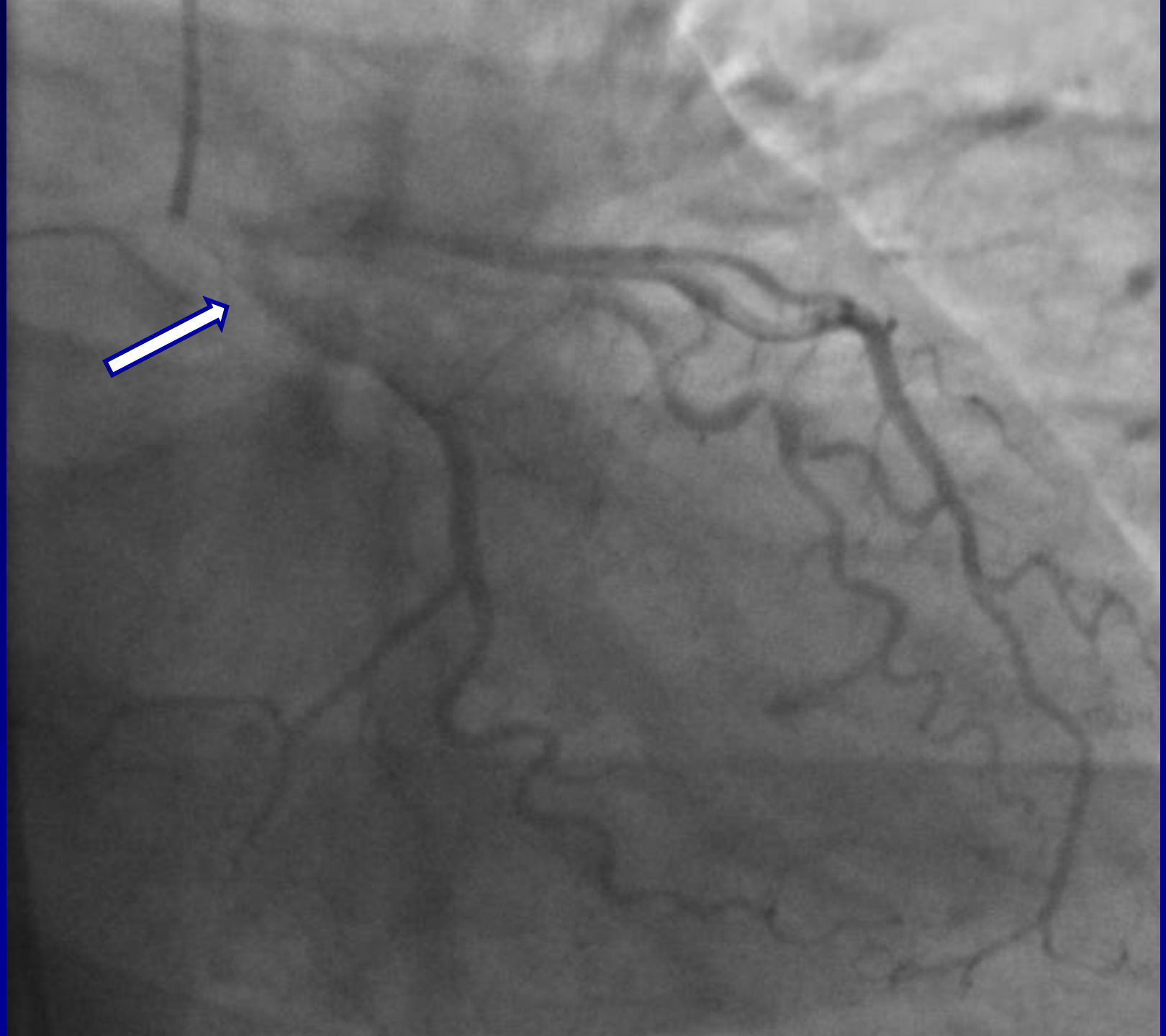


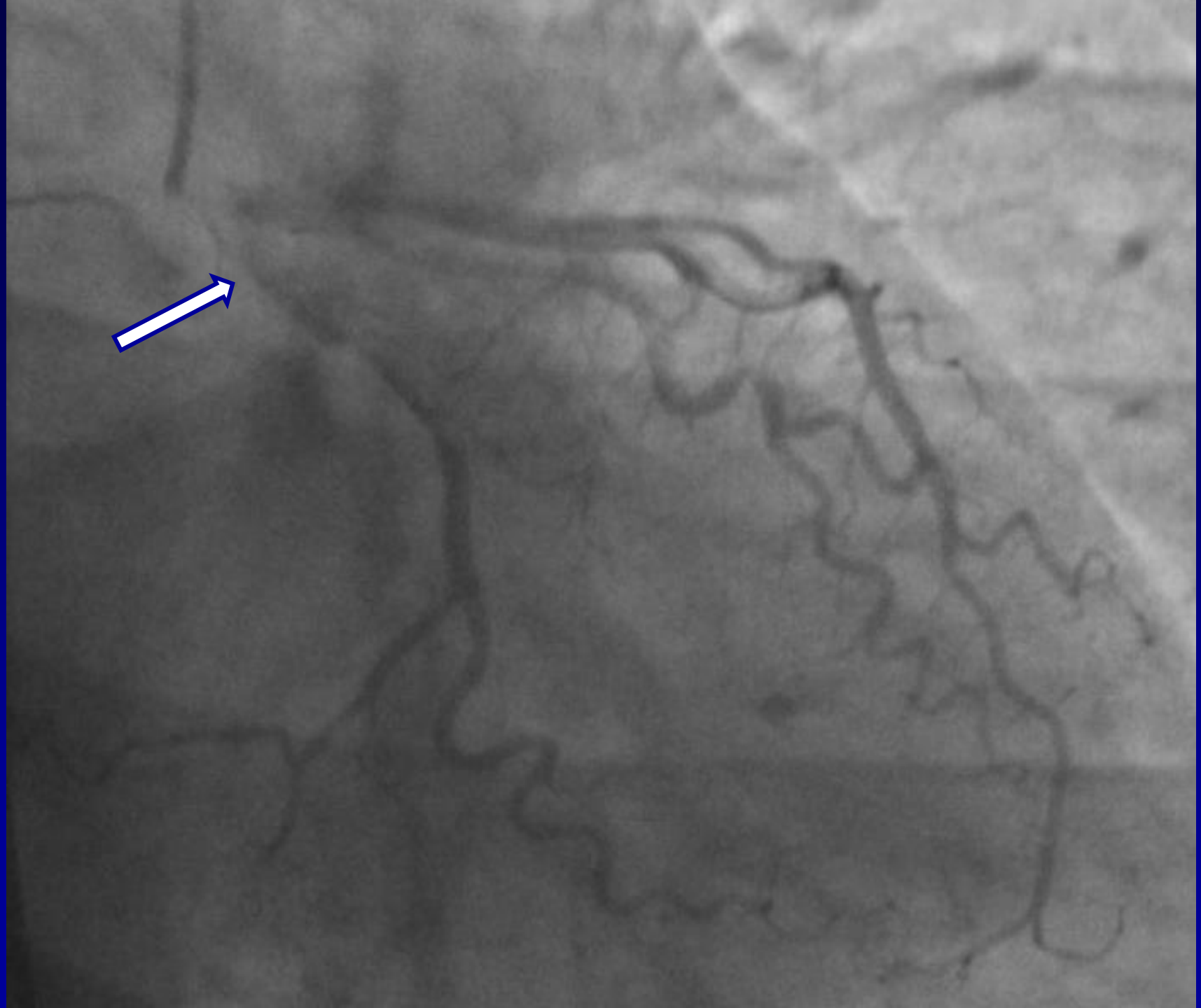


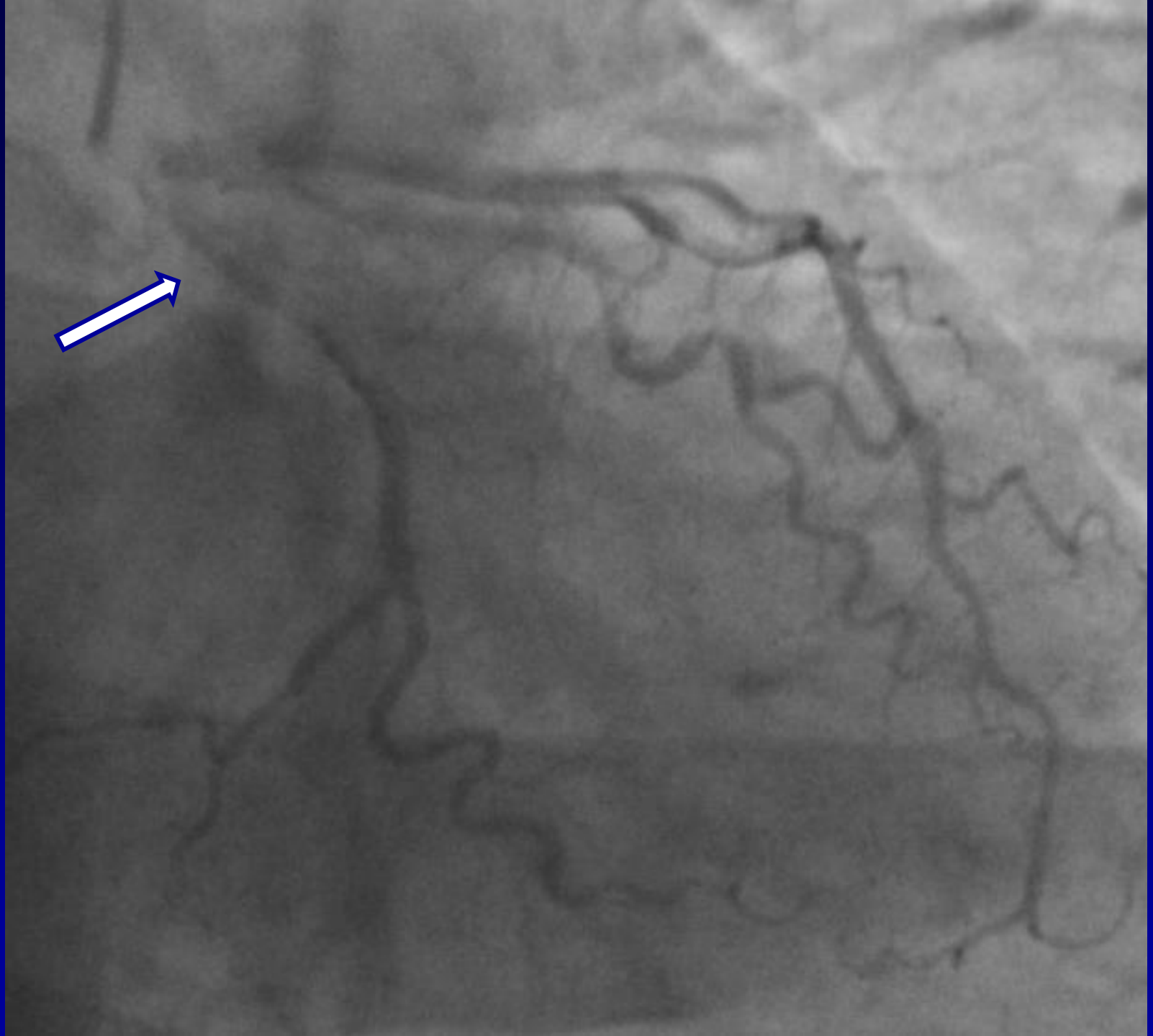


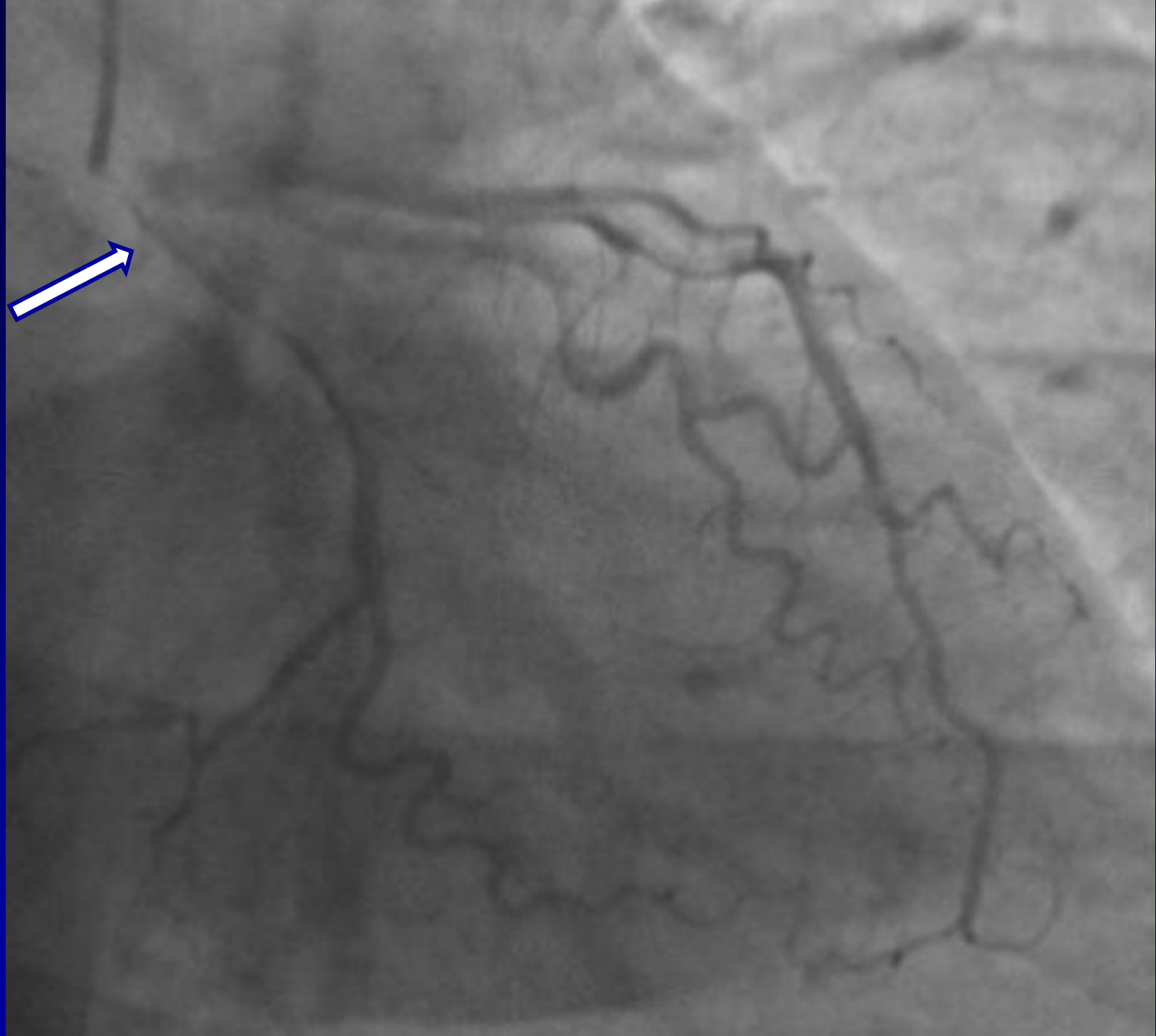


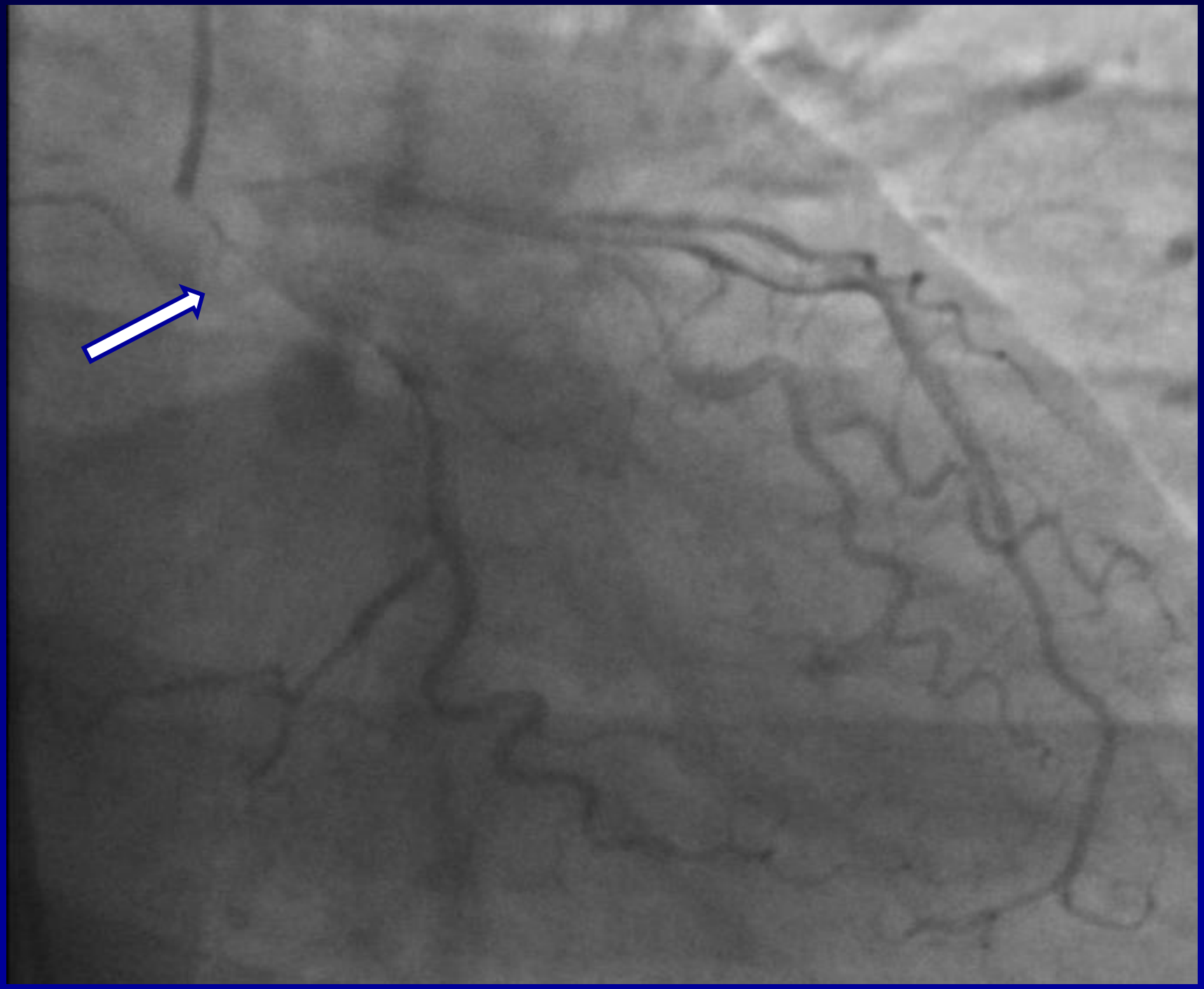


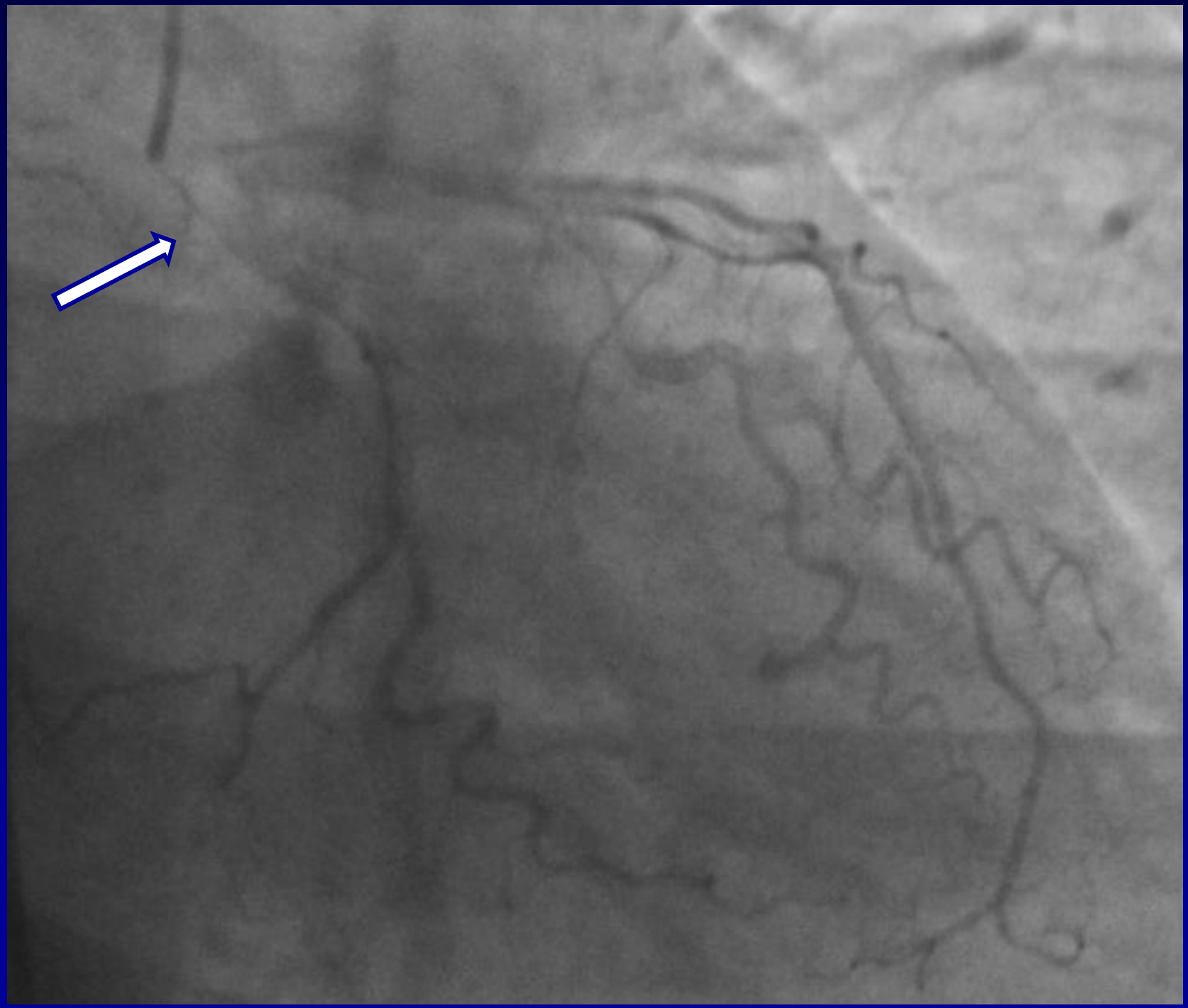


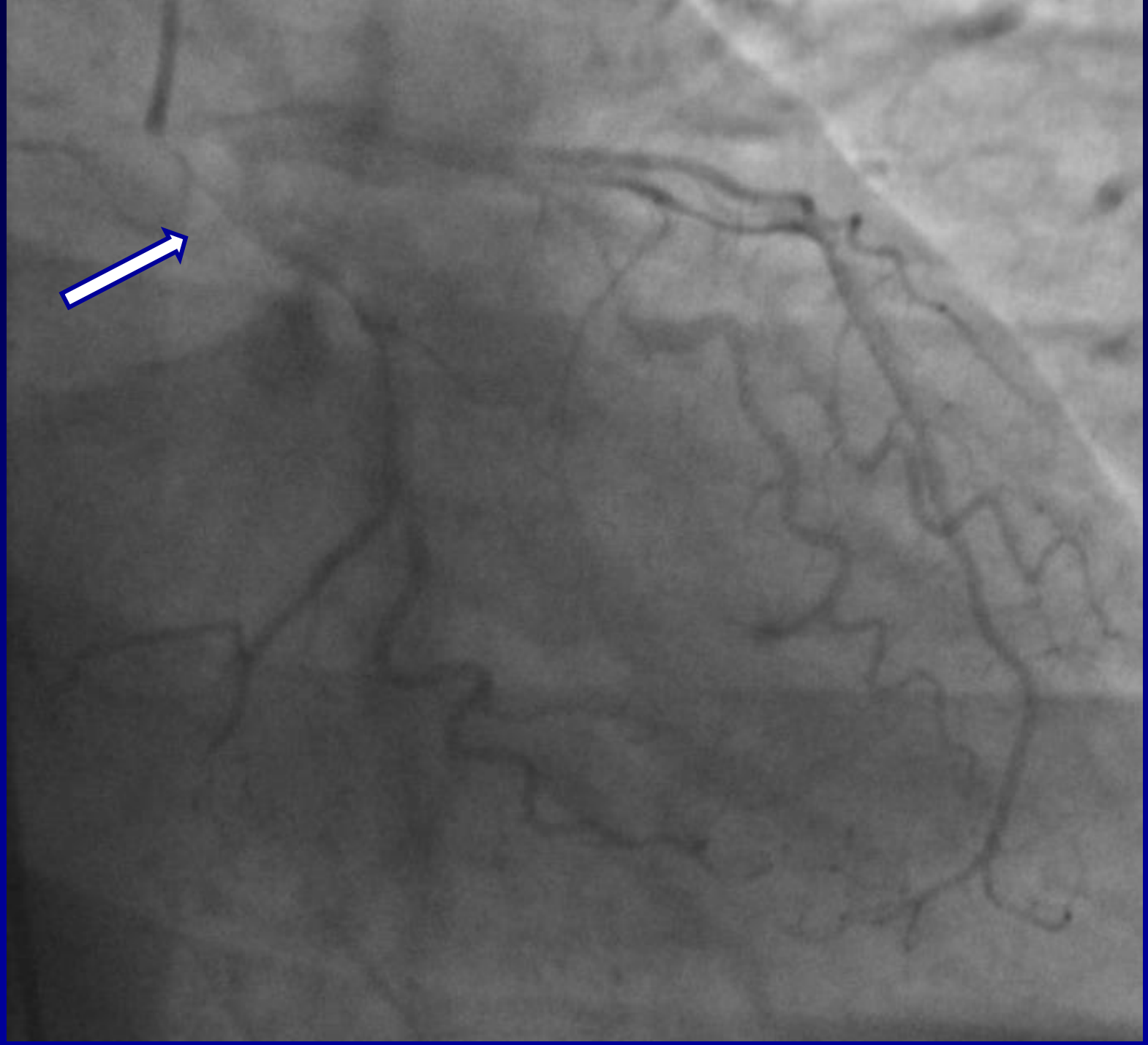


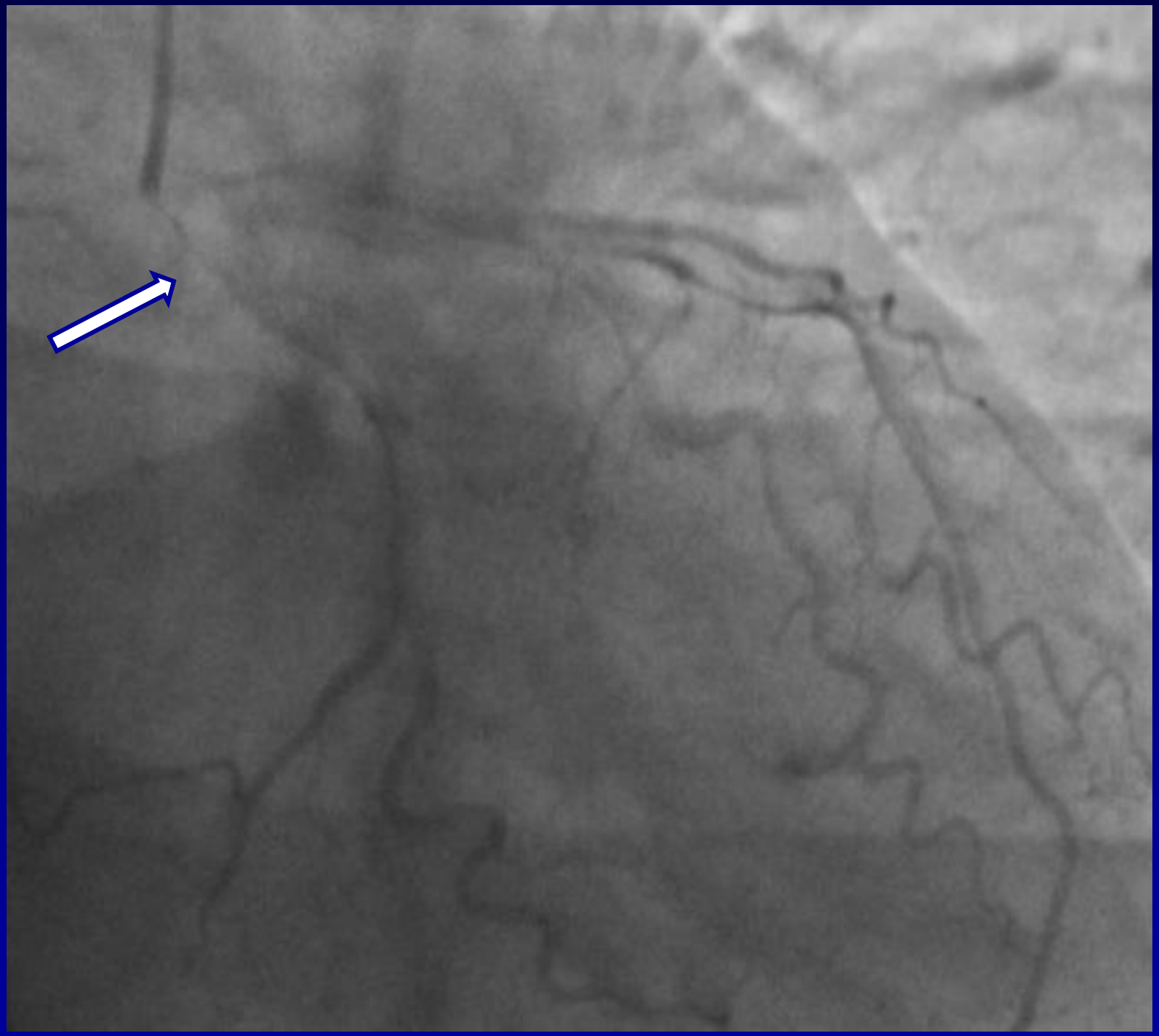


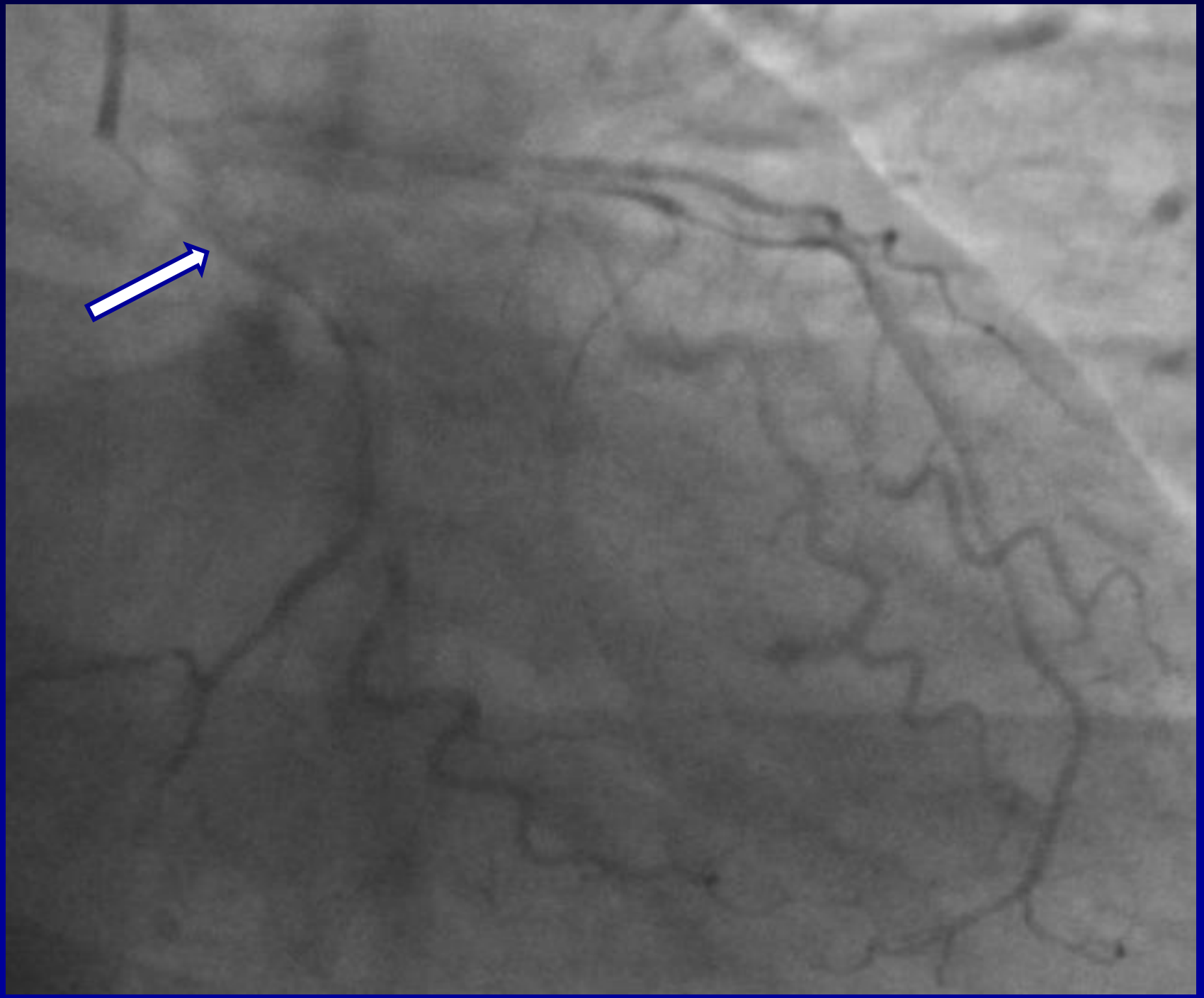


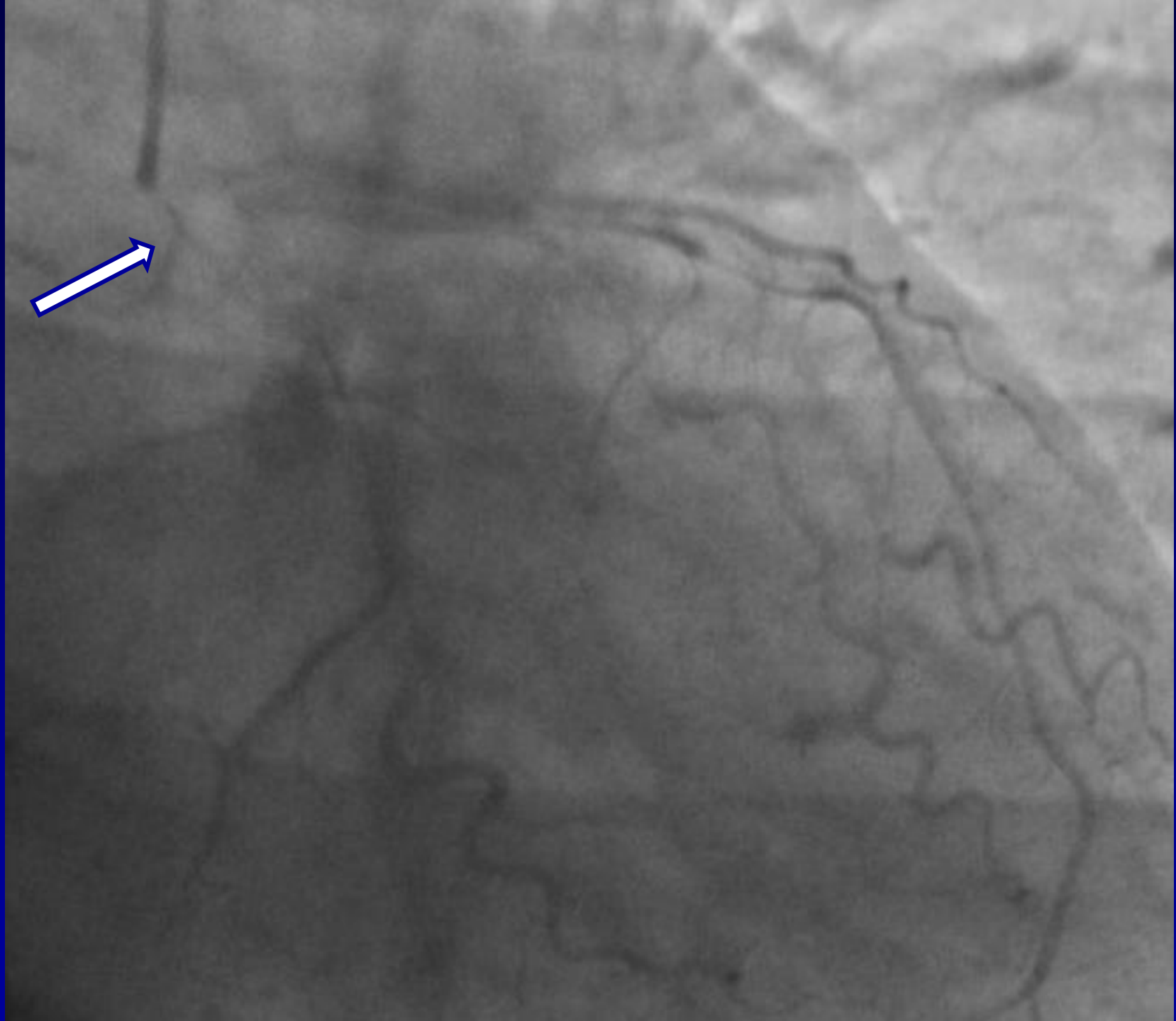


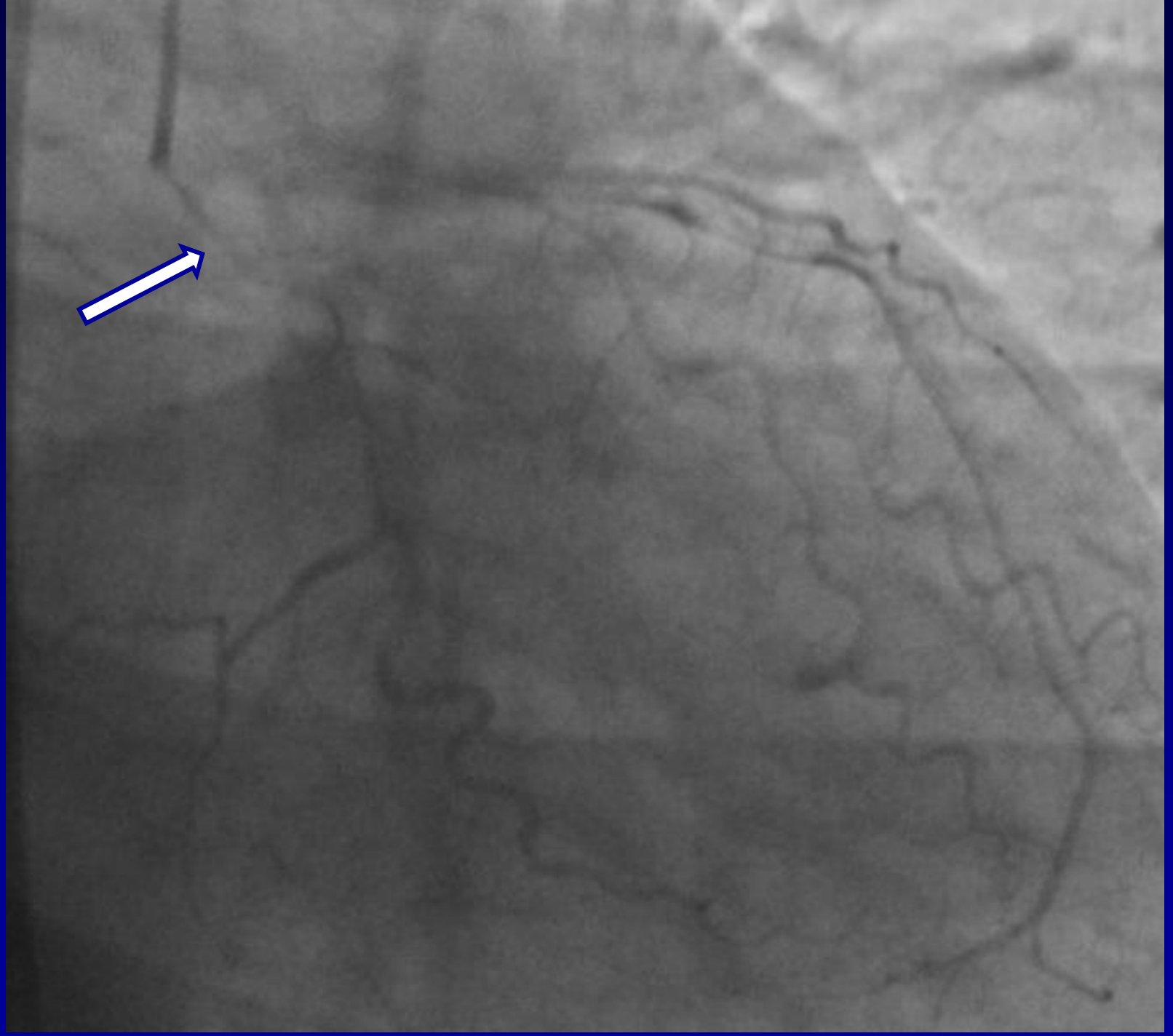


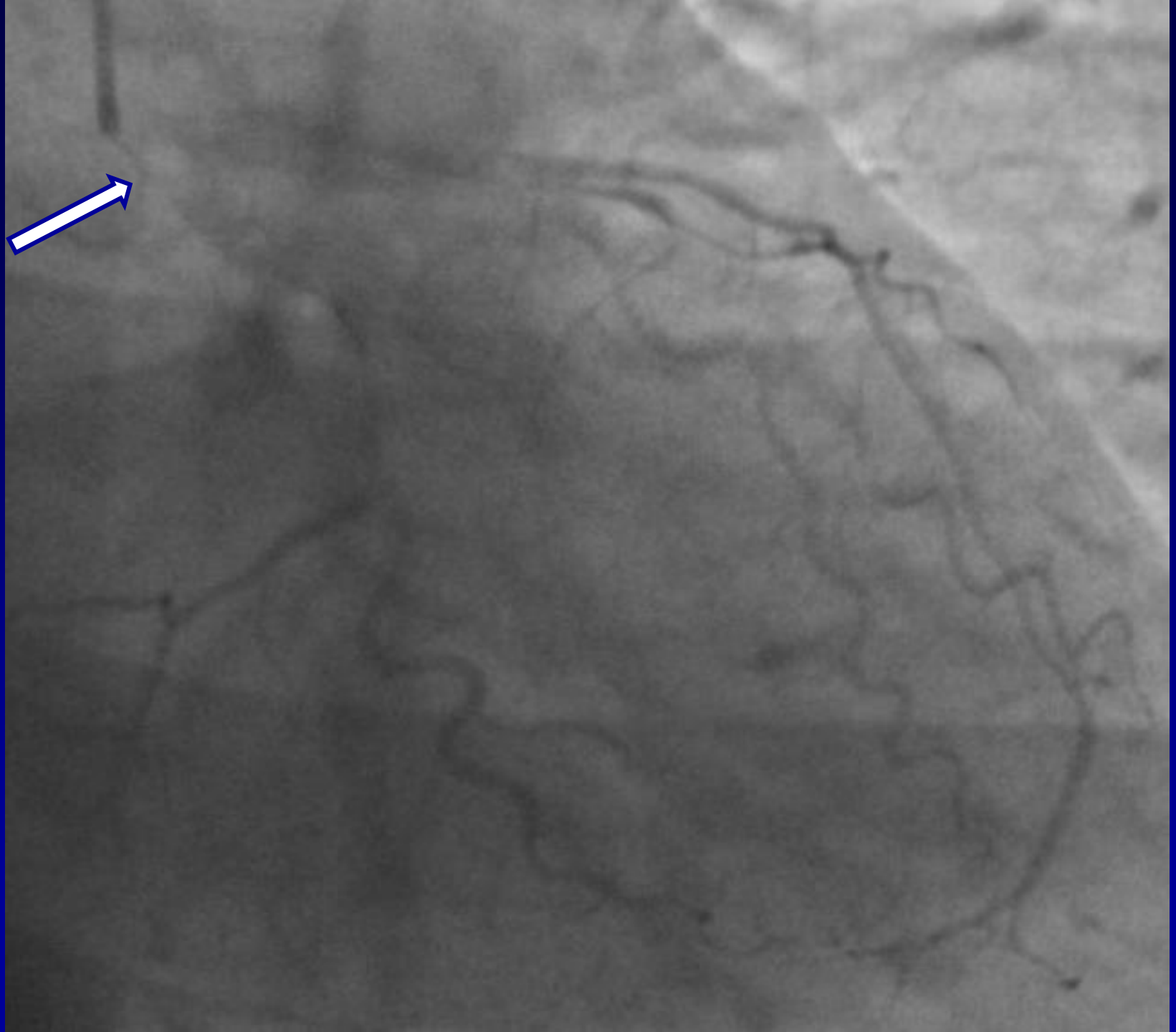






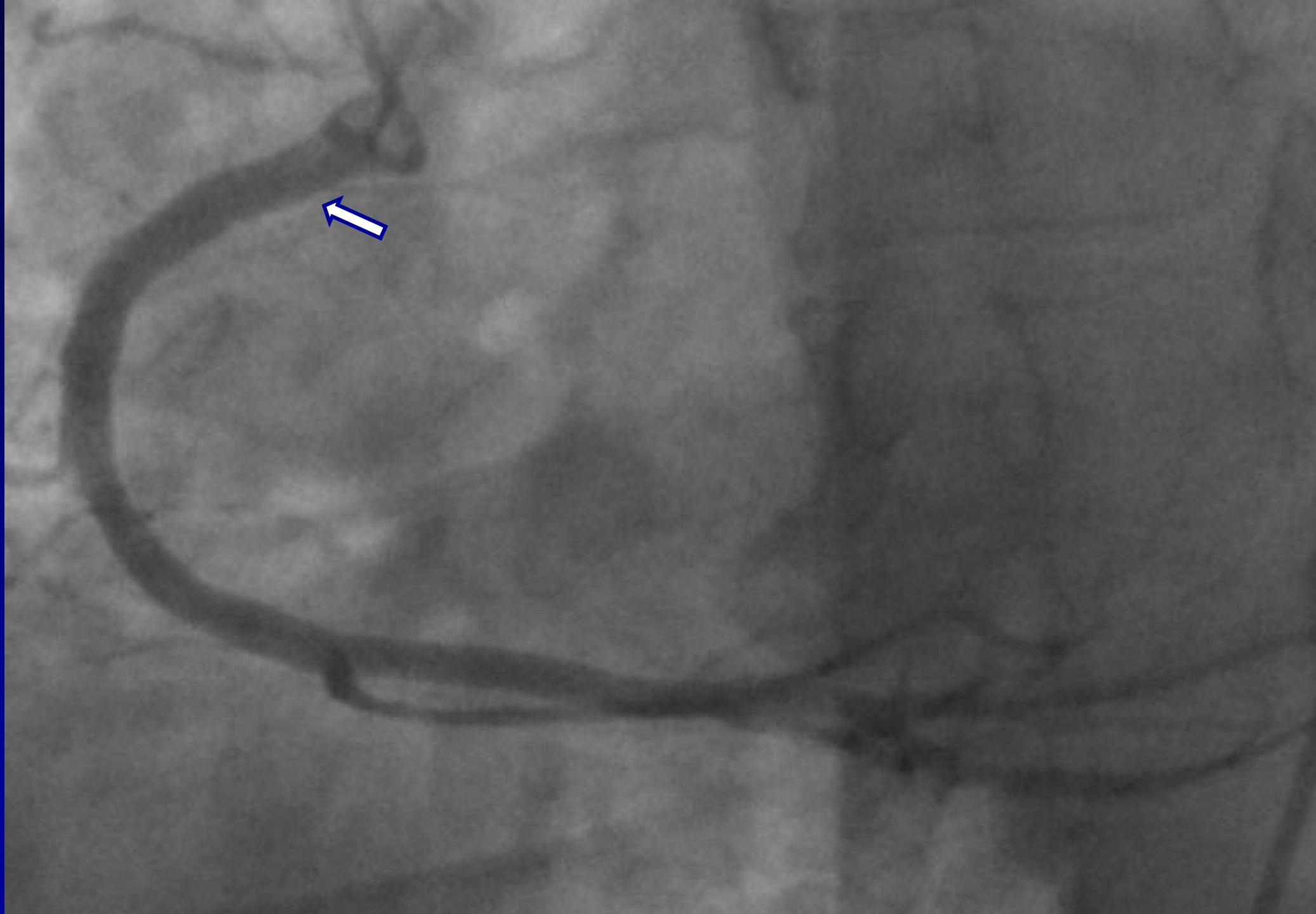


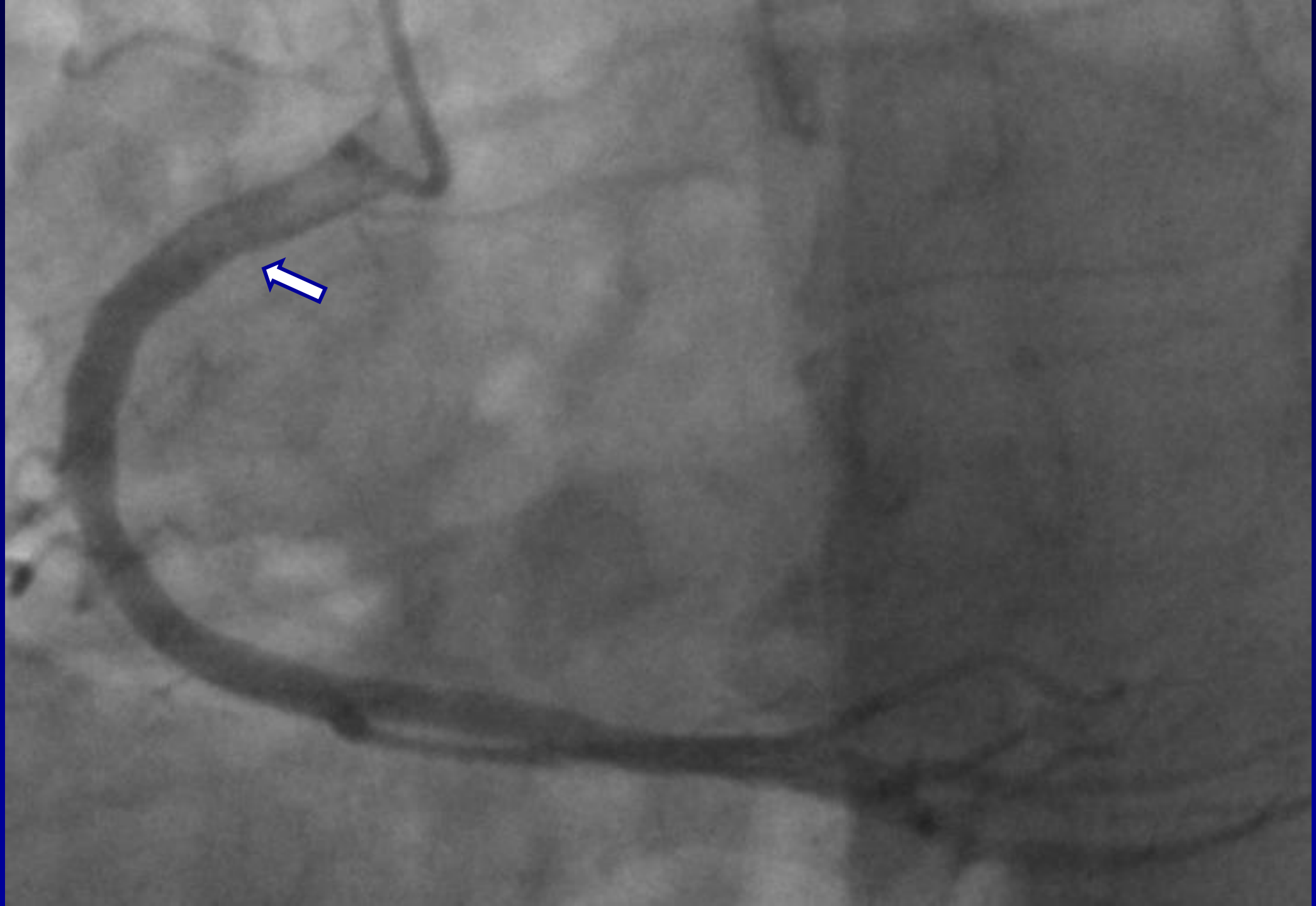


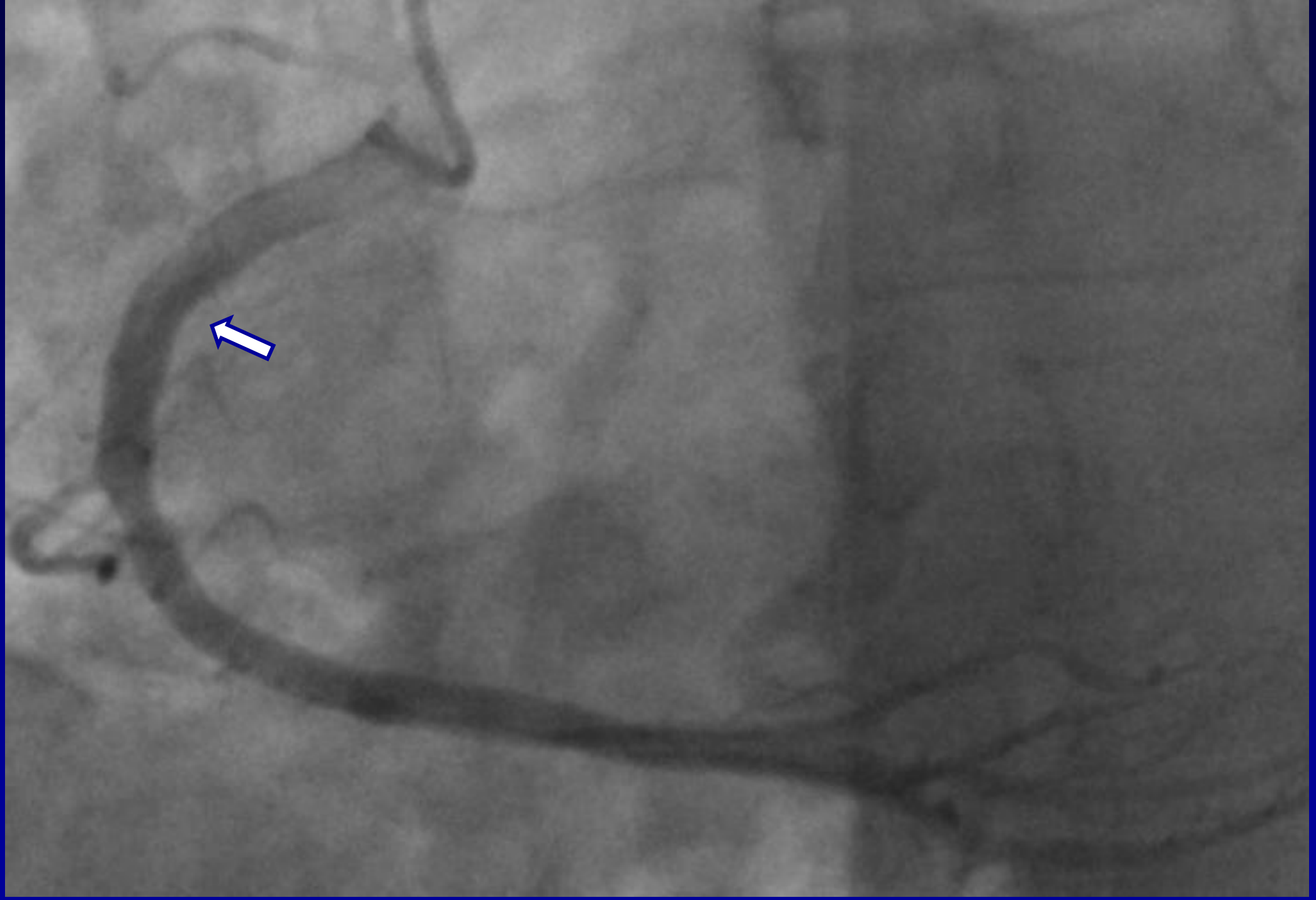


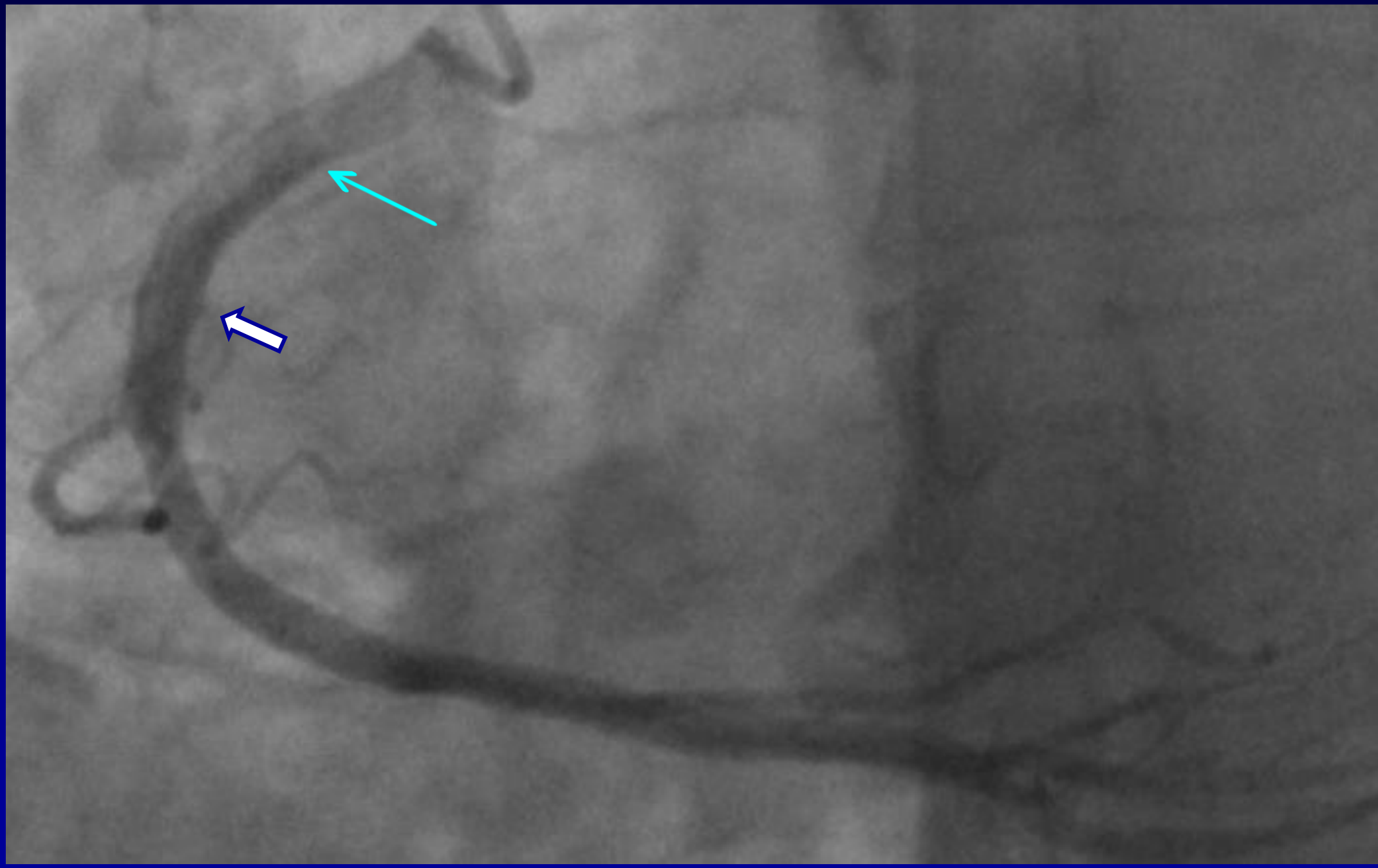
Background 2

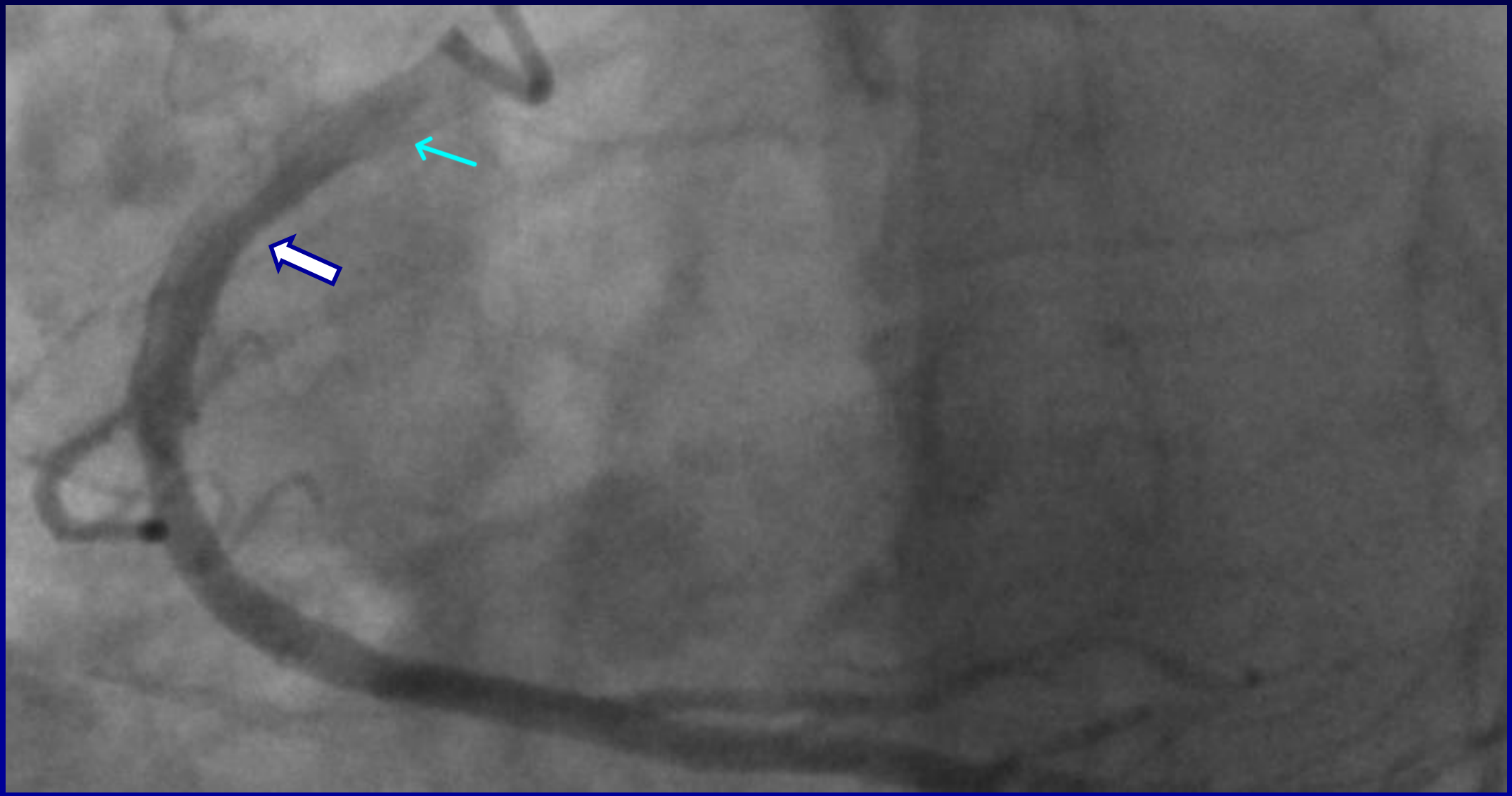
Abnormal flow dynamic = Presence of coronary plaque

