관상동맥 경련
Coronary Artery Spasm

서울대학교 의과대학 내과학 교실

박 영 배

Coronary Artery Spasm

Definition: Refers to a sudden intense vasoconstriction of an epicardial coronary artery that causes occlusion or near occlusion

Usual cause of variant angina but may be involved in other coronary syndromes

First described in 1959 by Prinzmetal M: Angina pectoris. I. A variant form of angina pectoris.

Prinzmetal M, Kennamer R, et al. Am J Med 1959;27:375-388.

Two pioneers:

Attilio Maseri and Hirofumi Yasue

Maseri A et al. Case of acute myocardial infarct without coronarographic changes. Boll Soc Ital Cardiol. 1972;17(12):1234-42.
Maseri A et al. Angina pectoris with ST seg elevation. Clinical, ECG and angiographic characteristics. Boll Soc Ital Cardiol. 1975;20(9):939-47.
Maseri A et al. Coronary spasm as a cause of acute myocardial ischemia in man. Chest.1975;68:625– 633.
Maseri A et al. Coronary vasospasm in angina pectoris. Lancet. 1977 Apr 2;1(8014):713-7.
Yasue H et al. Prinzmetal's angina: atropine suppression. Ann Intern Med. 1974 Apr;80(4):553.
Yasue H et al. Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. Circulation. 1974;50(3):534-9.

Pf. Maseri and Hammersmith Hospital

Coronary Artery Spasm

1986 - 1995

Young - Bae Park , M.D.

Professor

Division of Cardiology

Department of Internal Medicine

College of Medicine

Seoul National University

Subjects

Duration: April 1986 - December 1995

Total no. of CAG: 6806

Total no. of coronary a. spasm

: 273 (4.0%)

CAG: Coronary angiography

Comparison between variant angina and effort angina

	Variant Angina	Effort Angina
ST segment on ECG	usually elevated	usually depressed
Arrhythmia	usually occur(50%)	seldom occur
Ambulatory ECG	up to 90% ST change asymptomatic	75% ST depression symptomatic

	Variant Angina	Effort Angina
Pain	at rest	on exertion
	longer duration	shorter duration
	may occur in cyclic pattern	not cyclic
	midnight to 8 AM	6 AM to noon
Exercise tolerance	well preserved	decreased

Provocation test of Coronary Artery Spasm

1. Discontinue antianginal and antiplatelet agents

2. Baseline ECG and CAG

3. Temporary pacemaker insertion

4. Provocation

Ergonovine (IV or intracoronary)

Acetylcholine (intracoronary)

[12 lead ECG And CAG at the time of chest pain or 2 min. after administration]

5. Intracoronary nitroglycerin after demonstration of spasm at the end of the study

Diagnostic Criteria of Coronary Artery Spasm

1. Demonstration of transient narrowing in a coronary segment that initially appeared to be normal

2. Occurrence of transient total or near total obstruction in a normal coronary segment or at the fixed lesion

3. Prompt vasodilatory response of obstructed segments to the administration of nitroglycerin or spontaneous relief of the obstructed segment

Clinical Situation Where Spasm Provocation Is Helpful

1. **Rest pain** associated with
   - no preceding rise in HR & BP
   - cyclic recurrence in early morning
   - transient ST elevation or ventricular arrhythmias
   - nonspecific or no ECG change

2. **Angina** associated with
   - variable exercise threshold
   - ST elevation during stress test
   - syncope or ventricular arrhythmias

Contraindications to Spasm Provocation

1. **Absolute**
   - amenorrhea in premenopausal women
   - severe LV dysfunction
   - severe hypertension
   - severe aortic stenosis
   - significant left main coronary stenosis

2. **Relative**
   - recent MI (<5 days)
   - uncontrolled angina
   - uncontrolled ventricular arrhythmia

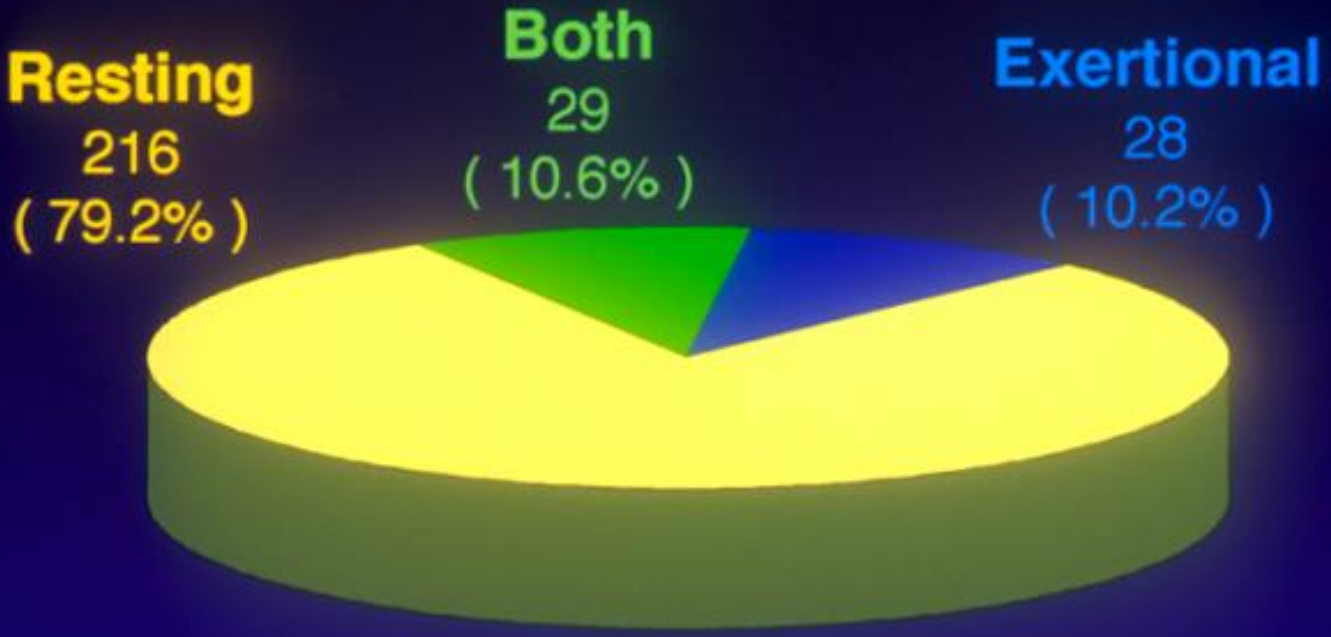
Age & Sex Distribution

N = 273

Age (yr.)	M no.	F no.	Total no.
21 - 30	3	0	3
31 - 40	15	3	18
41 - 50	58	17	75
51 - 60	103	22	125
61 - 70	39	6	45
71 - 80	6	1	7
Total	224	49	273

Nature of Chest Pain

N = 273



Development of Spasm

N = 273

	no.	%
Spontaneous	47	17.2
Provoked	226	82.8

Provocation Method

N = 226

Agent	Route	no.	%
EG	IV	122	54.0
EG	IC	60	26.5
Ach	IC	44	19.5

EG ; Ergonovine
Ach ; Acetylcholine
IV ; intravenous
IC ; intracoronary

Baseline CAG Finding

N = 273

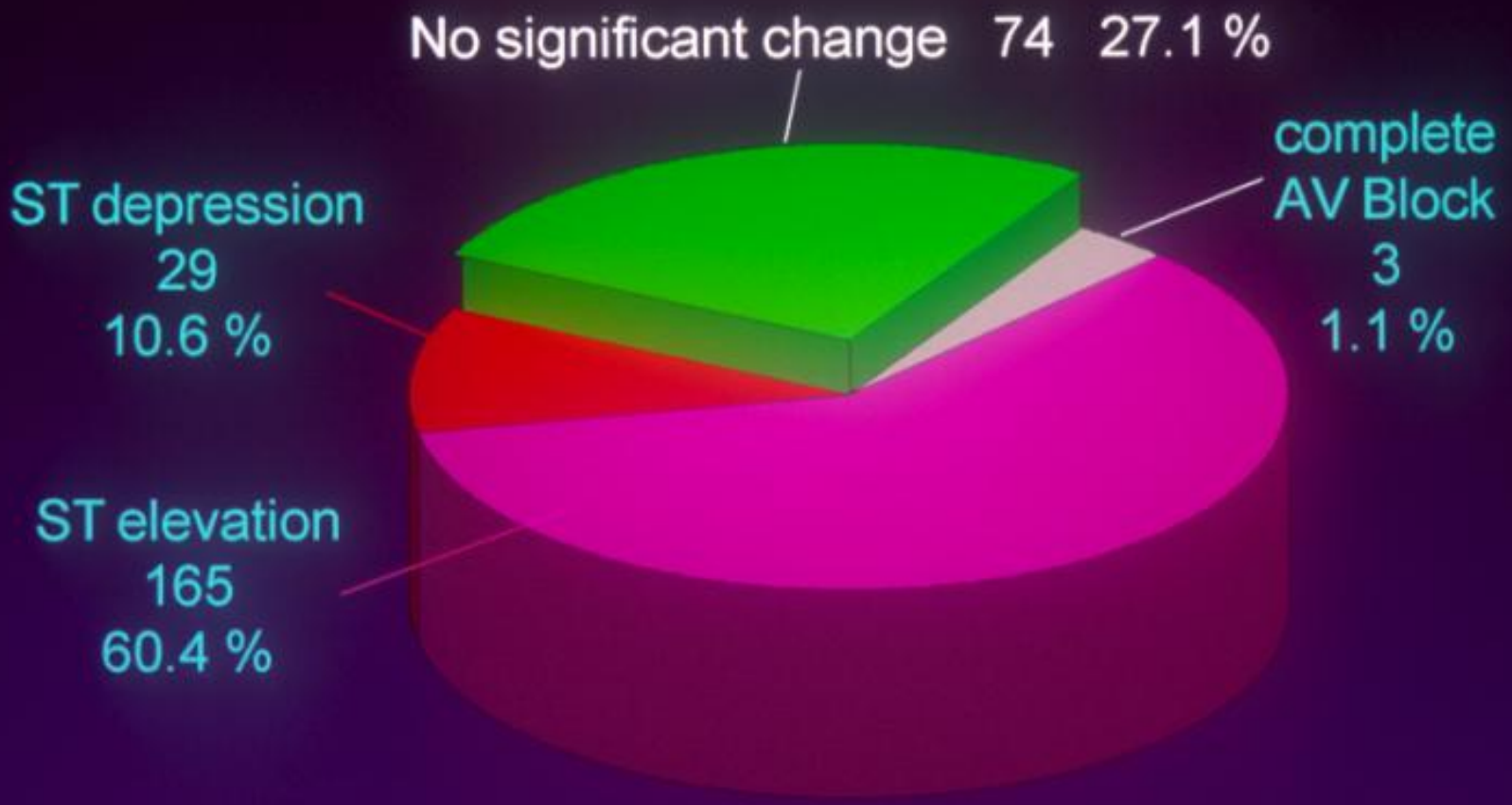
Normal CAG	**151** (55.3%)
Stenotic Lesion (+)	**122** (44.7%)
< 50%	56
50 - 75%	46
> 75%	20

Risk Factor

N = 273

	no.	%
Hypertension	81	34.1
Diabetes	37	15.6
Smoking	200	73.3

ECG Change


No significant change 74 27.1 %
complete AV Block 3 1.1 %
ST depression 29 10.6 %
ST elevation 165 60.4 %

ECG Change & Chest Pain

N = 273

		Chest Pain: Positive	Chest Pain: Negative	Total
ECG Change	Positive	196	3	199
	Negative	66	8	74
	Total	262	11	273

Time Onset of Chest Pain

N = 273

Time		no.	%
morning	(6A - 8A)	215	78.8
night	(10P - 6A)	43	15.8
daytime	(8A - 10P)	15	5.4

Location of Spasm

	no.	%
RCA	168	48.3
LAD	132	37.9
LCX	44	12.6
Lt. main	4	1.2
two sites	53	
three sites	16	