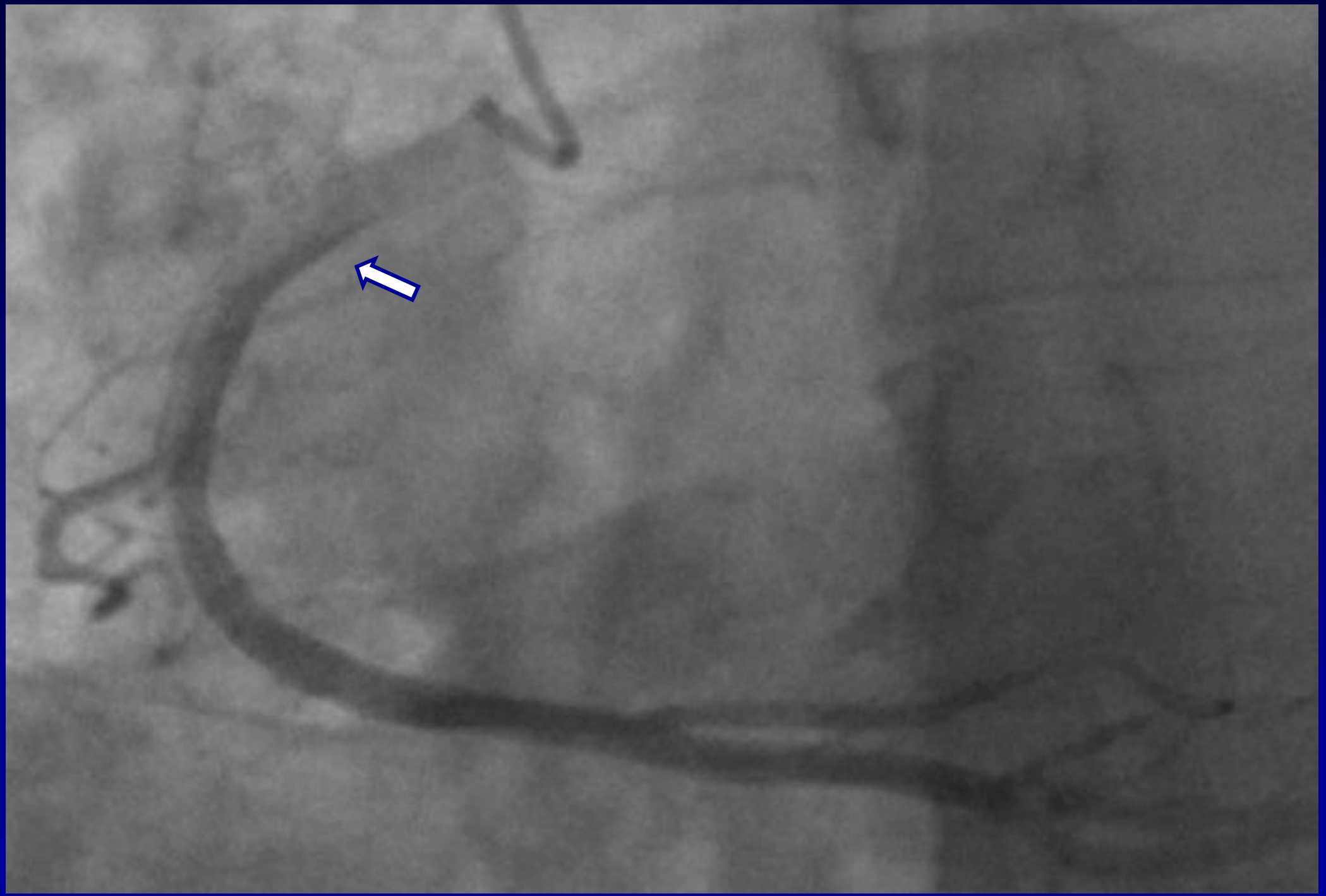


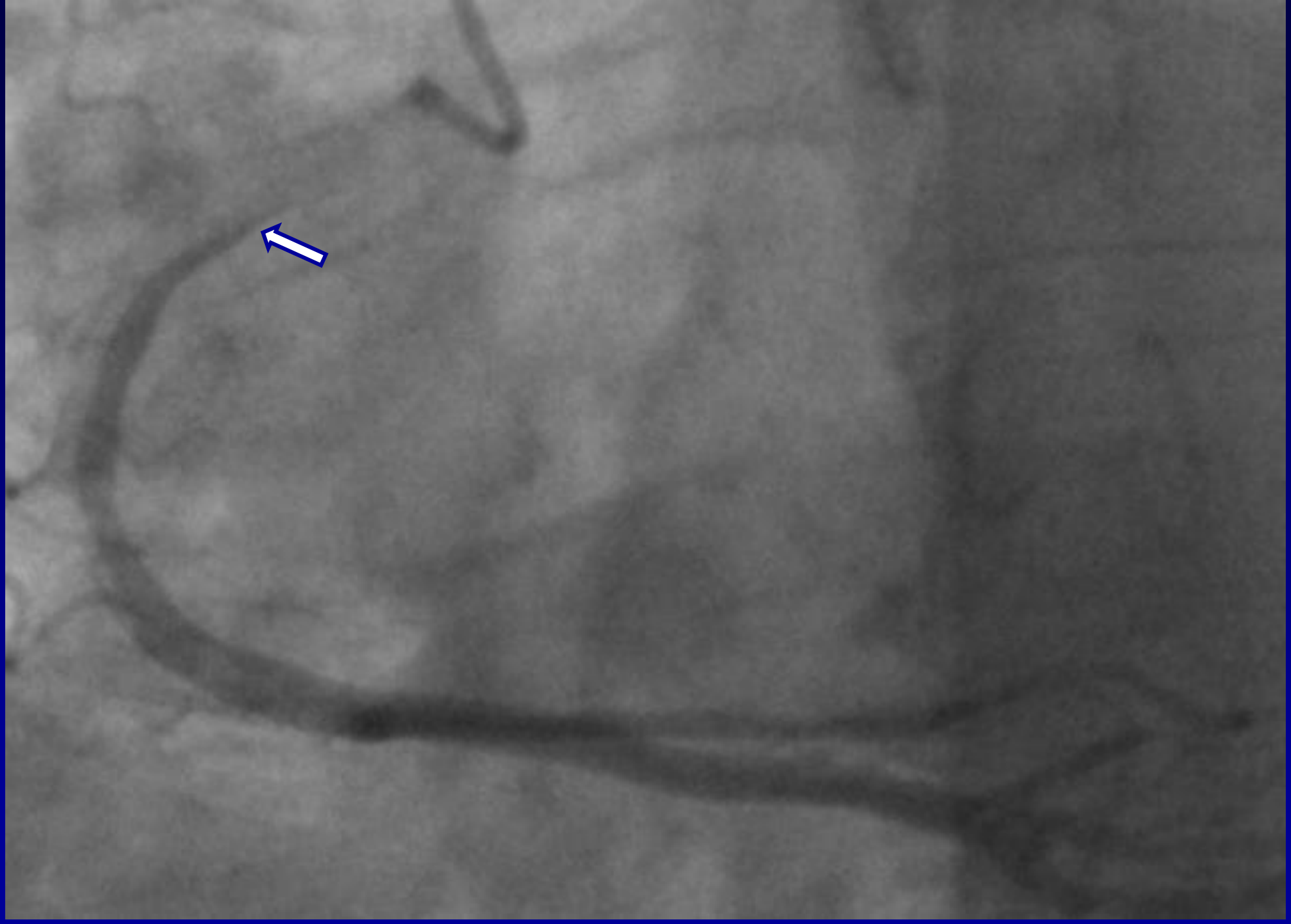


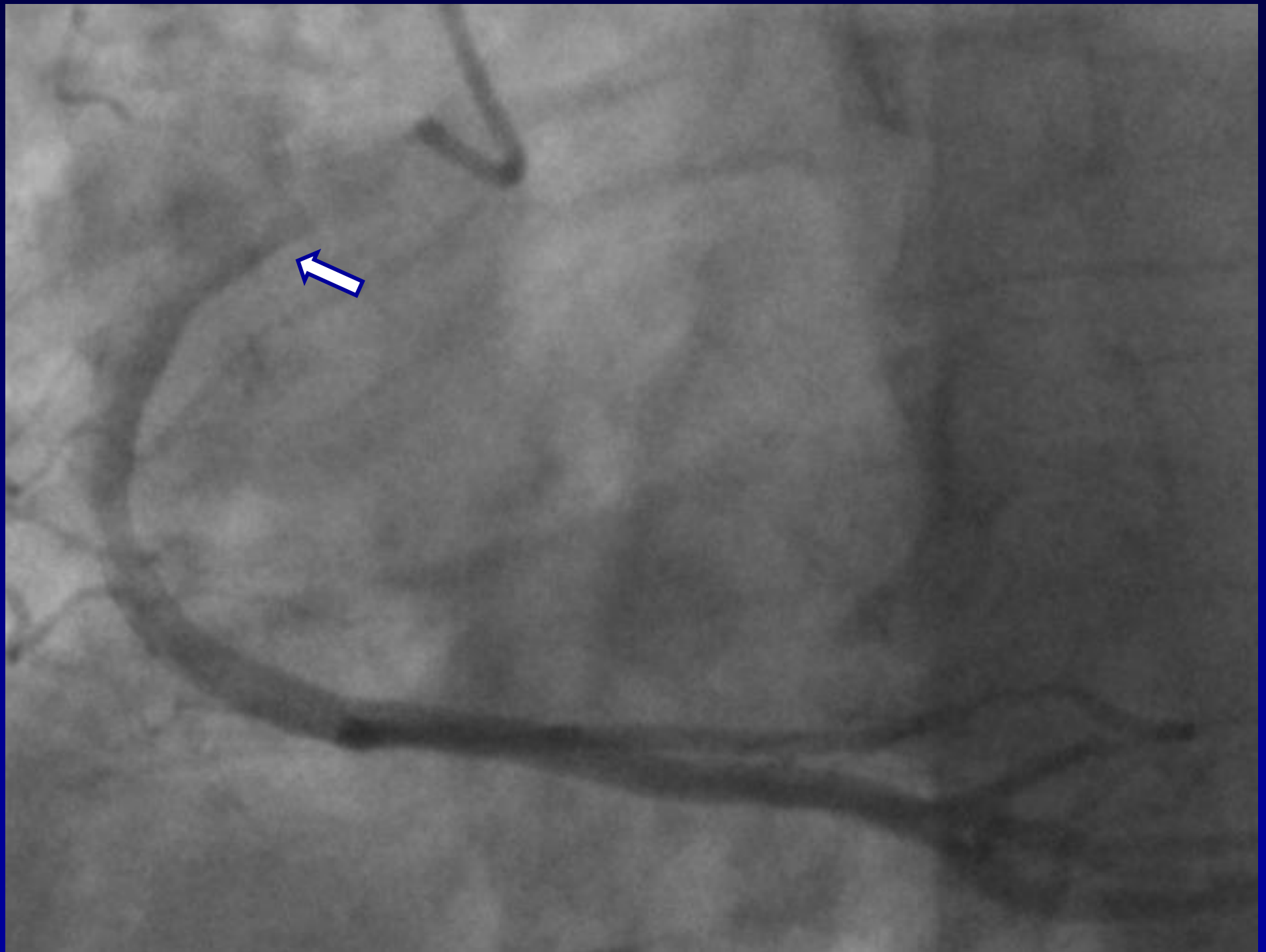


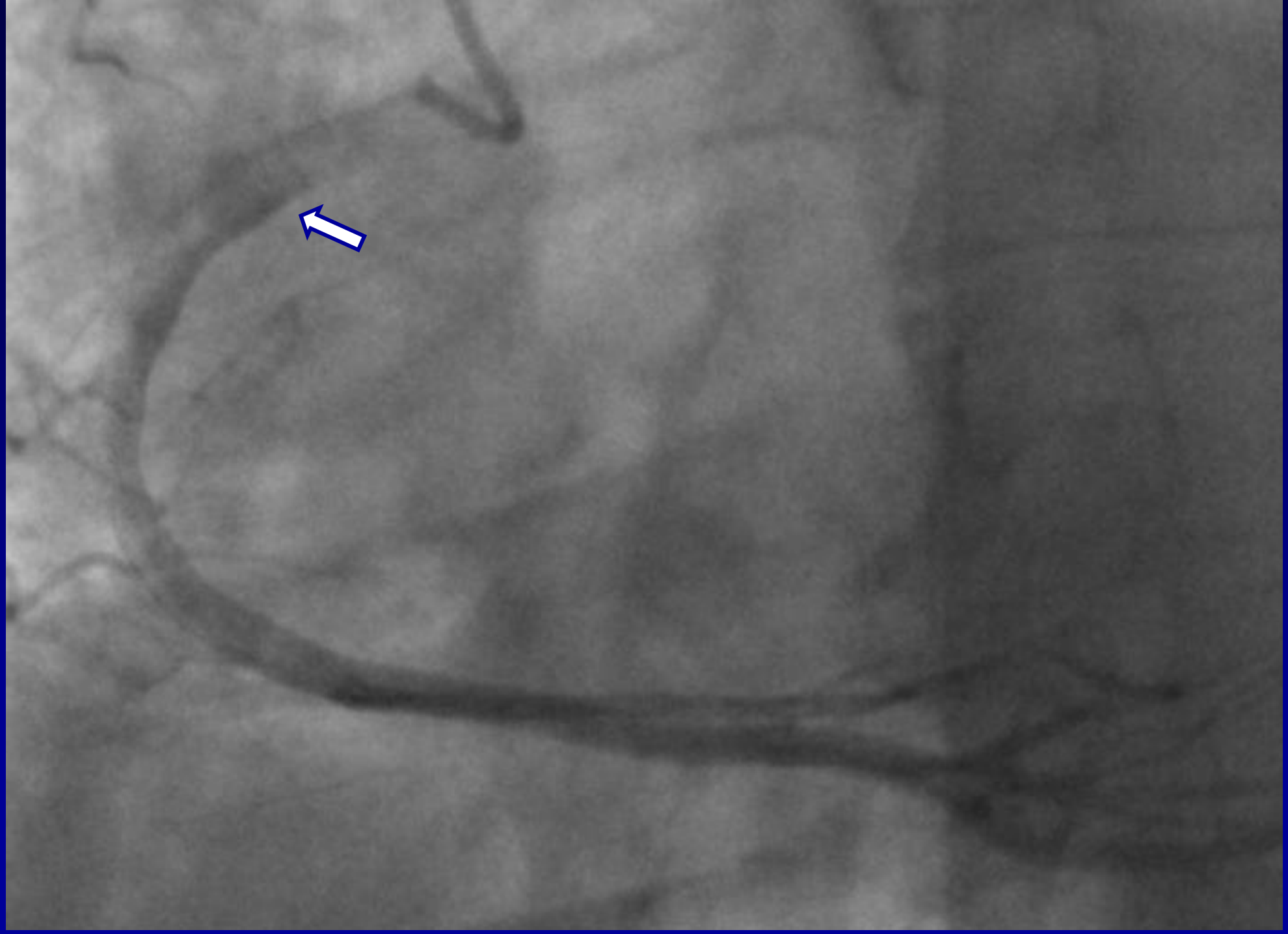


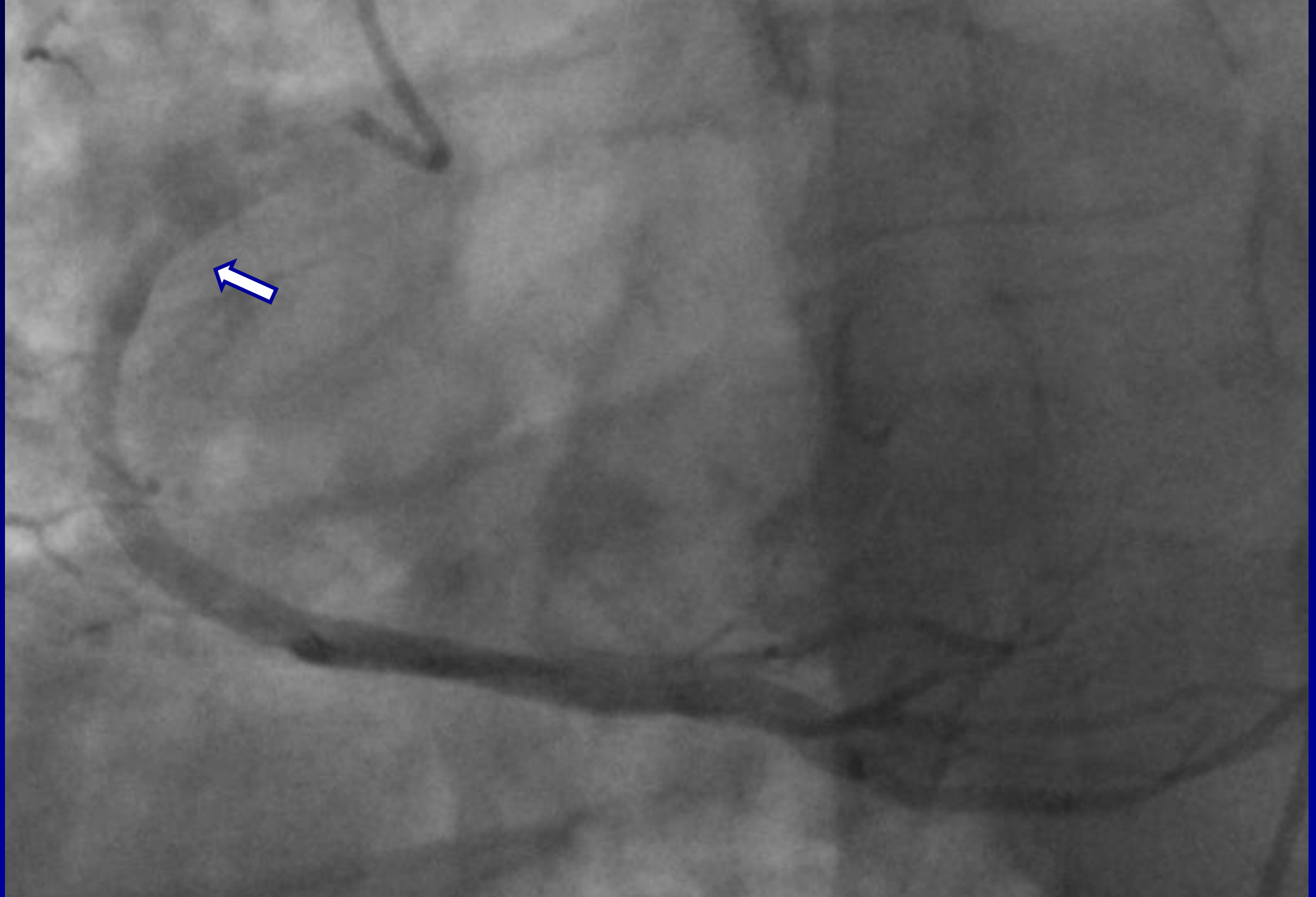


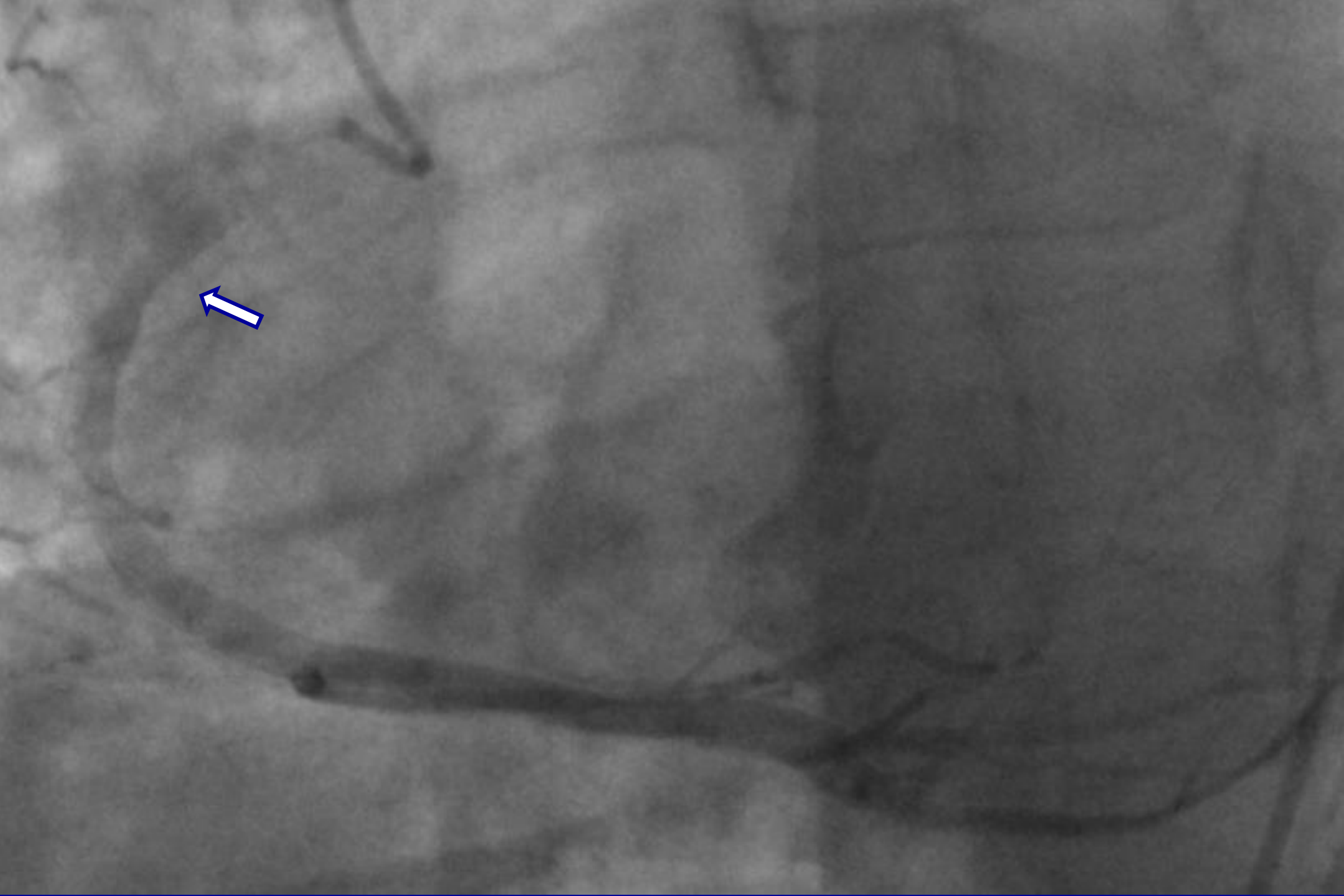


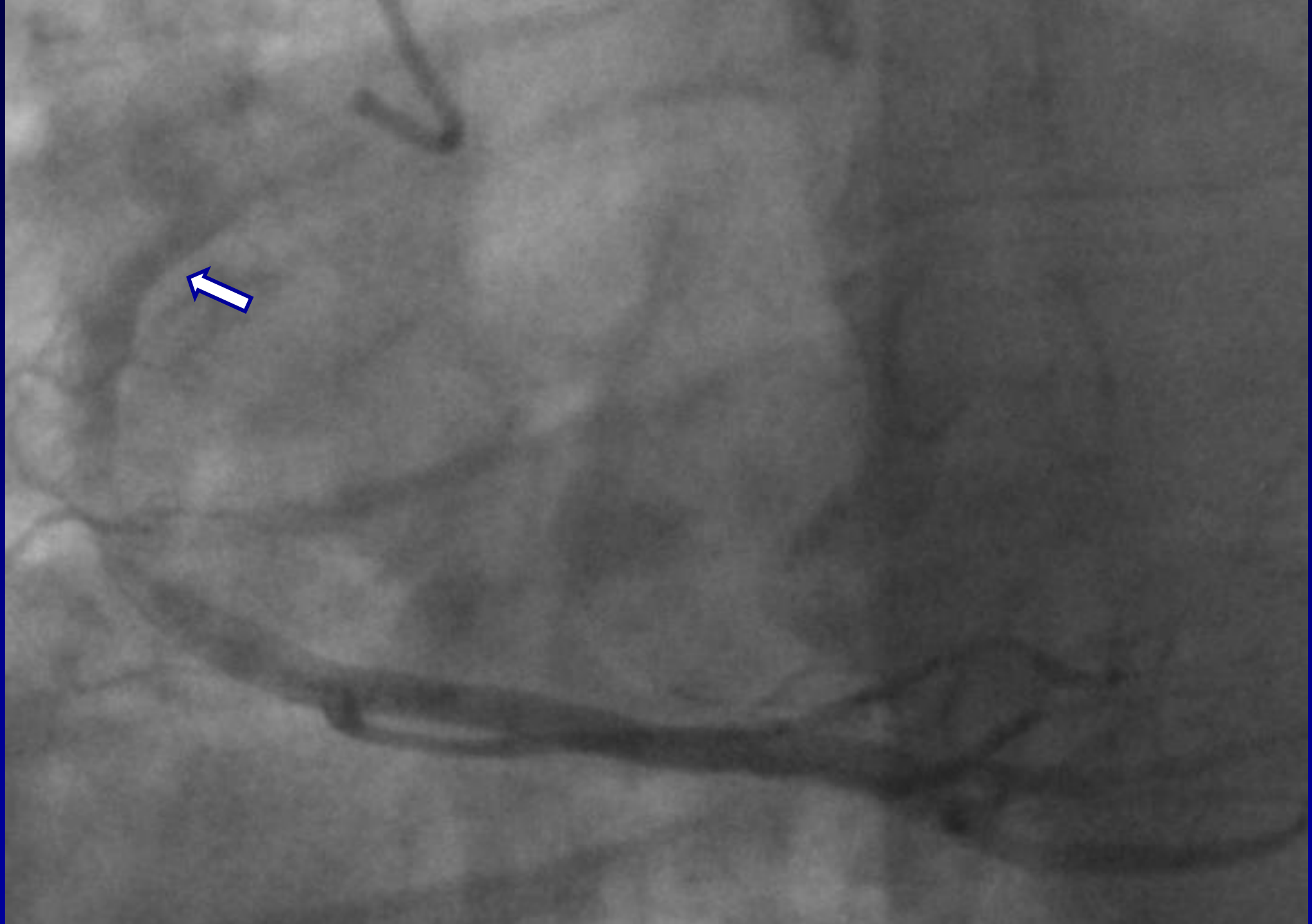


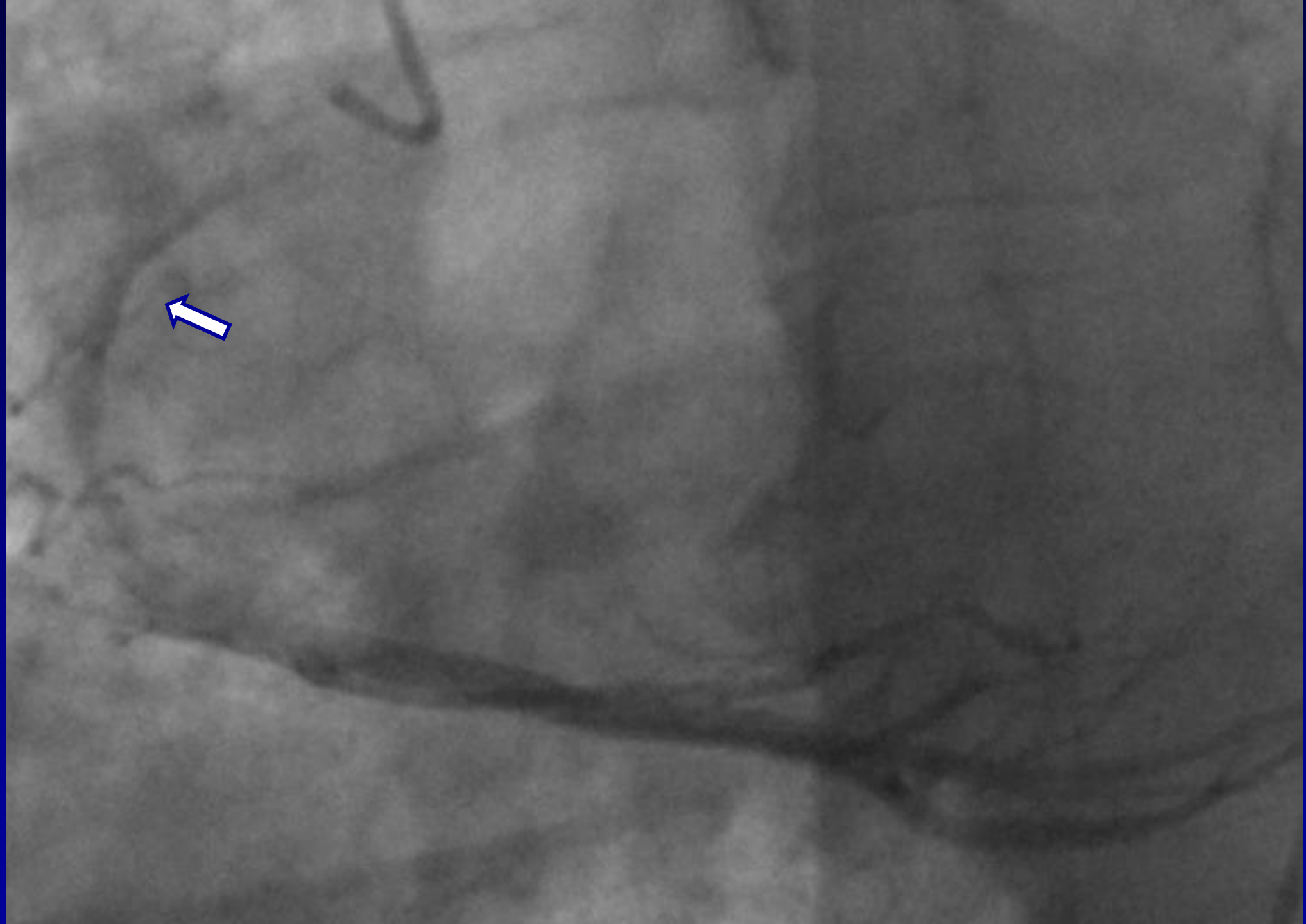


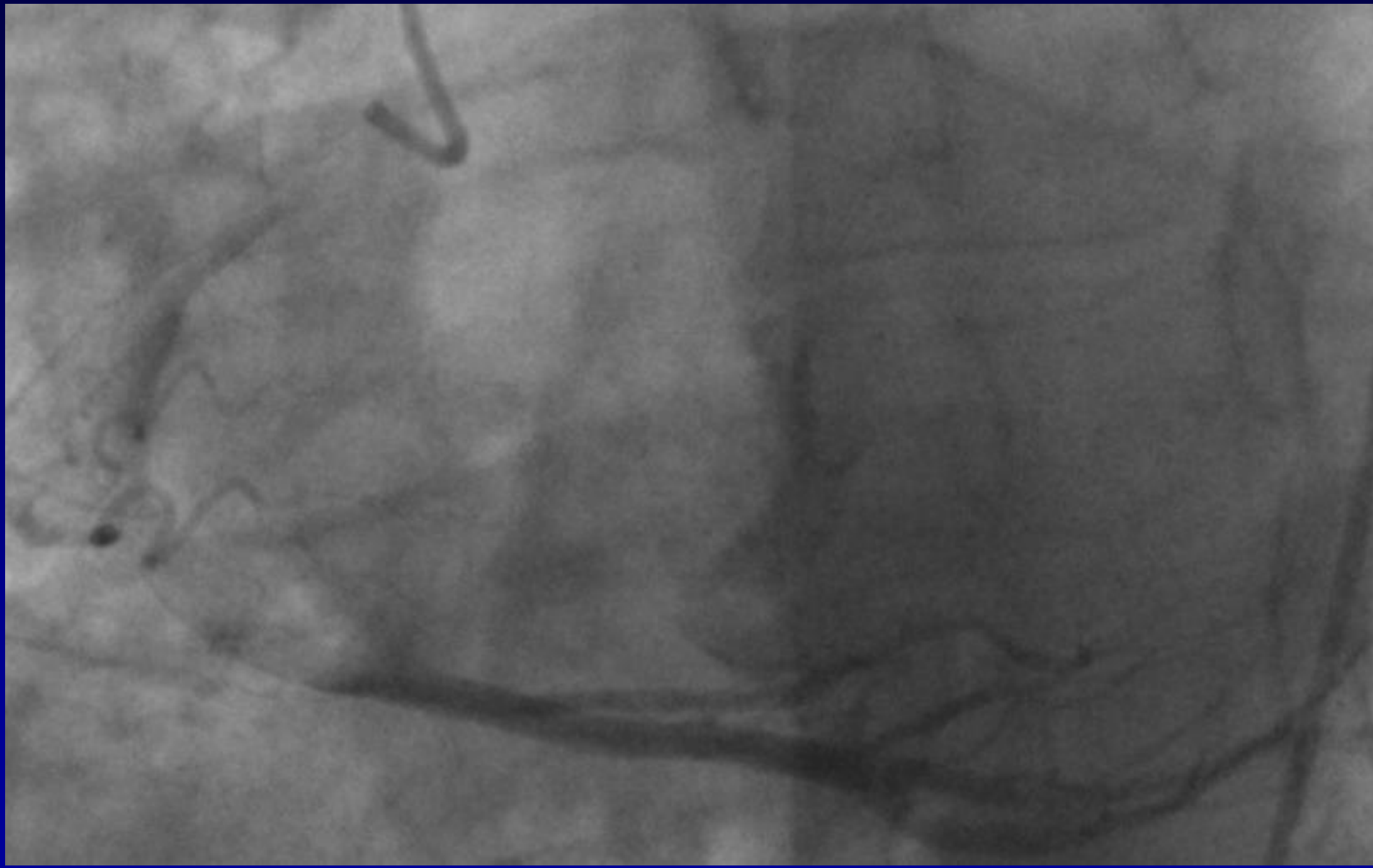


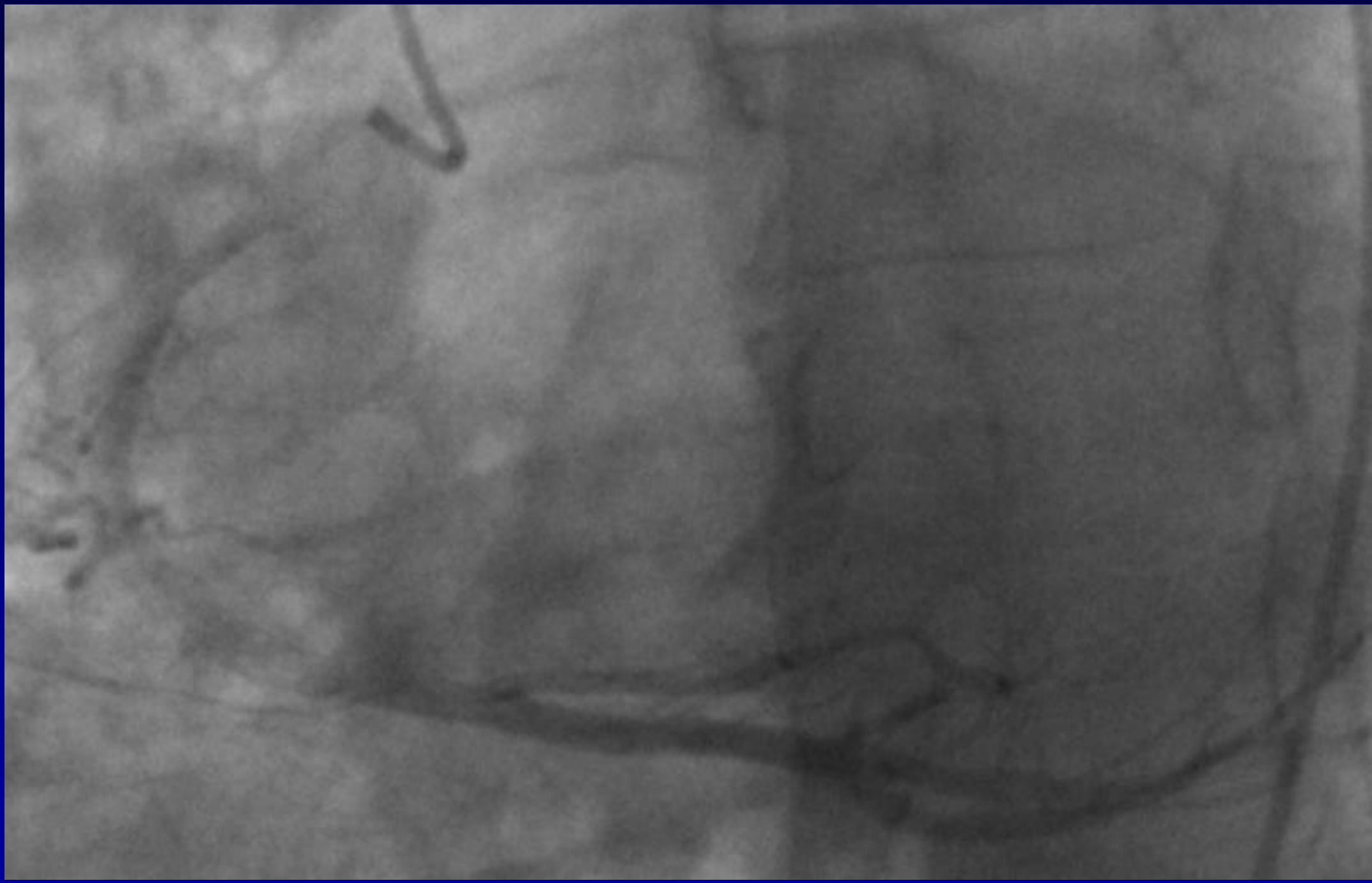


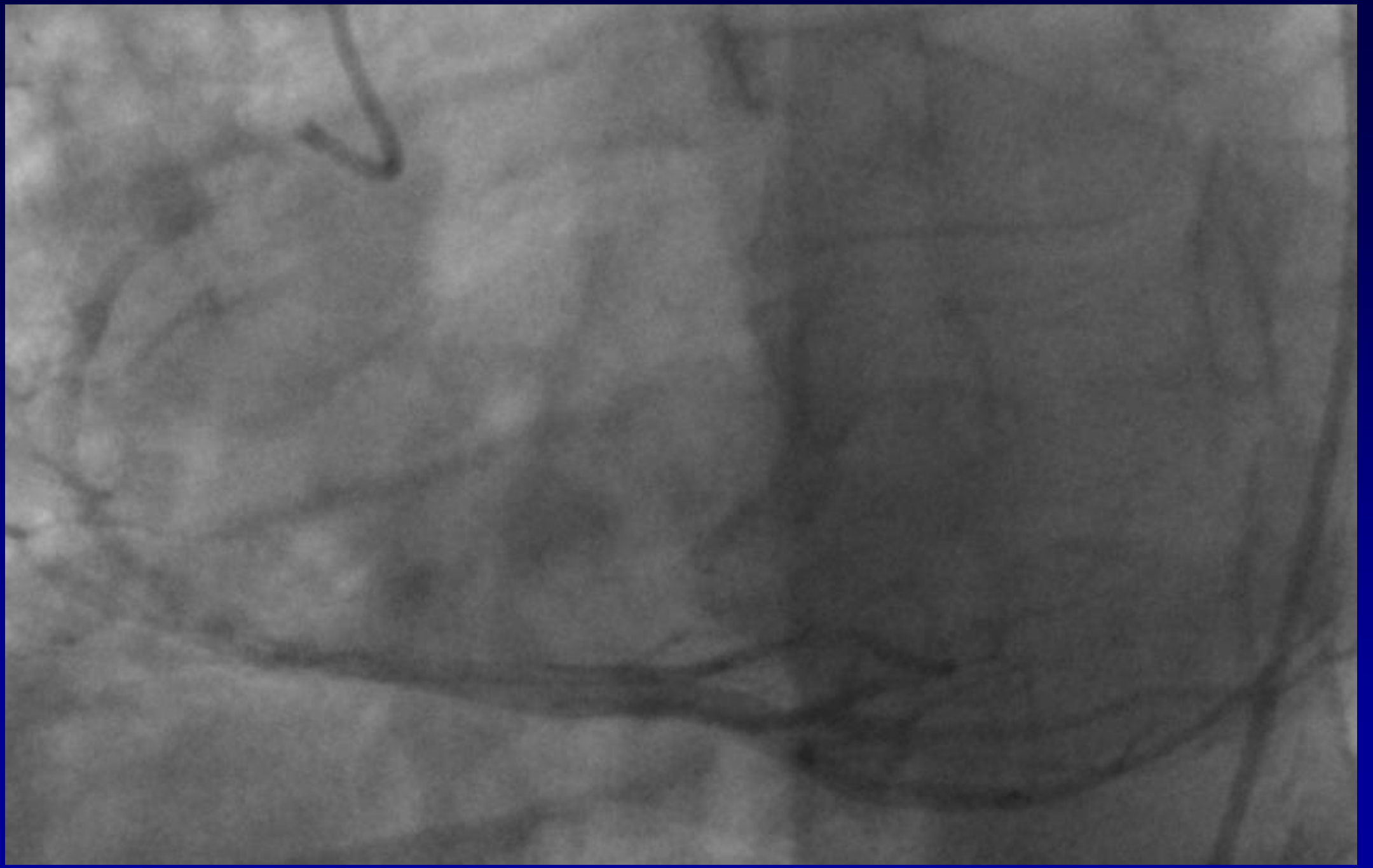


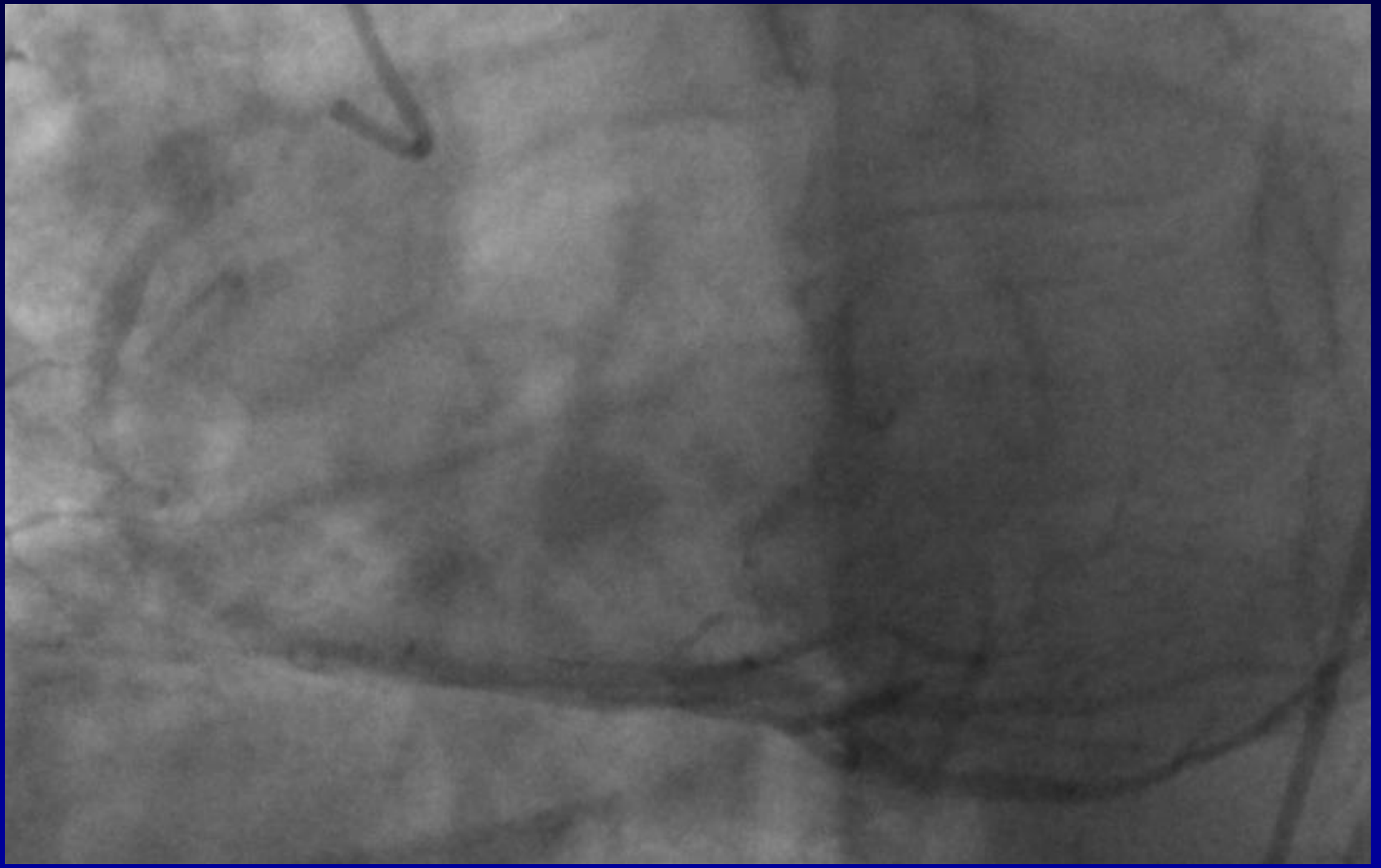


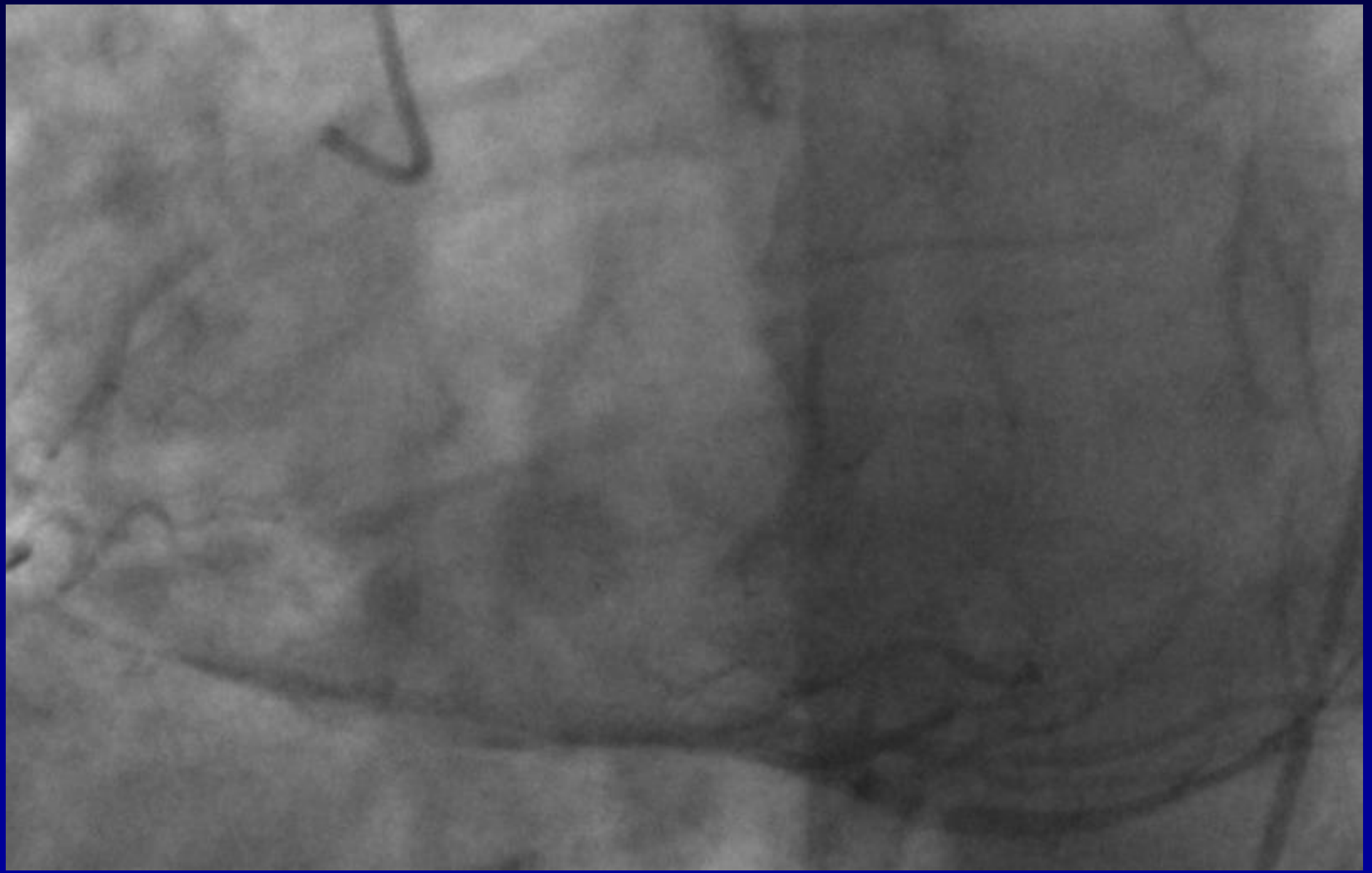


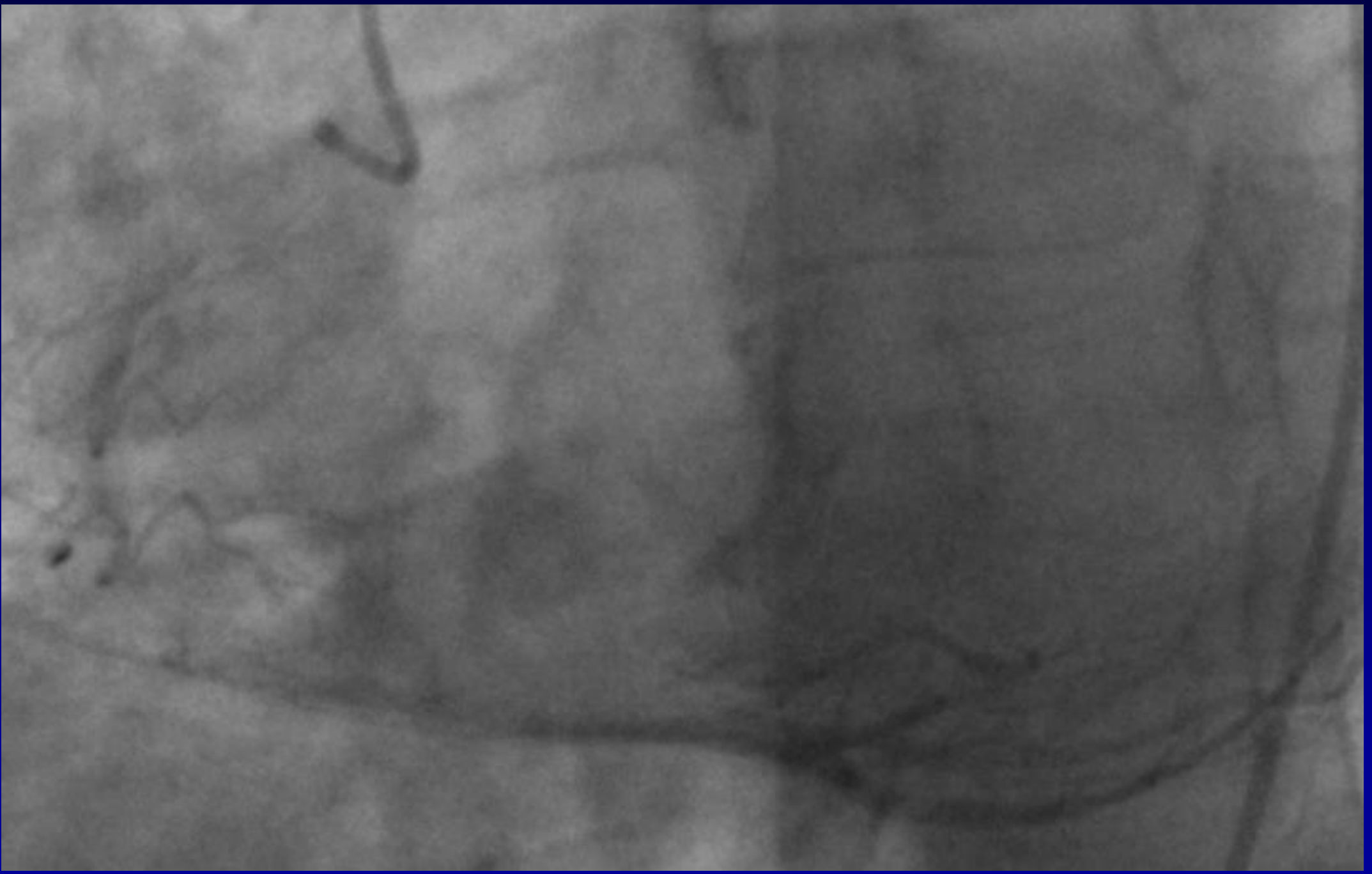


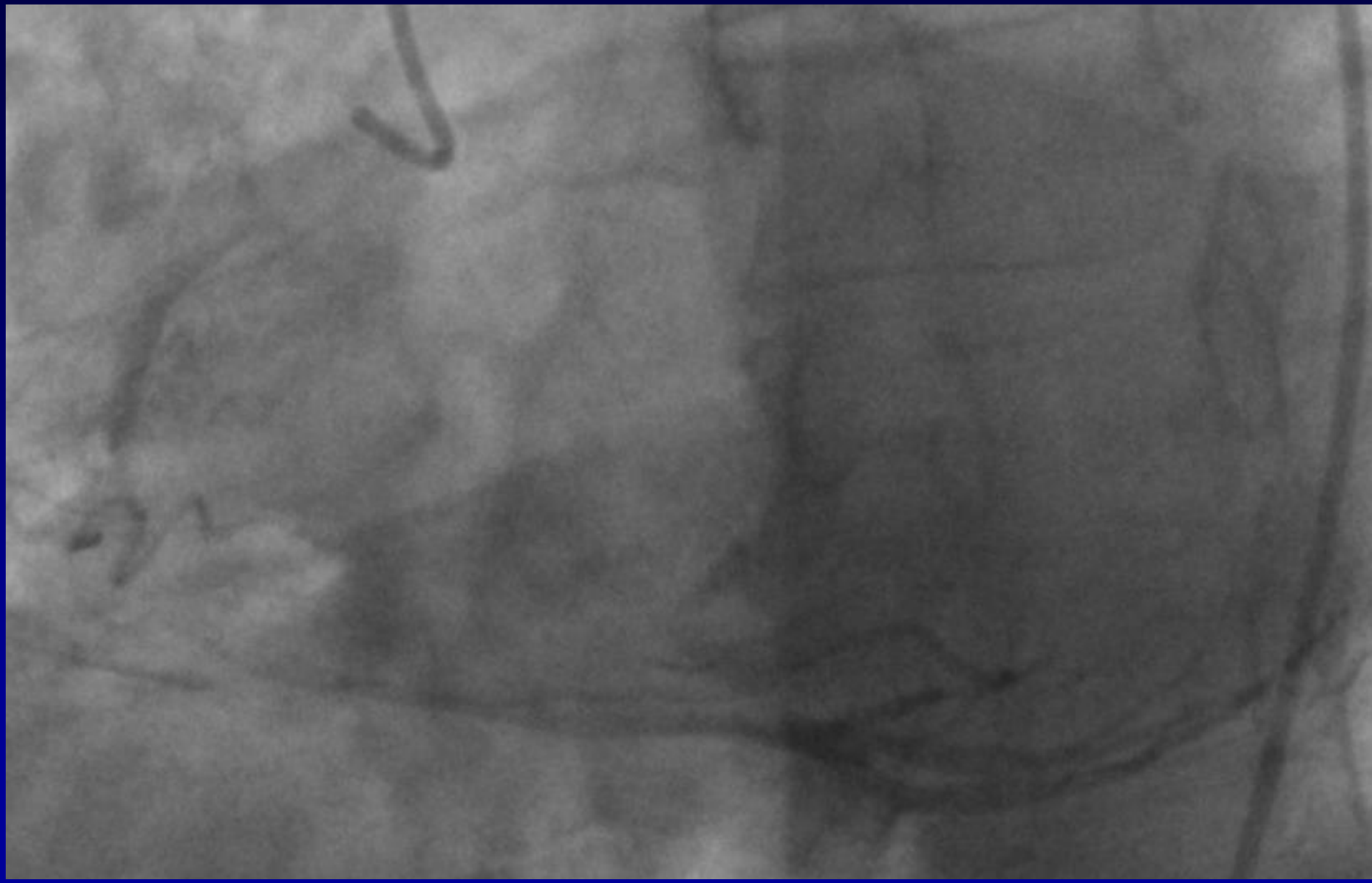


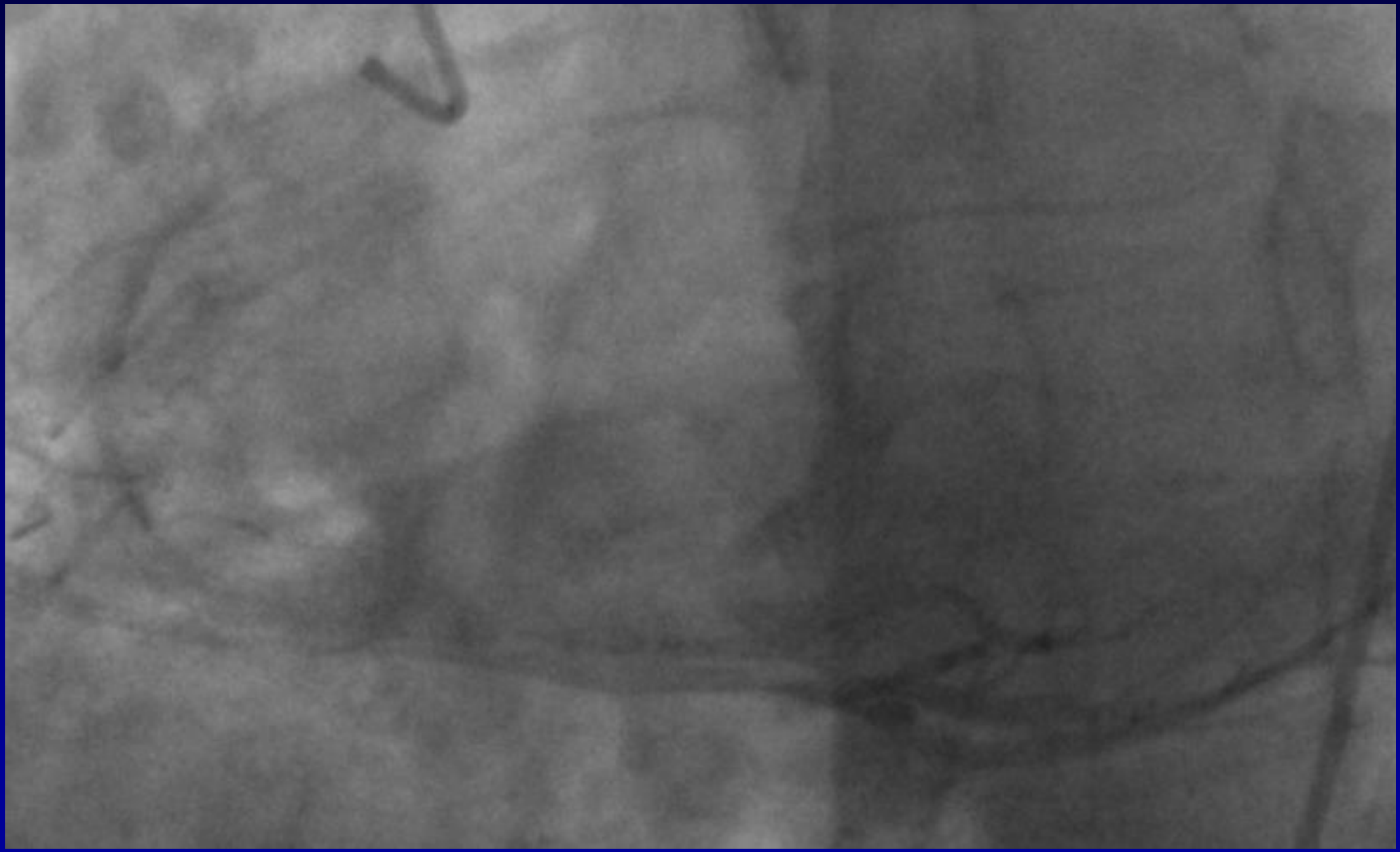


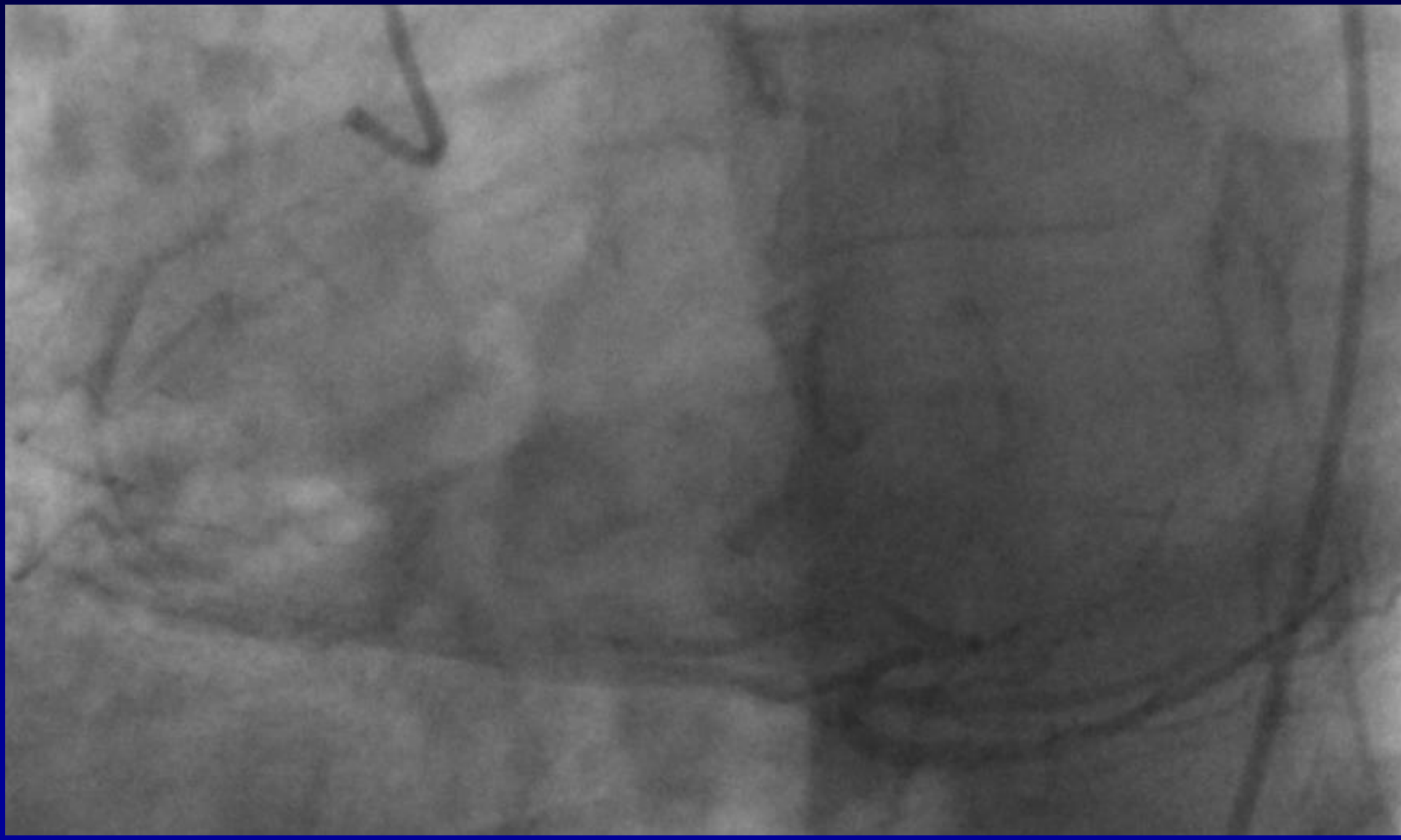


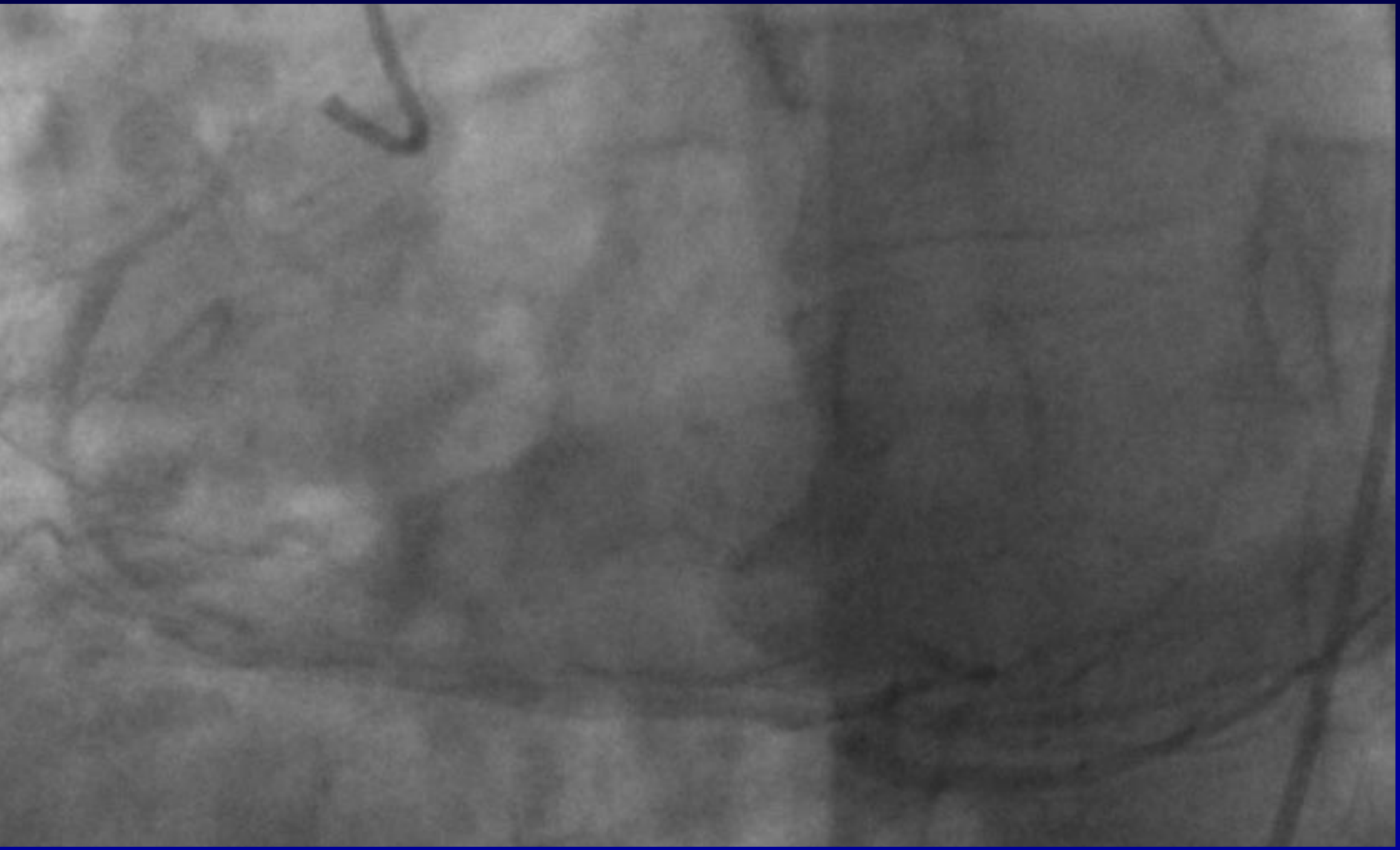


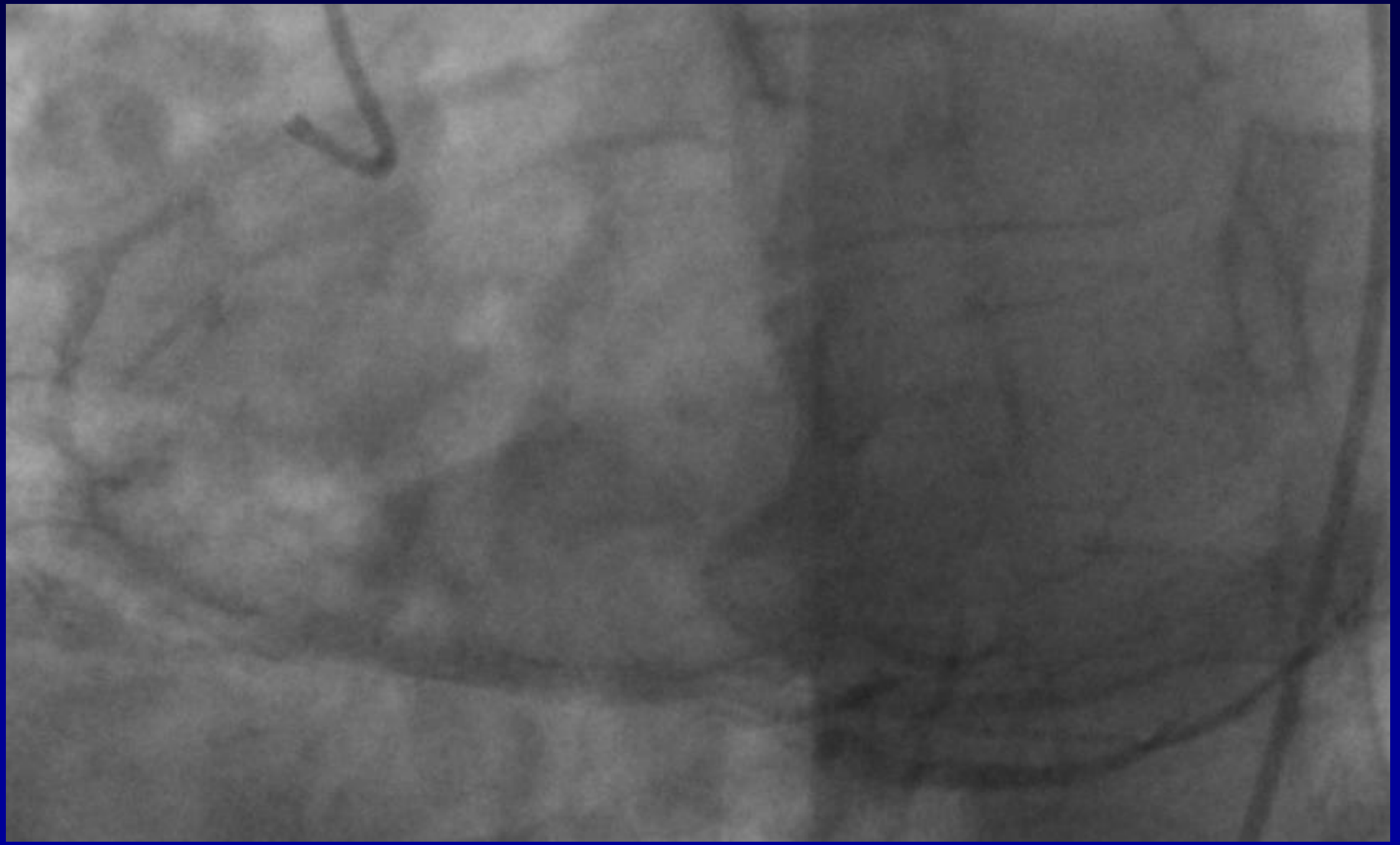


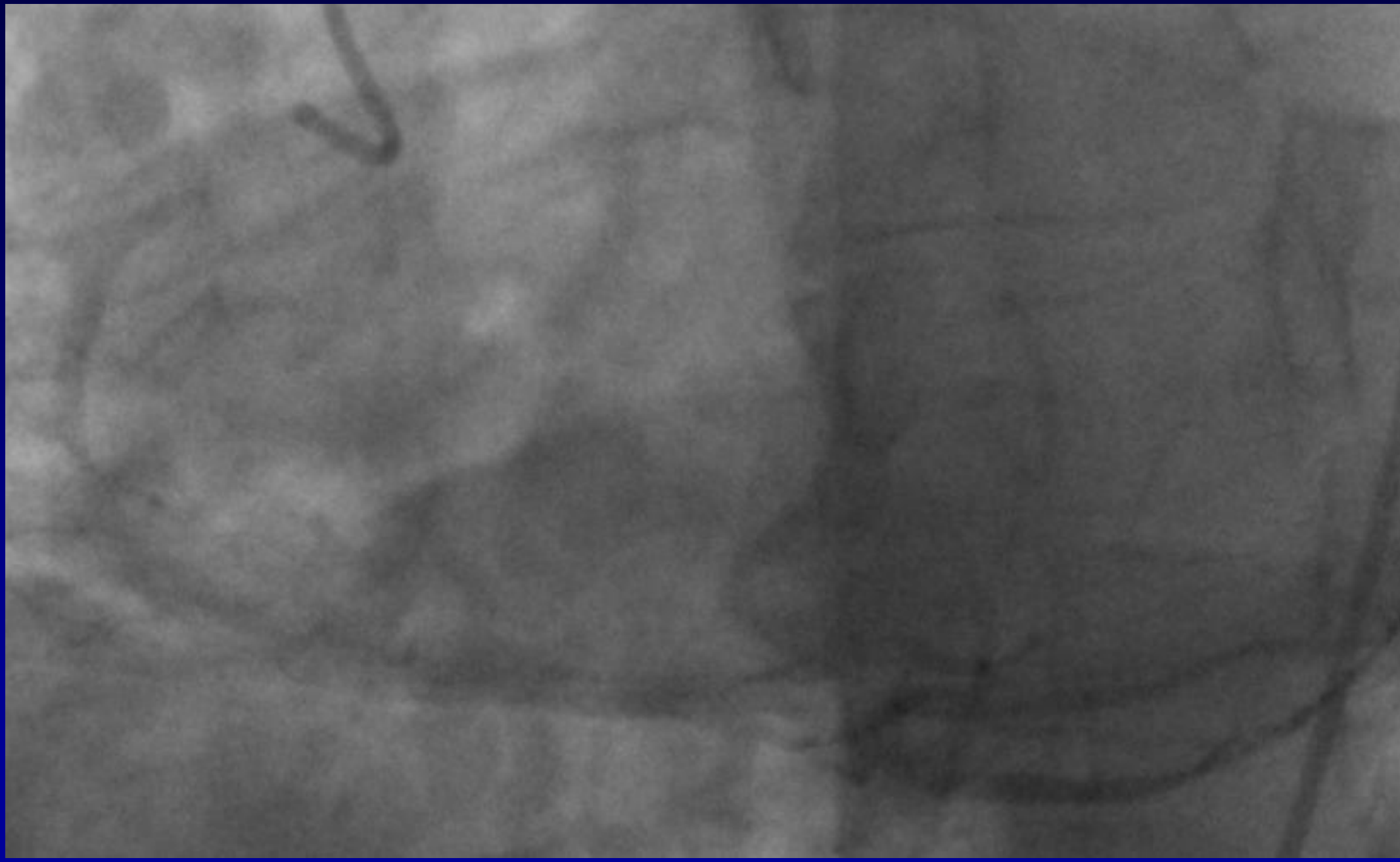


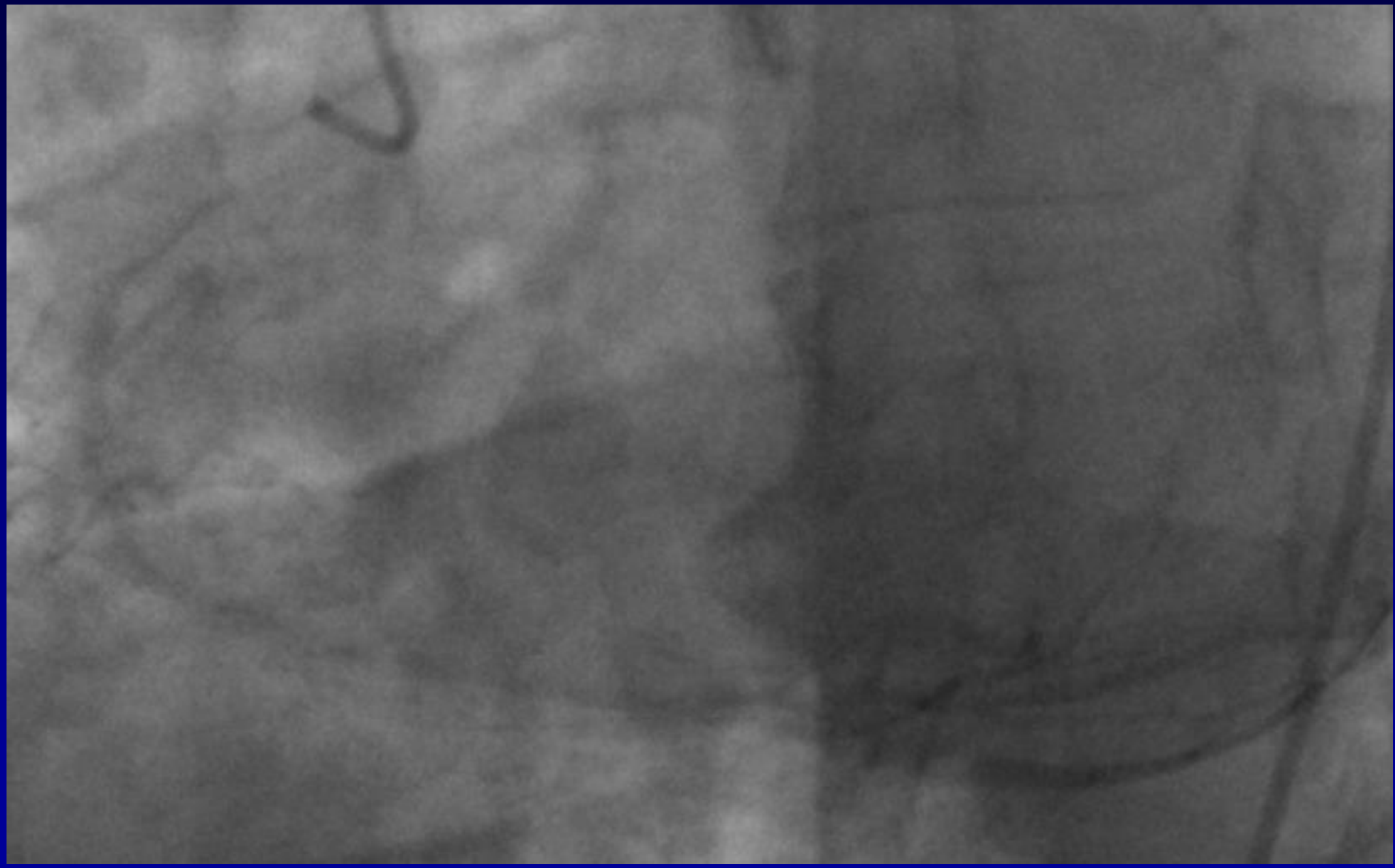


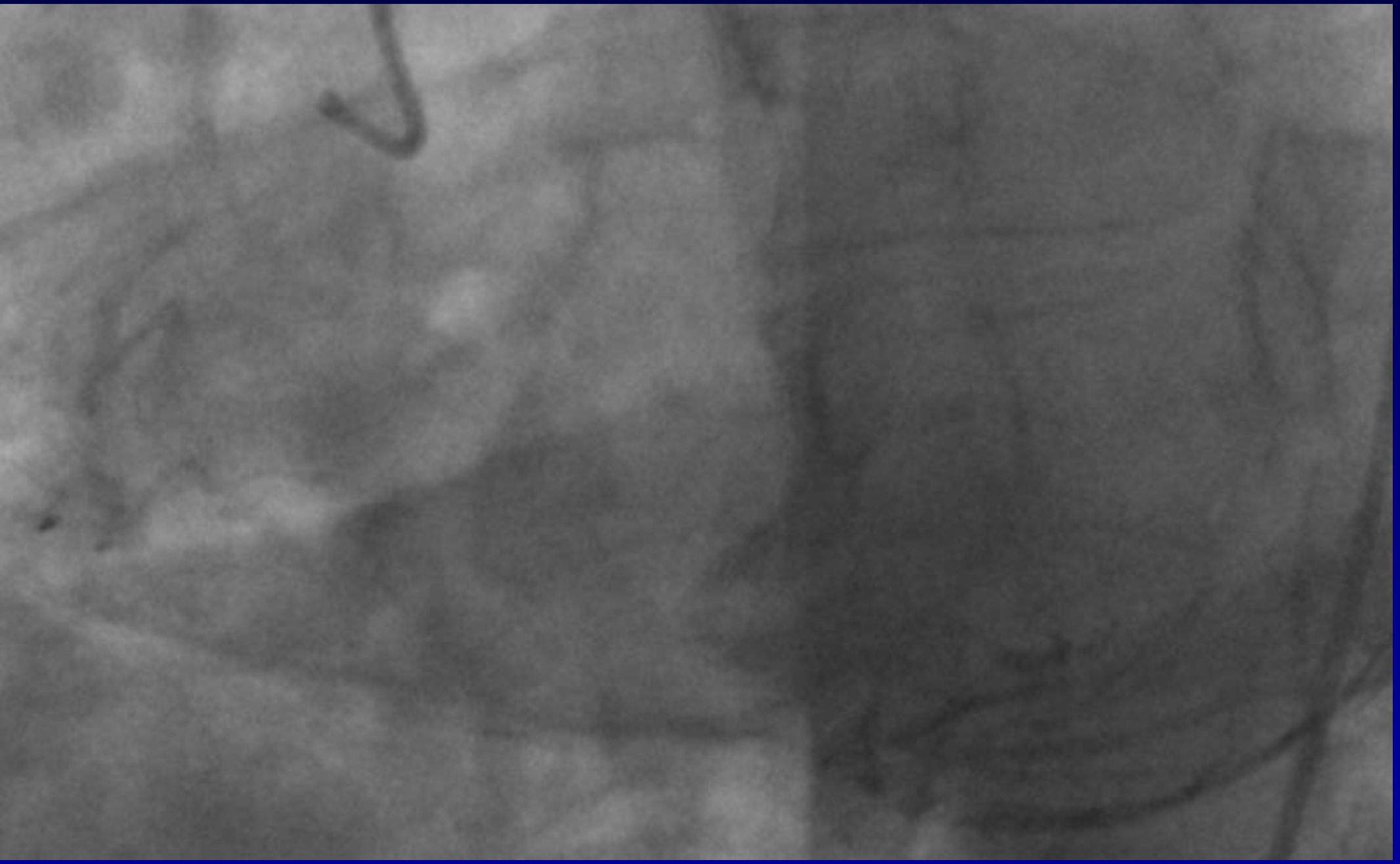


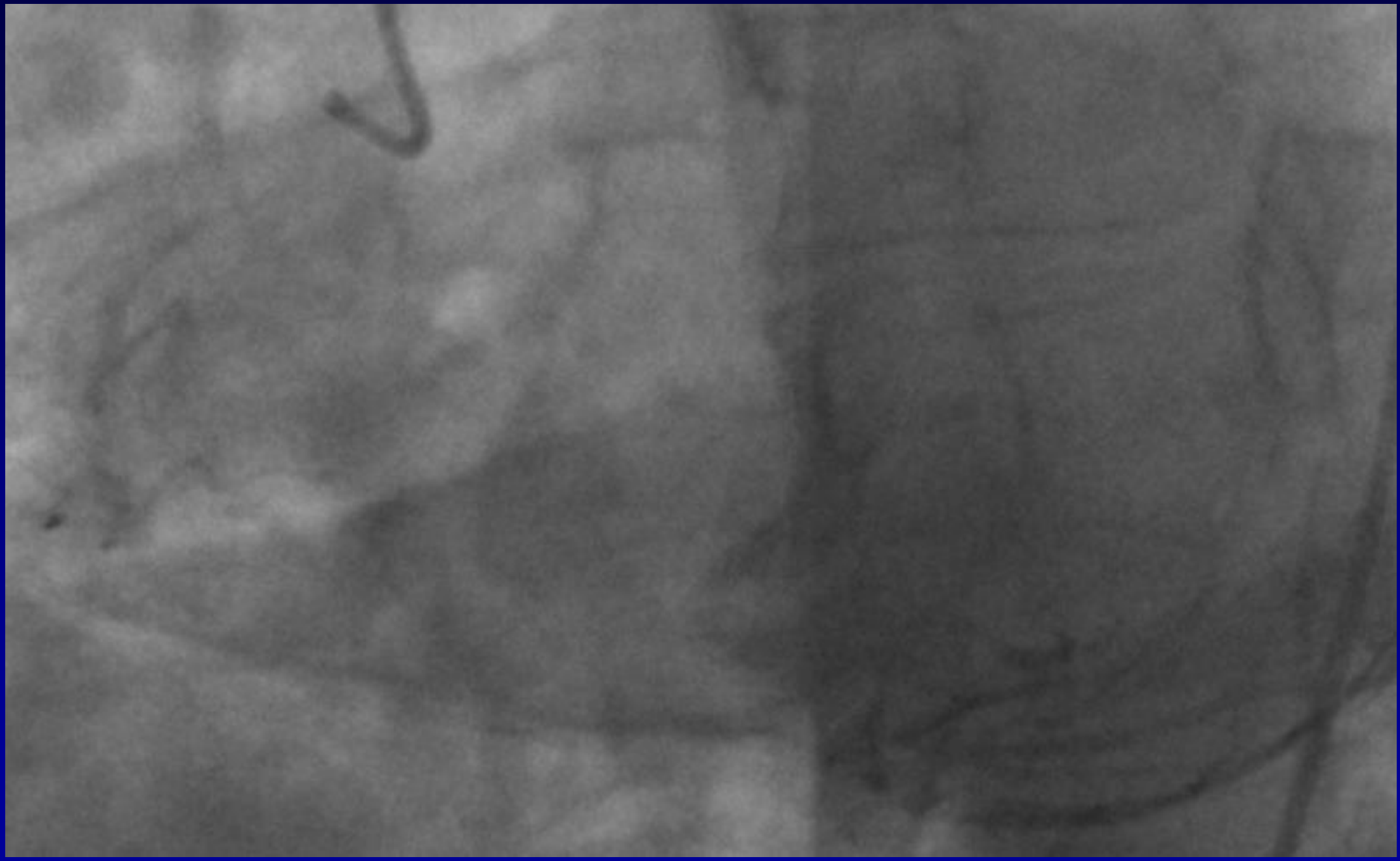


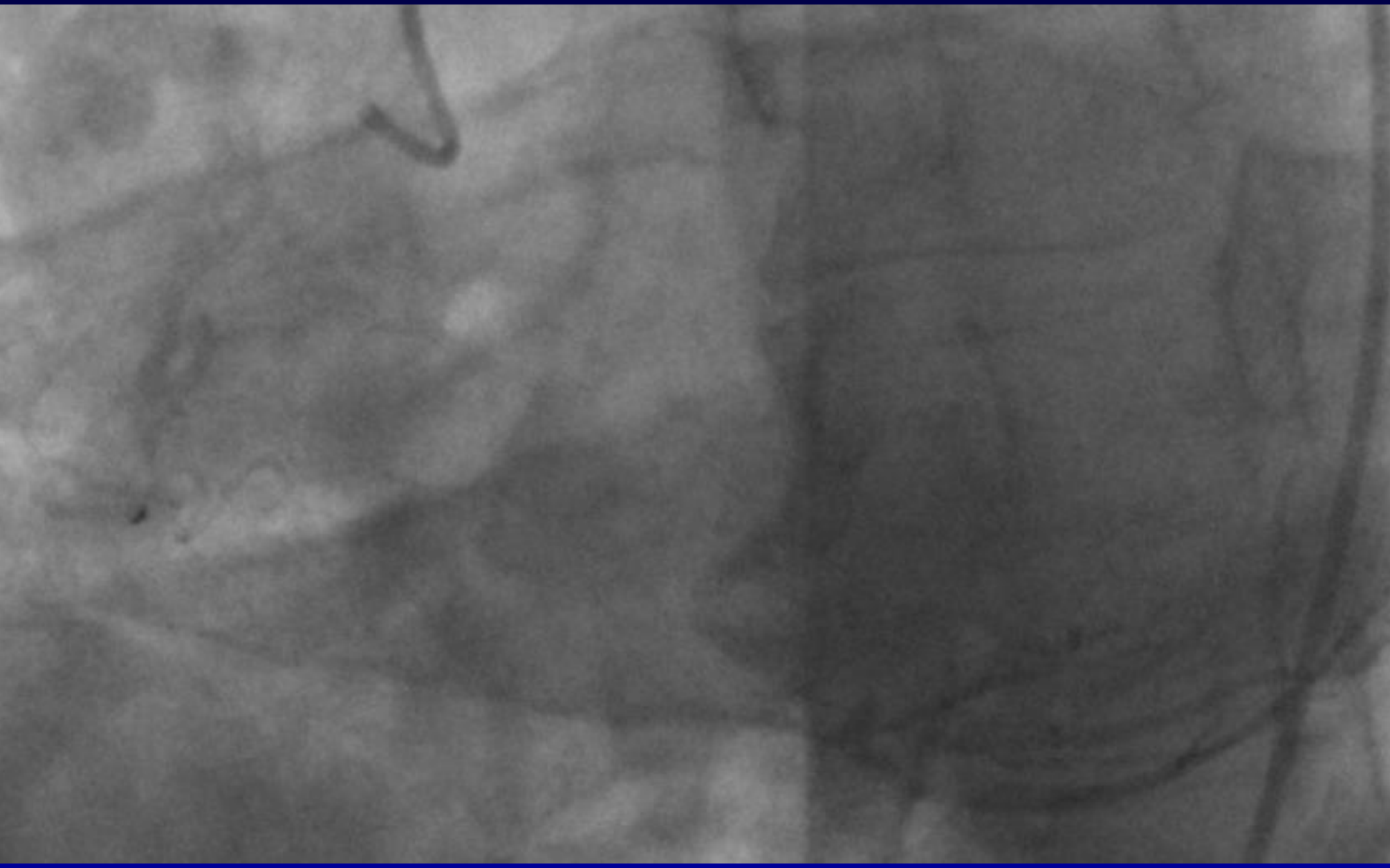




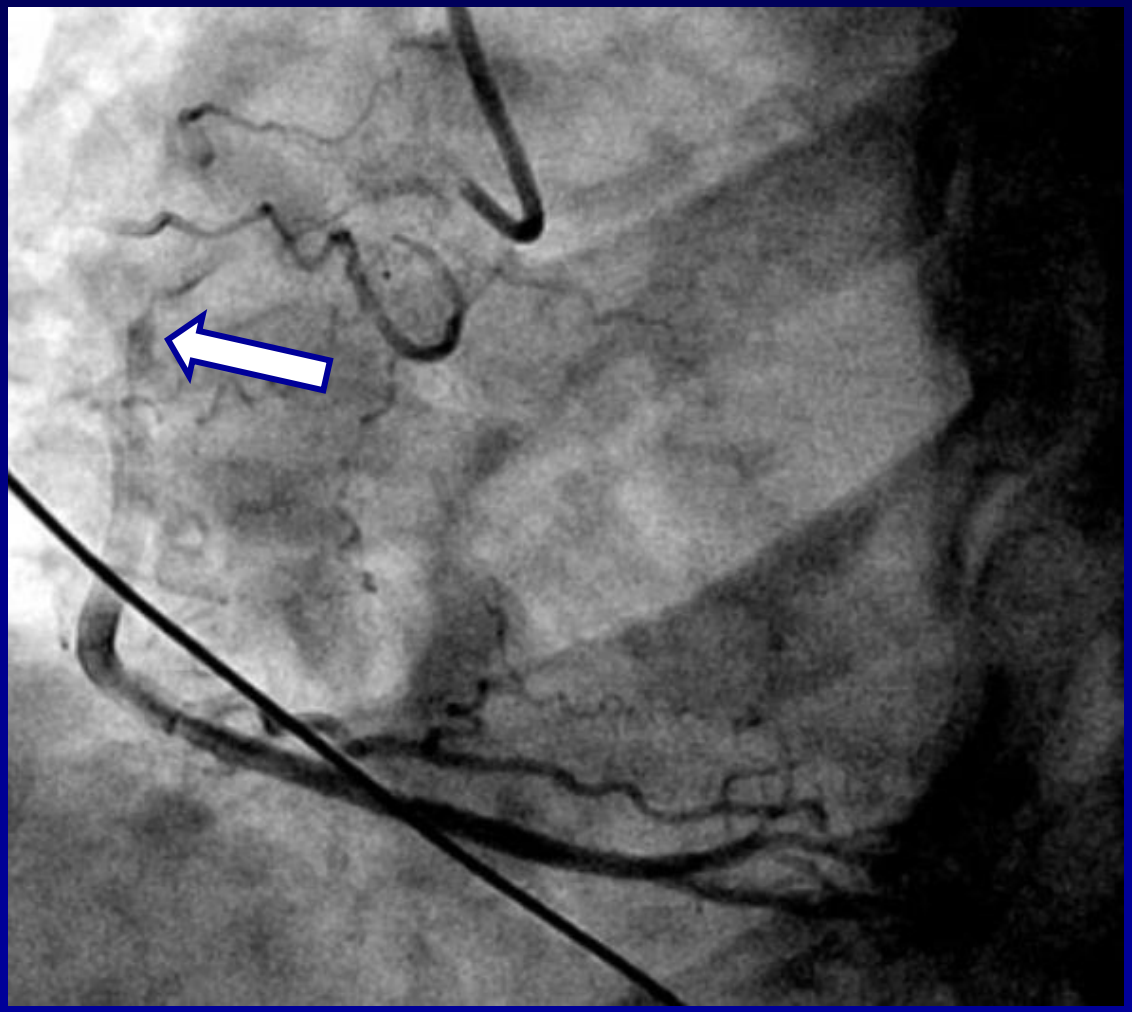




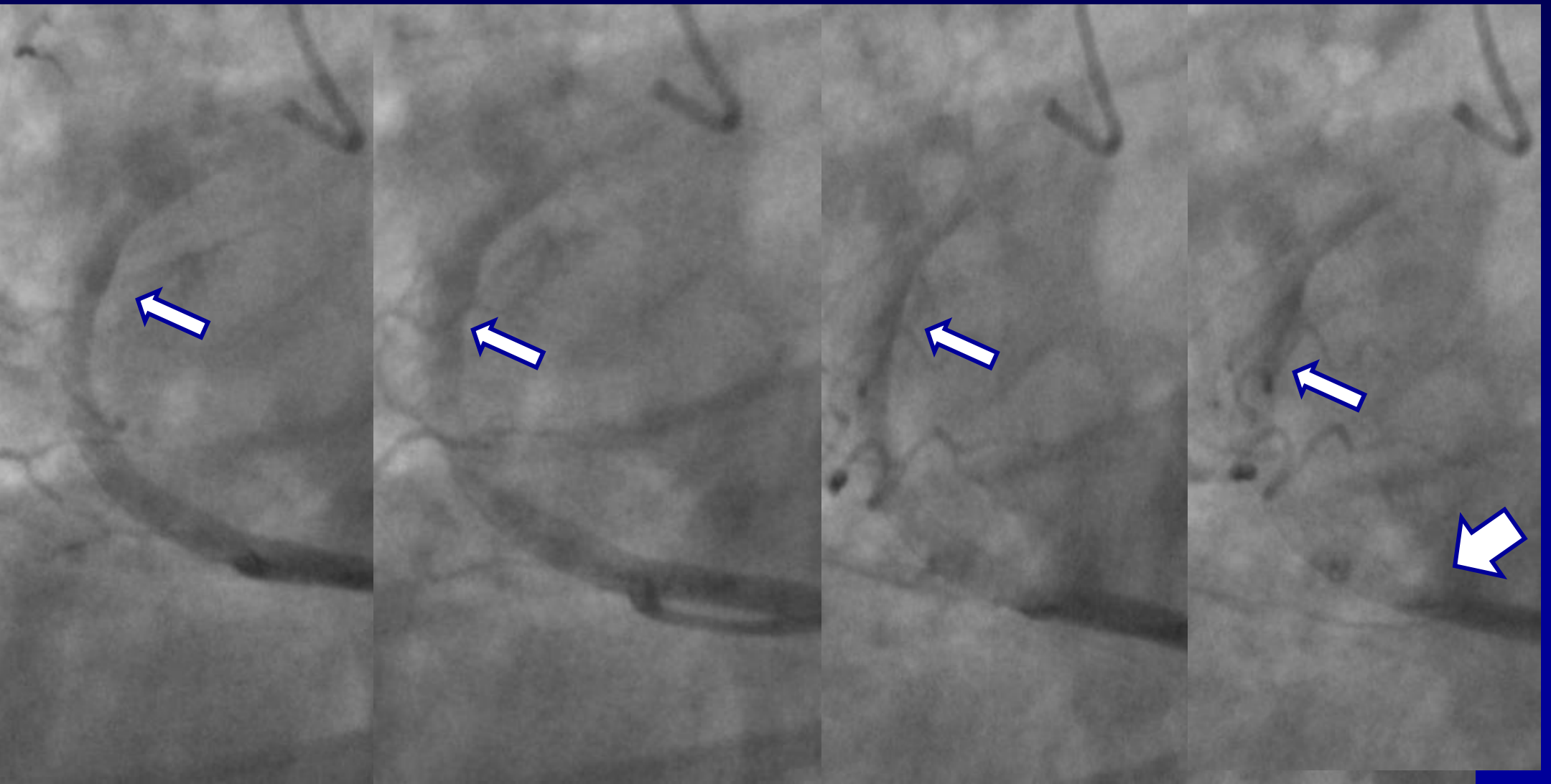


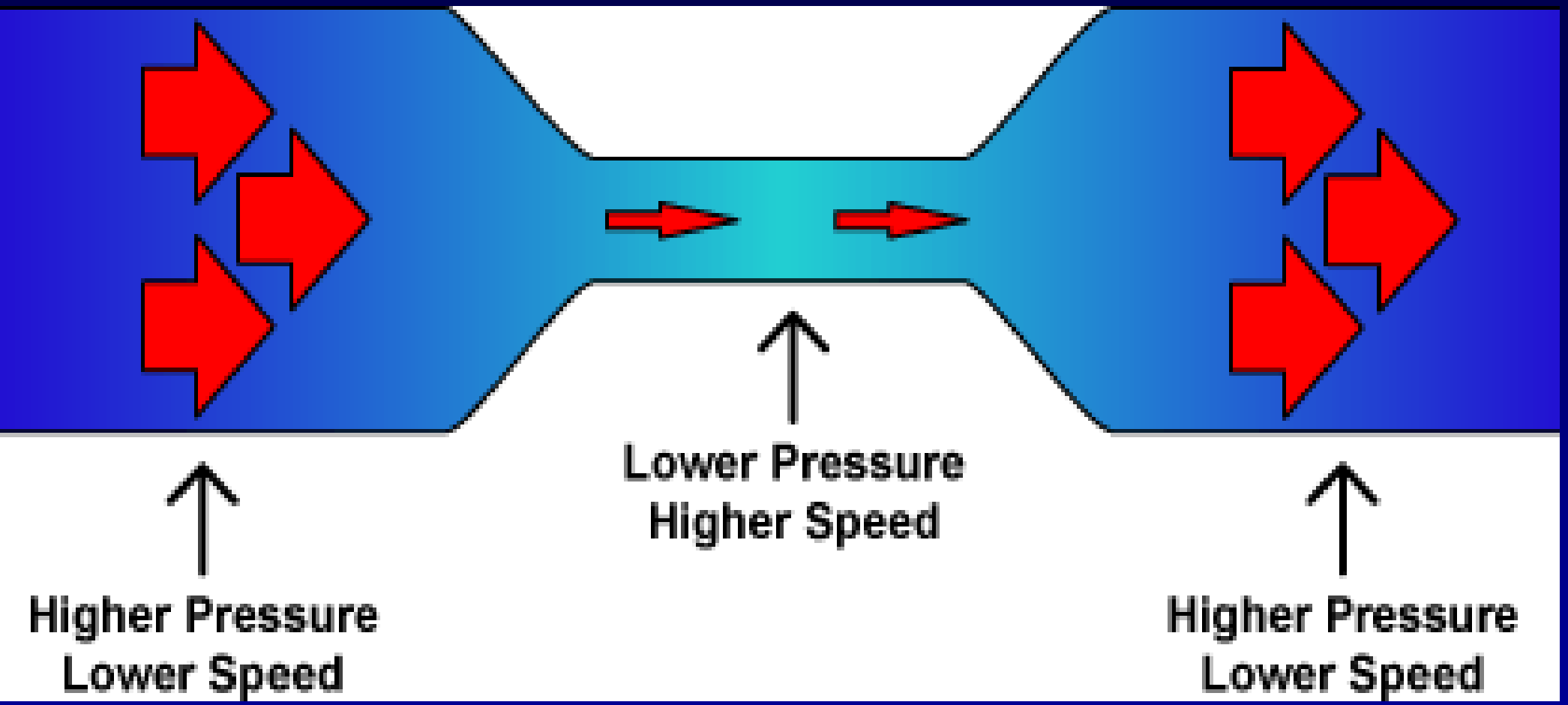


First Pathological Mechanism: Retention of Flow



2nd Pathological Mechanism: Reverse flow collides with the antegrade flow




Lower Pressure
Higher Speed
Higher Pressure
Lower Speed
Higher Pressure
Lower Speed

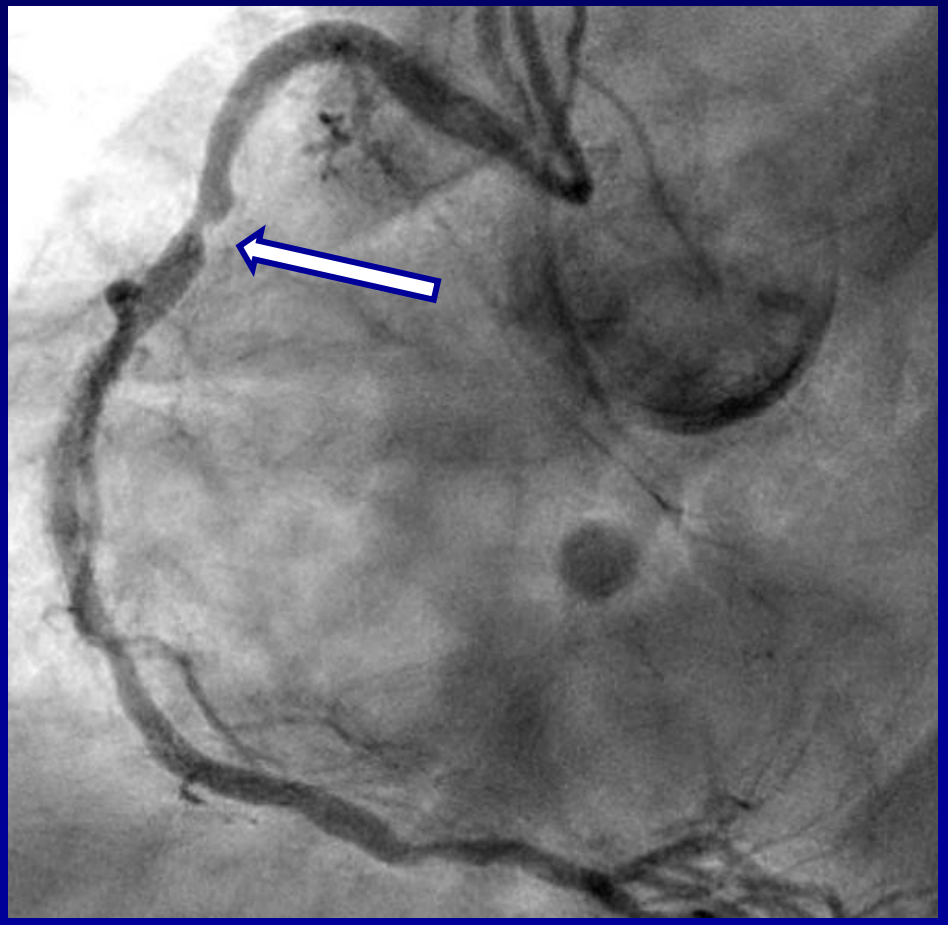
SUMMARY 2

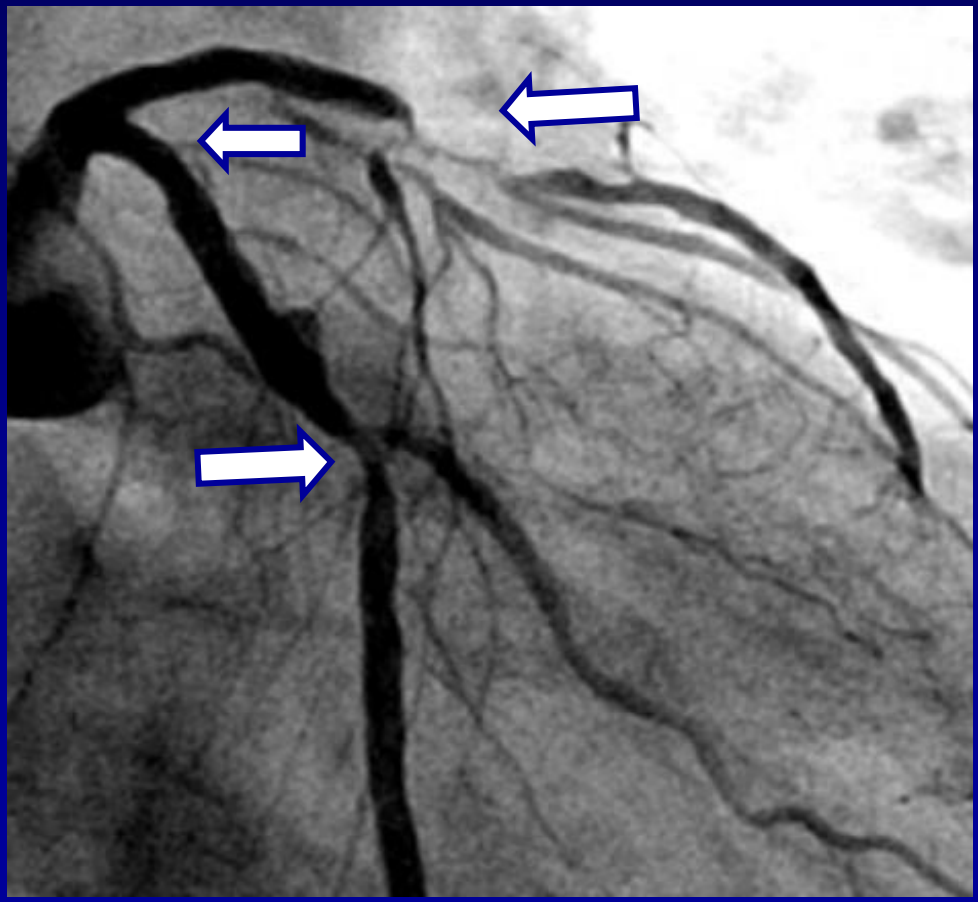
1. **STAGNANT FLOW AND TURBULENT FLOW (due to collision of antegrade and retrograde flow)** co-localize with the presence of atherosclerotic lesions

2. **This is the indirect evidence of the formation of coronary plaques** caused by mechanical injury to the endothelium and the birth of coronary plaques.

QUESTIONS: 2. Why at the mid segment?

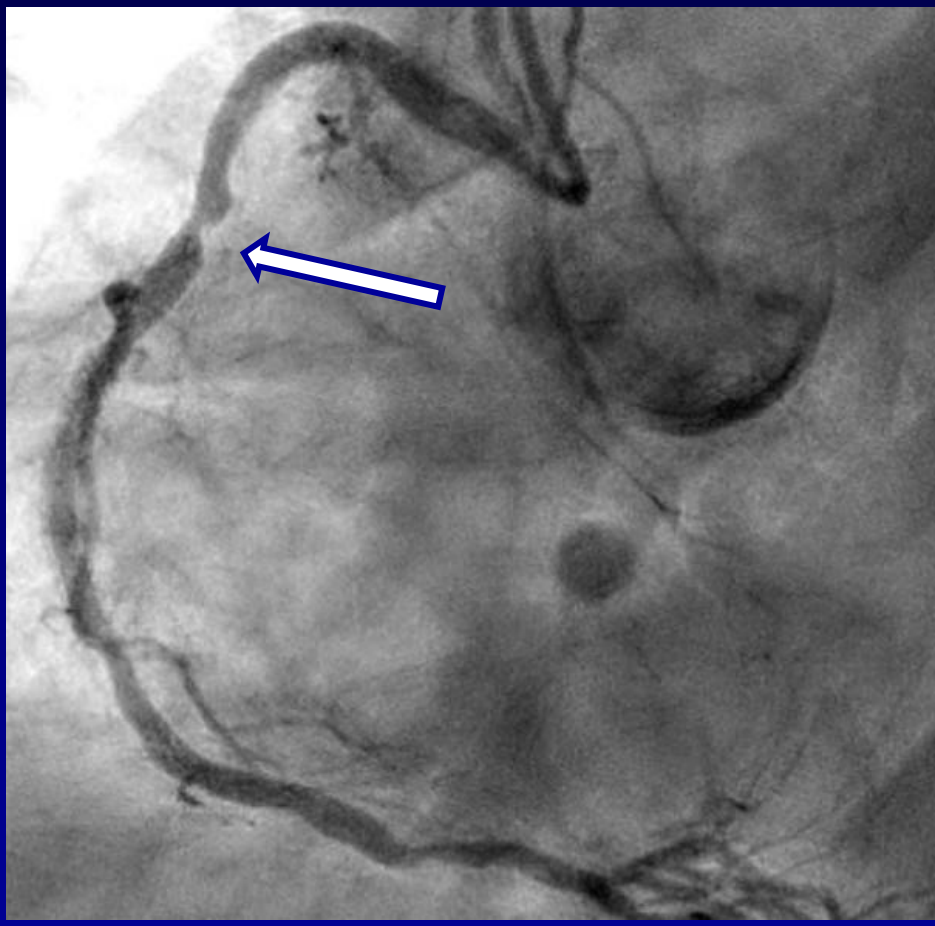
3. Why the lesion in the mid LCX is more severe than the lesion at the ostium of LCX?



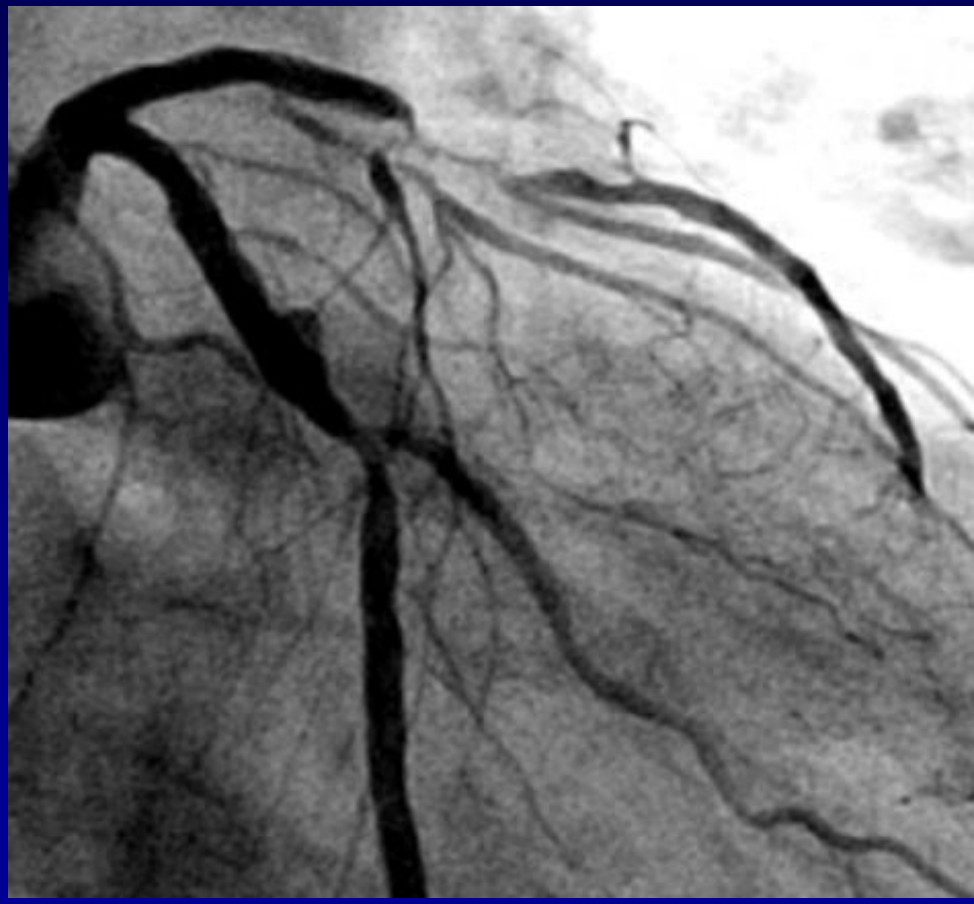


ANSWER : 2. Why at the mid segment?

Because during diastole, the flow moves forward. After 4 frames (0.06 seconds x 4= 0.24 seconds), the flow just arrives at the mid-segment, then the systole starts.
At that time, the collision happens and this is where the lesion is seen prominently



ANSWER : 3. Why the mid segment is more severe than the lesion at the ostium ?