ECG Change

ST seg. elevation

N = 165

lead	no.
II, III, aVF	87
I, aVL	7
V 1, 2 & 3	40
V 4, 5 & 6	31

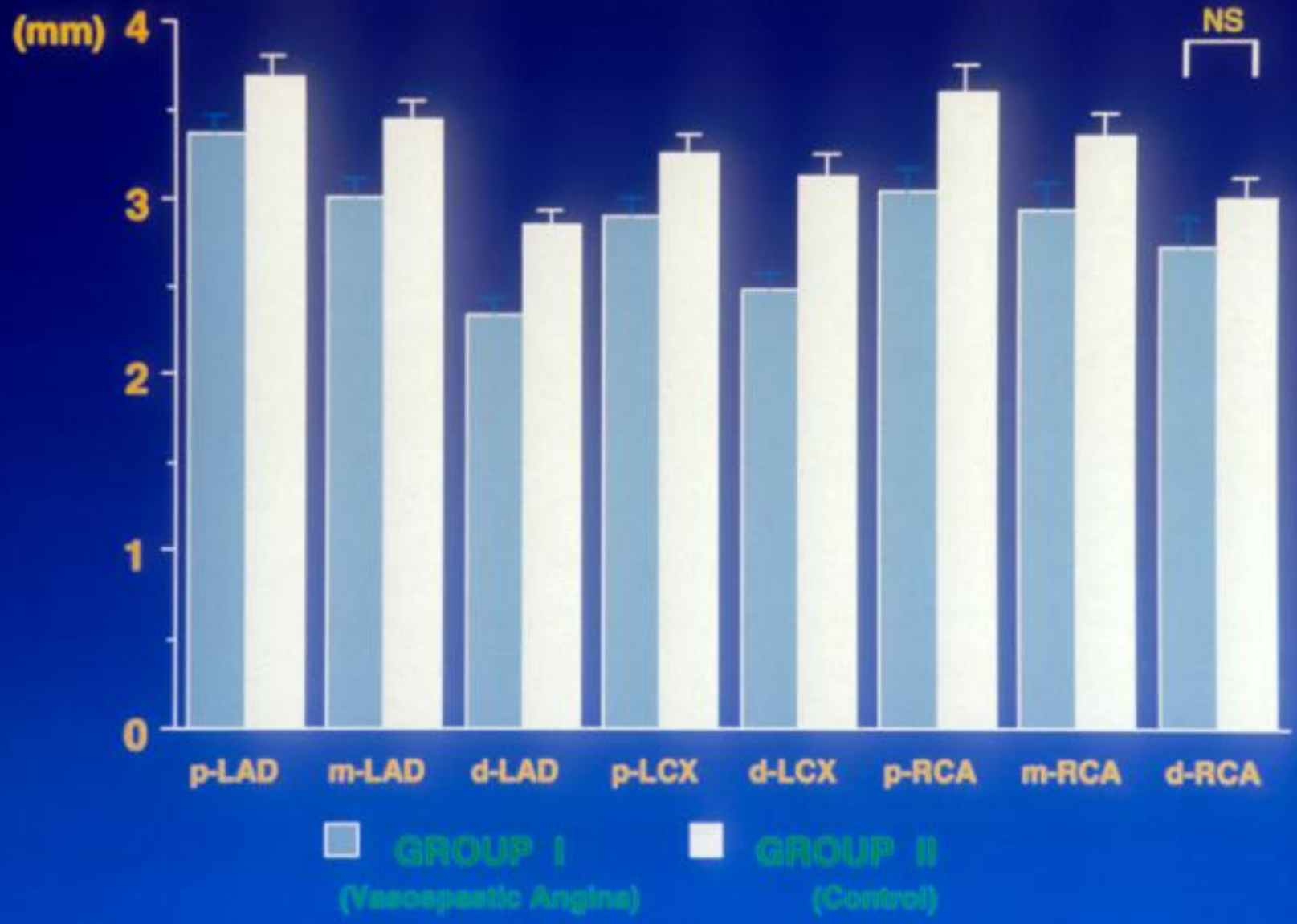
ECG Change

ST seg. depression

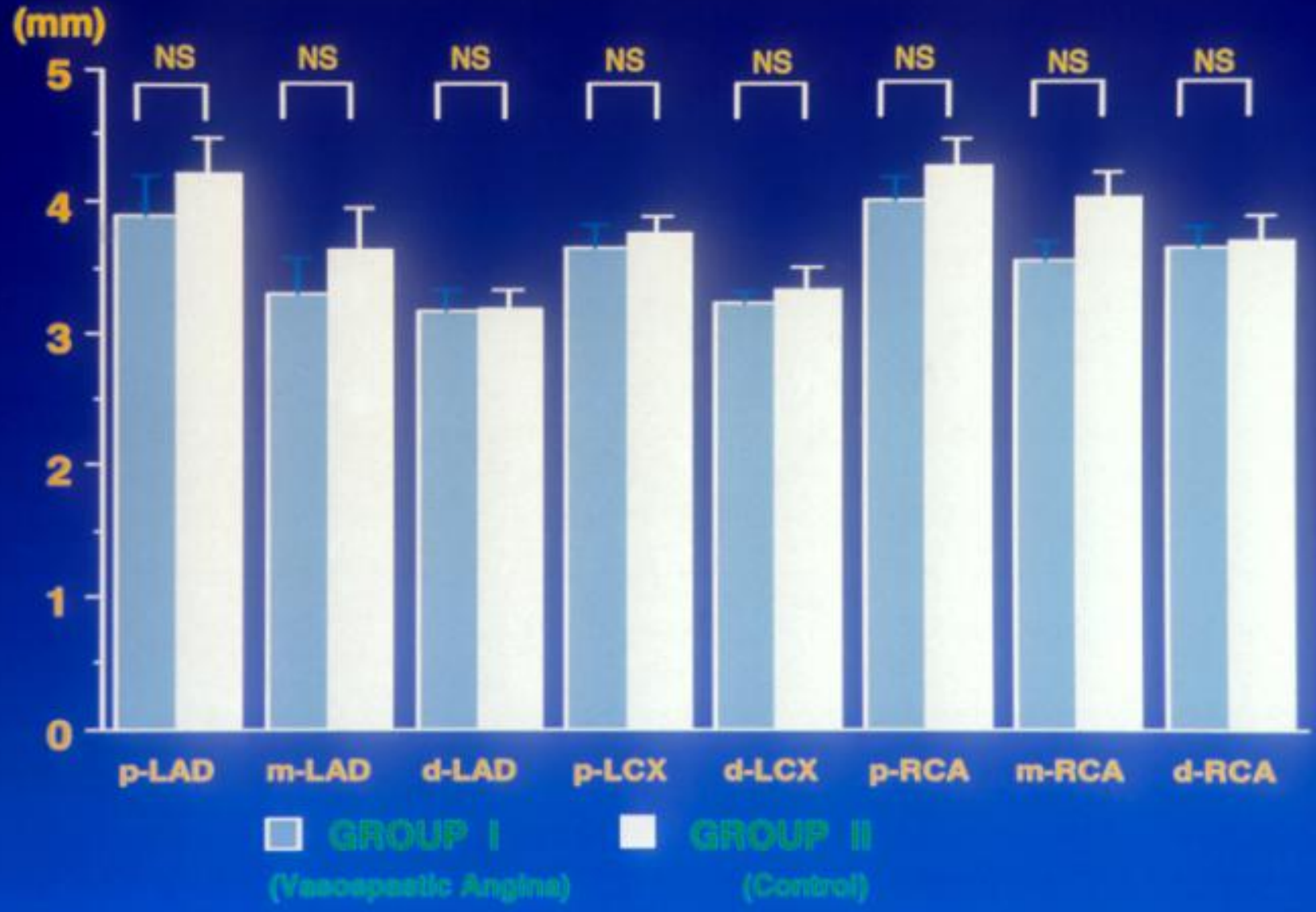
N = 29

lead	no.
II, III, aVF	14
I, aVL	3
V 1, 2 & 3	3
V 4, 5 & 6	9

Basal Coronary Artery Diameter



Coronary Artery Diameter after NG



Vasomotor Tone Ratio

$$\frac{\text{diameter after nitroglycerin - basal diameter}}{\text{diameter after nitroglycerin}} \times 100$$

Vasomotor Tone Ratio (%)

Location		Group I	Group II	p value
LAD	proximal	25.5 ± 11.3	14.0 ± 2.3	< 0.05
	mid	14.2 ± 6.6	1.5 ± 7.0	< 0.05
	distal	26.6 ± 10.2	7.0 ± 3.8	< 0.05
LCX	proximal	16.2 ± 6.5	9.7 ± 3.2	< 0.05
	distal	23.0 ± 8.2	10.8 ± 5.7	< 0.05
RCA	proximal	29.3 ± 5.7	7.1 ± 7.1	< 0.05
	mid	27.6 ± 7.0	12.3 ± 3.8	< 0.05
	distal	28.2 ± 5.6	13.0 ± 9.1	< 0.05
Total		24.5 ± 2.7	8.6 ± 1.9	< 0.01

Group I : Vasospastic angina **Group II : Control** **MEAN ± S.E.**

NS : Not Significant

Summary-1

1. Coronary artery spasm was documented in 273 (4.0%) out of 6806 patients who had coronary angiograms.
2. The most prominent clinical symptom was the typical chest pain which occurred during midnight to early morning at rest.
3. Coronary artery spasm occurred on normal looking coronary artery most frequently, however, spasm occurred on fixed lesion more often if the fixed stenosis was found on coronary angiogram, regardless of severity of the stenosis.

Summary-2

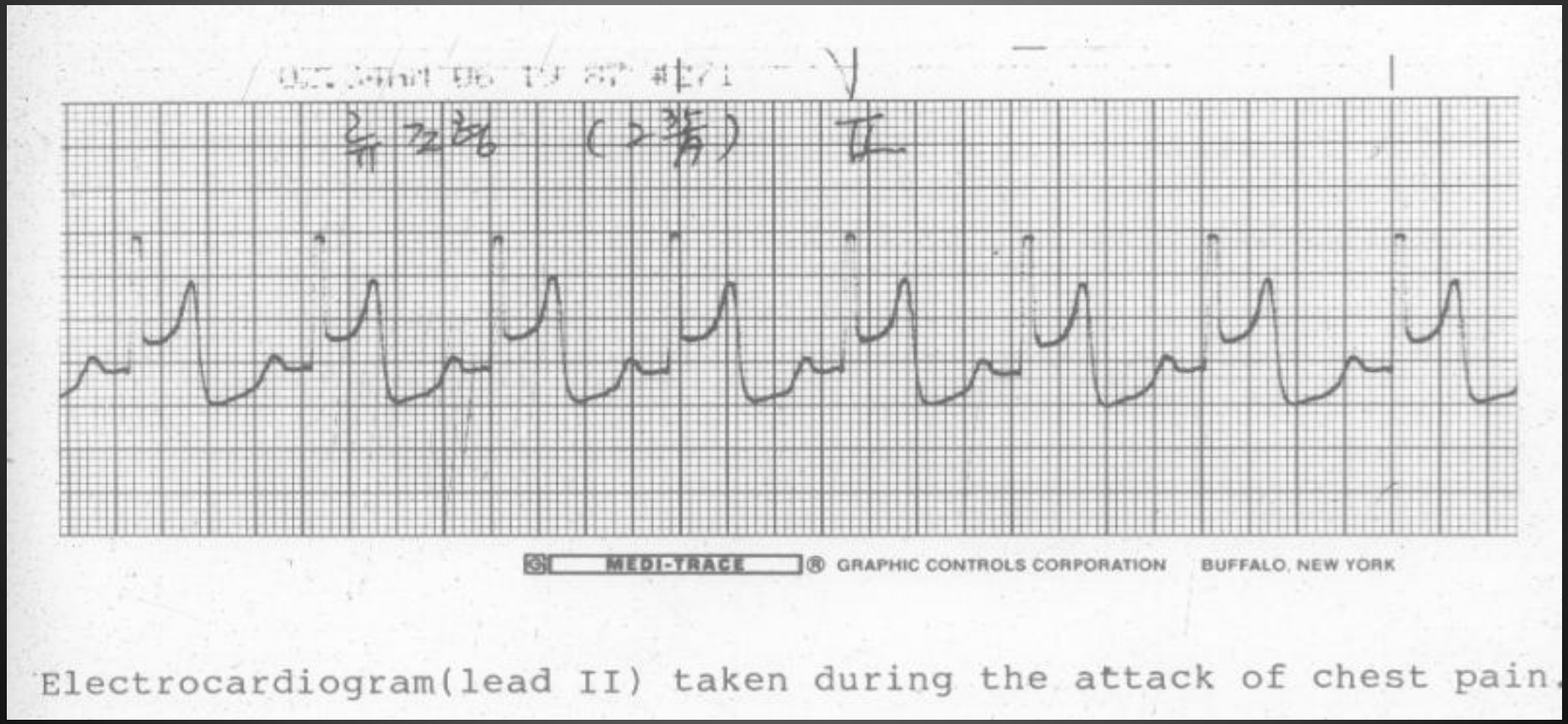
4. Spasm without ECG changes and chest pain occurred in 8 cases (2/47 Sp, 1/44 ACH, 3/122 IV EG, 2/60 IC EG), and it may be an evidence of silent myocardial ischemia.

5. Spasms on the right coronary artery were the most frequently demonstrated, and those on left anterior descending artery and left circumflex artery were followed in decreasing order of frequency.