Because in the ostial lesion, the injury was caused by one single mechanism (Retention of flow)

While at the midsegment, the injuries were caused by 2 mechanisms (A. collision of antegrade and retrograde flow) (Retention of flow)

The architecture of the coronary arteries predisposes the arteries to have plaques

Figure 1. Right anterior oblique caudal view of high-grade ostial circumflex artery and moderate left anterior descending artery stenoses.

http://www.vasculardiseasemanagement.com/content/radial-access-pci-children-obstructive-coronary-artery-disease

CAD in Twins

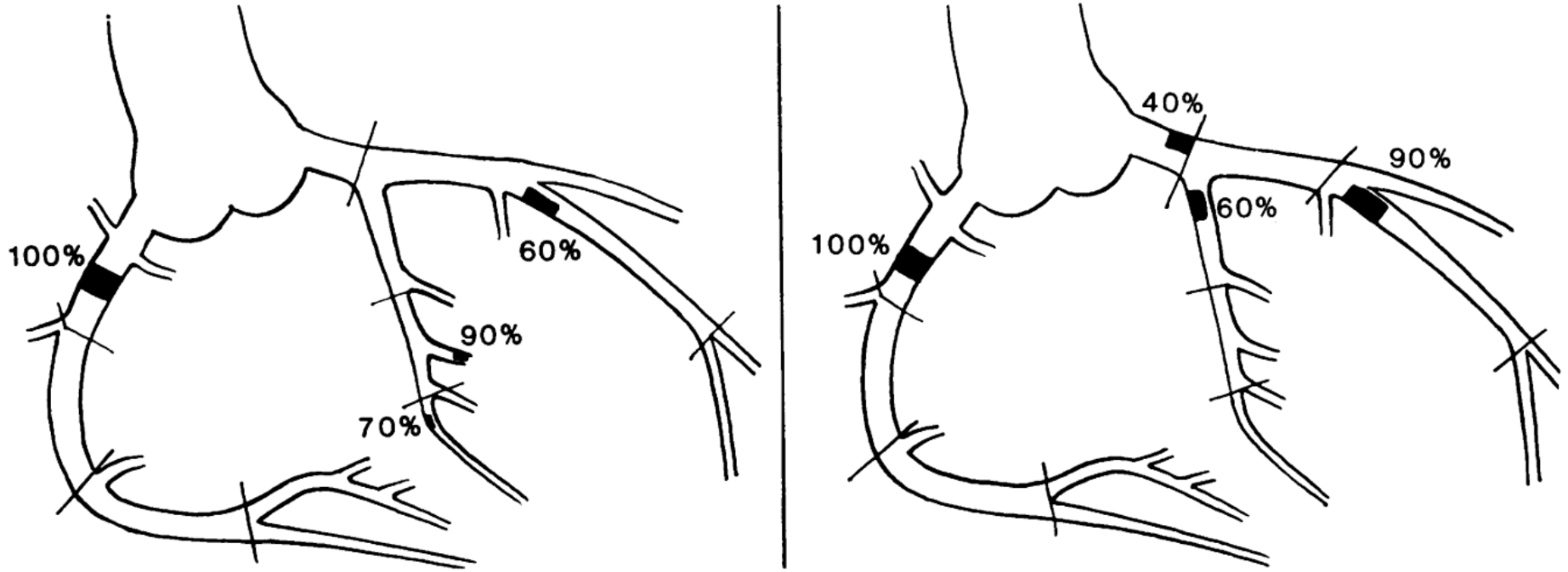
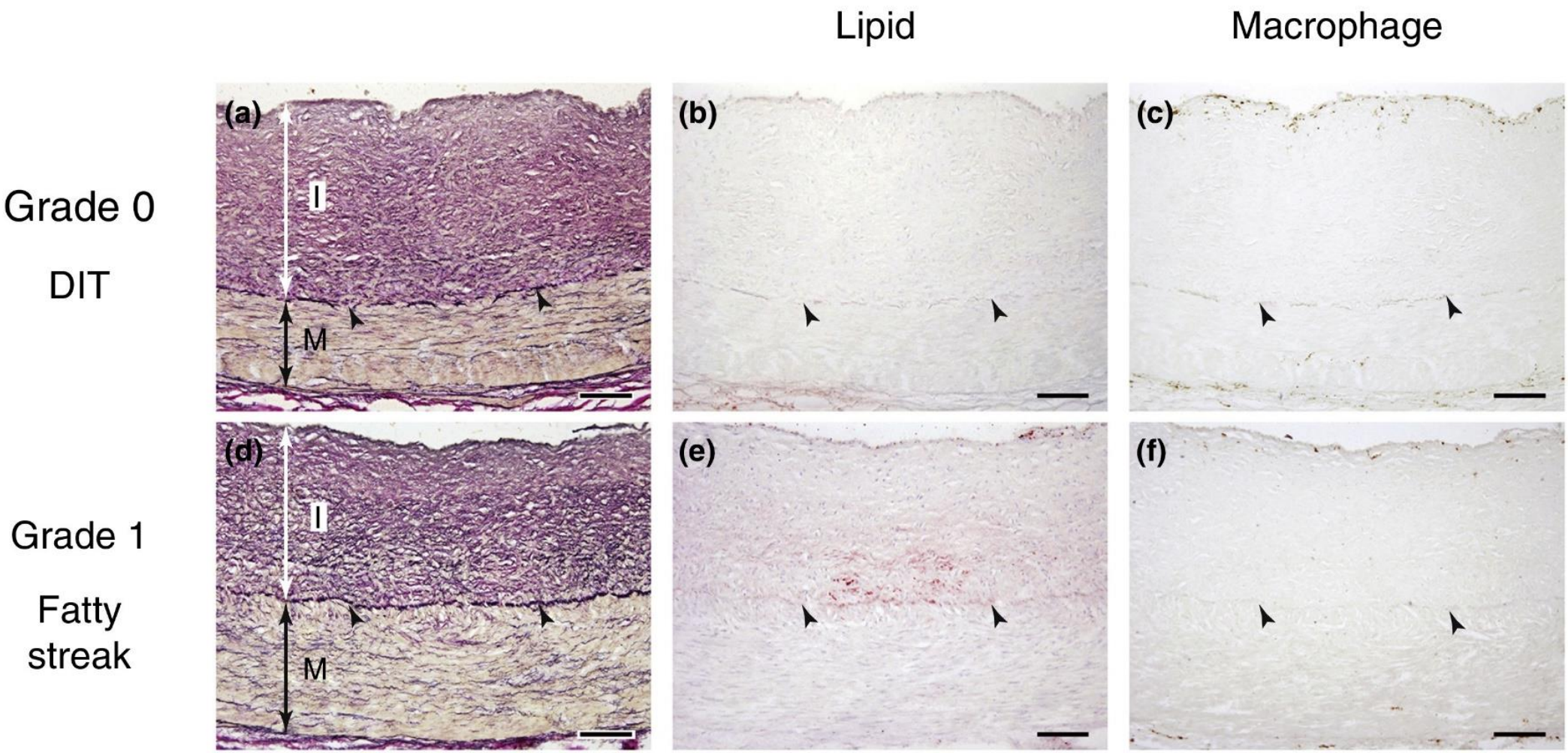


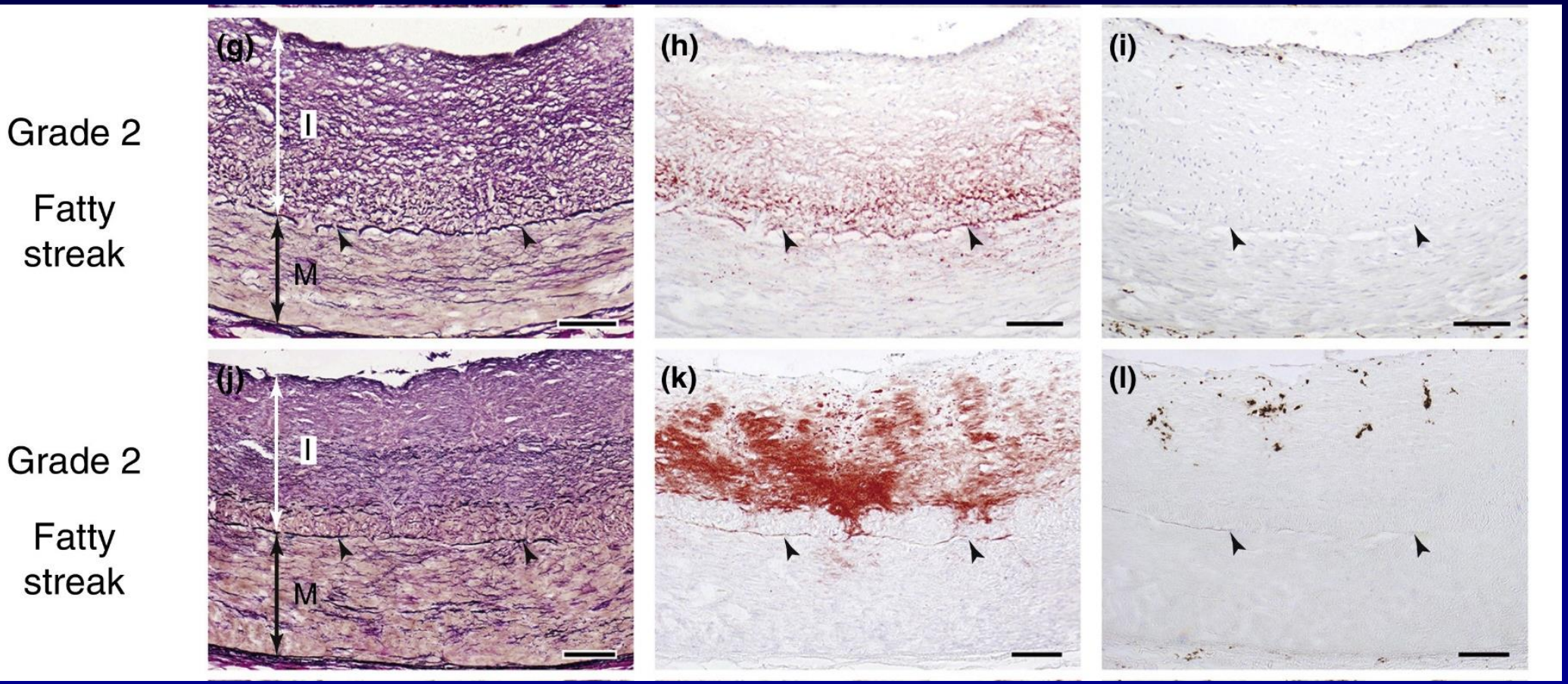
Fig. 2 *Schematic representation of coronary anatomy in the second twin pair.* Left, *case 3.* Right, *case 4.*

QUESTION 3

What is the role of LDL cholesterol and other conventional risk factors?



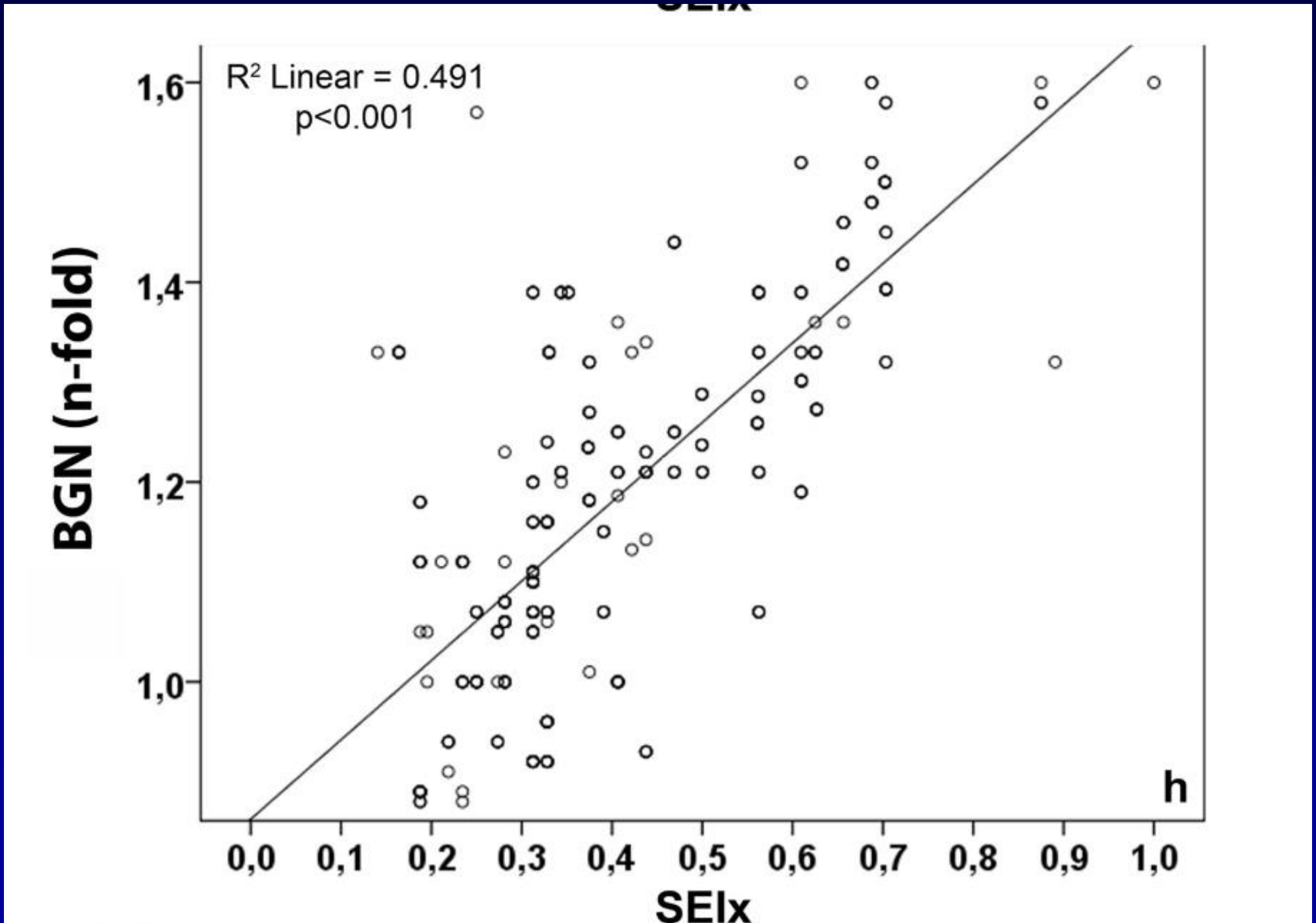
Yutaka Nakashima. Arteriosclerosis, Thrombosis, and Vascular Biology. Early Human Atherosclerosis, Volume: 27, Issue: 5, Pages: 1159-1165, DOI: (10.1161/ATVBAHA.106.134080)



Yutaka Nakashima. Arteriosclerosis, Thrombosis, and Vascular Biology. Early Human Atherosclerosis, Volume: 27, Issue: 5, Pages: 1159-1165, DOI: (10.1161/ATVBAHA.106.134080)

QUESTION 4

If LDL cholesterol is not the first perpetrator, what is the role of other conventional risk factors?
How do they contribute to the formation of coronary plaques?


R² Linear = 0.491
p<0.001
BGN (n-fold)
1,6
1,4
1,2
1,0
0,0
0,1
0,2
0,3
0,4
0,5
0,6
0,7
0,8
0,9
1,0
SEIx
h

Clin Chim Acta. 2009 Aug;406(1-2):89-93. doi: 10.1016/j.cca.2009.05.024. Epub 2009 Jun 10.

Biglycan expression in hypertensive subjects with normal or increased carotid intima-media wall thickness.

Sardo MA[1], Mandraffino G, Campo S, Saitta C, Bitto A, Alibrandi A, Riggio S, Imbalzano E, Saitta A.

Author information

1 Department of Internal Medicine, University of Messina,Via Camiciotti, 82, 98123-Messina, Italy.

Abstract

BACKGROUND: Biglycan (BGN), an extracellular matrix proteoglycan, has been shown to convey pro-inflammatory signals. In the present study we investigated BGN expression and its correlation with plasma levels of inflammatory markers in hypertensive subjects with or without alteration of carotid intima media thickness (IMT).

METHODS: We evaluated 123 untreated essential hypertensives with no additional risk factors for atherosclerosis nor signs of cardiovascular disease and 40 controls. Hypertensives were classified according to a normal (< or =1 mm) or increased (>1 mm) IMT. BGN-mRNA and protein expression were measured in unstimulated, LPS- and Angiotensin II (Ang-II)-stimulated blood monocytes. Plasma concentrations of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-alpha) and high sensitivity-C-reactive protein (hs-CRP) were also measured.

RESULTS: We found increased levels of IL-6, TNF-alpha, hs-CRP, and BGN-mRNA and protein in hypertensives vs controls (1.72+/-0.60 vs 1 n-fold, and 3.60+/-0.75 vs 1 n-fold, both $p<0.001$). However, BGN expression was not significantly different between hypertensives with IMT < or =1 mm and >1 mm. Furthermore, in vitro addition of Ang II enhanced basal BGN-mRNA (in hypertensives: 3.57+/-1.08 vs 1.72+/-0.60 n-fold, $p<0.001$) and protein (in hypertensives: 4.92+/-0.42 vs 3.41+/-0.75, $p<0.001$) expression in monocytes.

CONCLUSIONS: Our data provide evidence of an enhanced expression of BGN in essential hypertension. In addition we suggest that Ang II

58 YO male patient just had PCI of RCA a week before

1. No HTN
2. Age 58
3. No diabetes
4. No smoking
5. LDL =58mg%

What is the next question to ask?

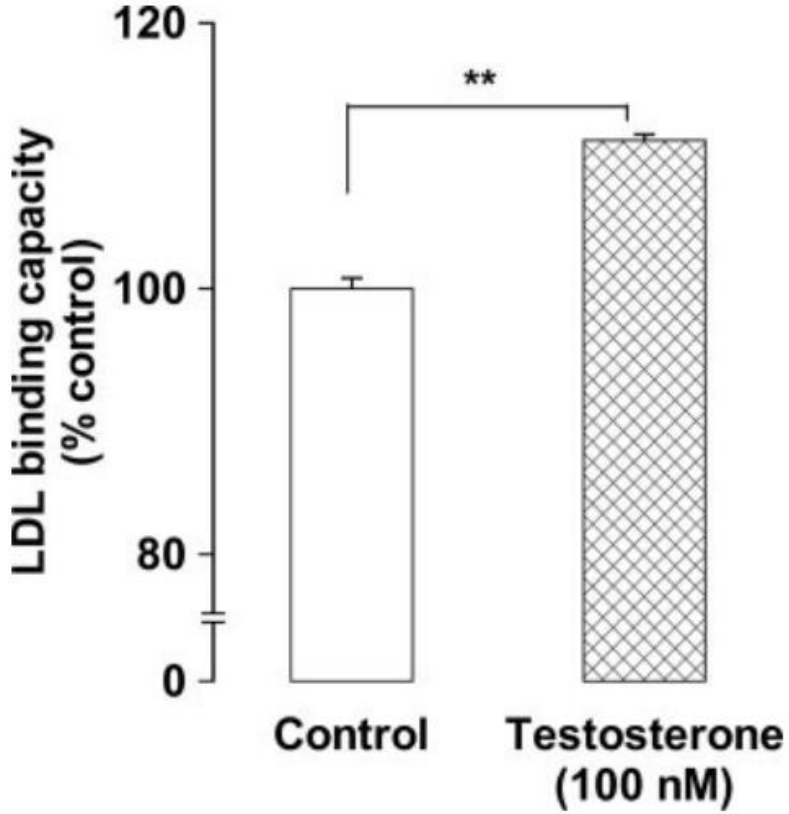


FIG. 5. T-treated VSMCs synthesize proteoglycans with increased binding capacity to LDL. Human VSMCs were treated with and without T (100 nM) and metabolically labeled with [^{35}S]sulfate. Radiolabeled proteoglycans were applied to separate LDL affinity columns and eluted with 1 M NaCl. The amount of radioactivity eluted from the column was expressed as a percentage of the amount applied to the column. The control was set at 100% LDL binding capacity and proteoglycan-LDL binding from T-treated cells was expressed as a percentage of the control. Data are the mean ± SEM of three experiments. **, $P < 0.01$.

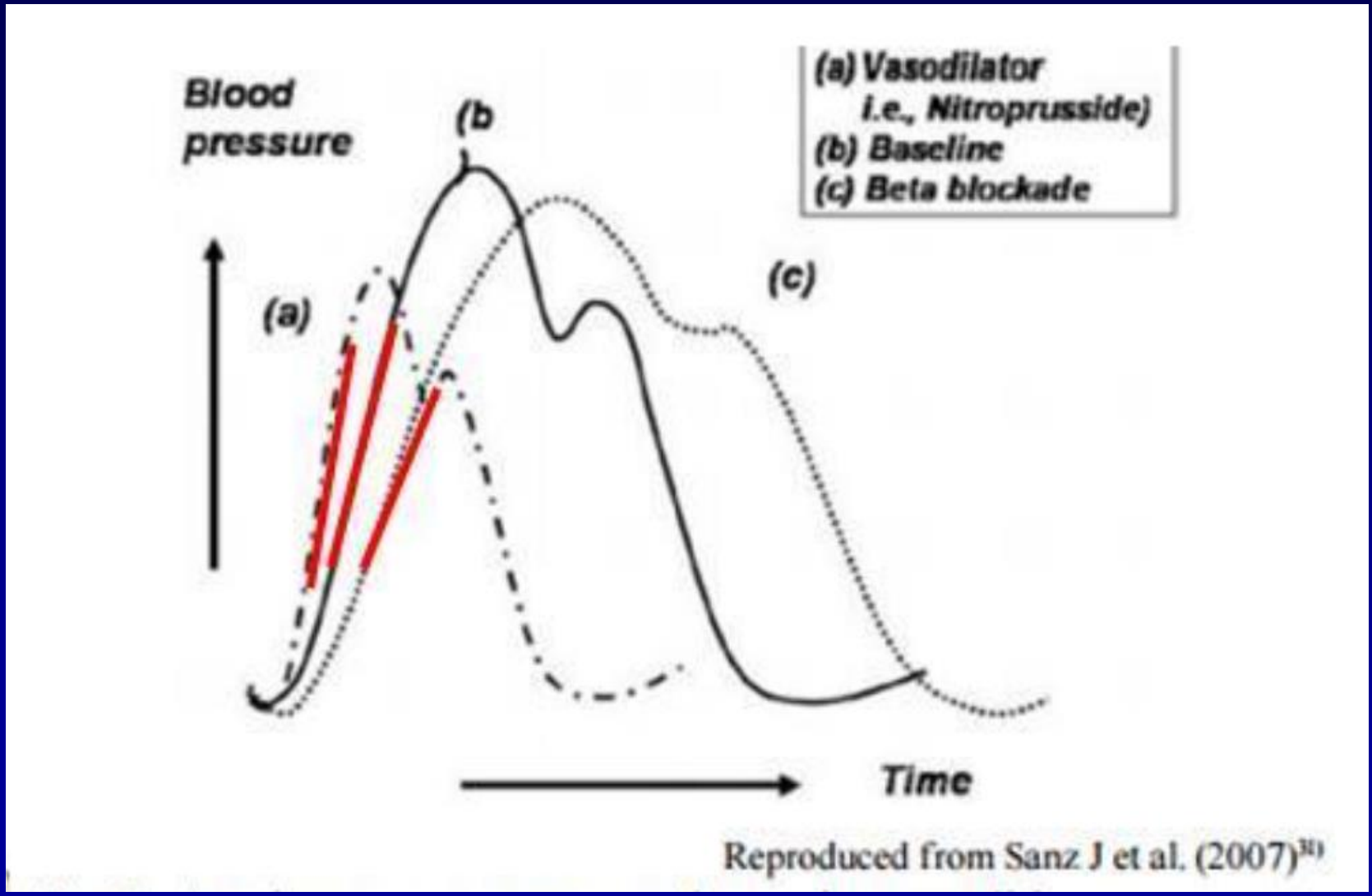
APPLICATIONS:
What can attenuate the brisk rate of rise dP/dT of the systolic blood pressure?

EXERCISE

Perfect Blood Pressure: No large gap between systolic and diastolic BP

BETA BLOCKERS

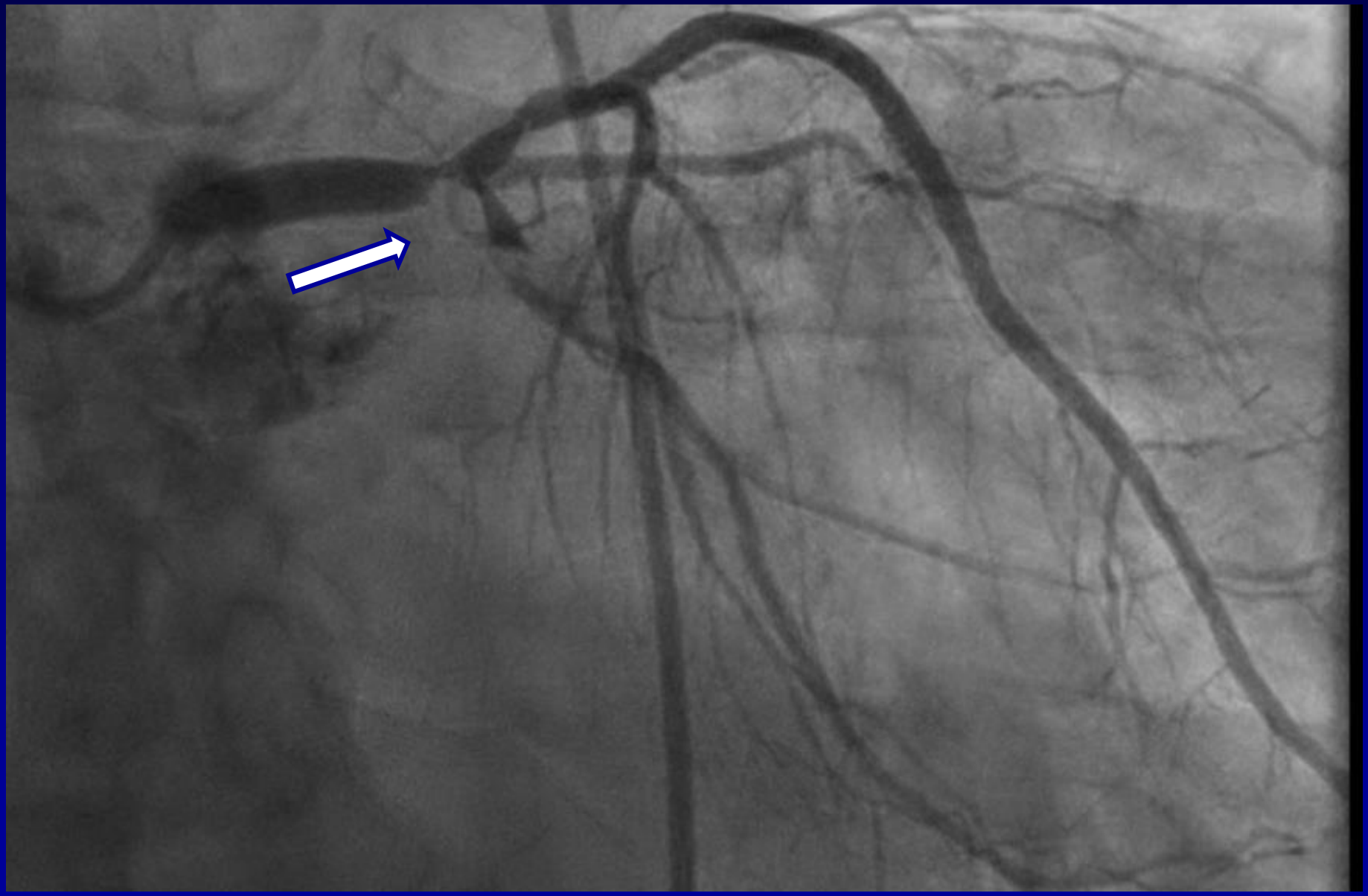
MECHANISM OF BETA BLOCKADE



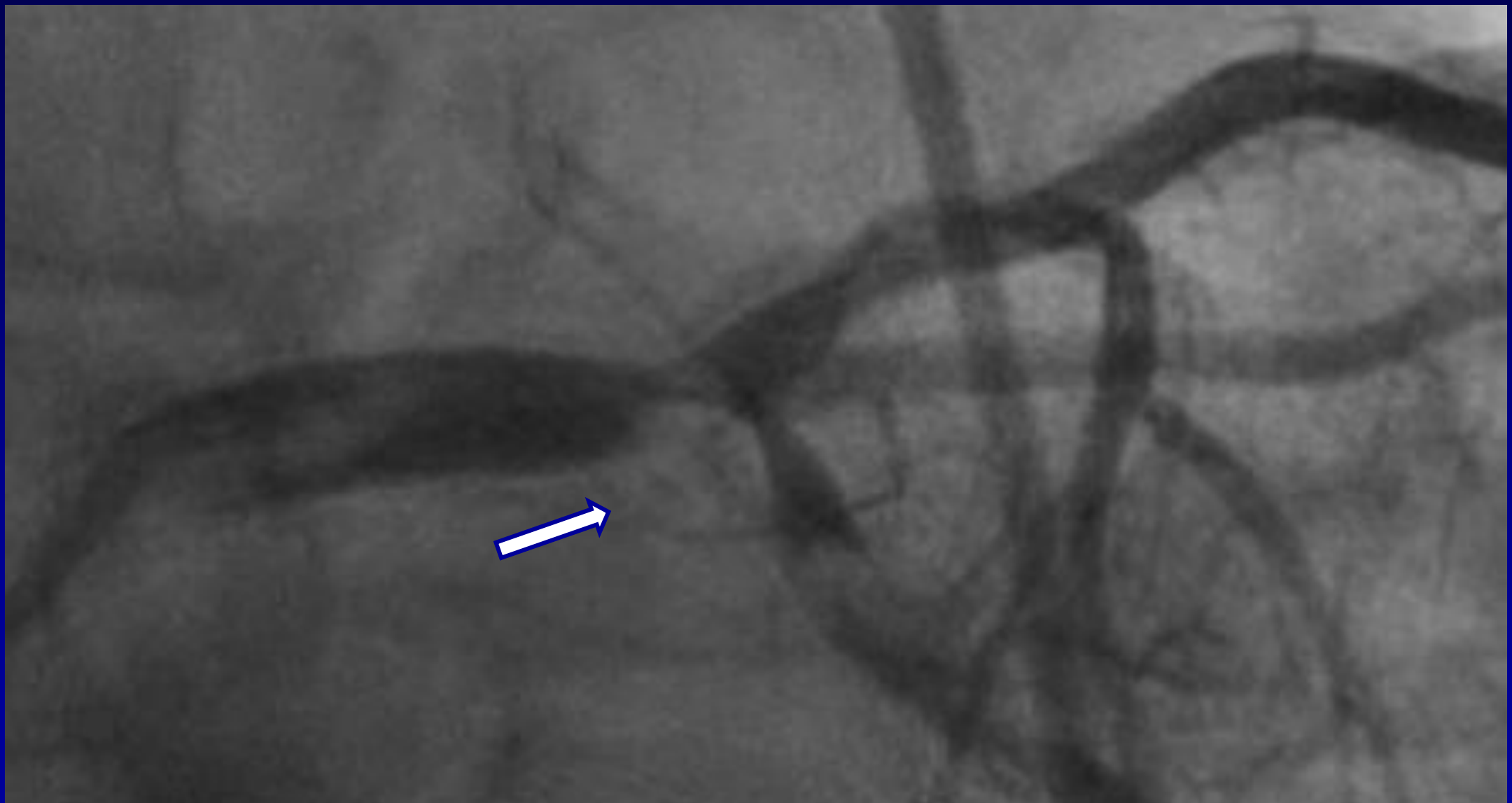
Reproduced from Sanz J et al. (2007)[31]

ONGOING RESEARCH

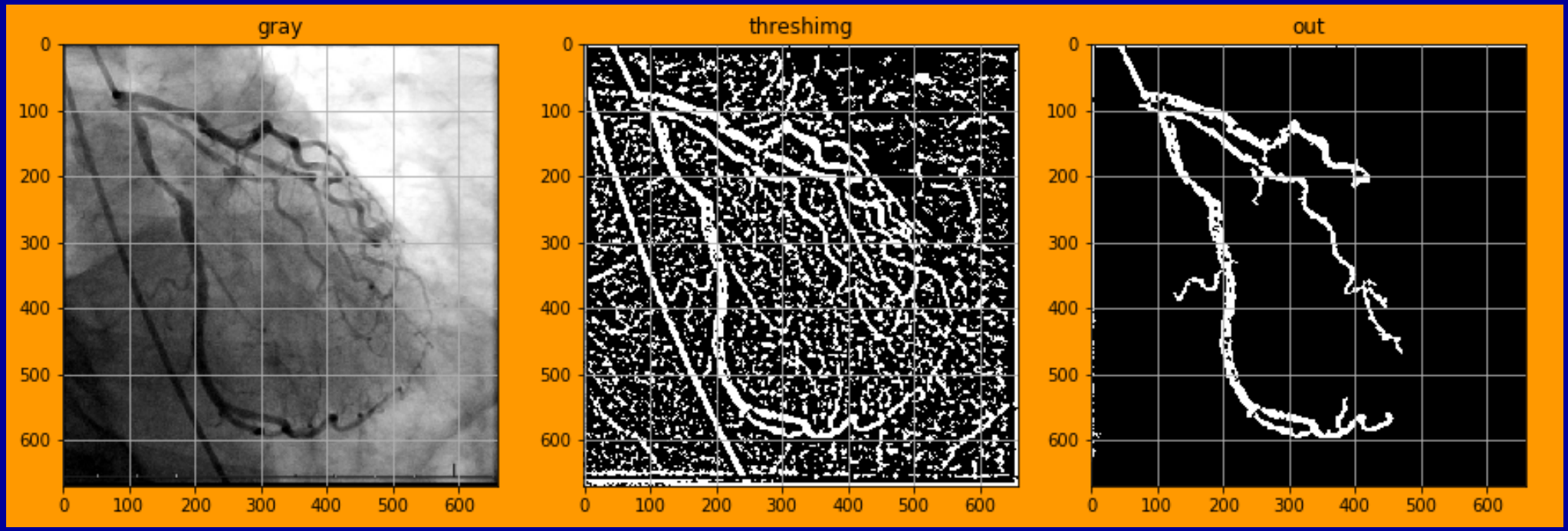
Question 4. Will the plaque rupture in a near future?

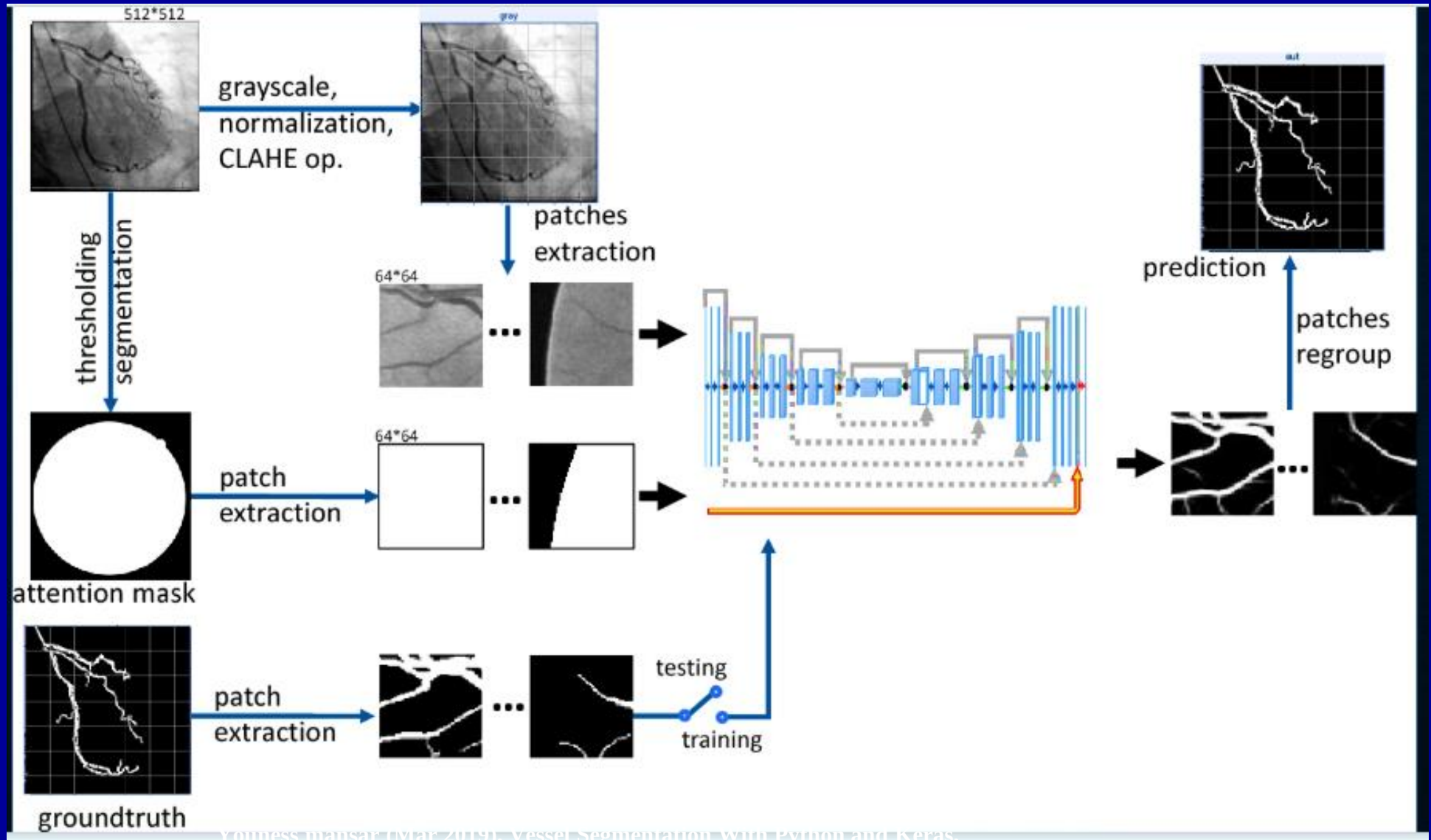


Answer 4. Is the flow turbulent at the entry slope of the plaque?



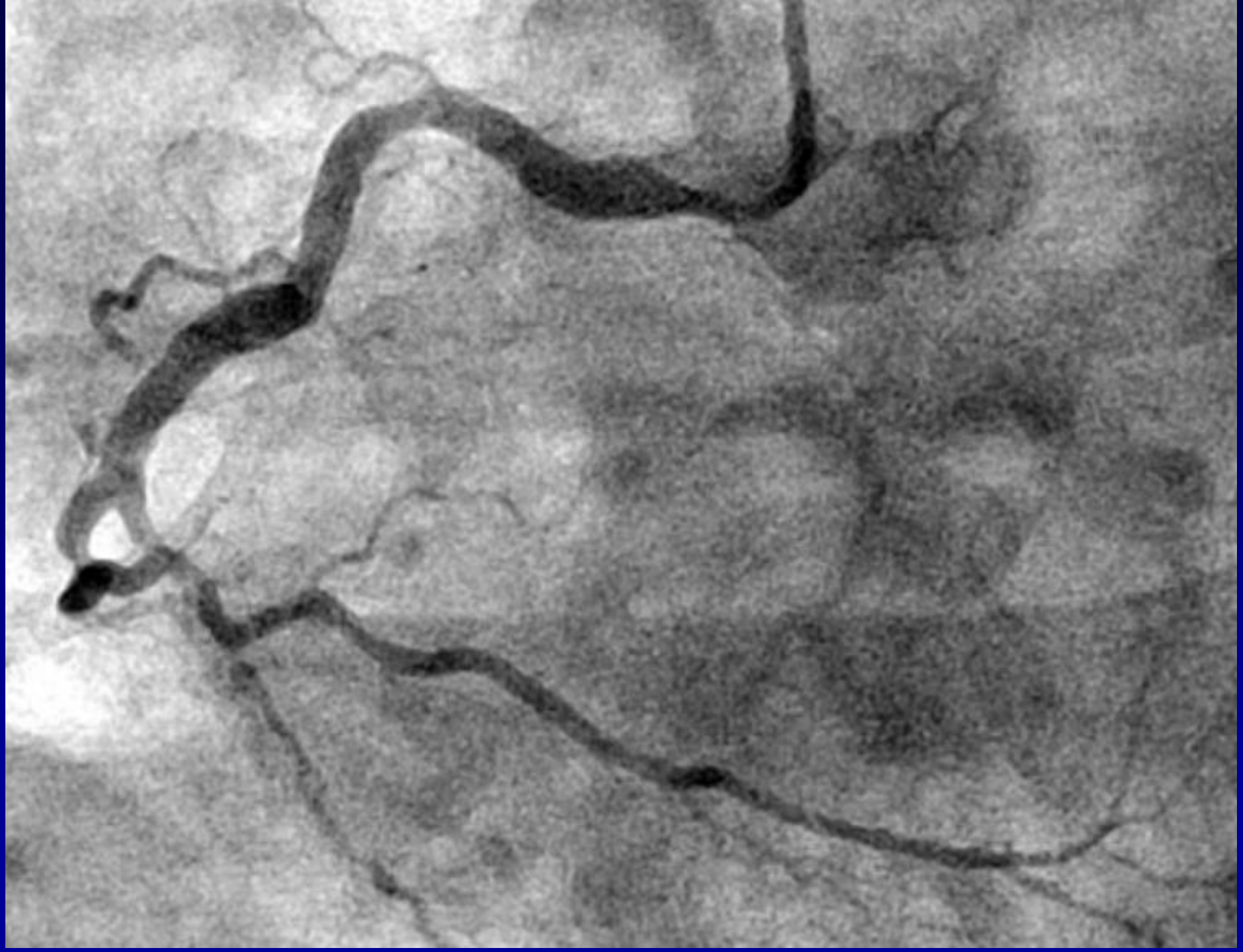
MEDICAL IMAGING SEGMENTATION

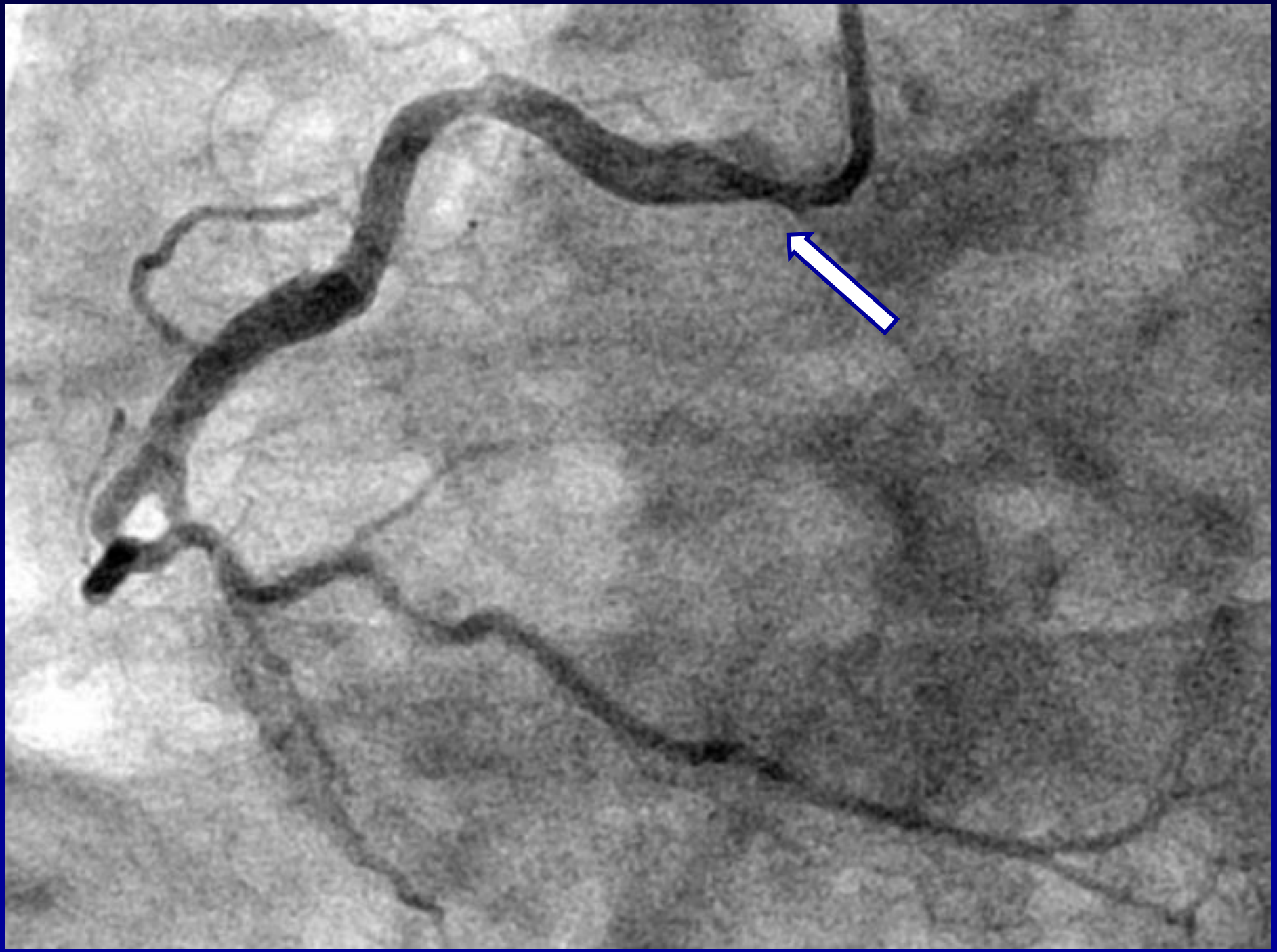


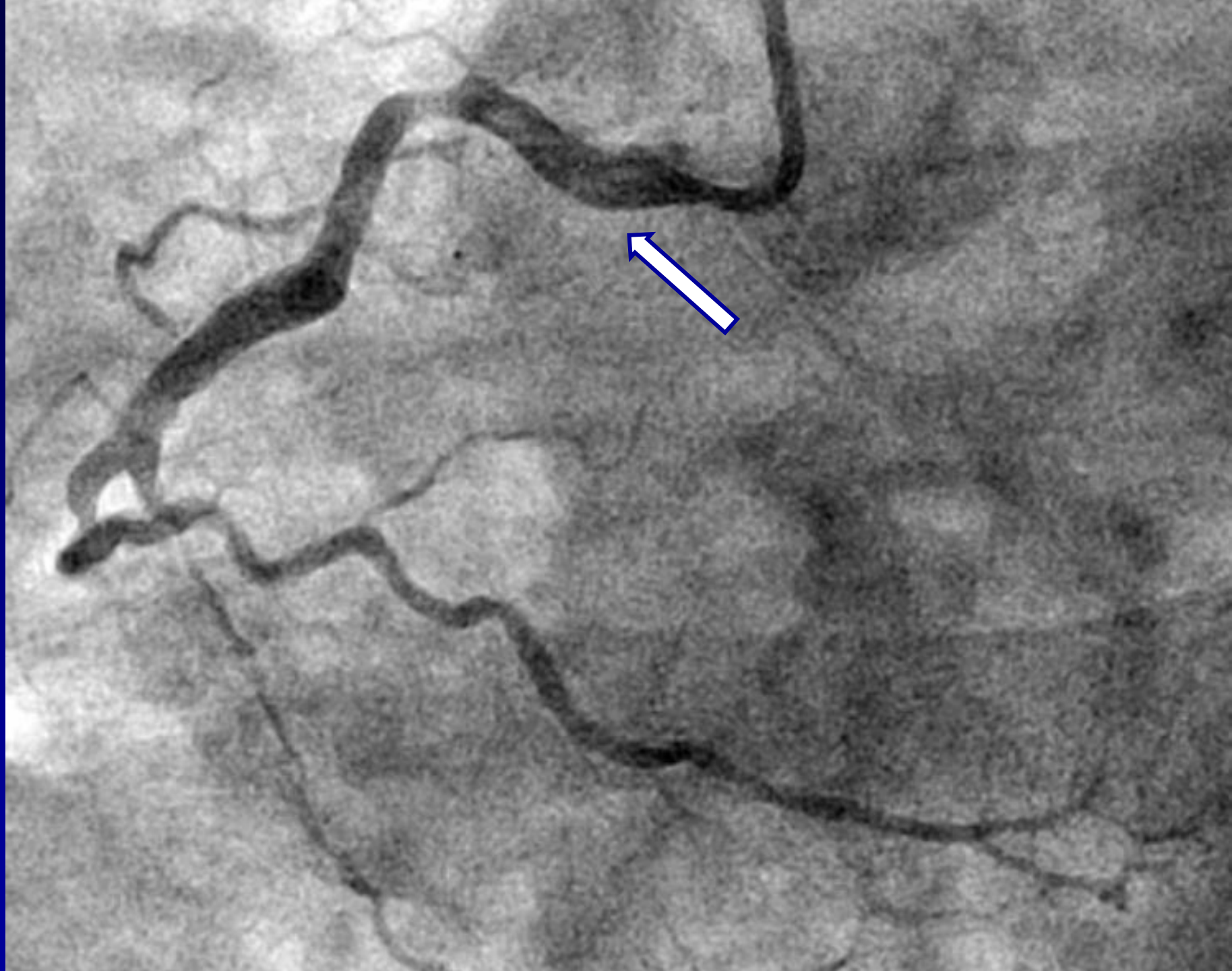


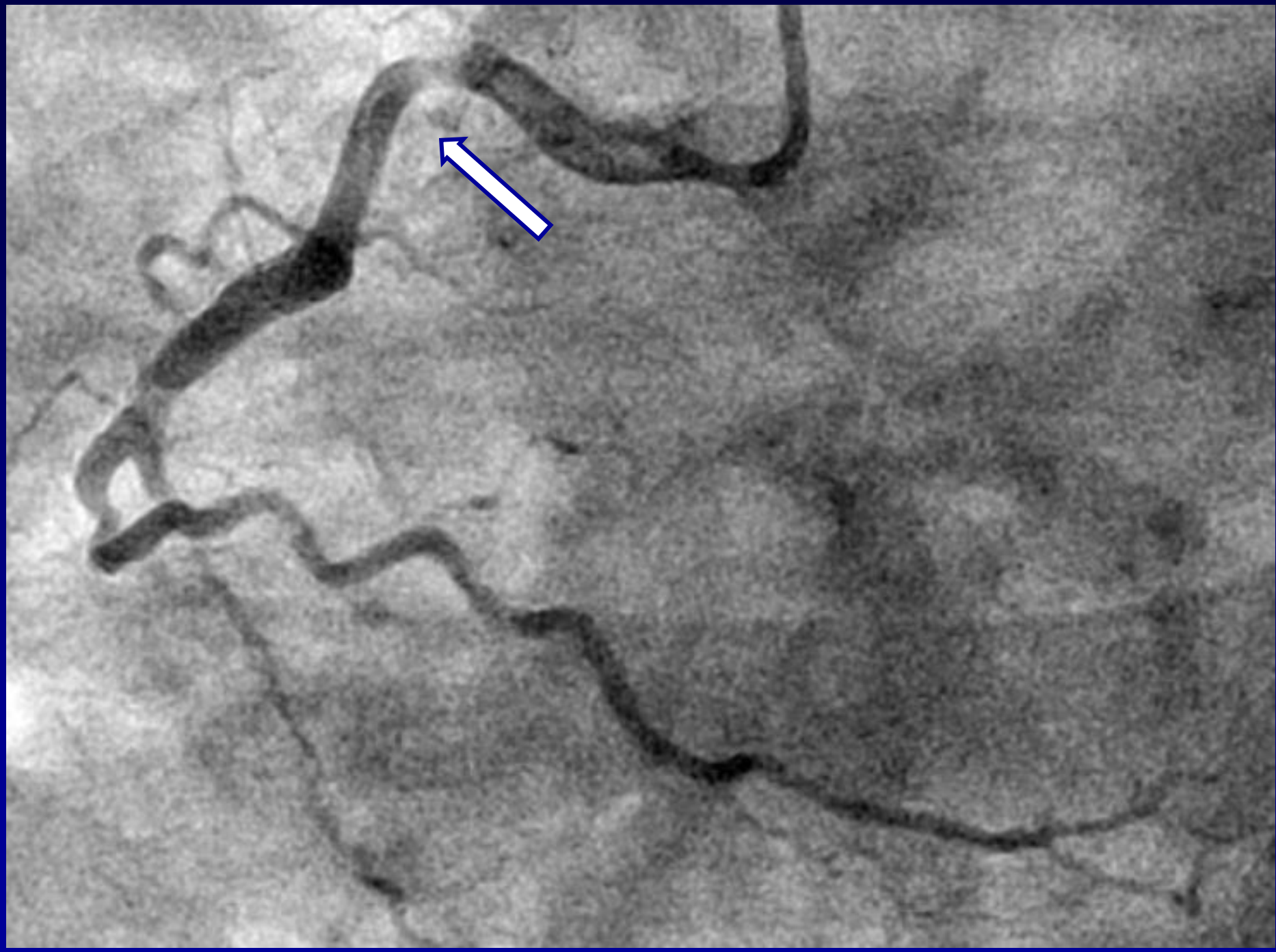
Youness Mansar (Mar 2019), Vessel Segmentation With Python and Keras,
https://towardsdatascience.com/vessel-segmentation-with-python-and-keras-722f9fb71b21