Cases

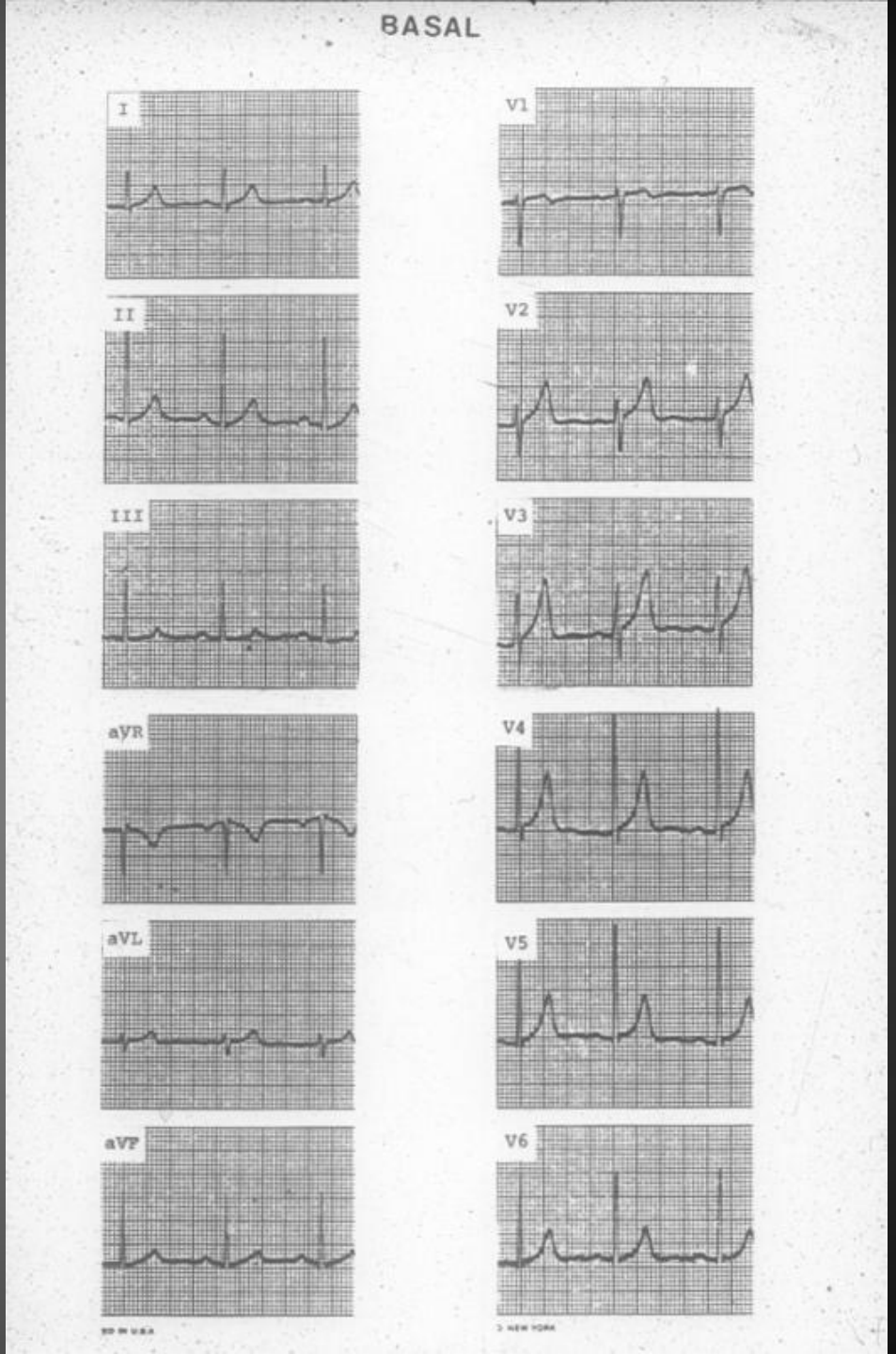
55YO Male: 고등학교 교장 선생님
(Recurrent early morning chest pain)

CCU ECG monitoring 중 chest pain +



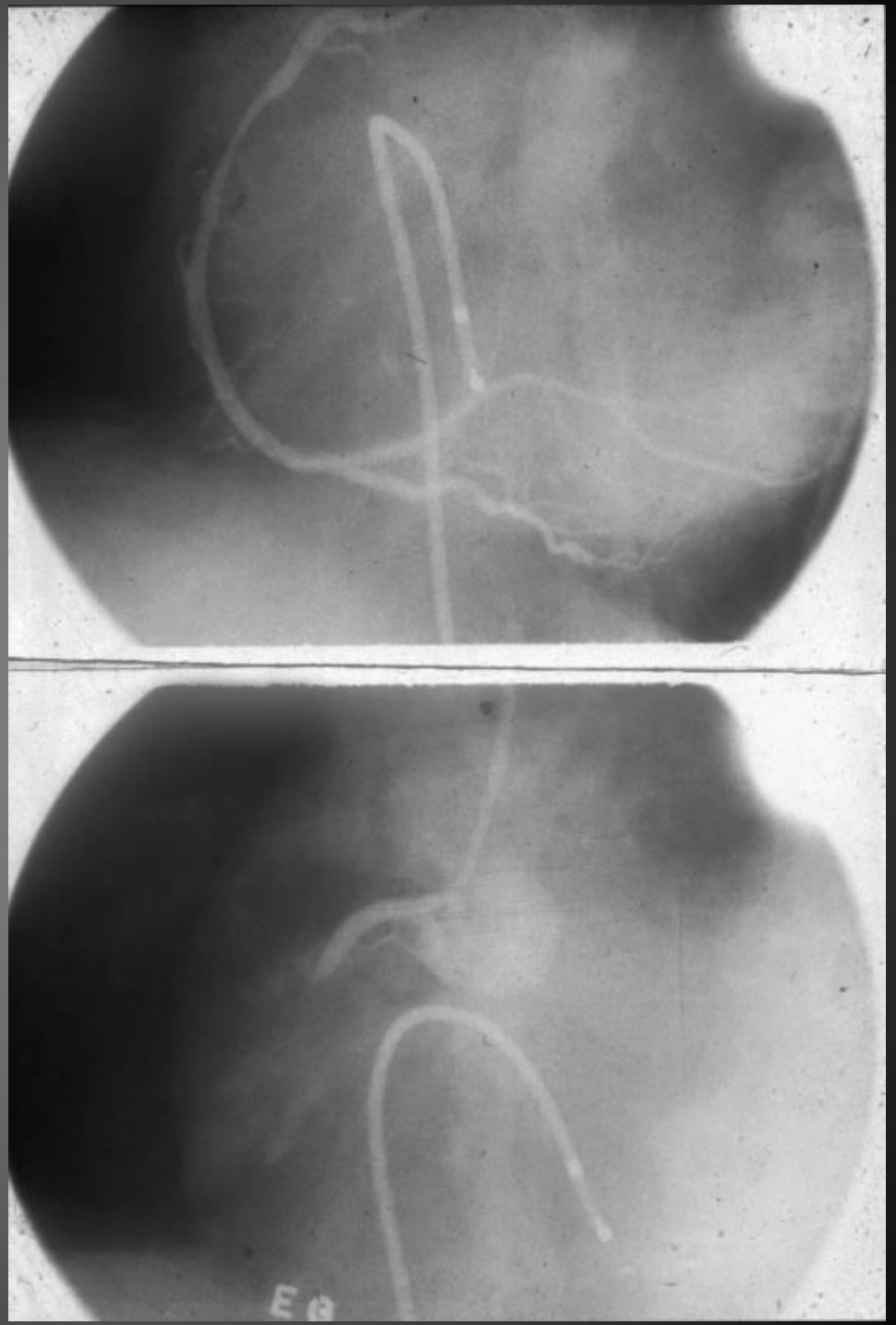
Electrocardiogram(lead II) taken during the attack of chest pain.

Baseline ECG

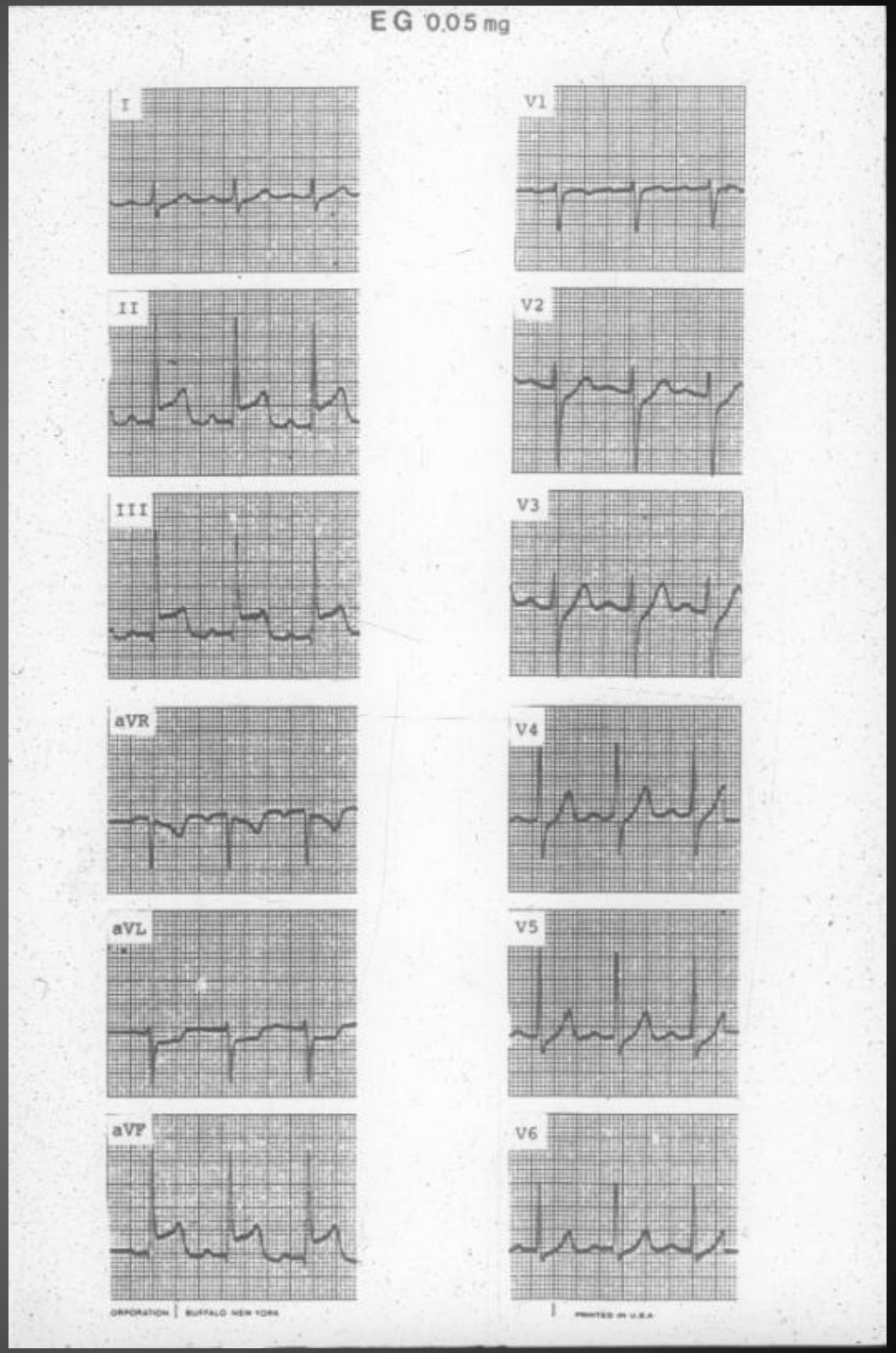


Baseline CAG

After ergonovine IV

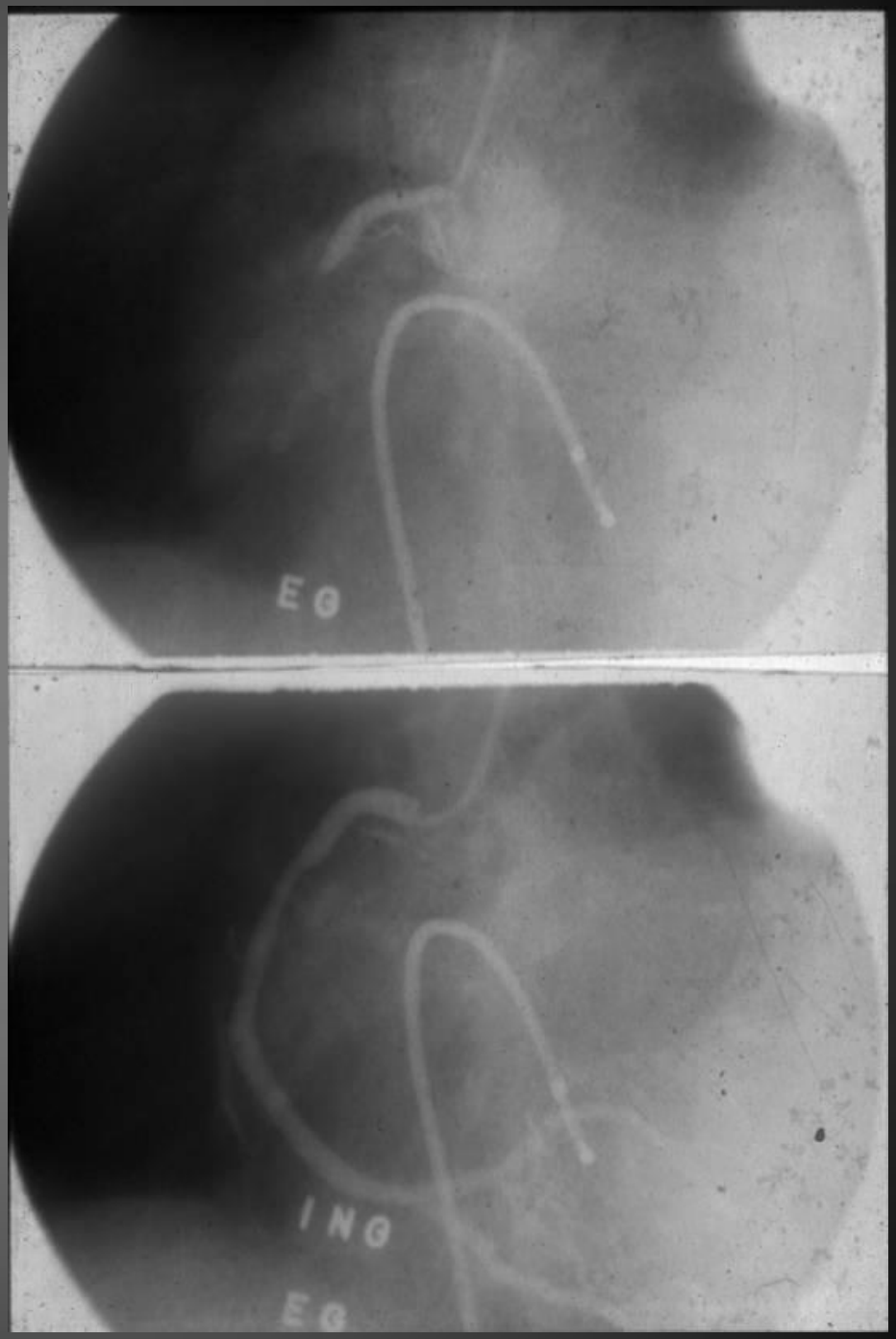


ECG during EG provocation

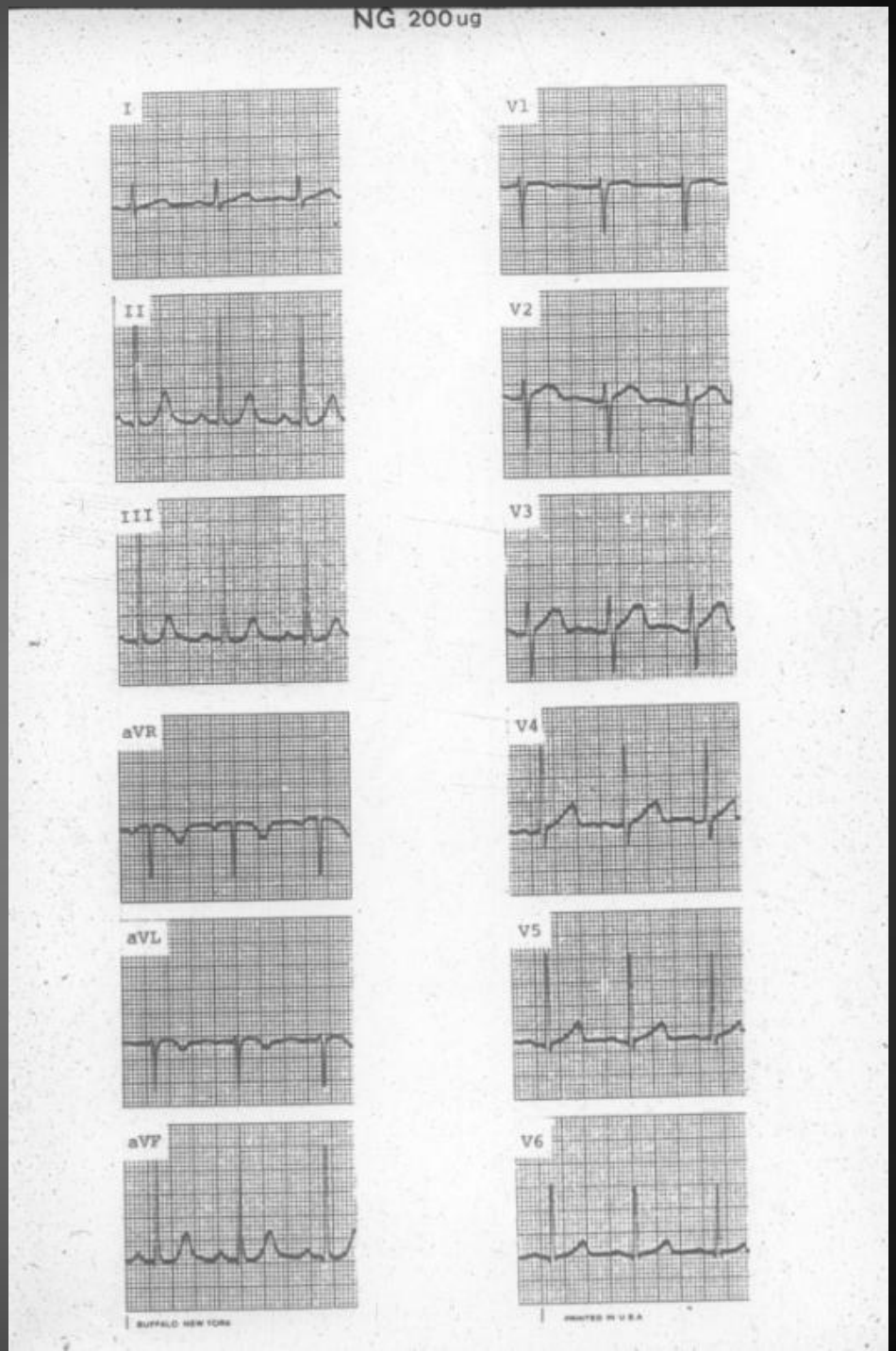


EG provocation

After ICNG

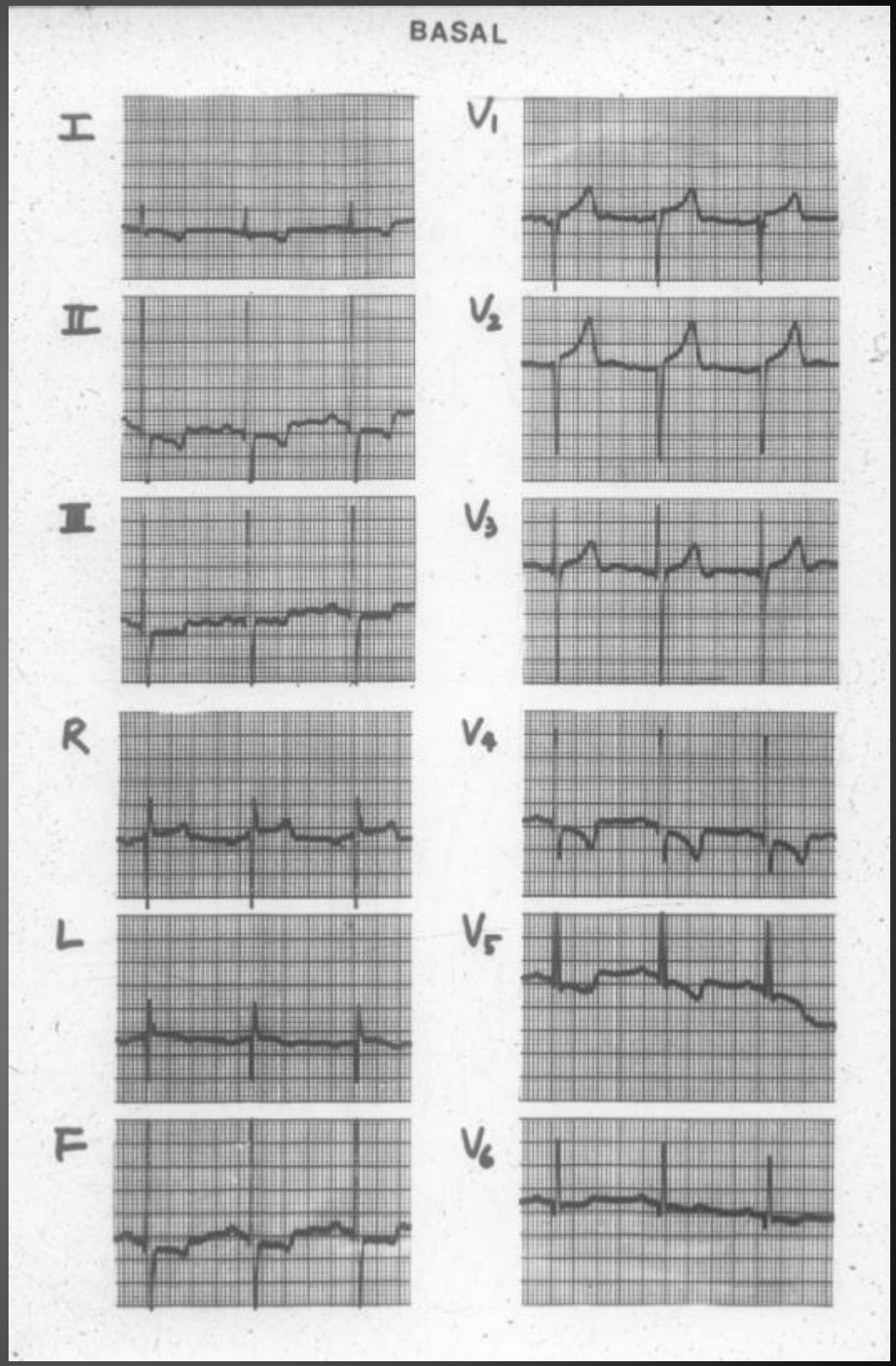


ECG after ICNG

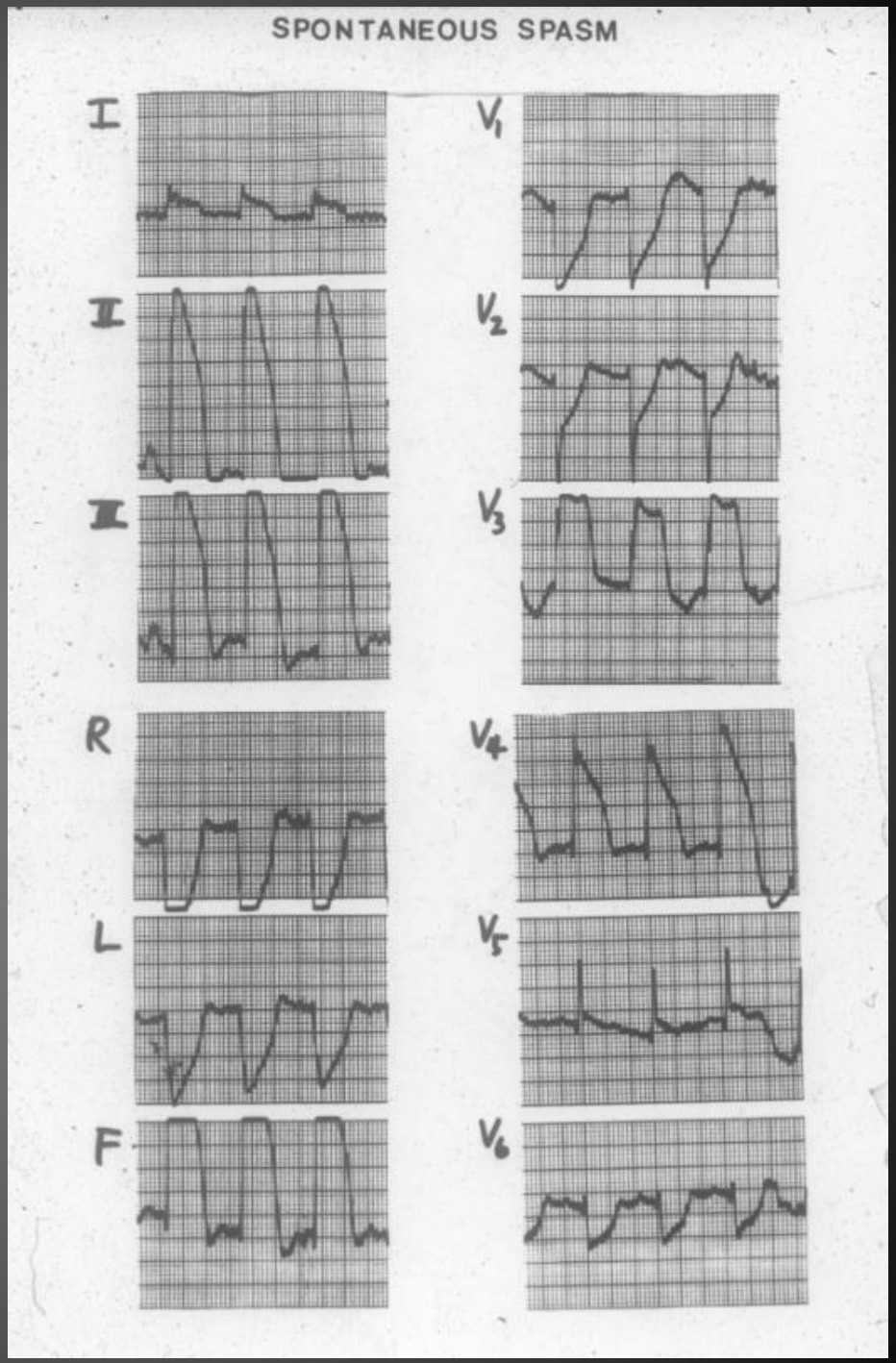


Case of severe spontaneous coronary artery spasm

Baseline ECG

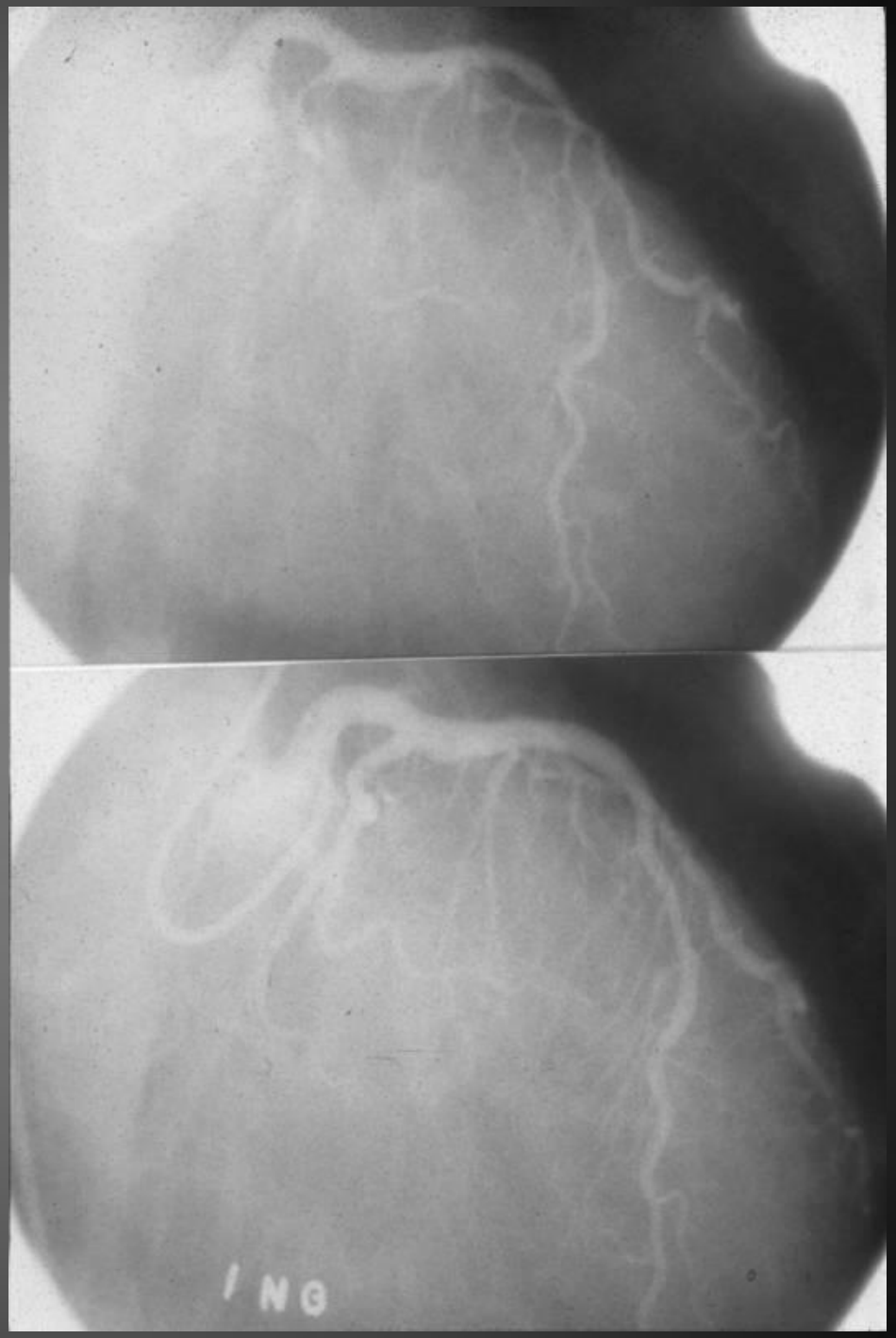


ECG during chest pain (spontaneous spasm)