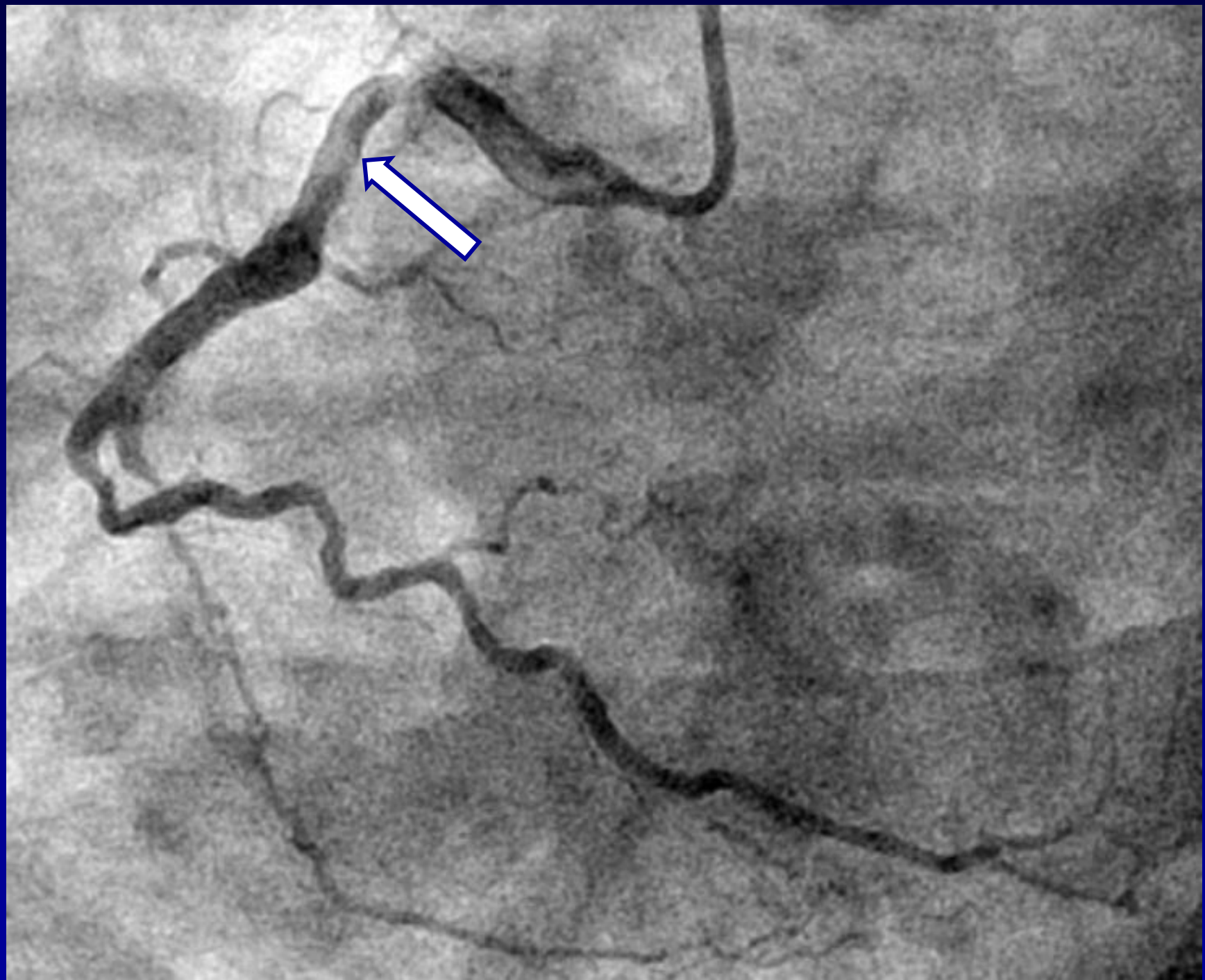
John K
RCA 72 frames before PCI

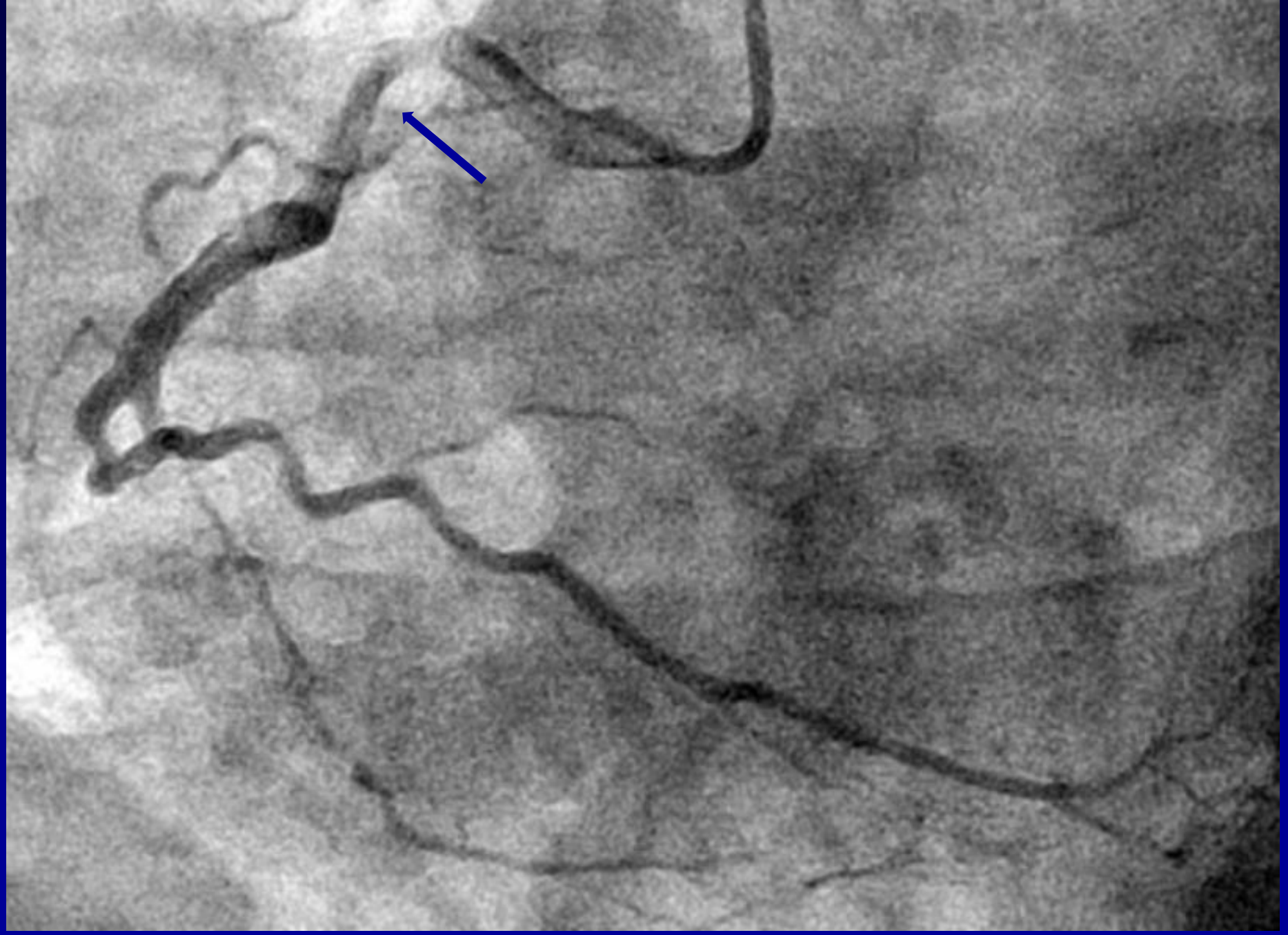


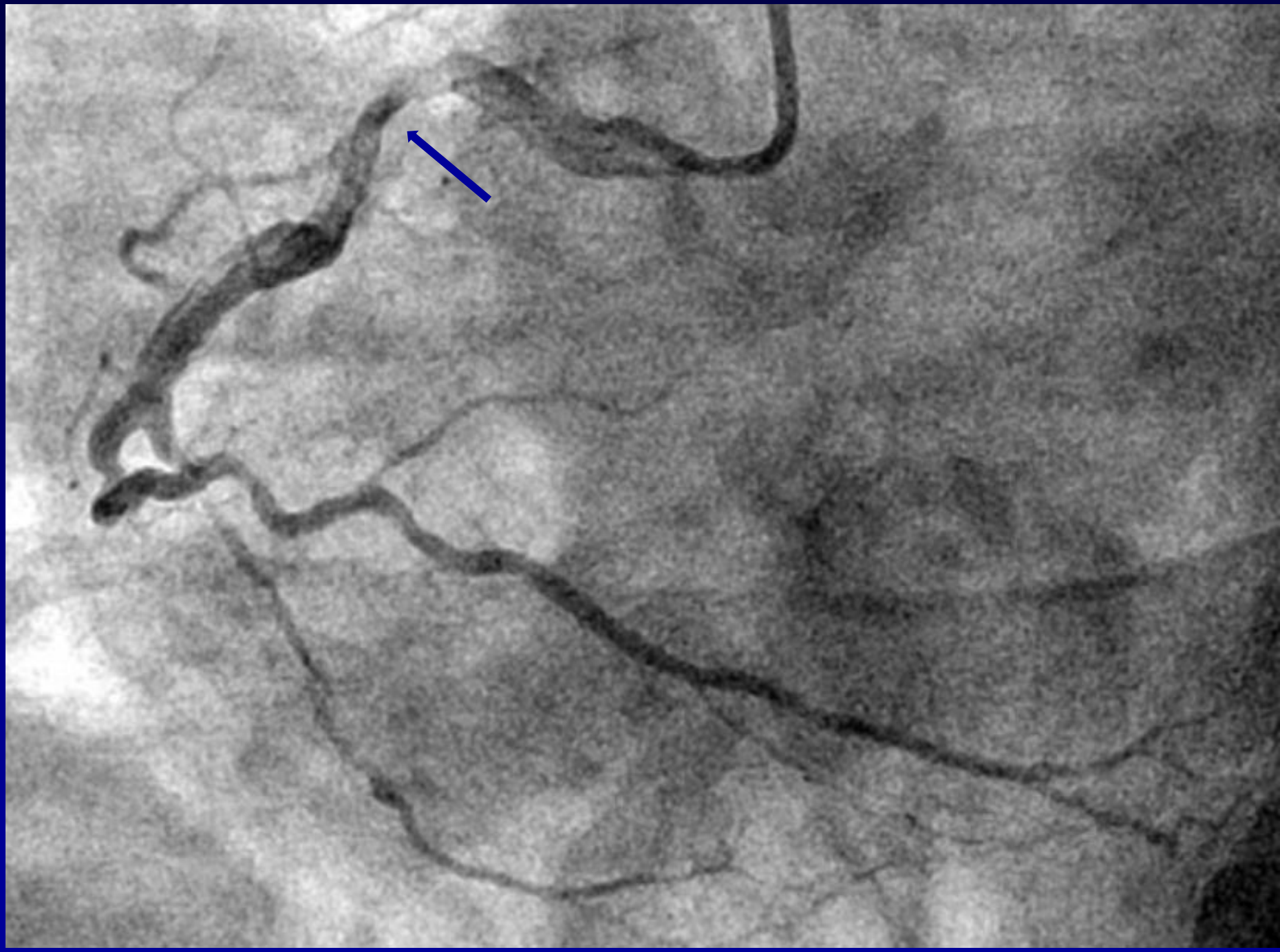


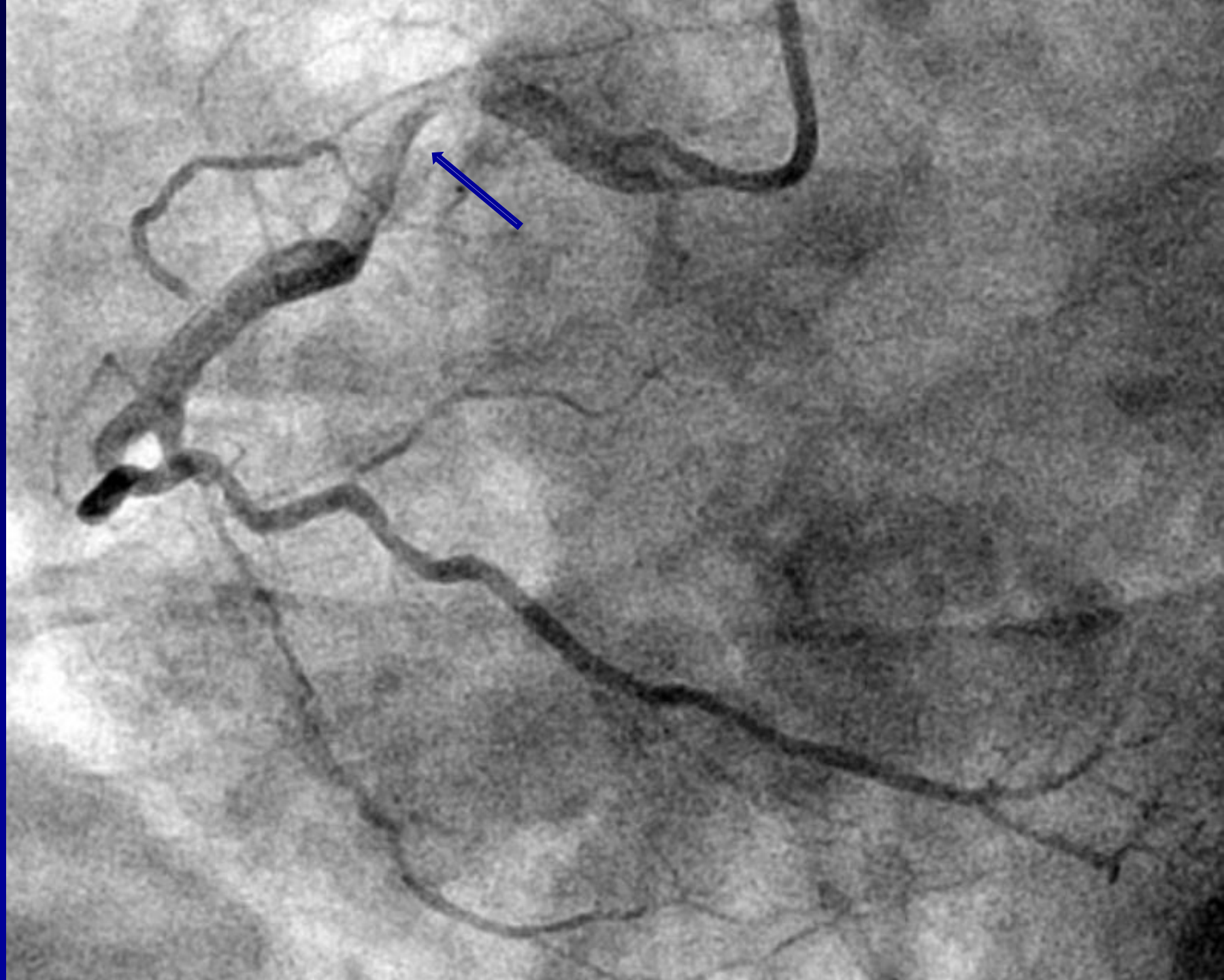


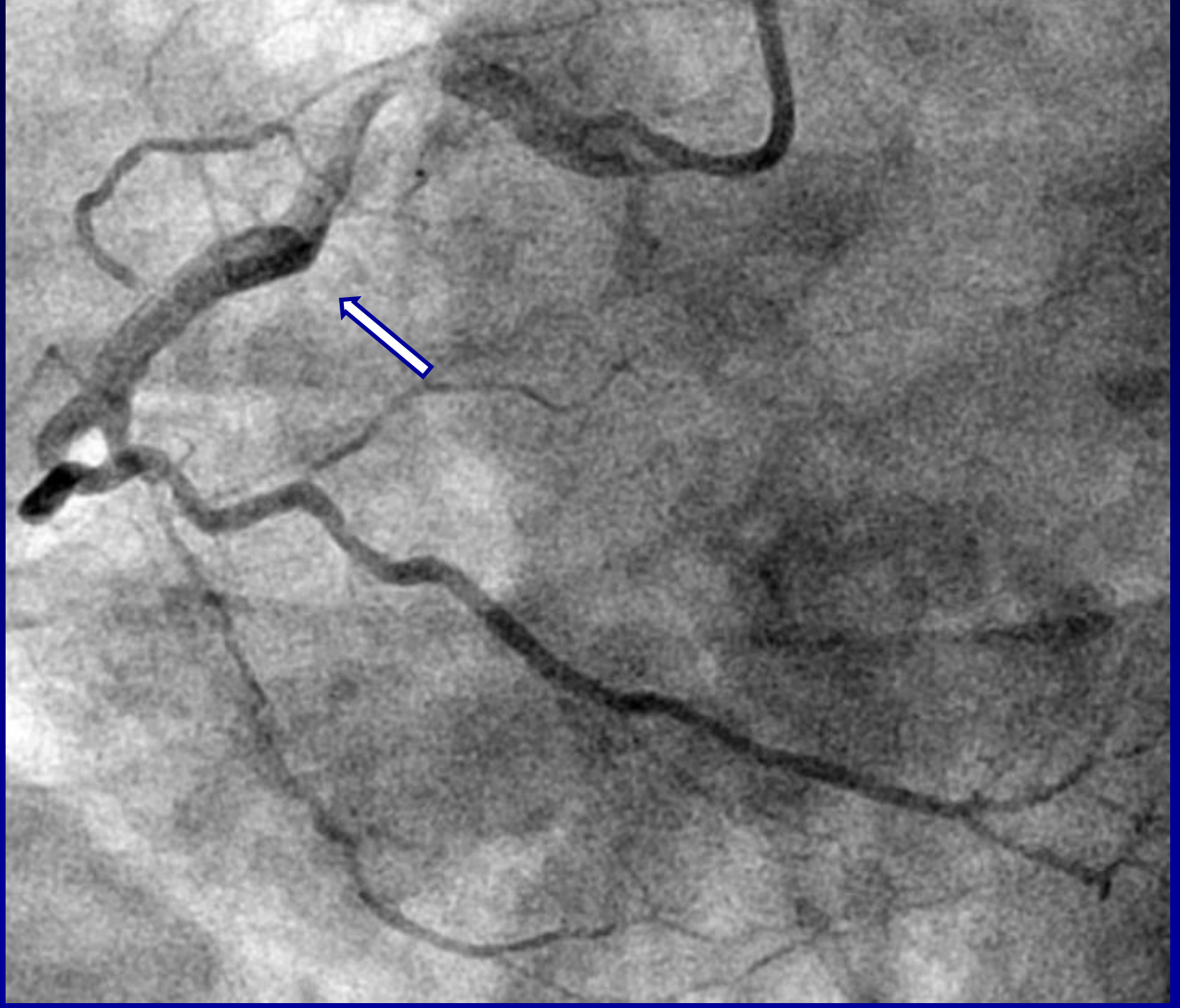


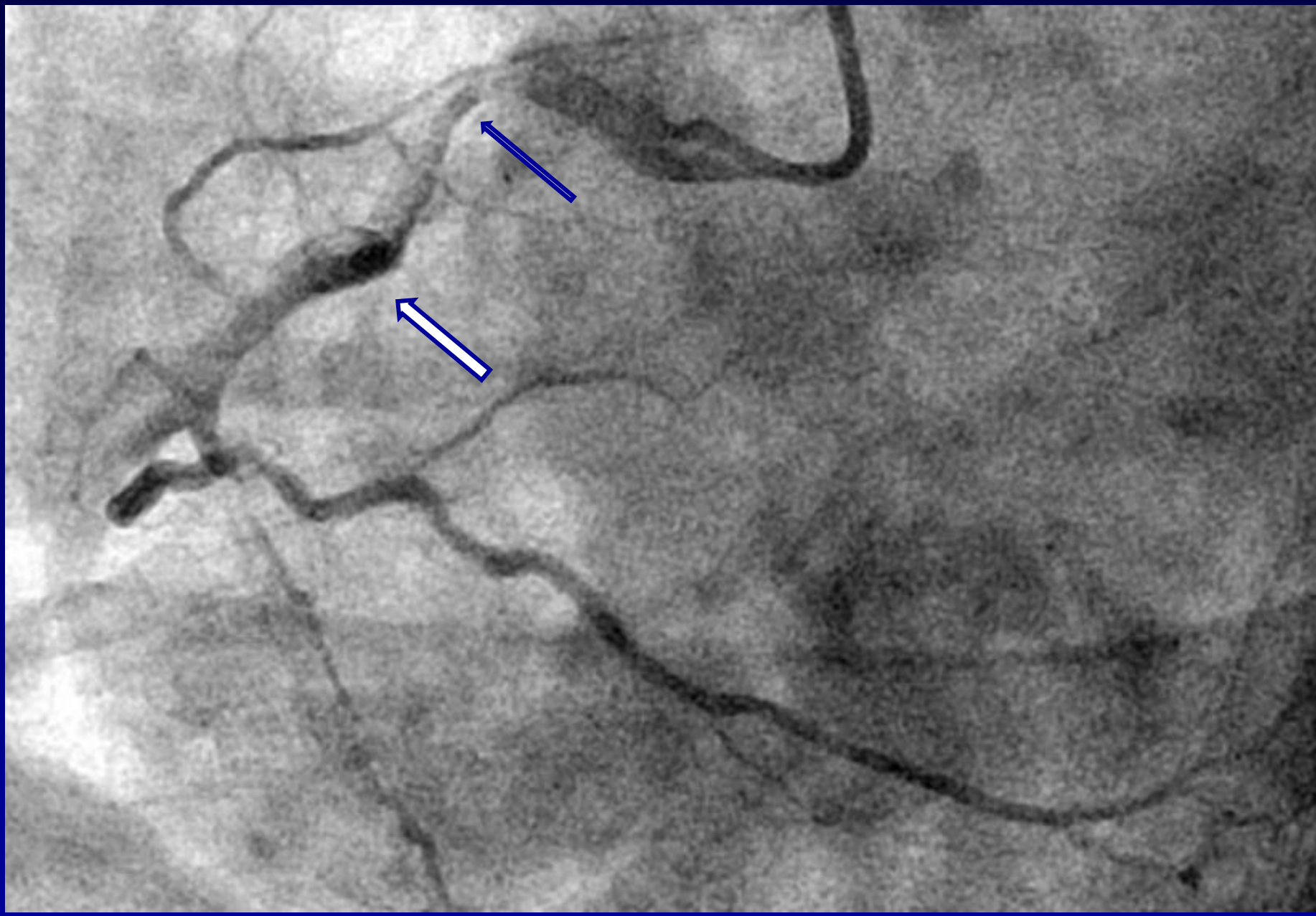


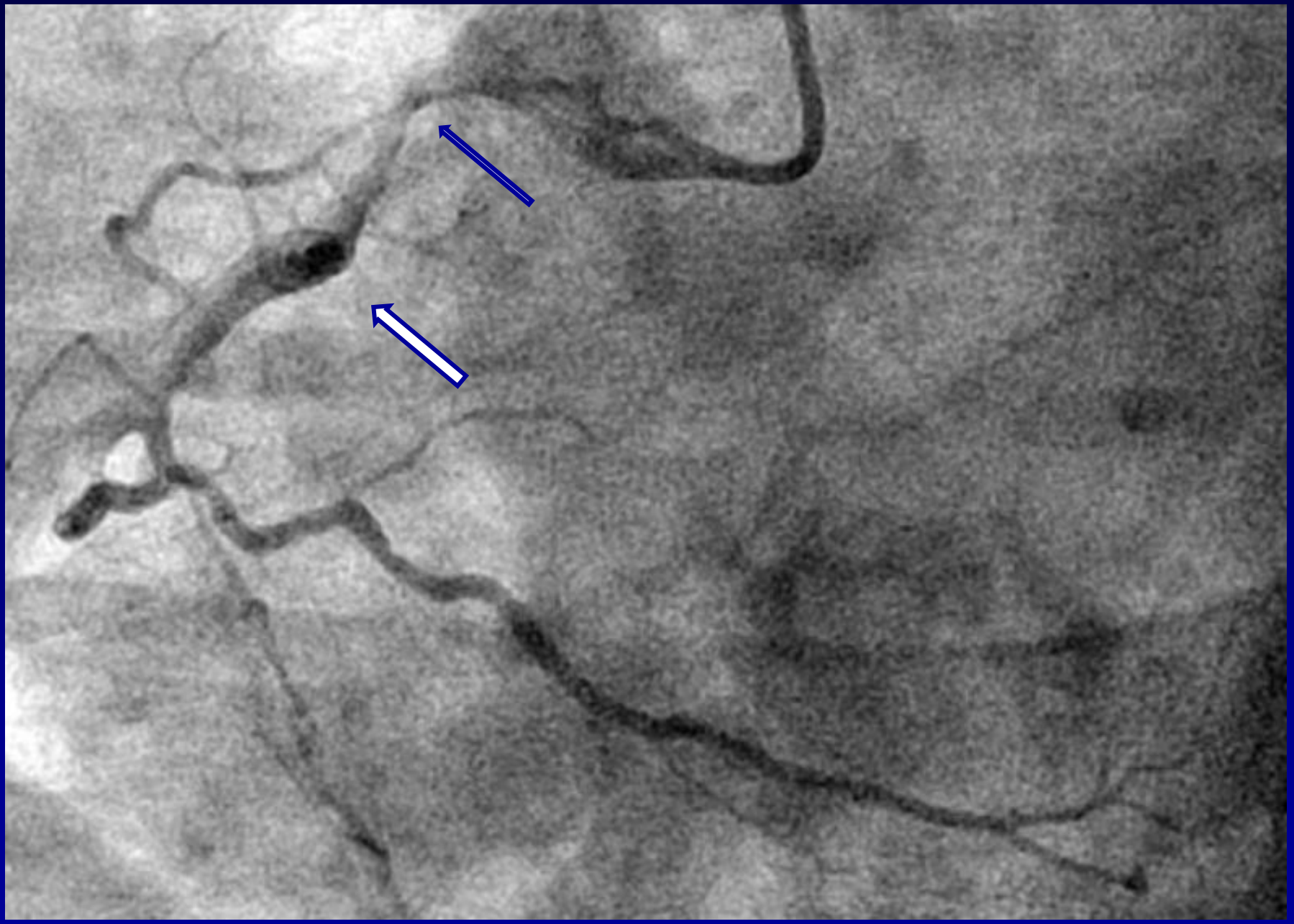


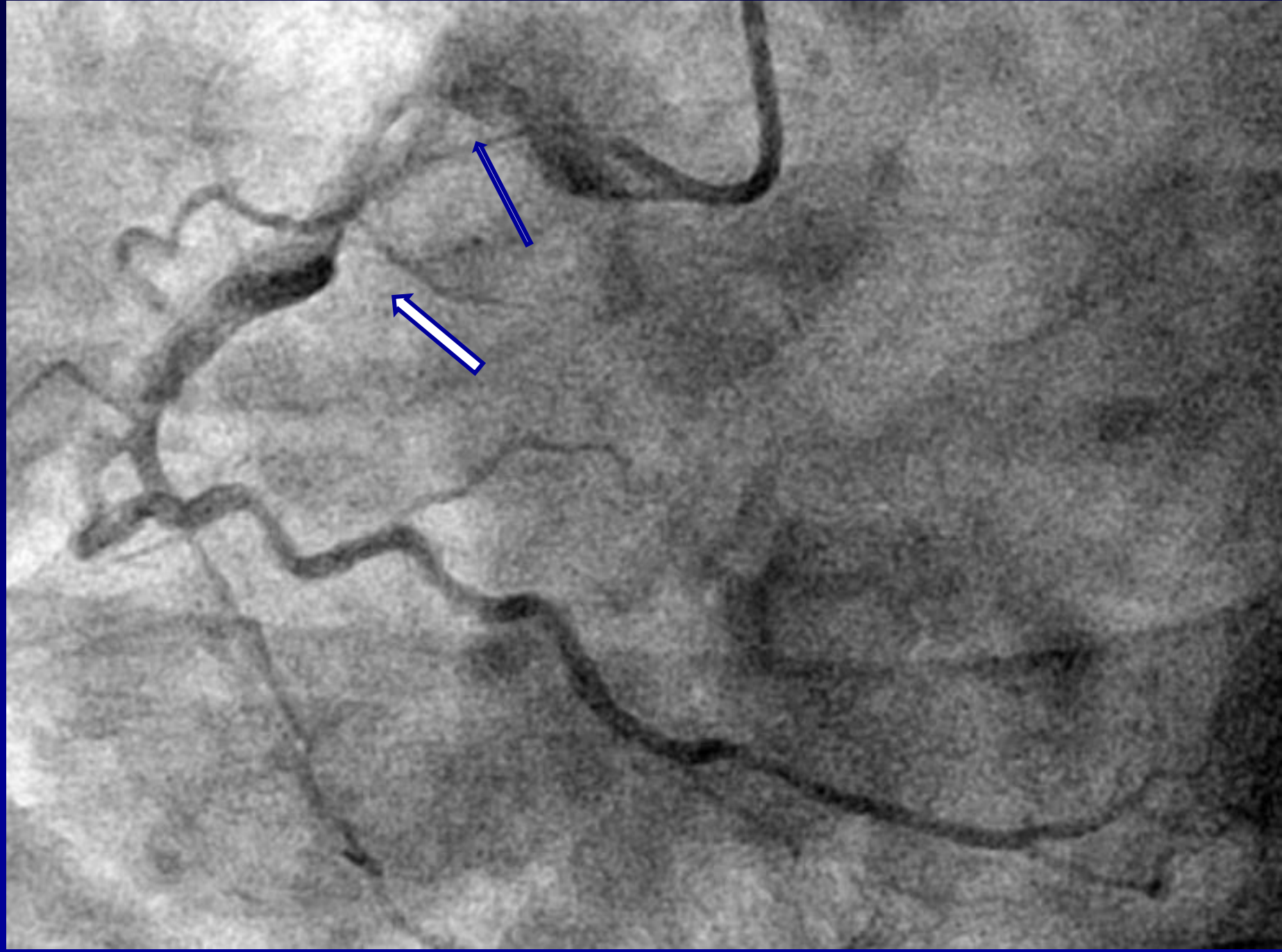


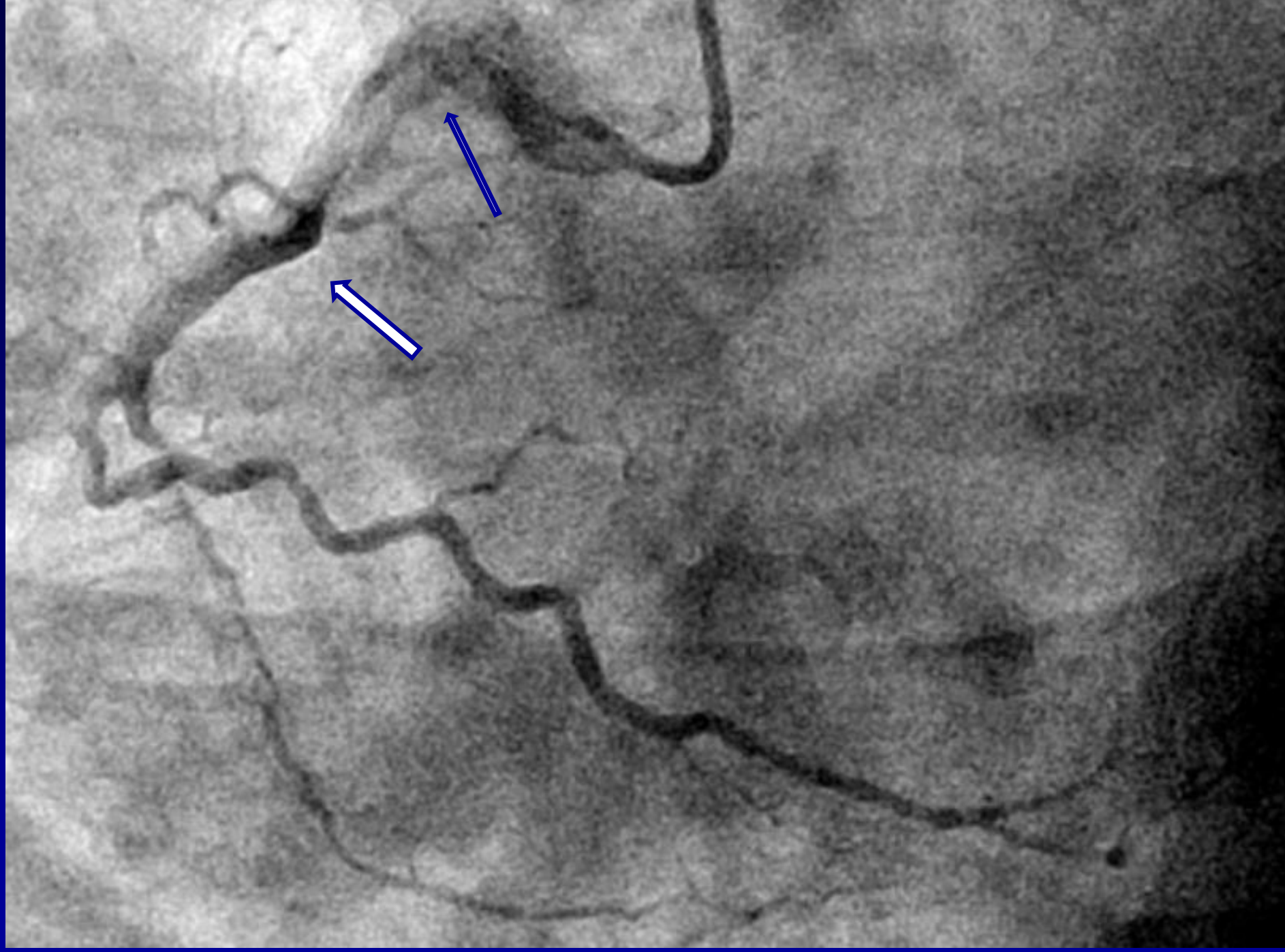


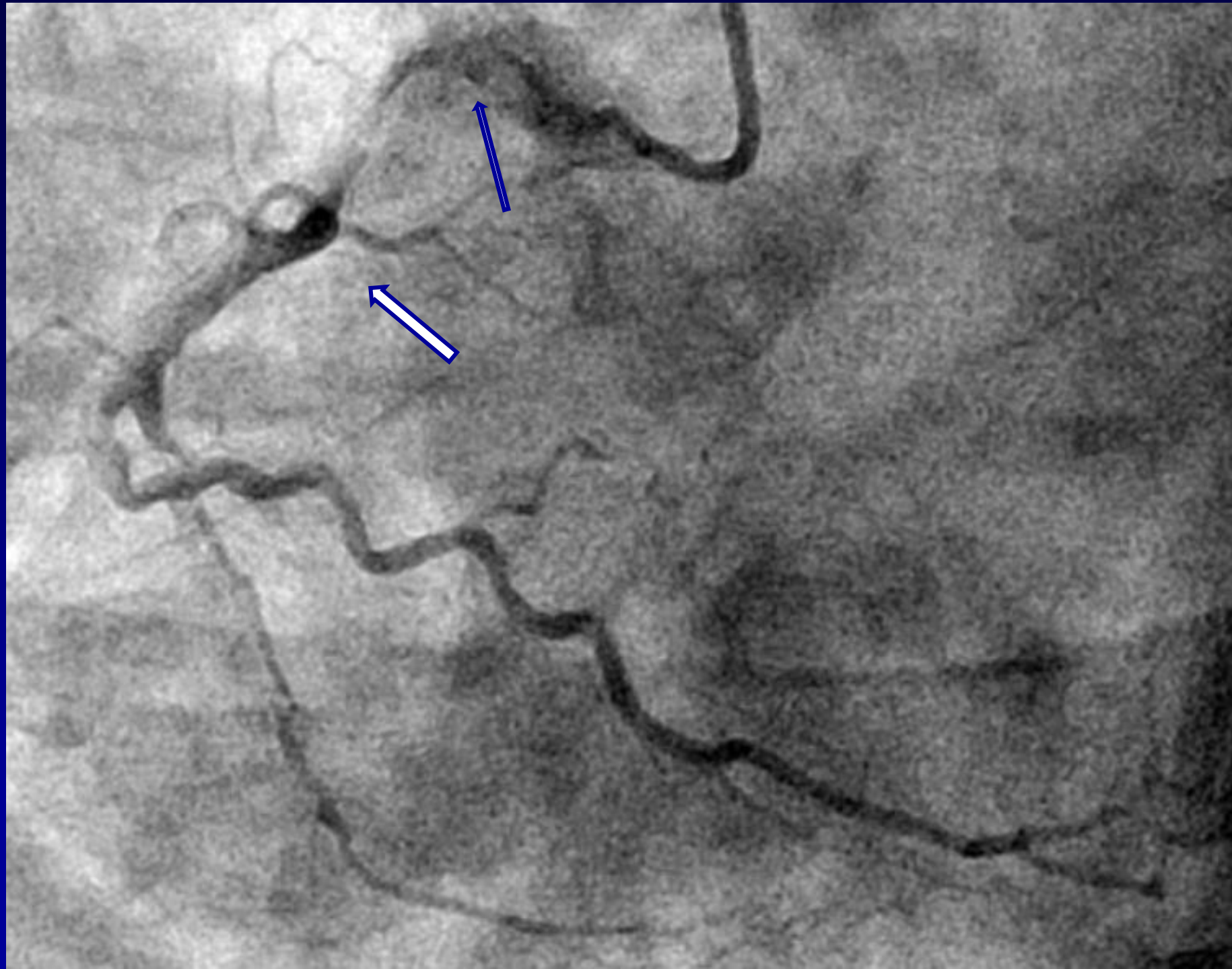


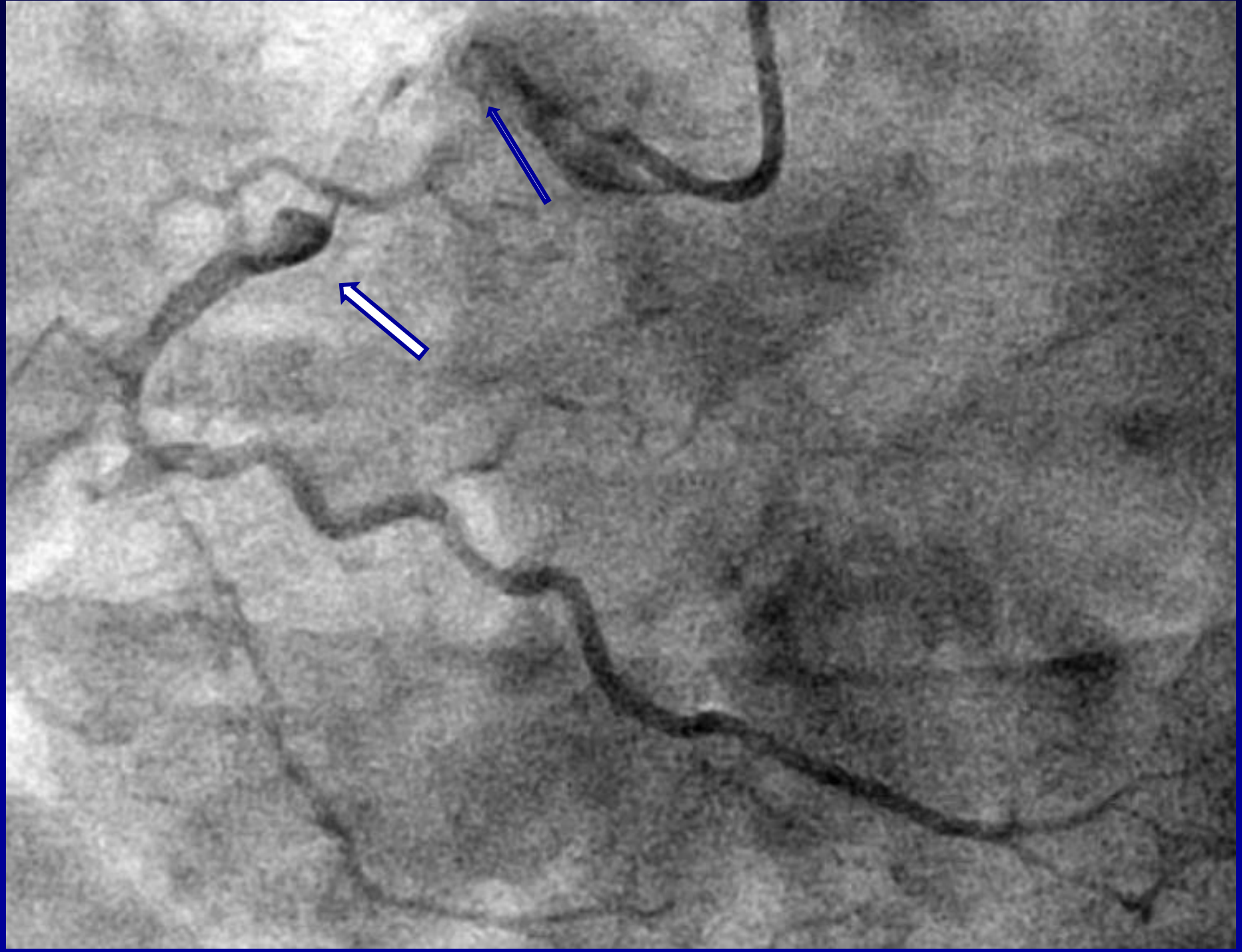


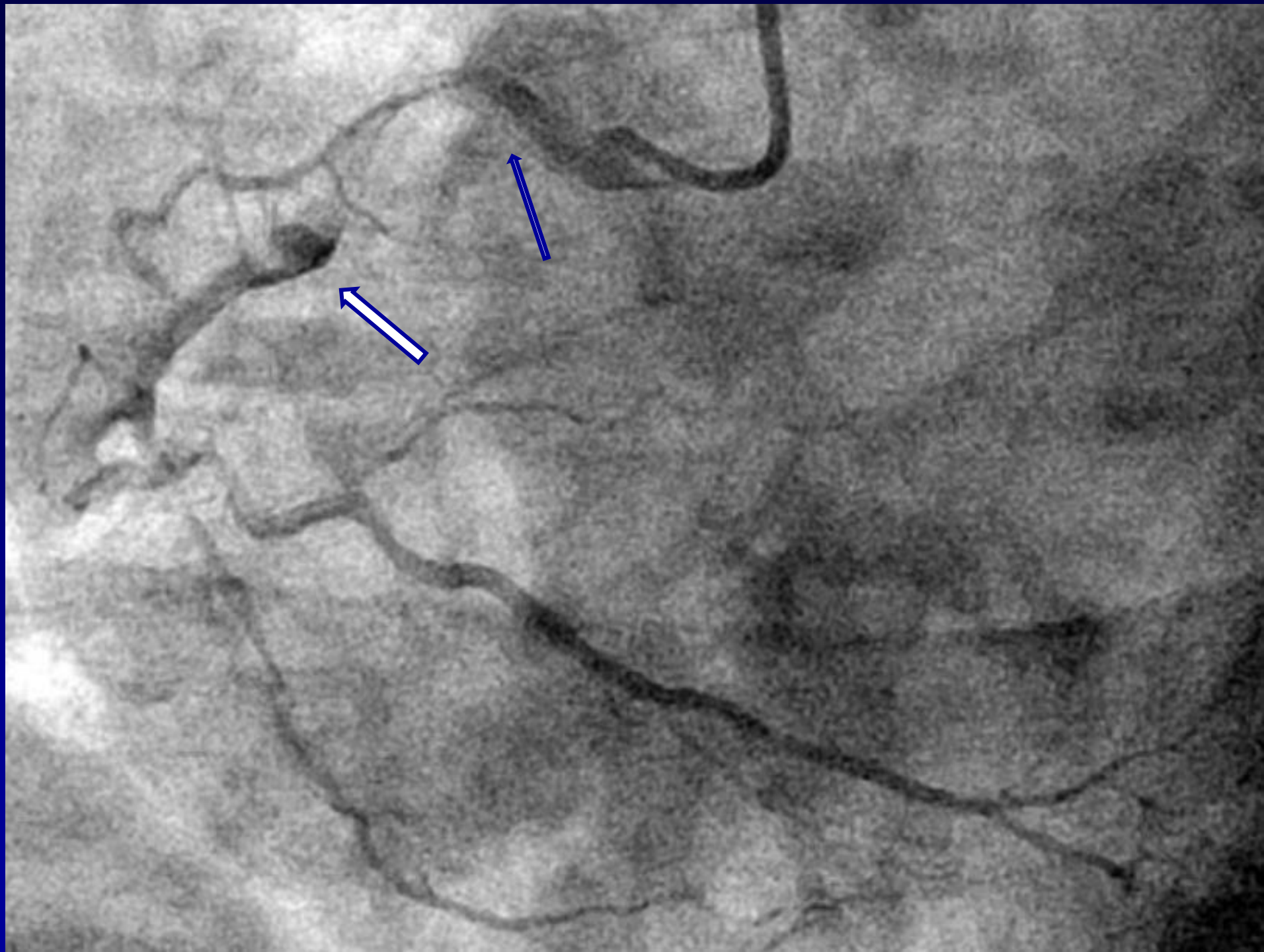


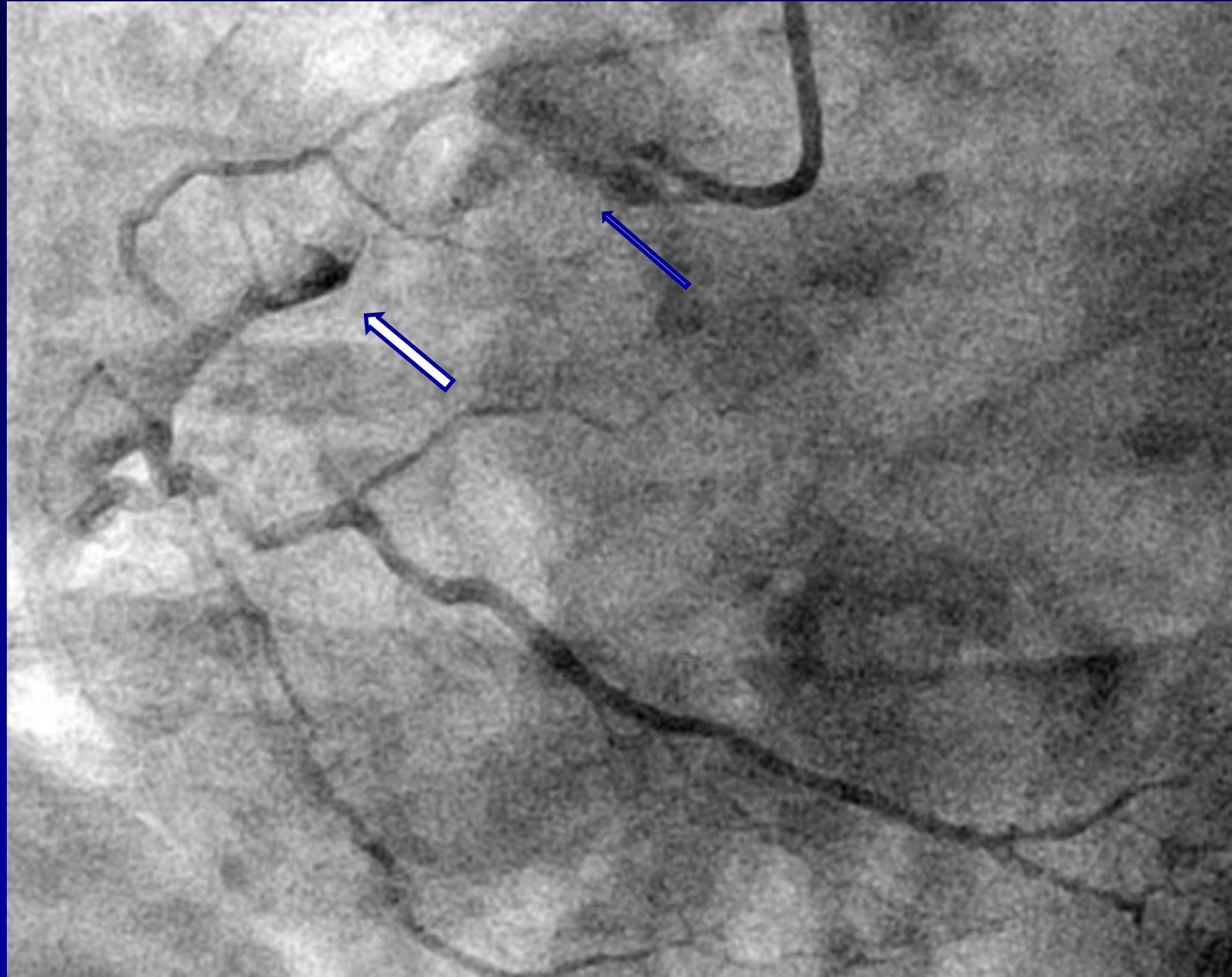


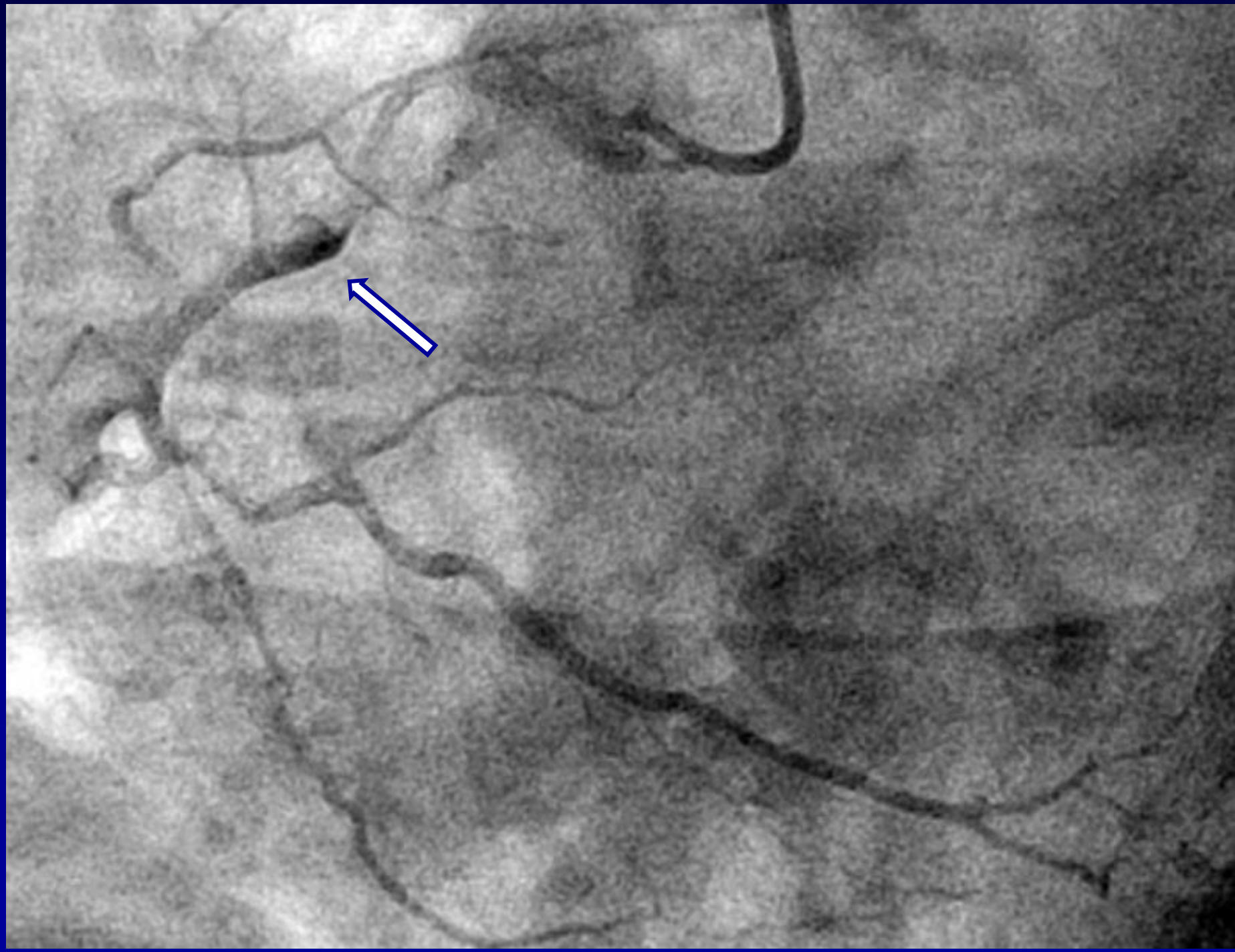


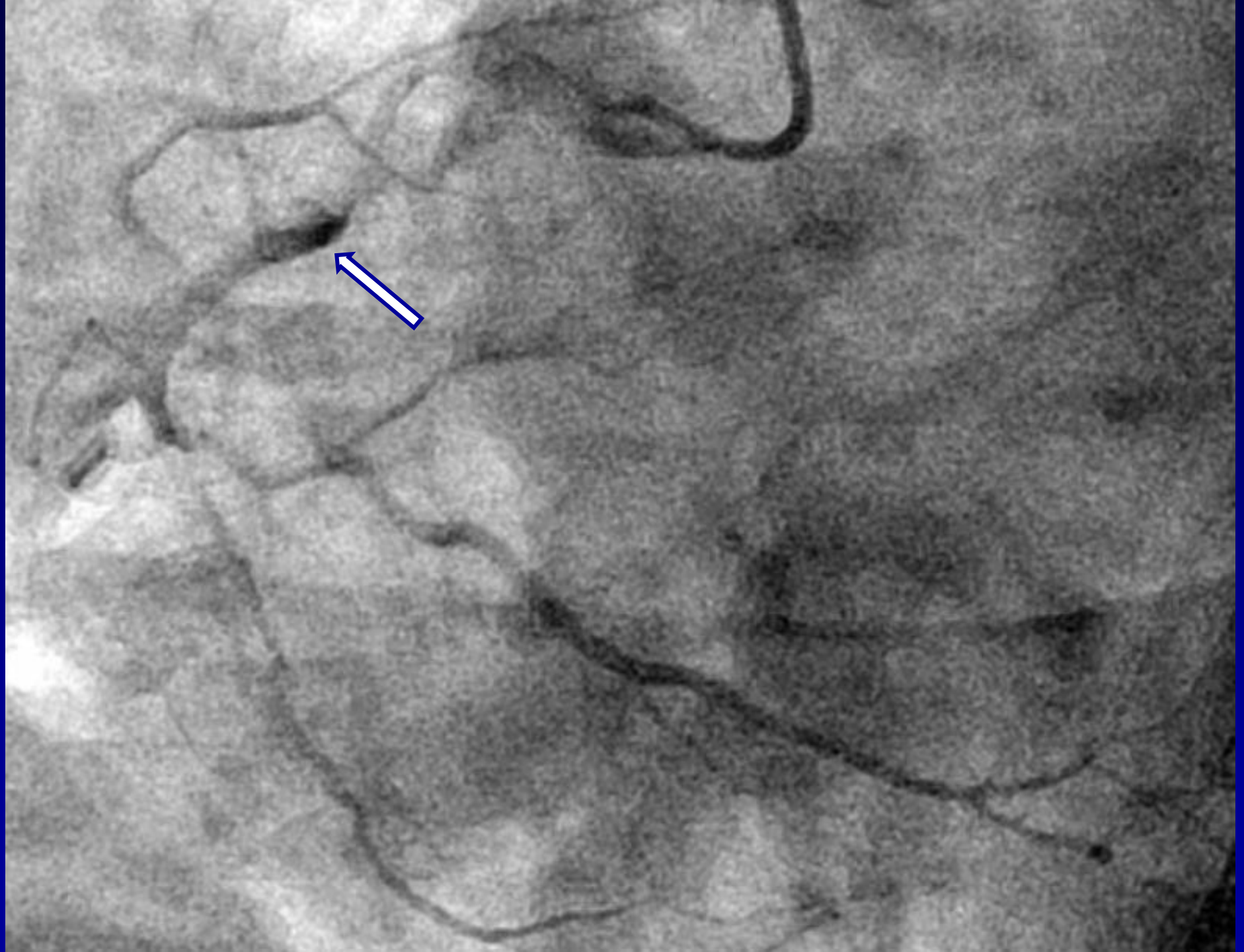