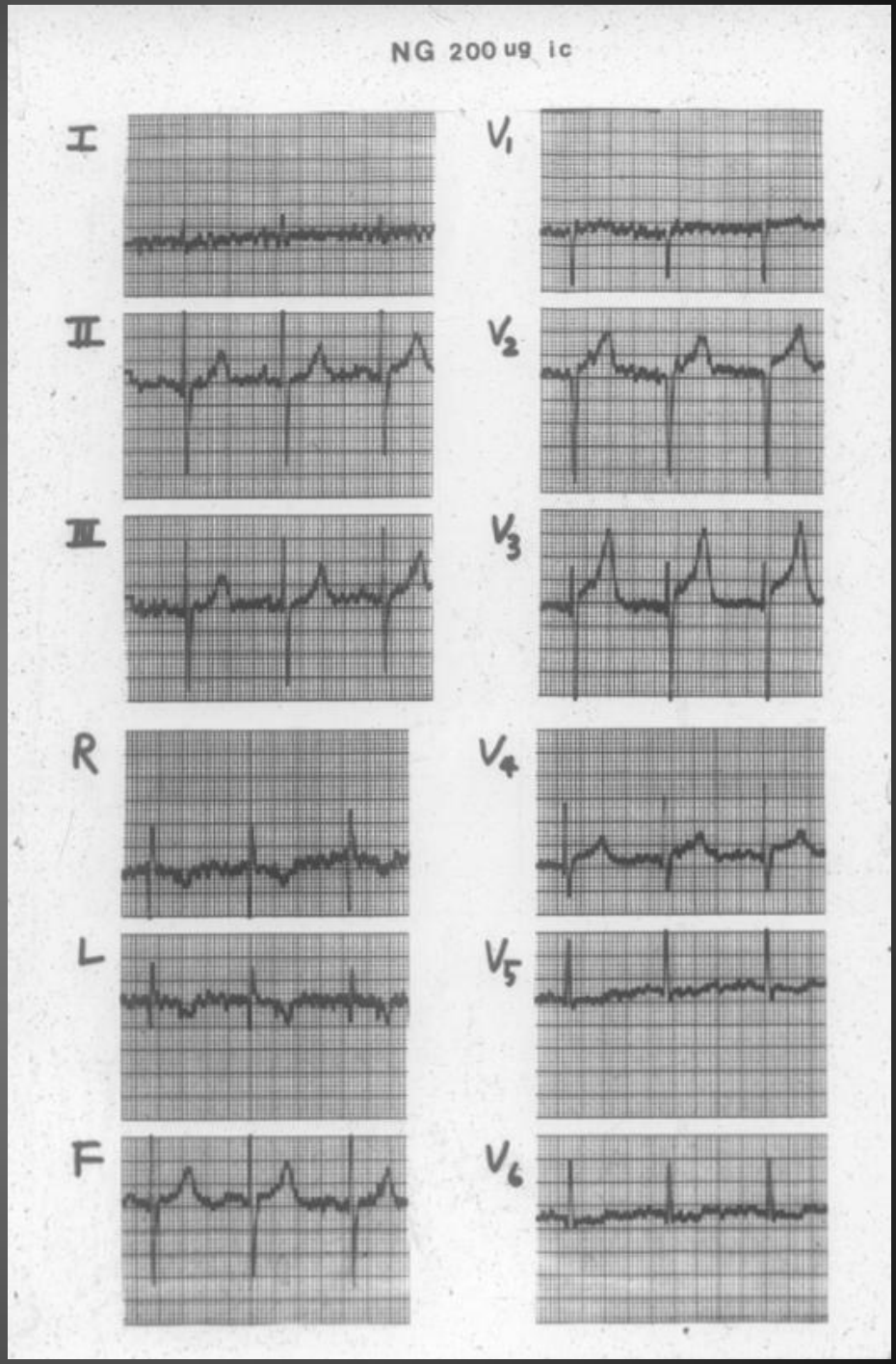


CAG during spontaenous spasm: pLCx near total, mLAD tight >90% stenosis

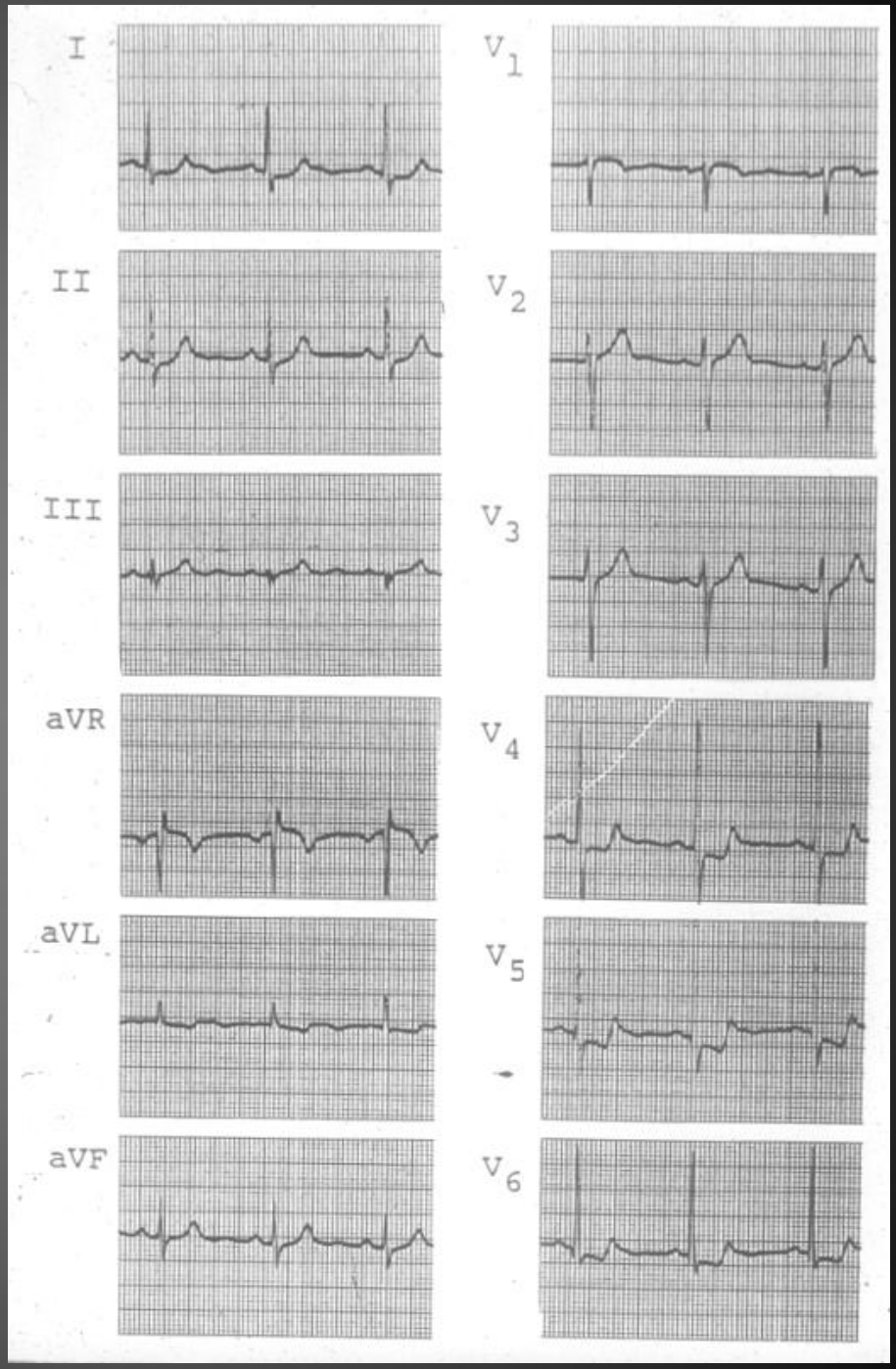
After ICNG



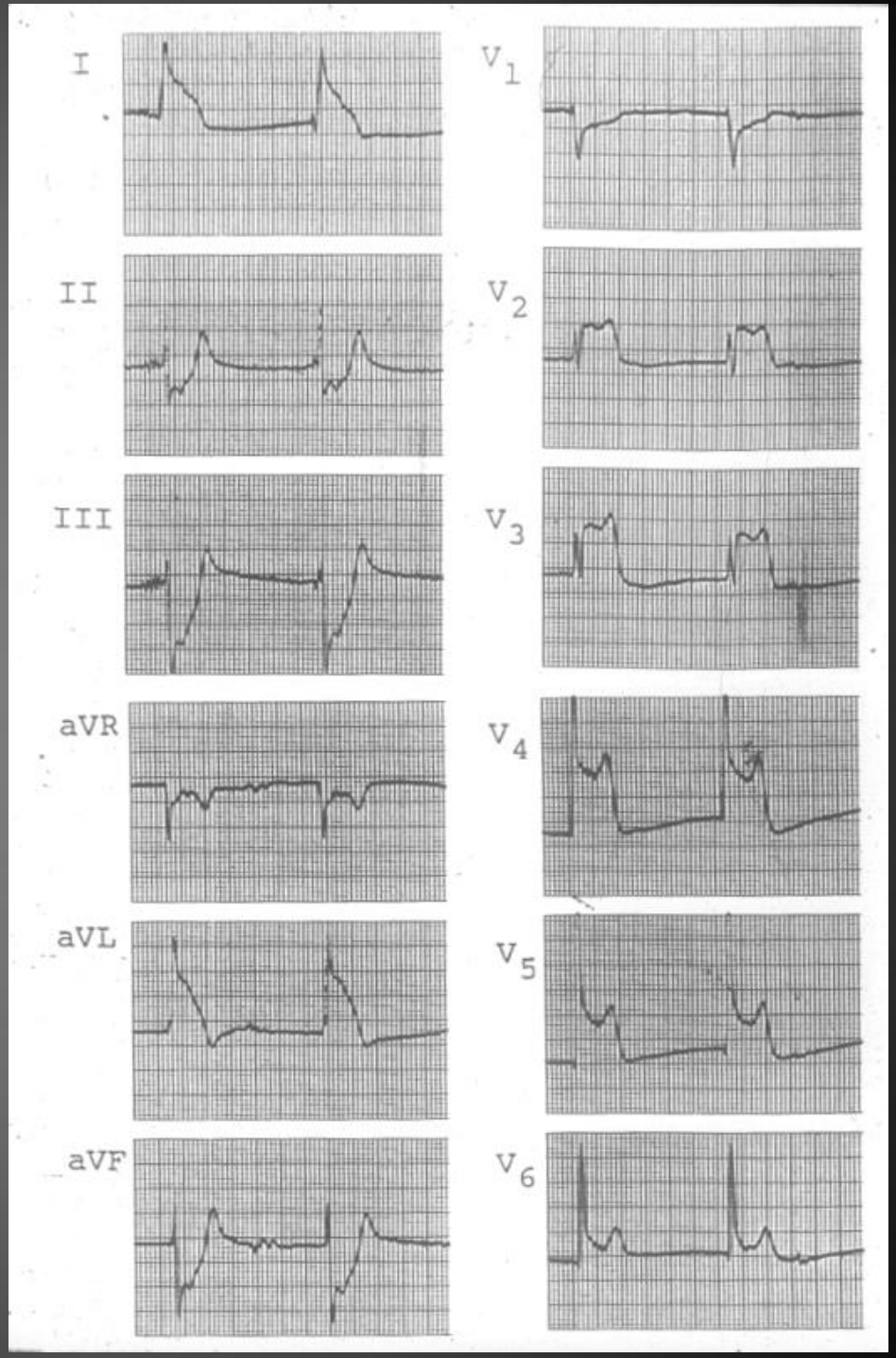
ECG after ICNG



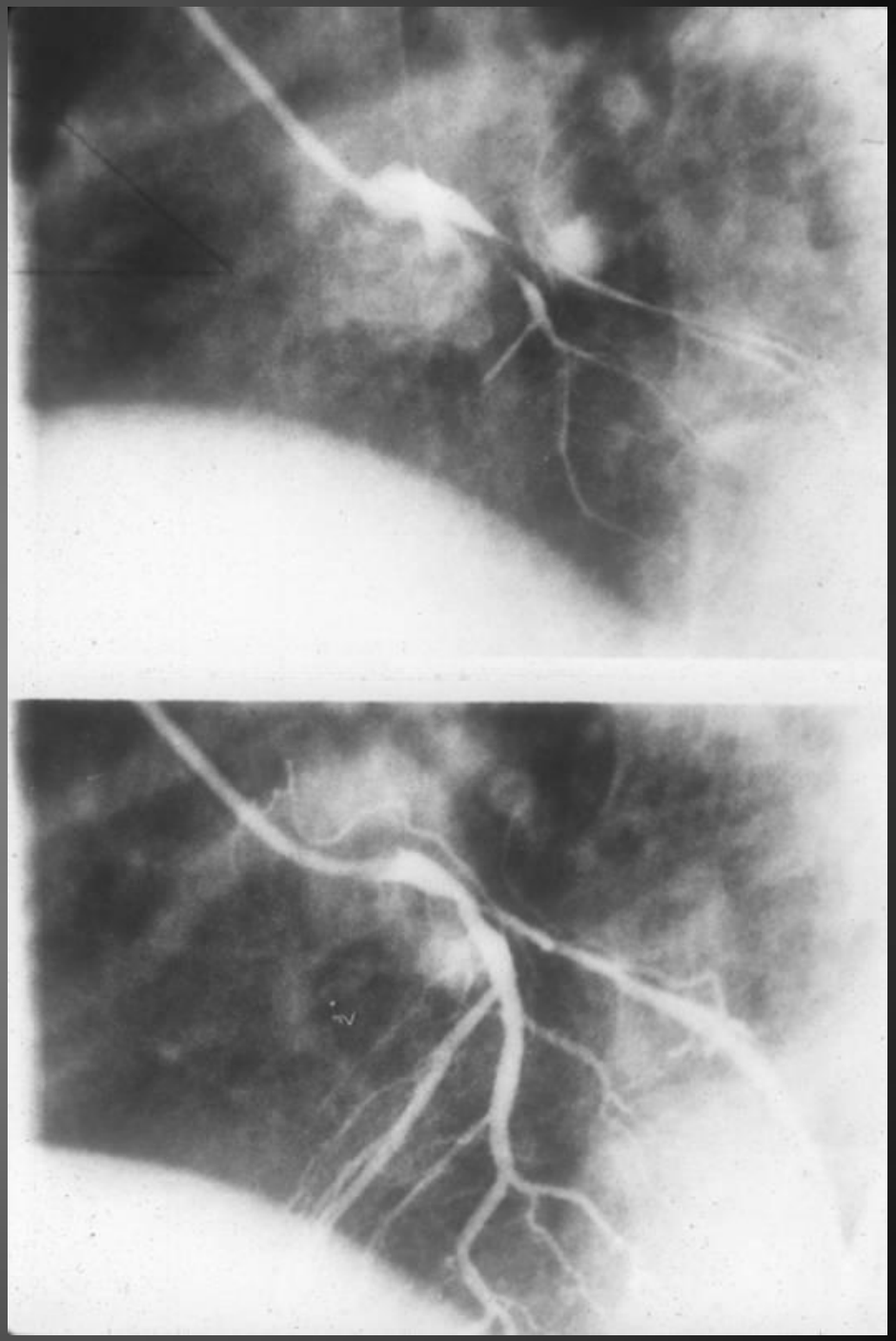
Baseline ECG
: ST depression



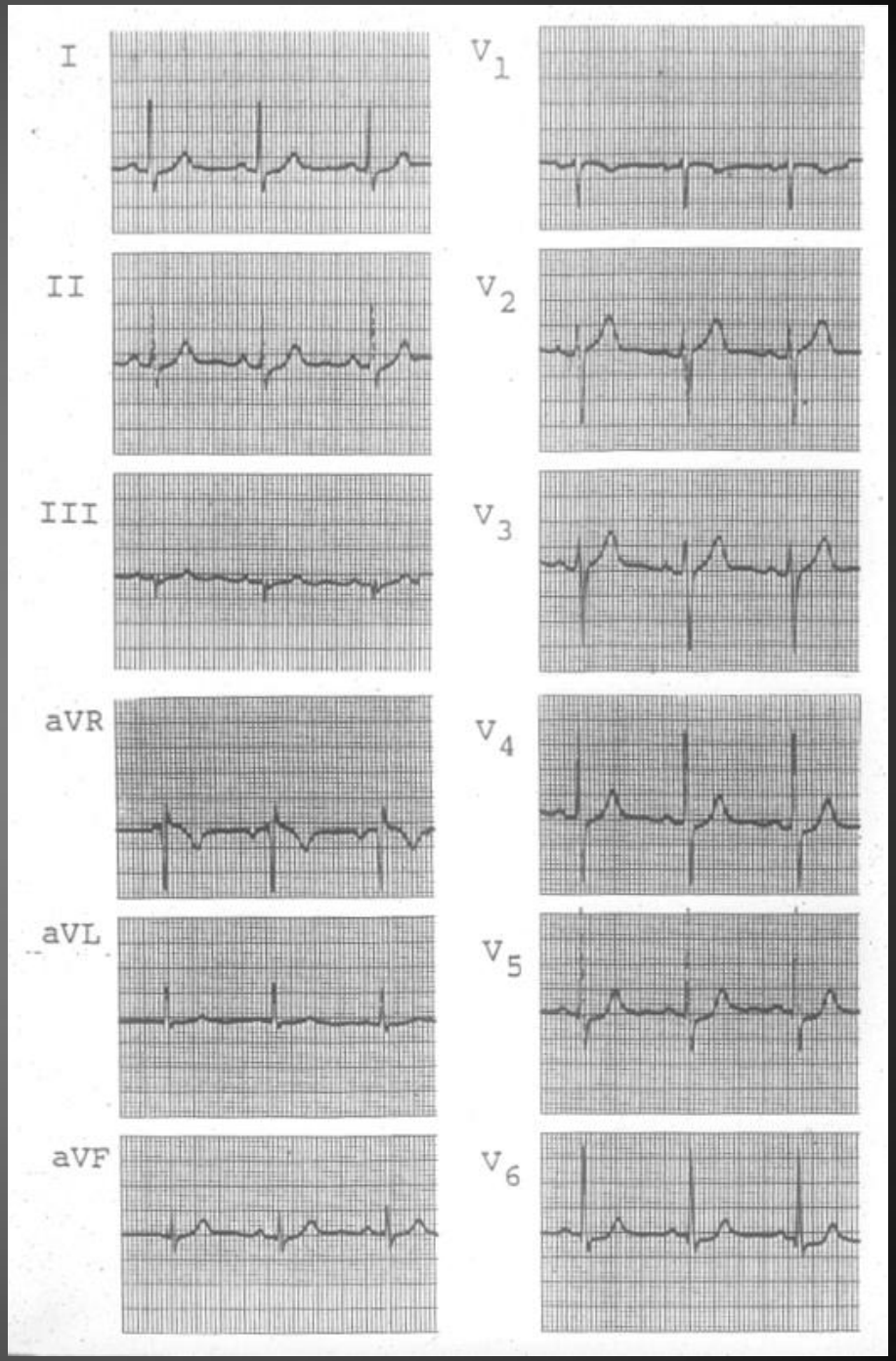
ECG during chest pain (spontaneous spasm)



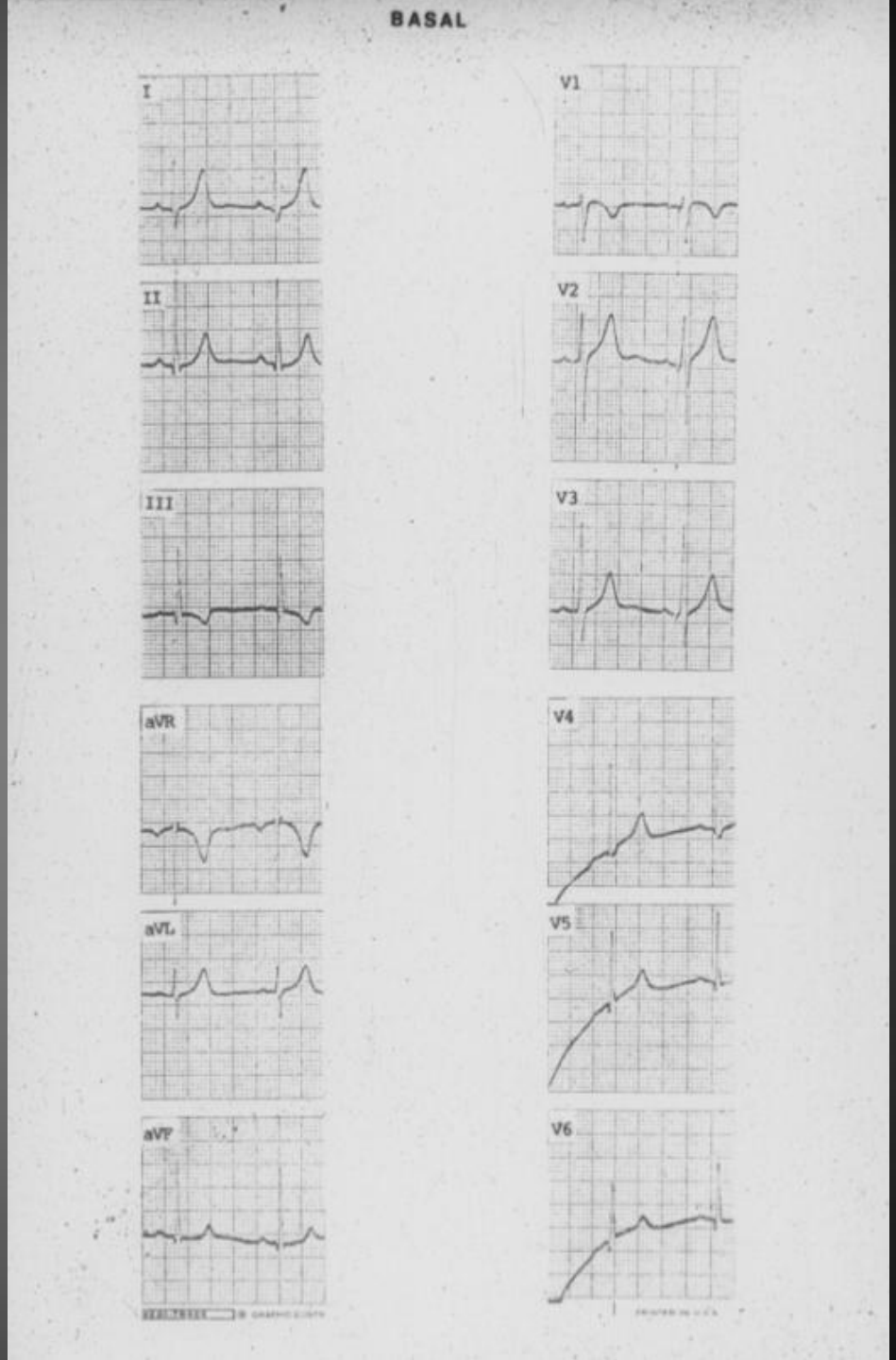
CAG
(spontaneous spasm)