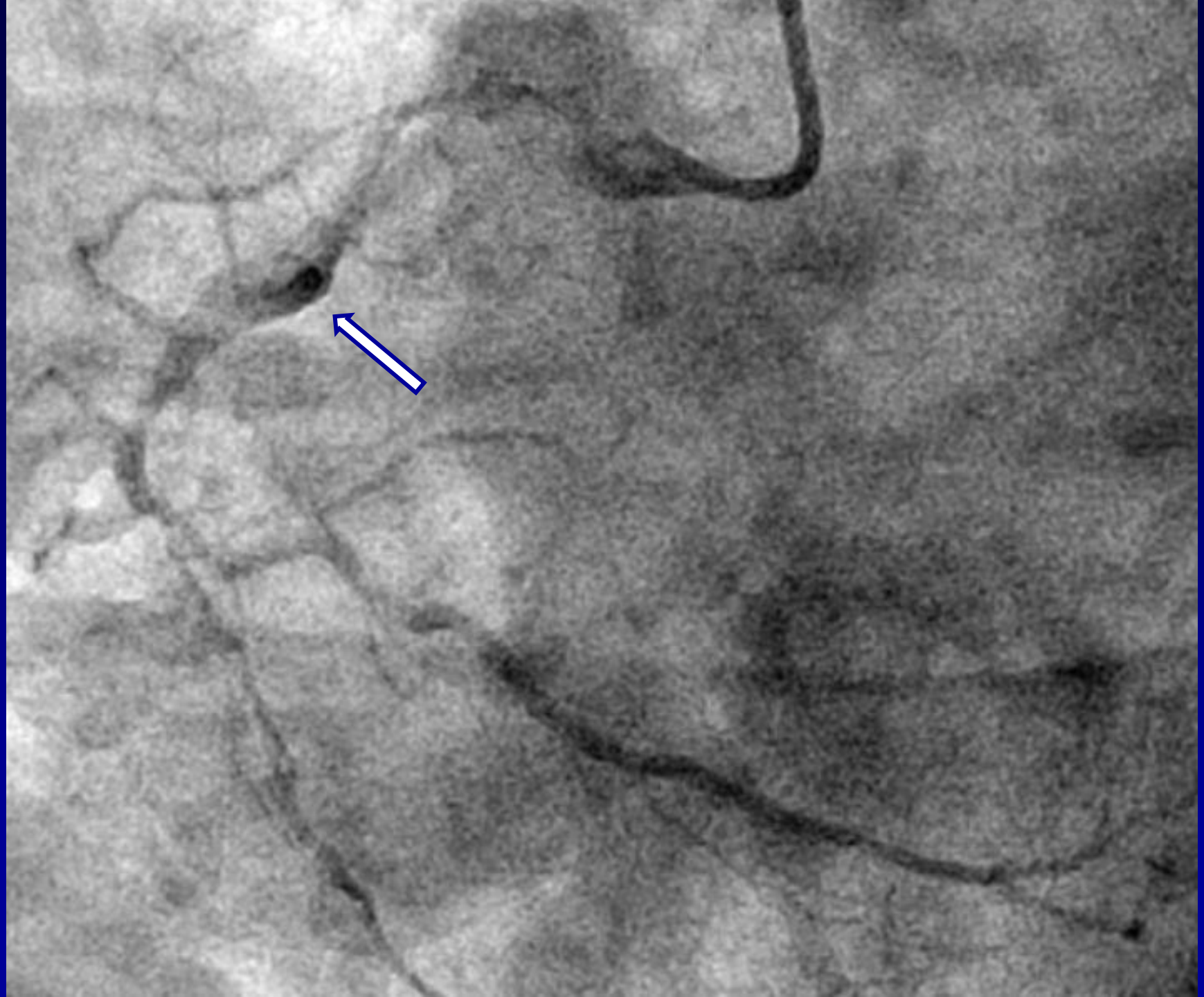


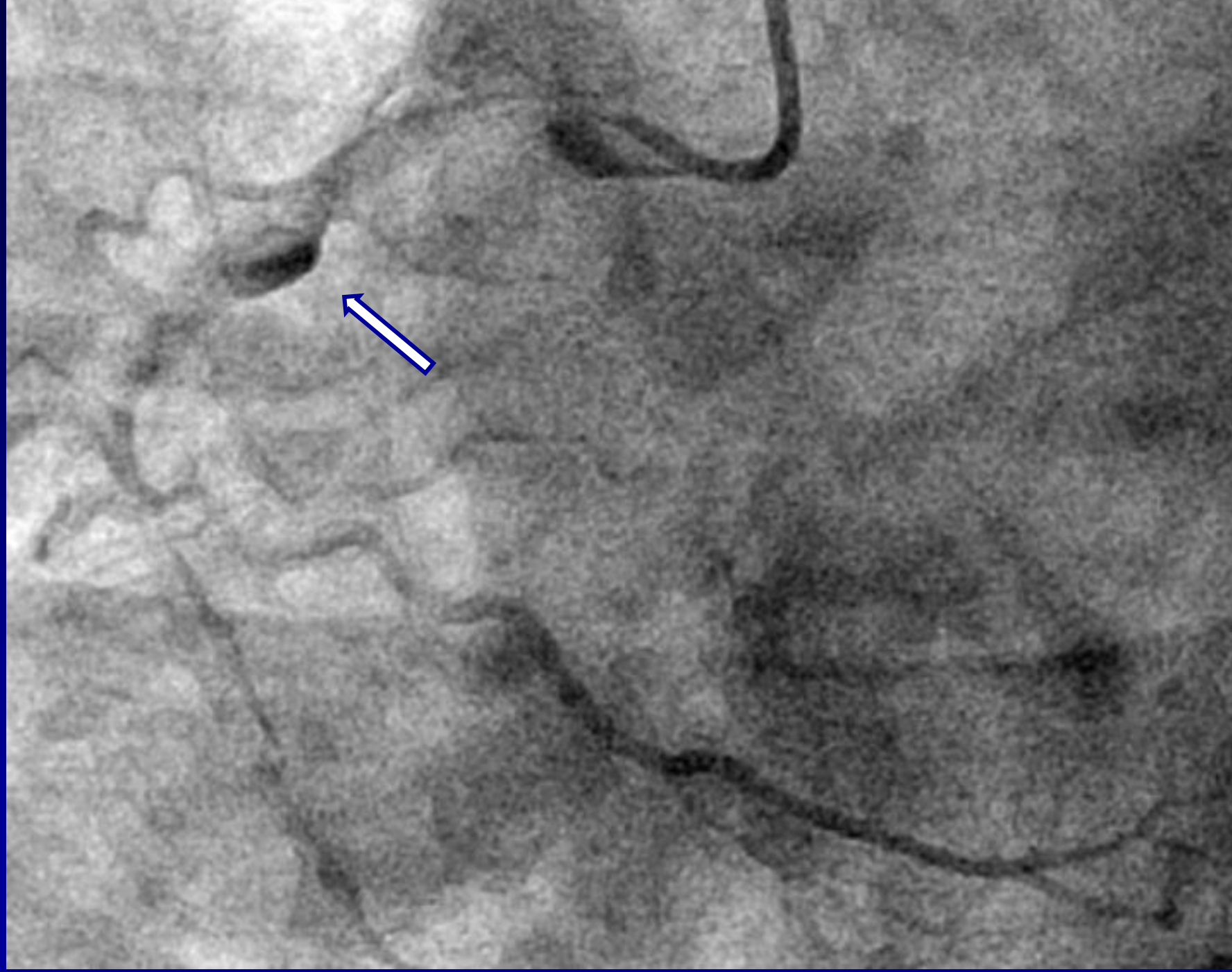




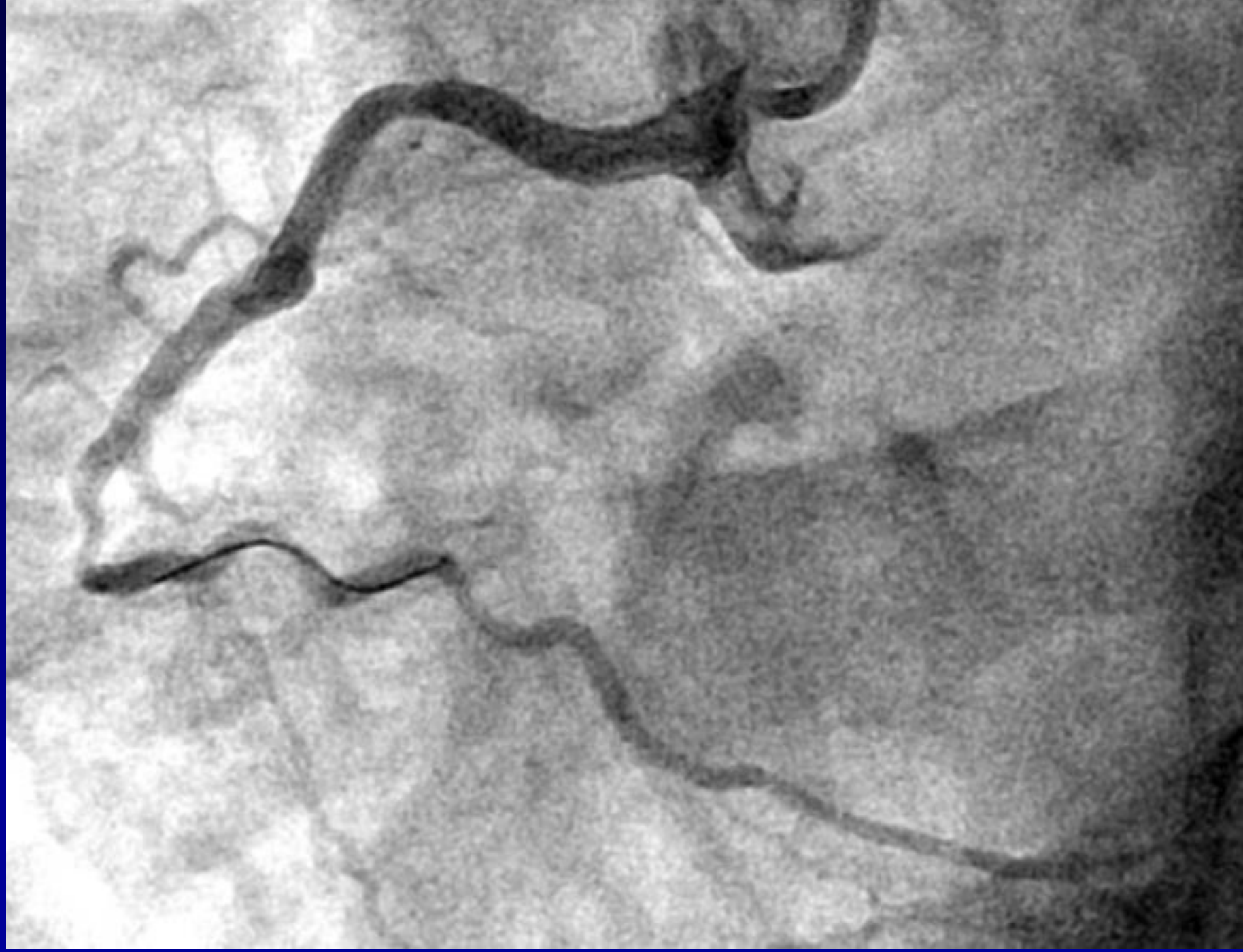


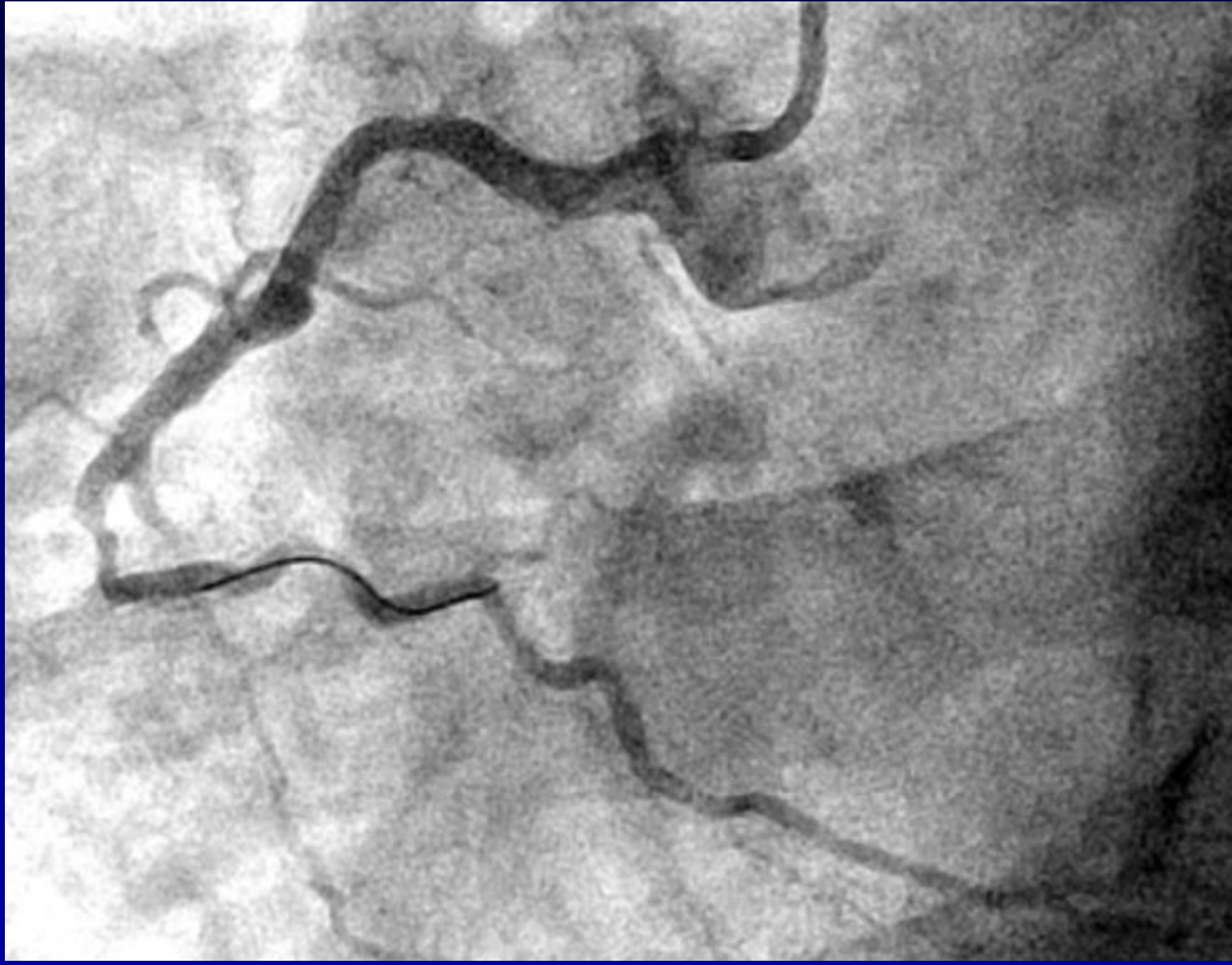


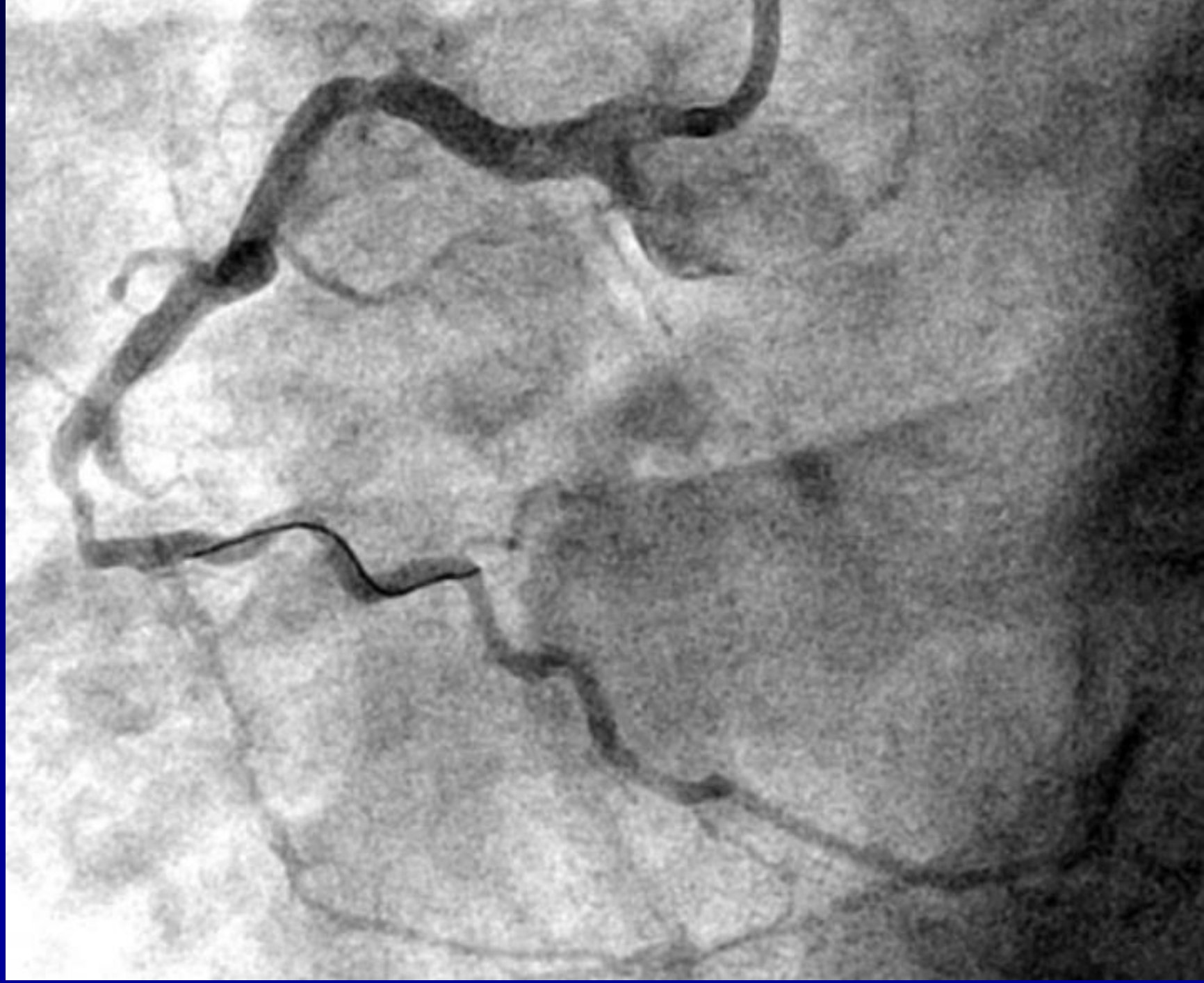


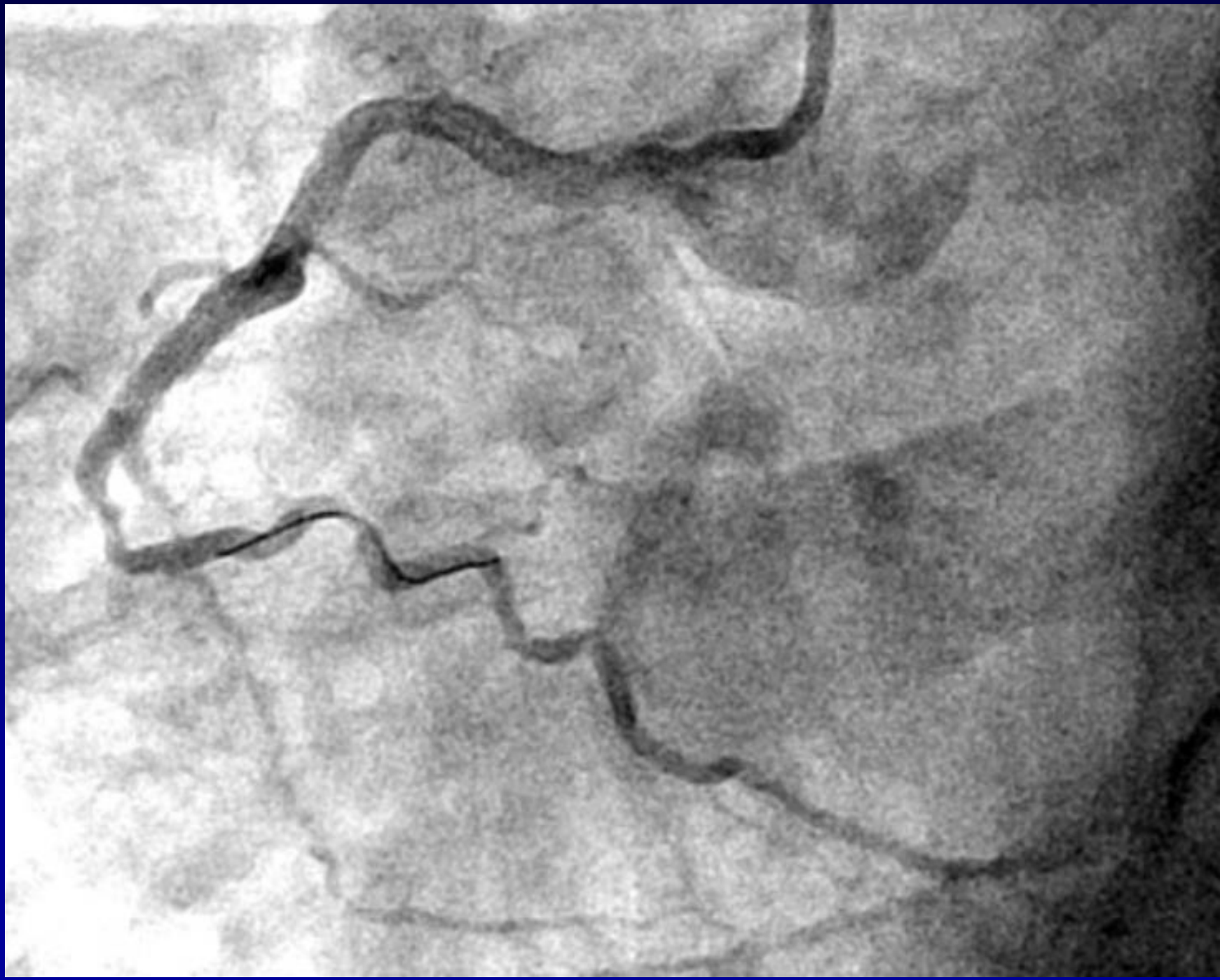


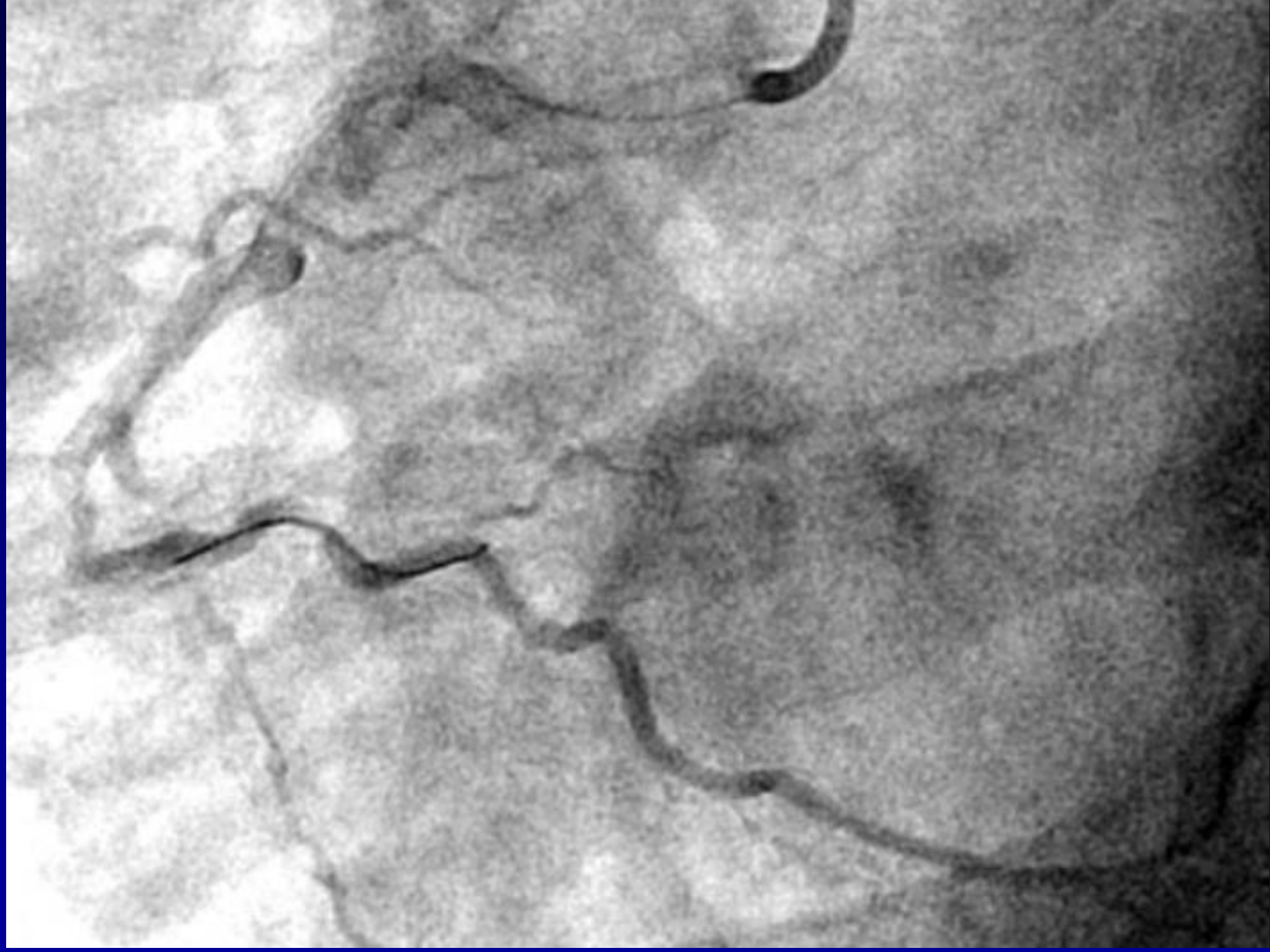
John K
RCA After PCI

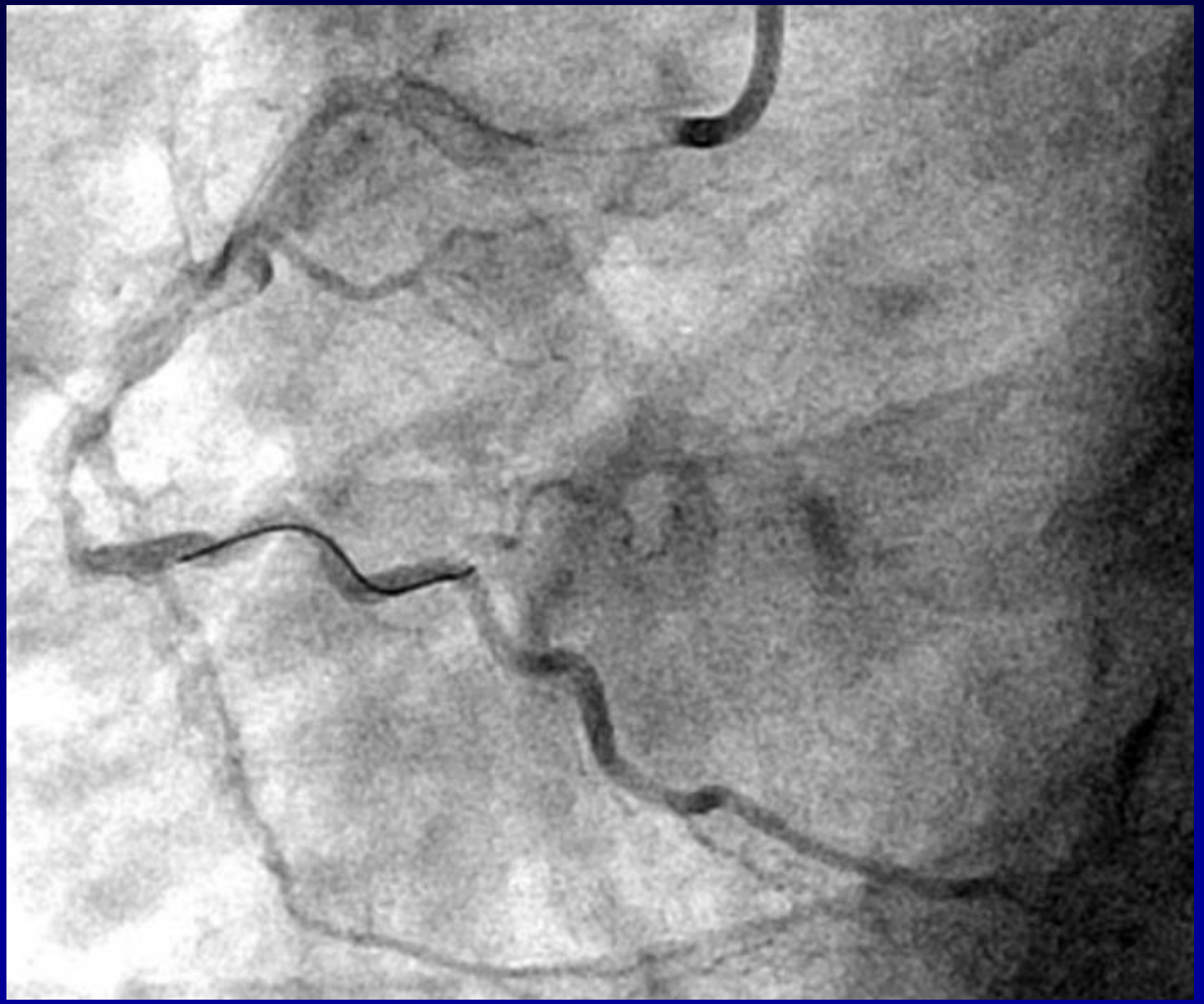


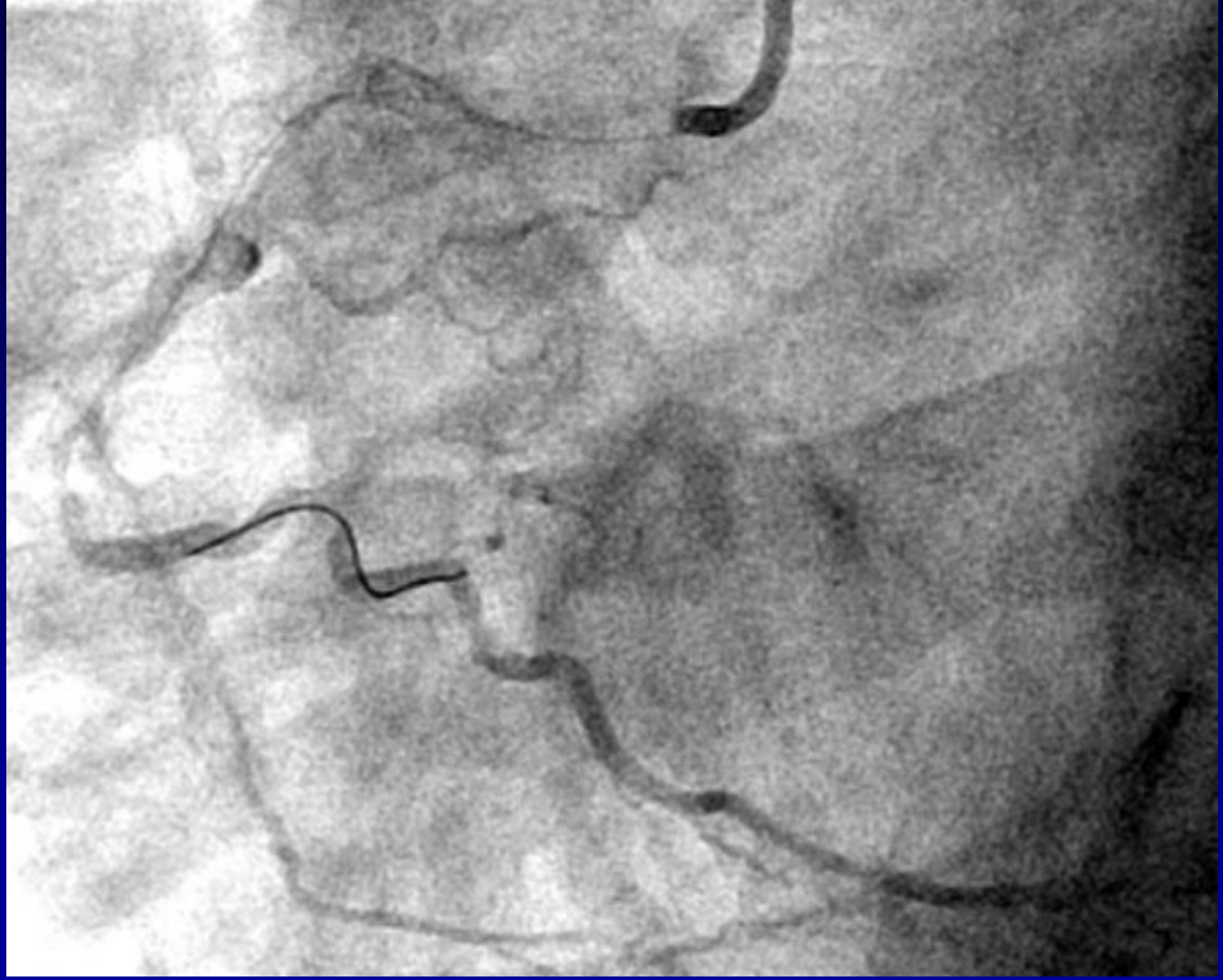


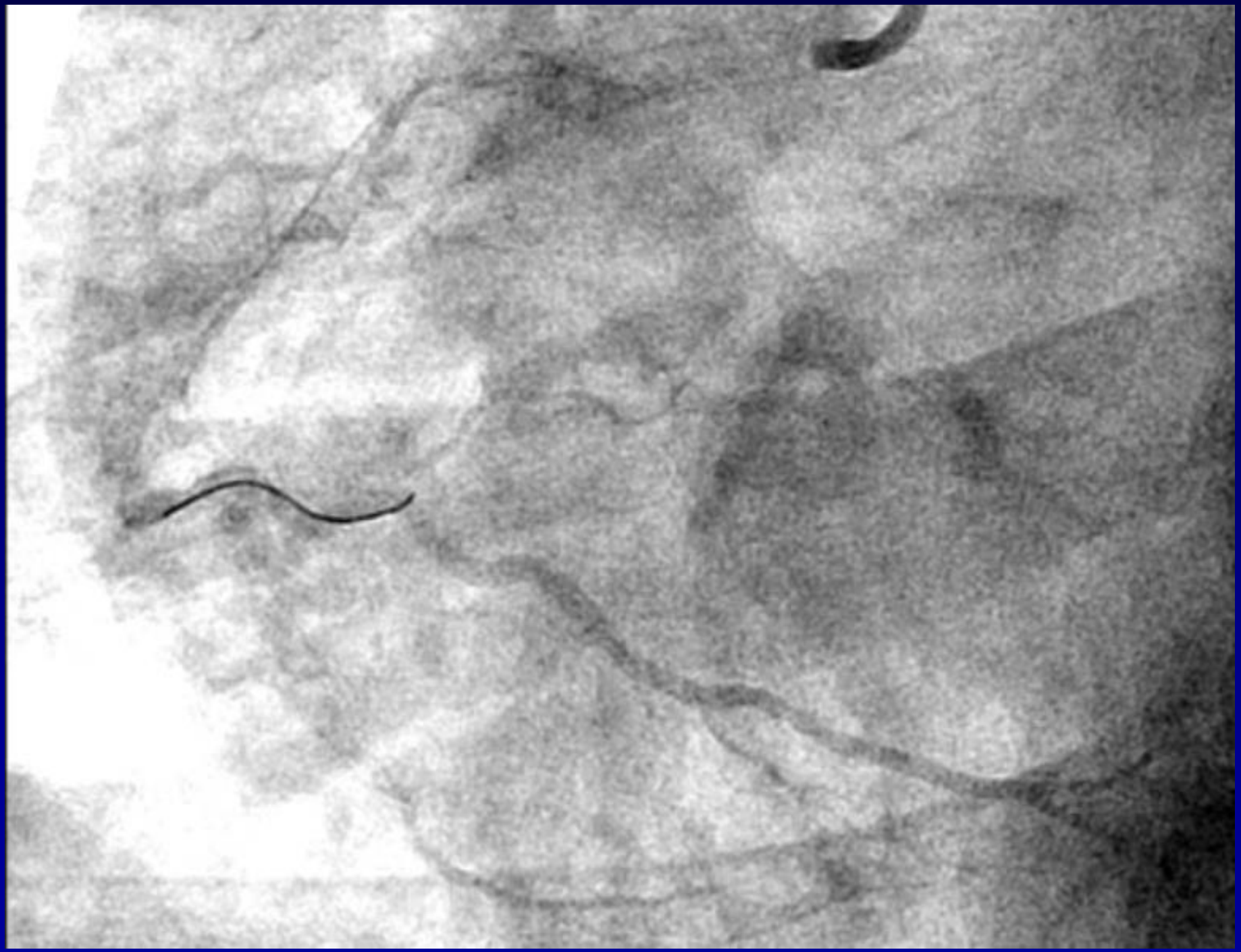


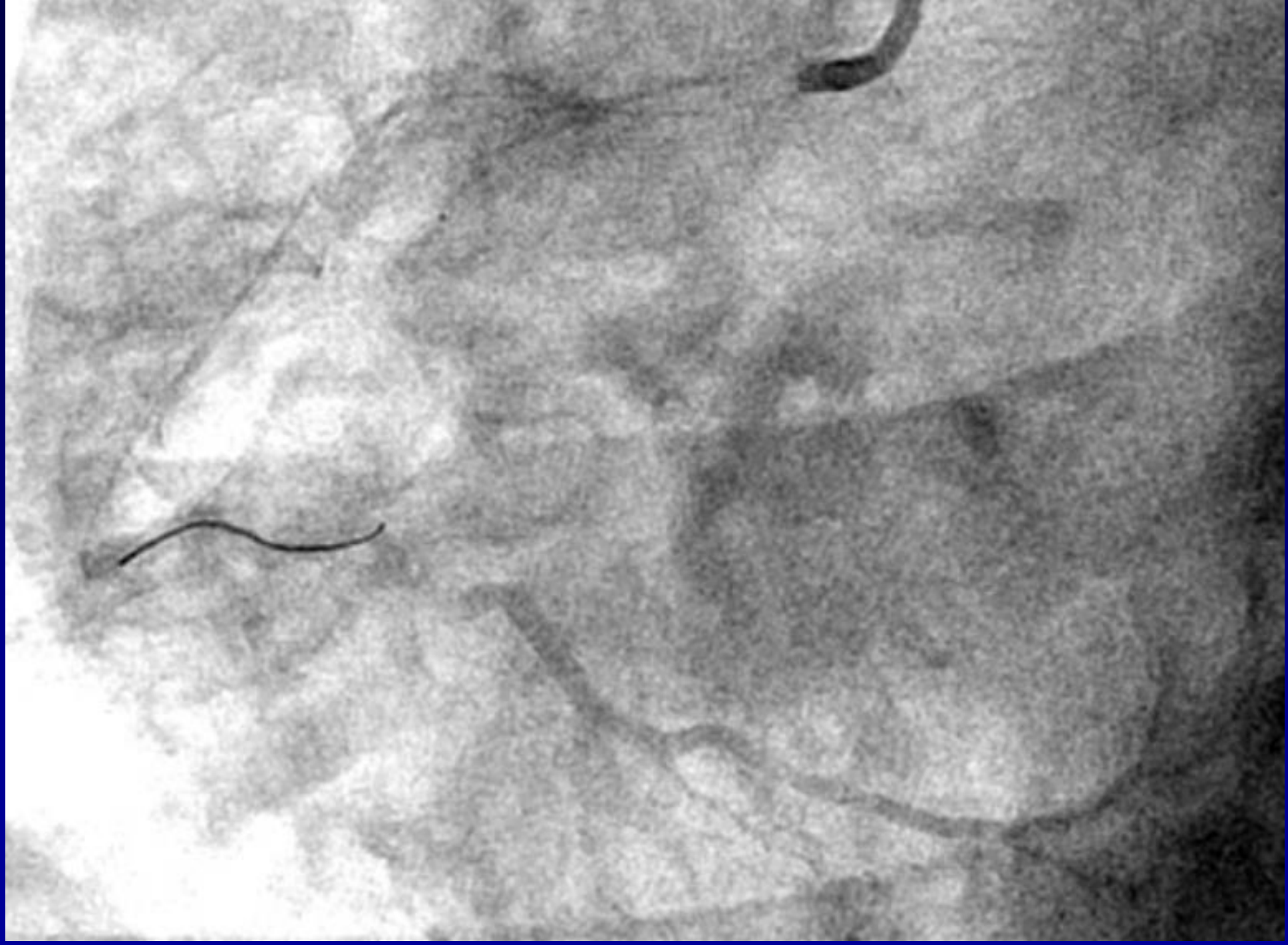


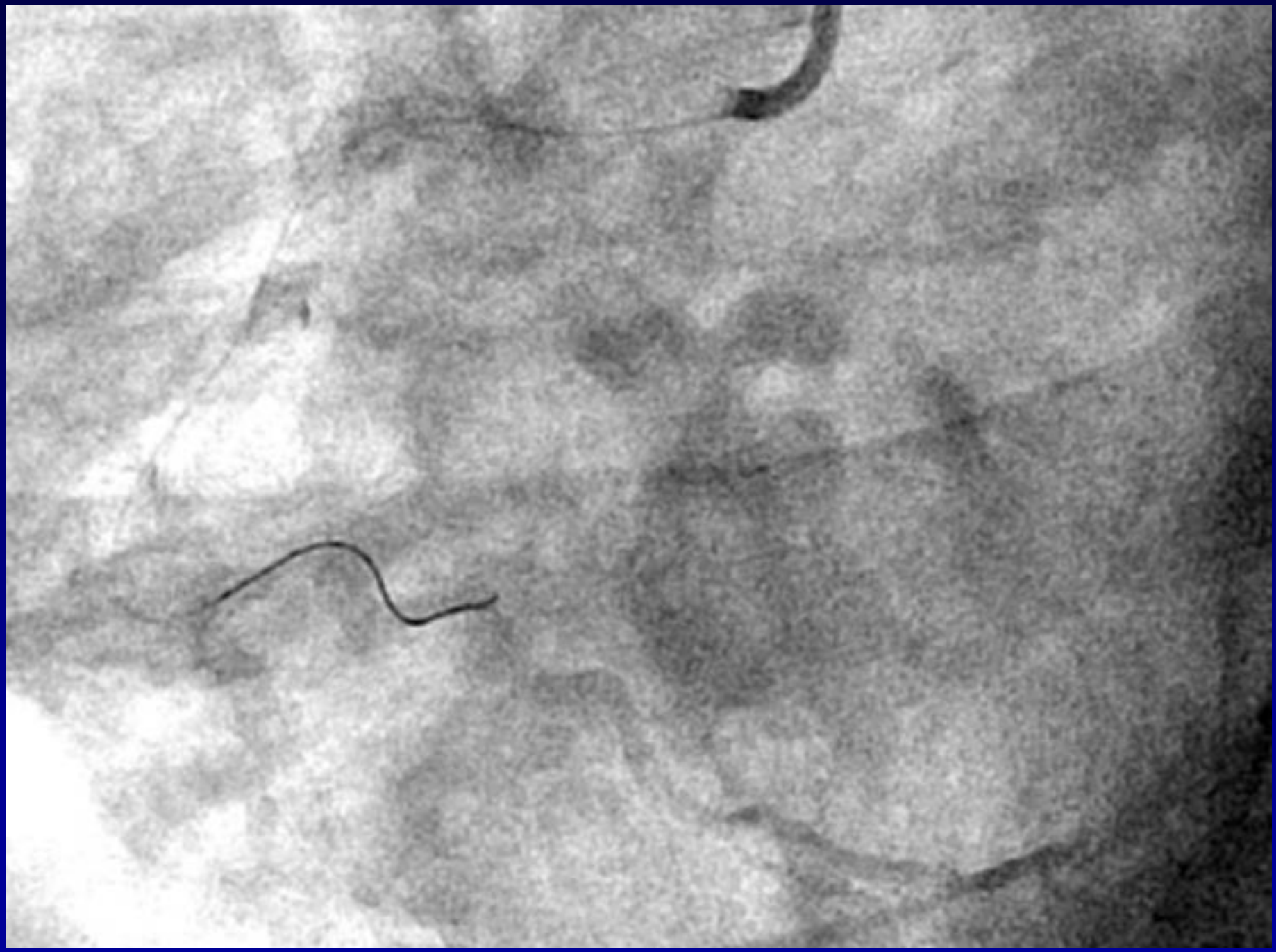








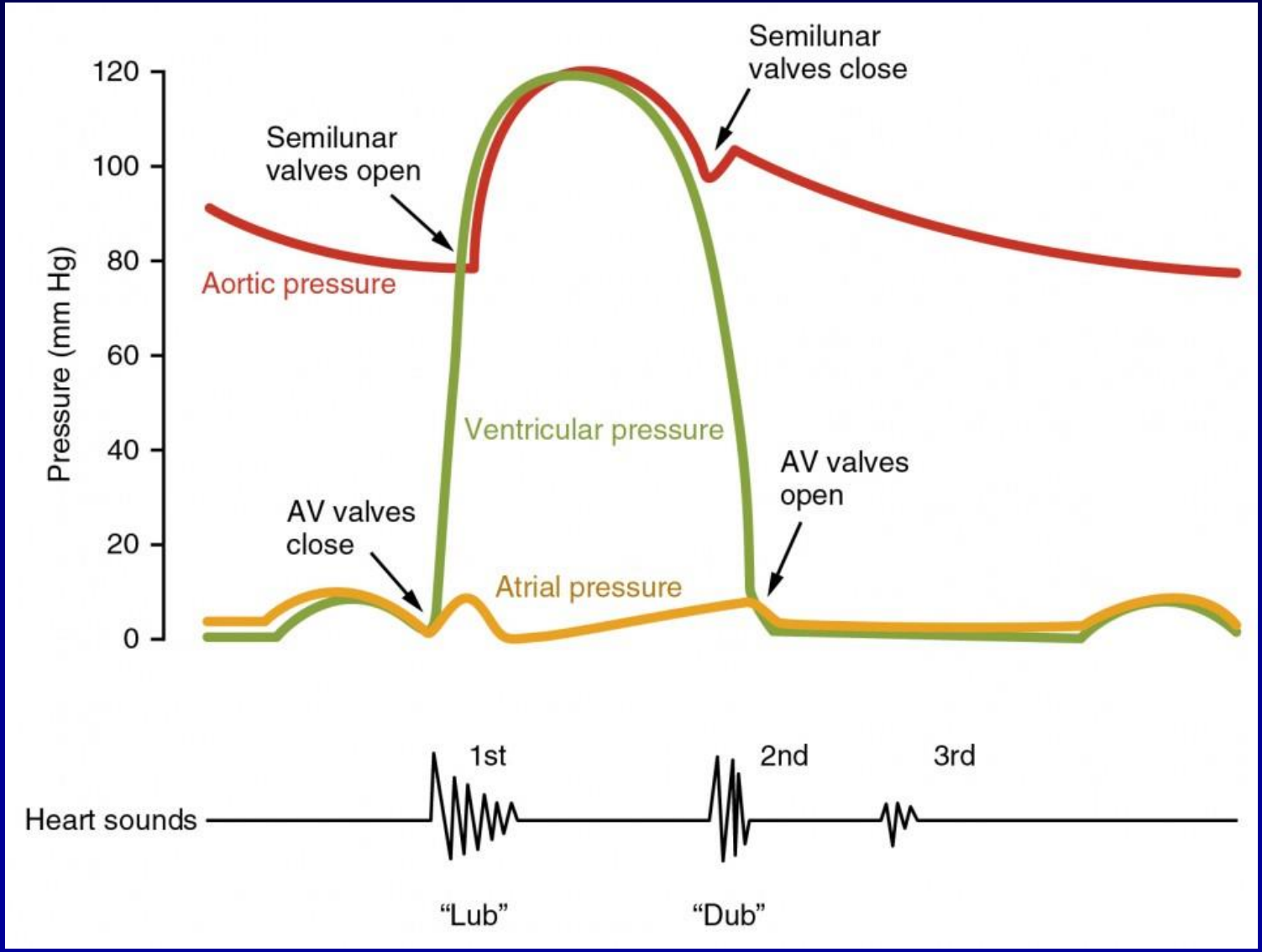




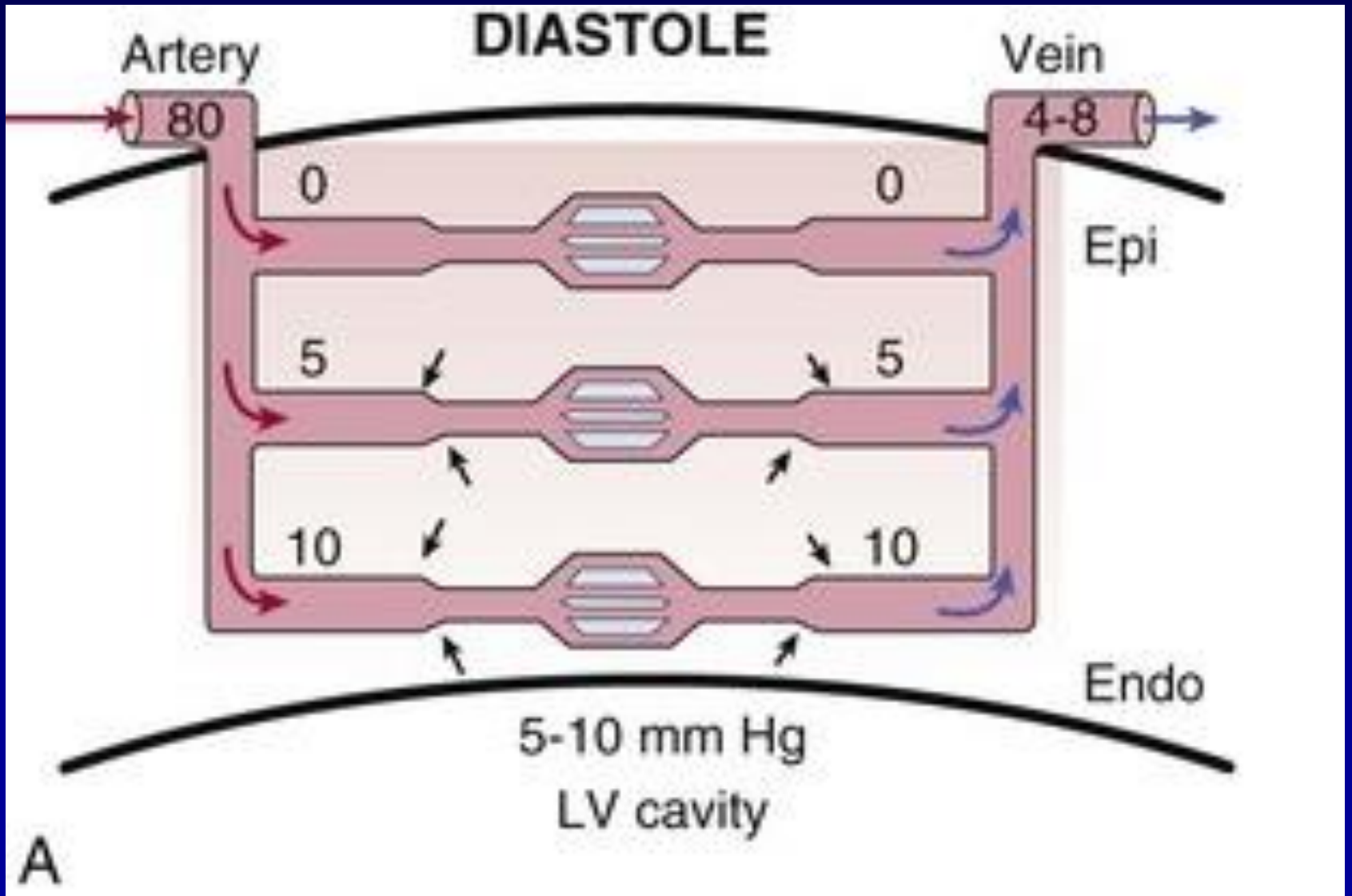
Does elimination of stagnant flow and reversed flow confirm perfect FFR ?