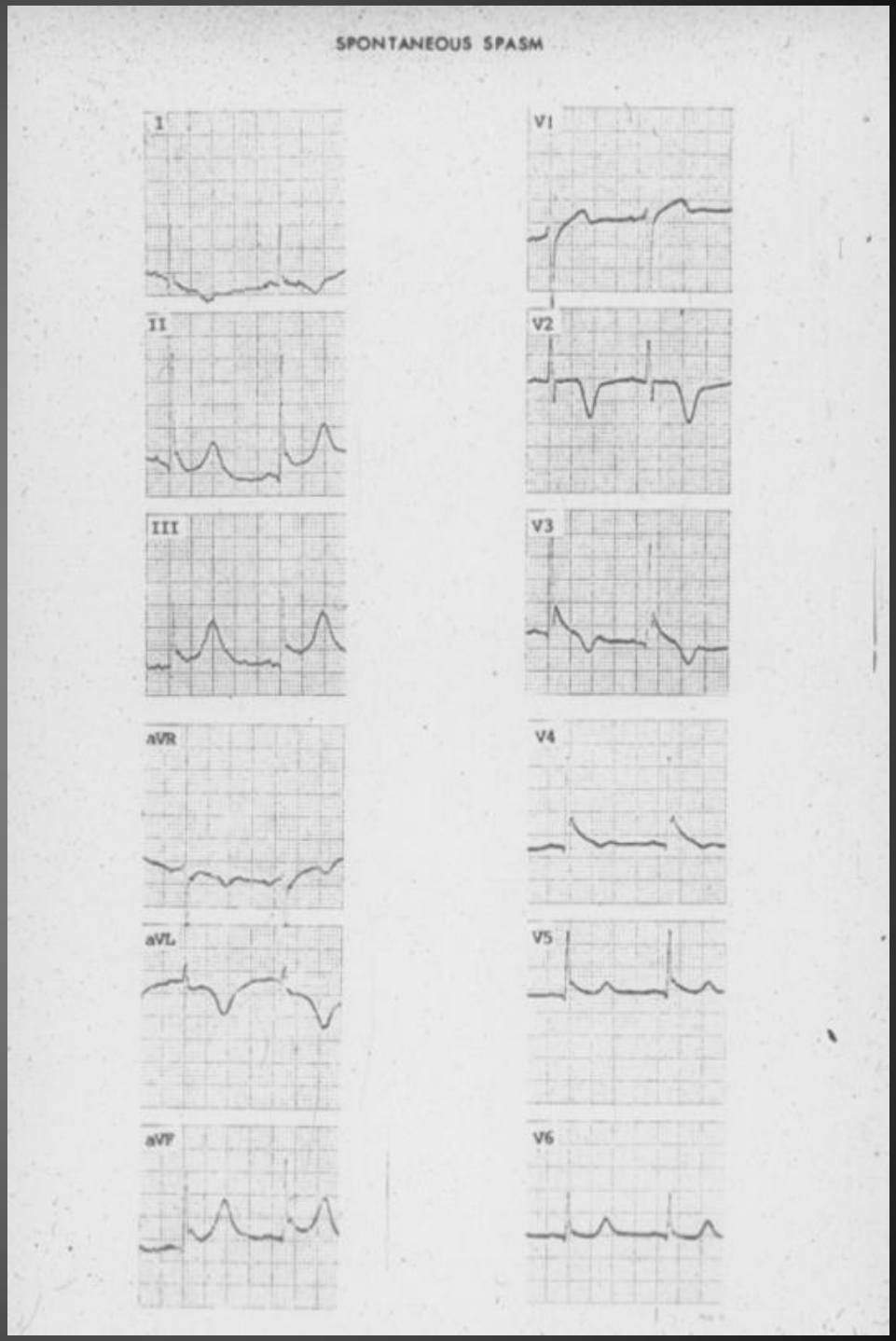
After ICNG



Baseline ECG

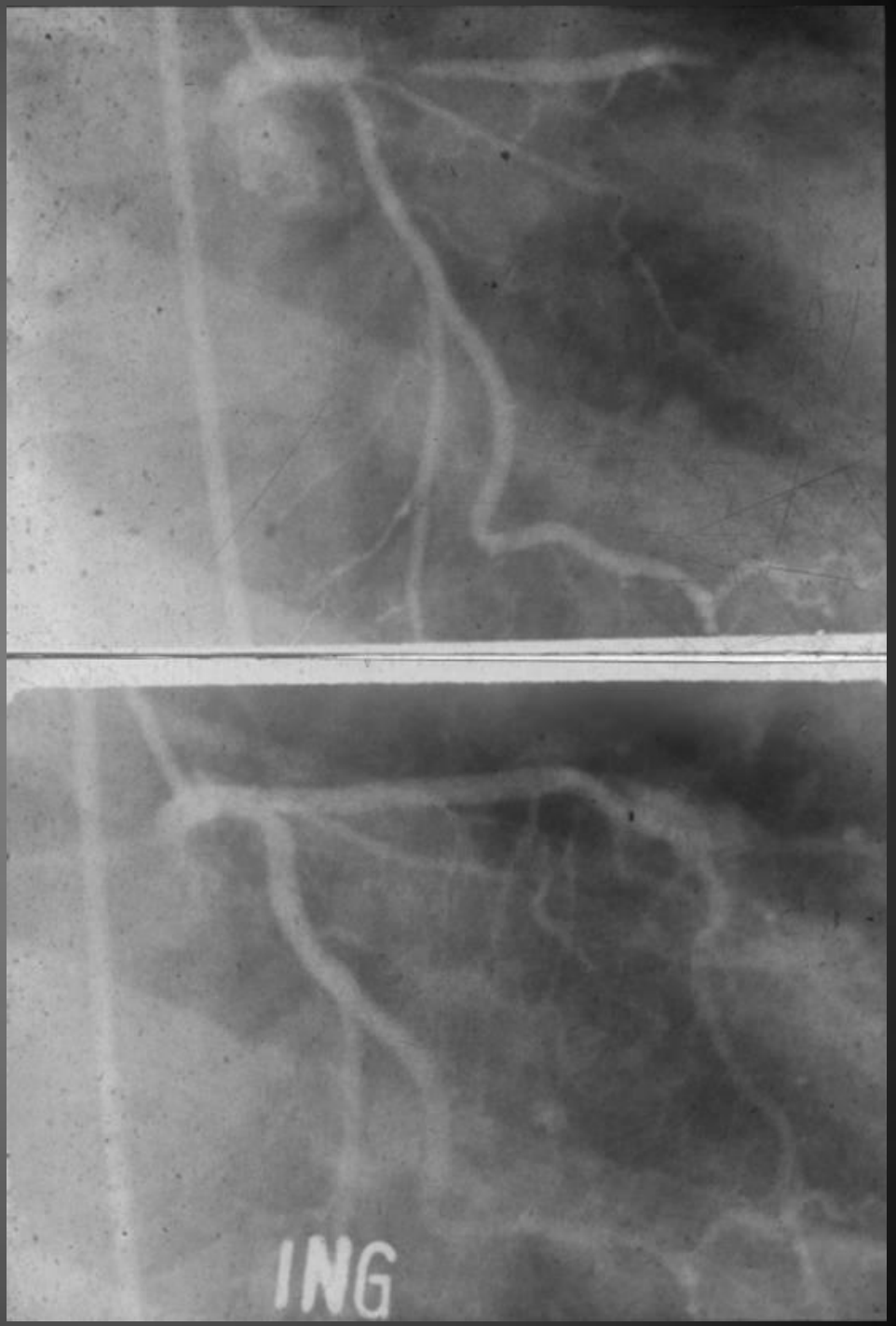


ECG during spontaneous spasm

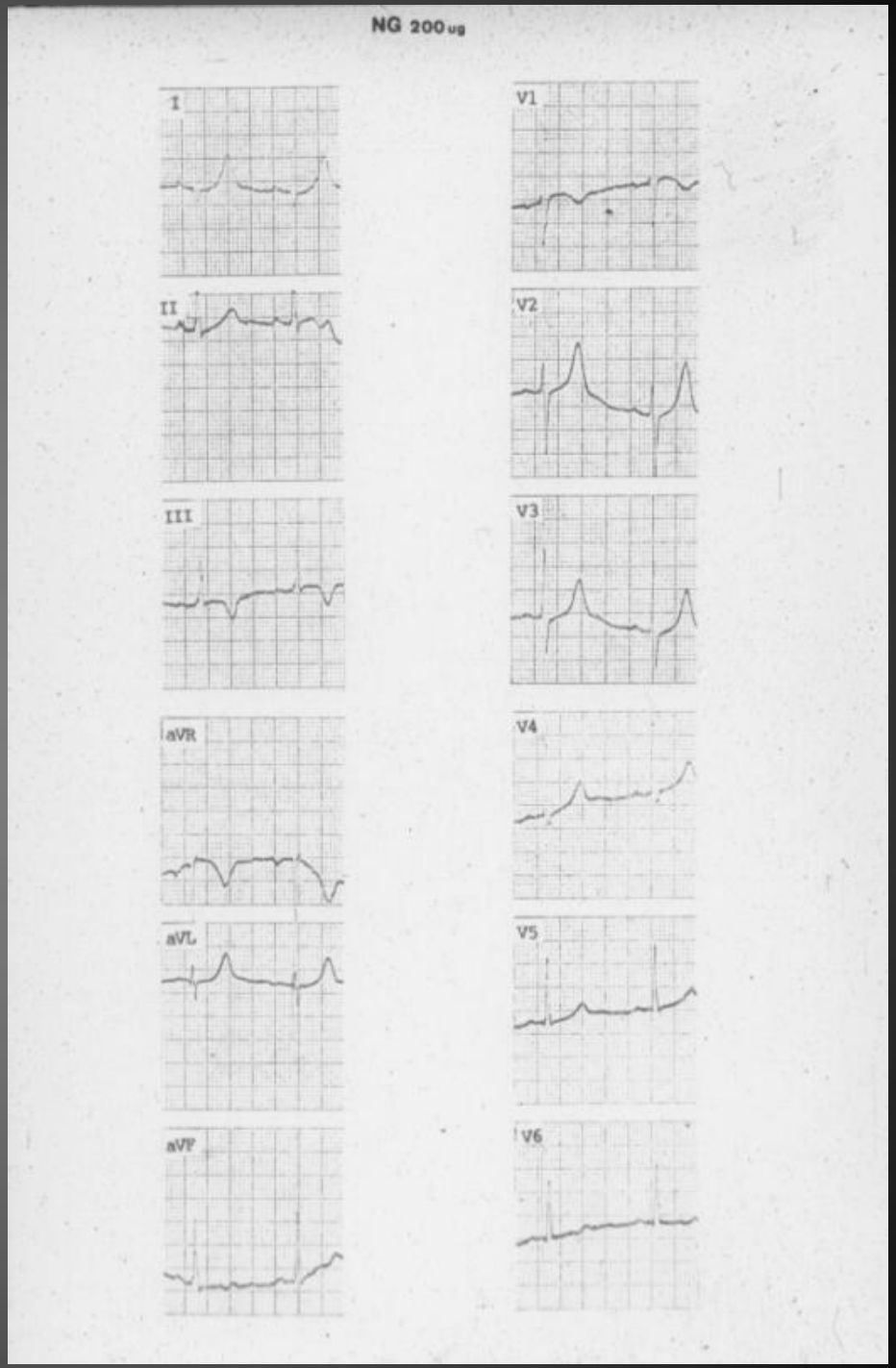


Baseline CAG:
spasm in LAD ostium

After ICNG



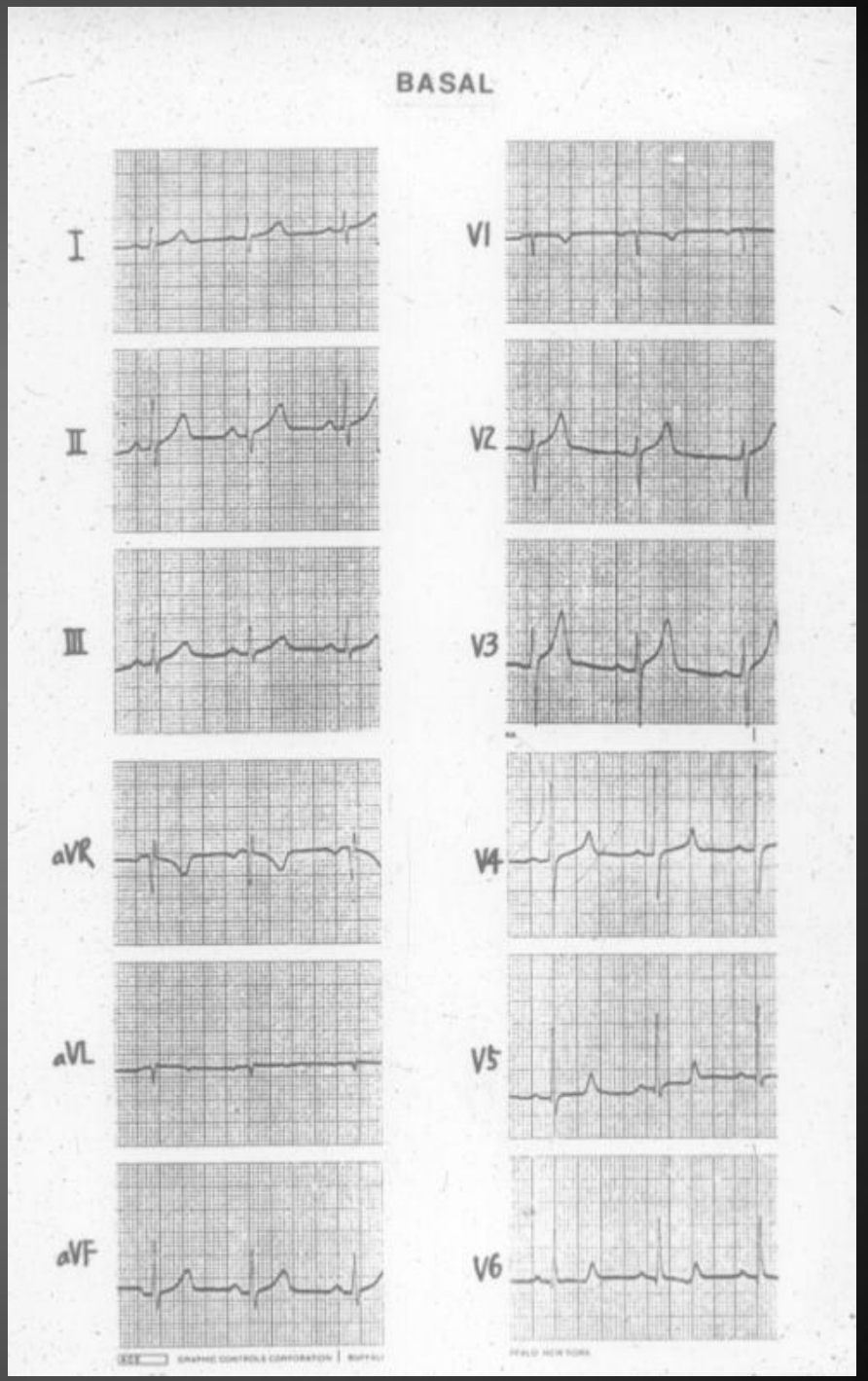