CONCLUSIONS

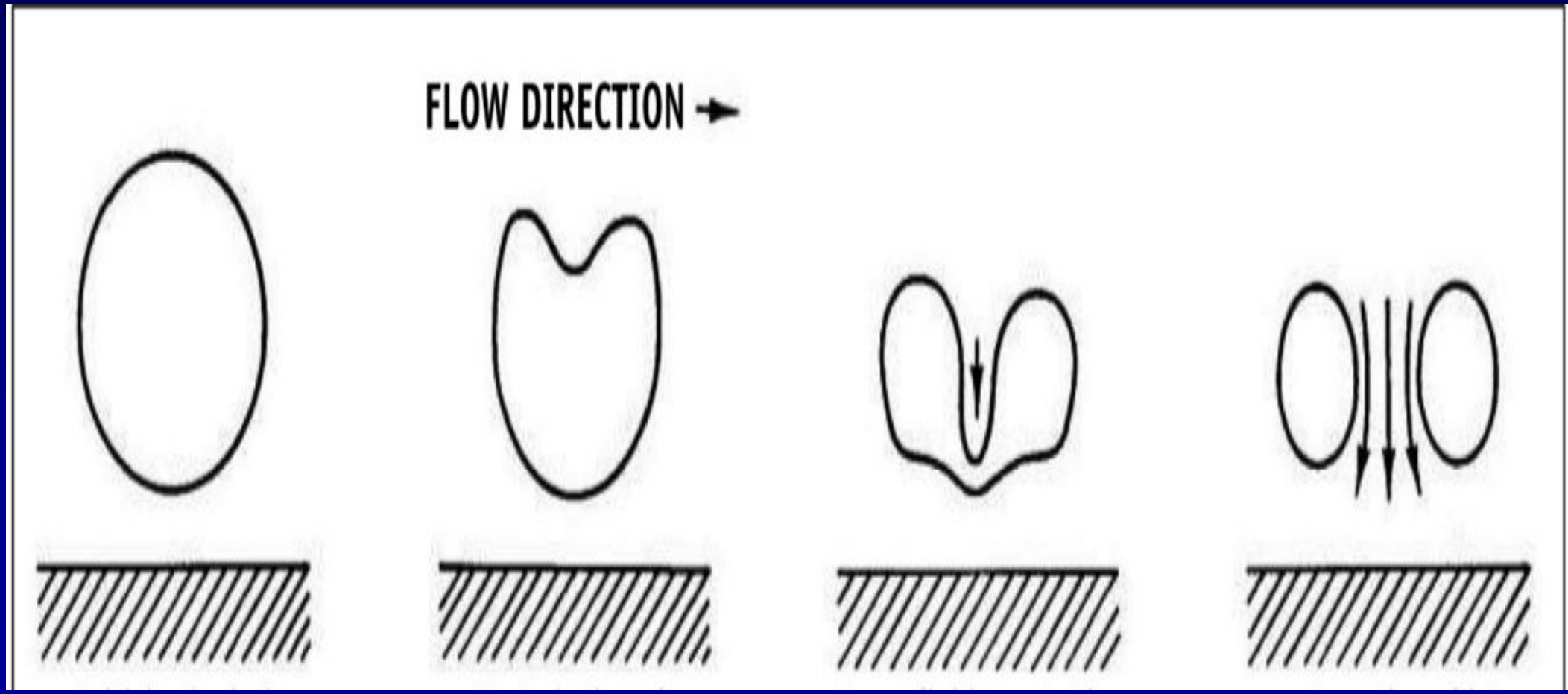
Change of Pressure



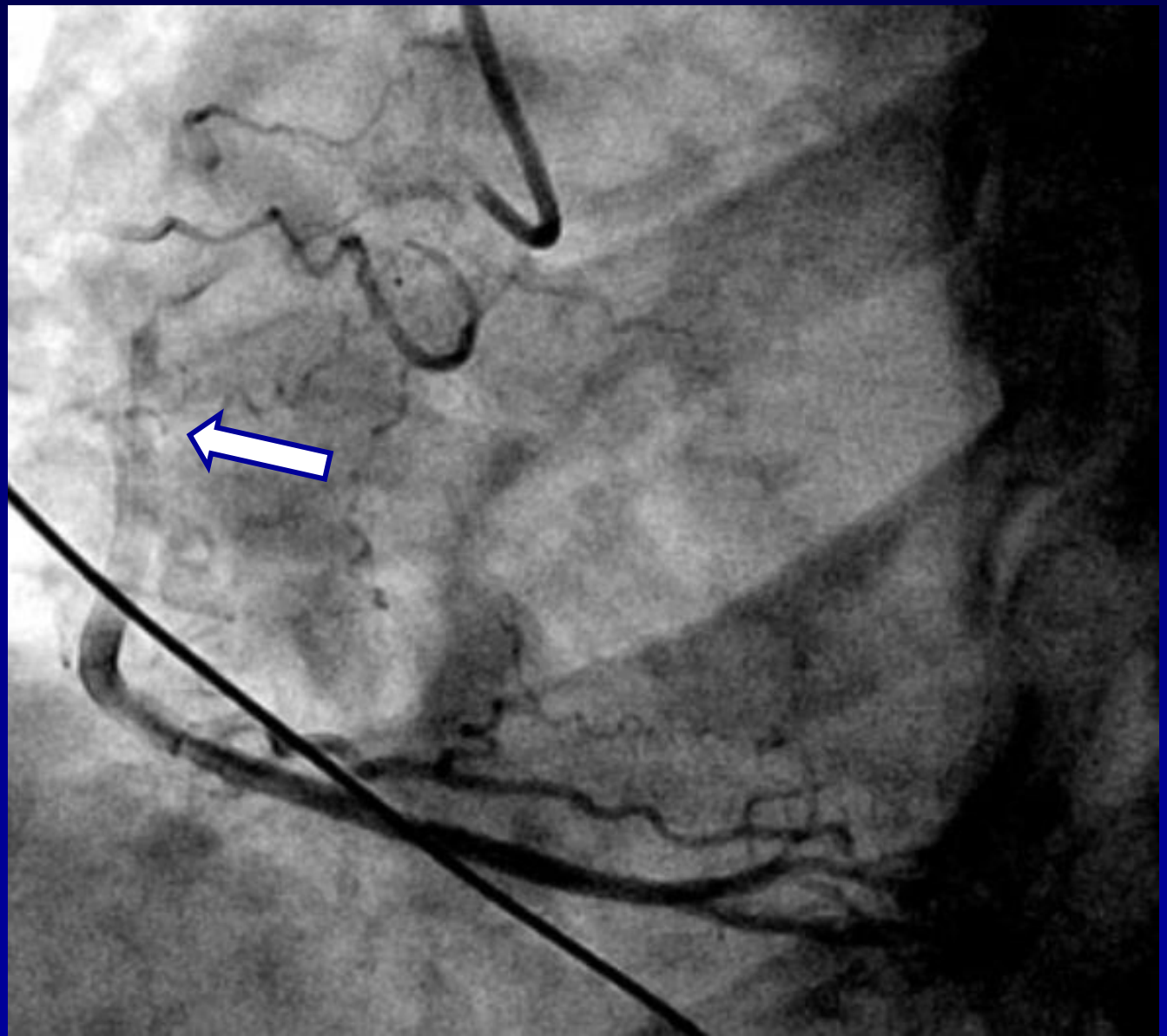
Change of Pressure



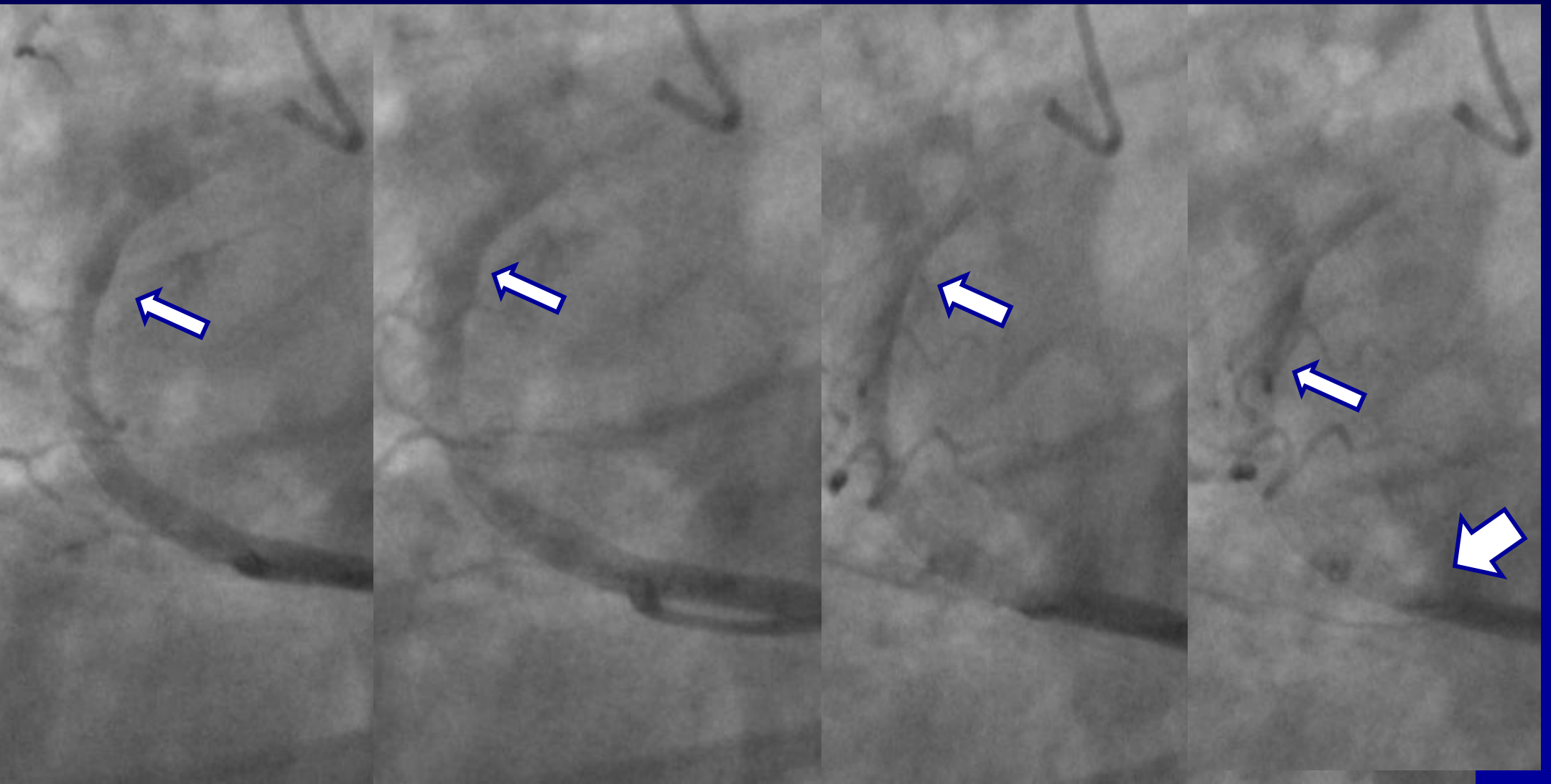
Bubble Ruptures Cause Microjet



Stagnant Flow



Collision of Antegrade and Retrograde Flow



NO SMOKING

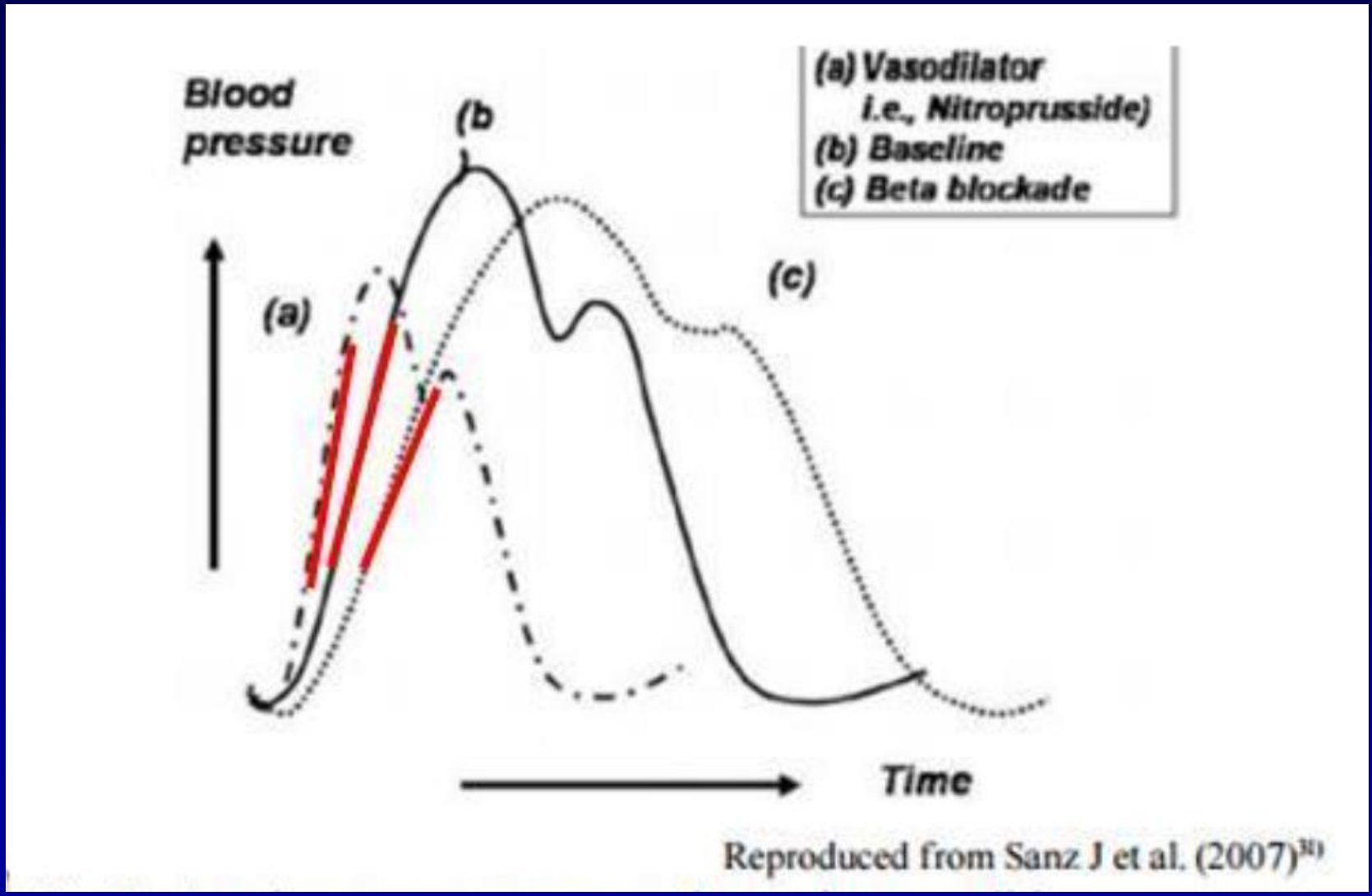
EXERCISE

Perfect Blood Pressure: No large gap between systolic and diastolic BP

STATINS


90 Tablets
Lipitor®
10 mg*
Parke-Davis
90 tablets
40 mg
PRAVACHOL®
(pravastatin
sodium) Tablets
Rx only
Bristol-Myers
Squibb Company
Zocor® 10 mg
(Simvastatin)
90 Tablets

MECHANISM OF BETA BLOCKADE



Reproduced from Sanz J et al. (2007)[31]

Thank You for Your Attention