ECG after ICNG



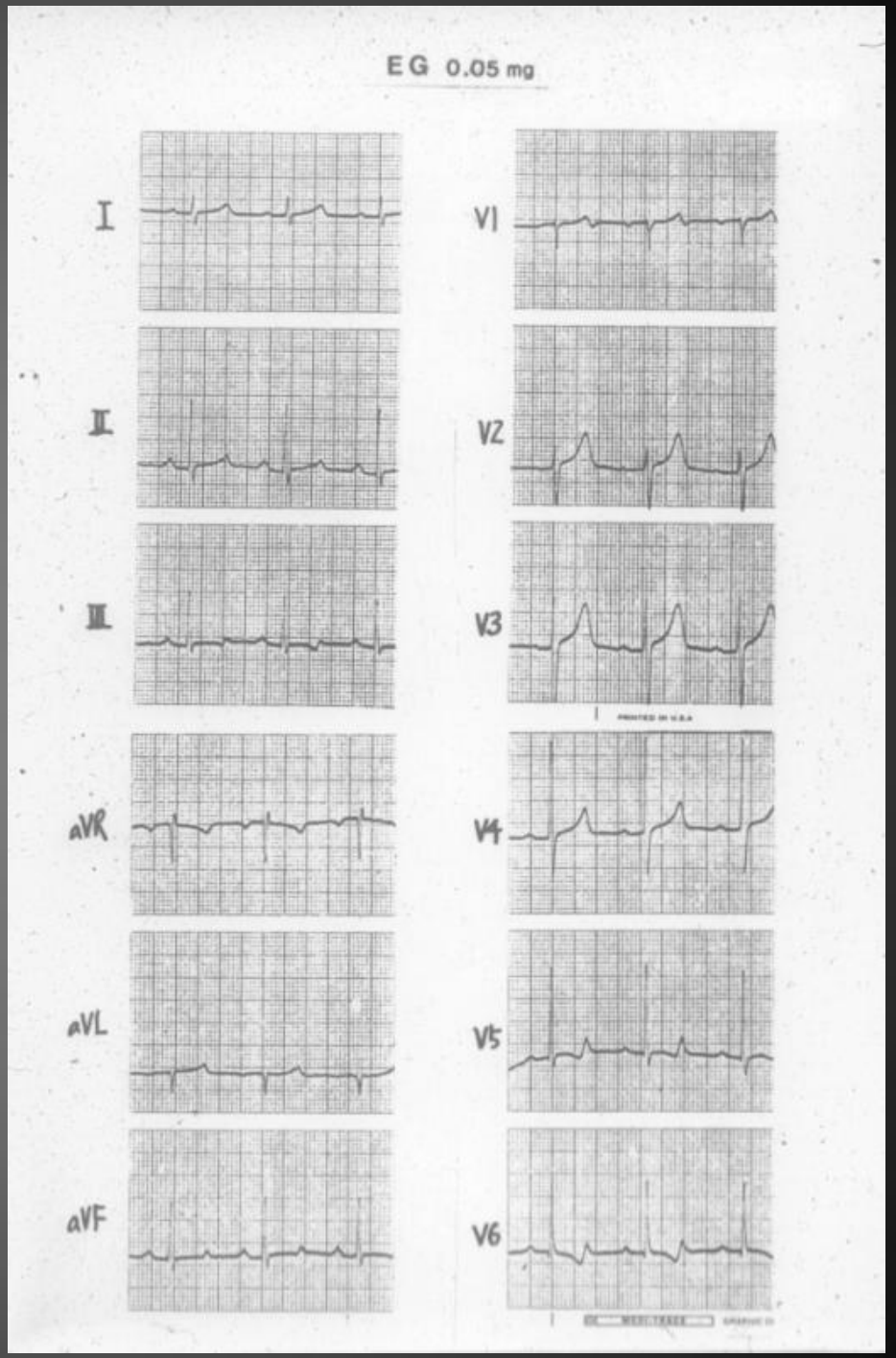
Spasm in a fixed lesion

: Mechanism of unstable angina and AMI

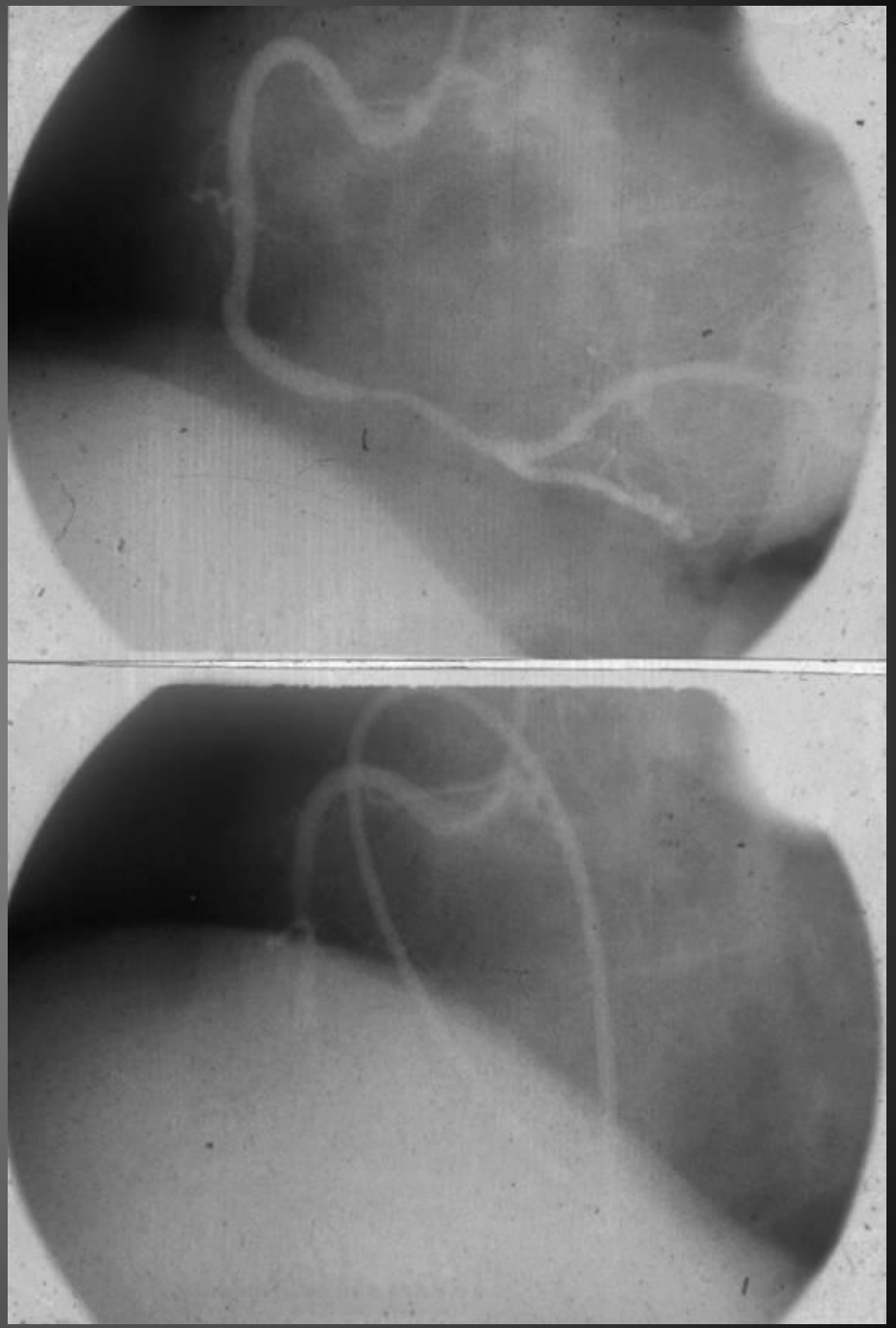
Baseline ECG



After EG provocation

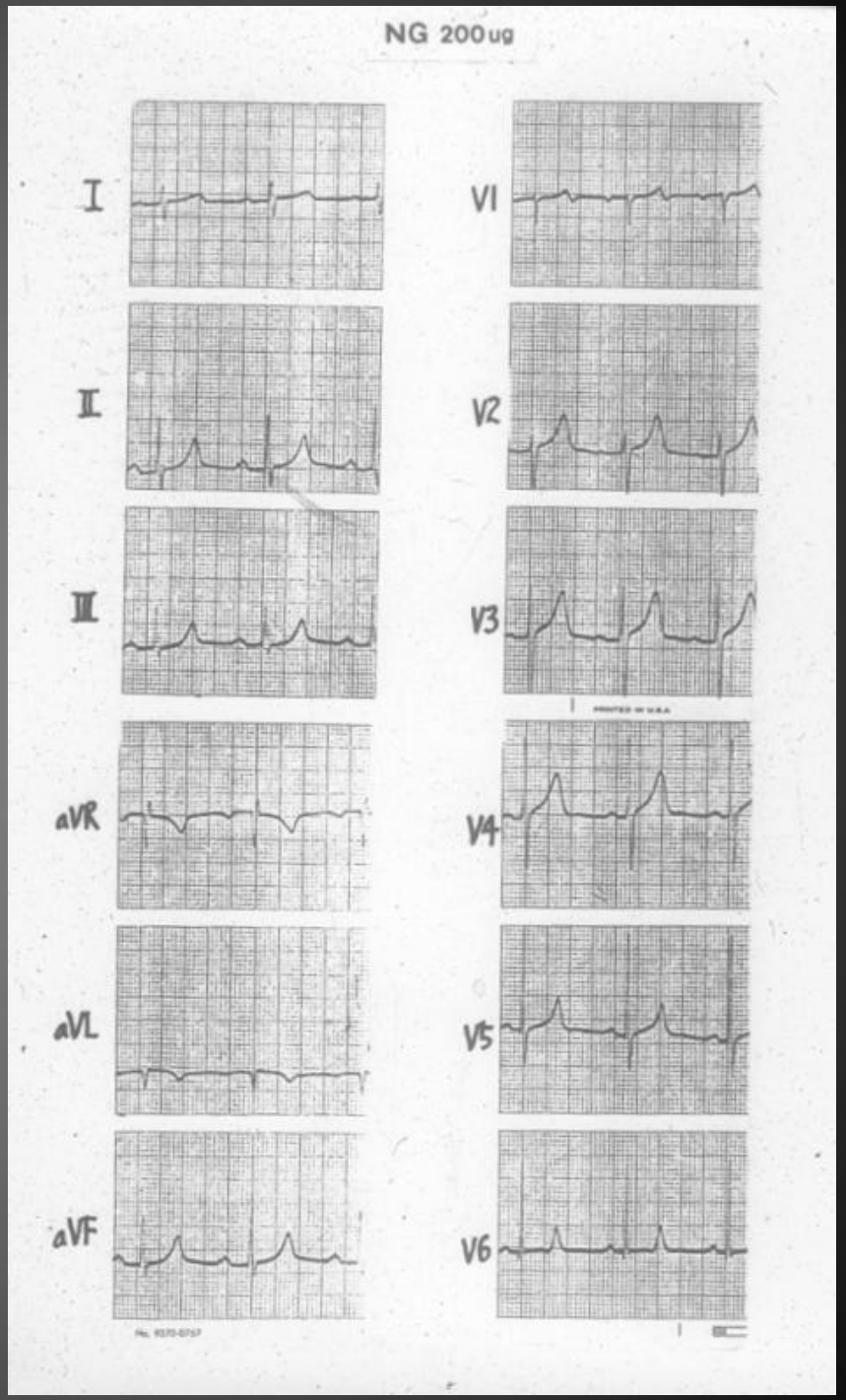


Baseline CAG:



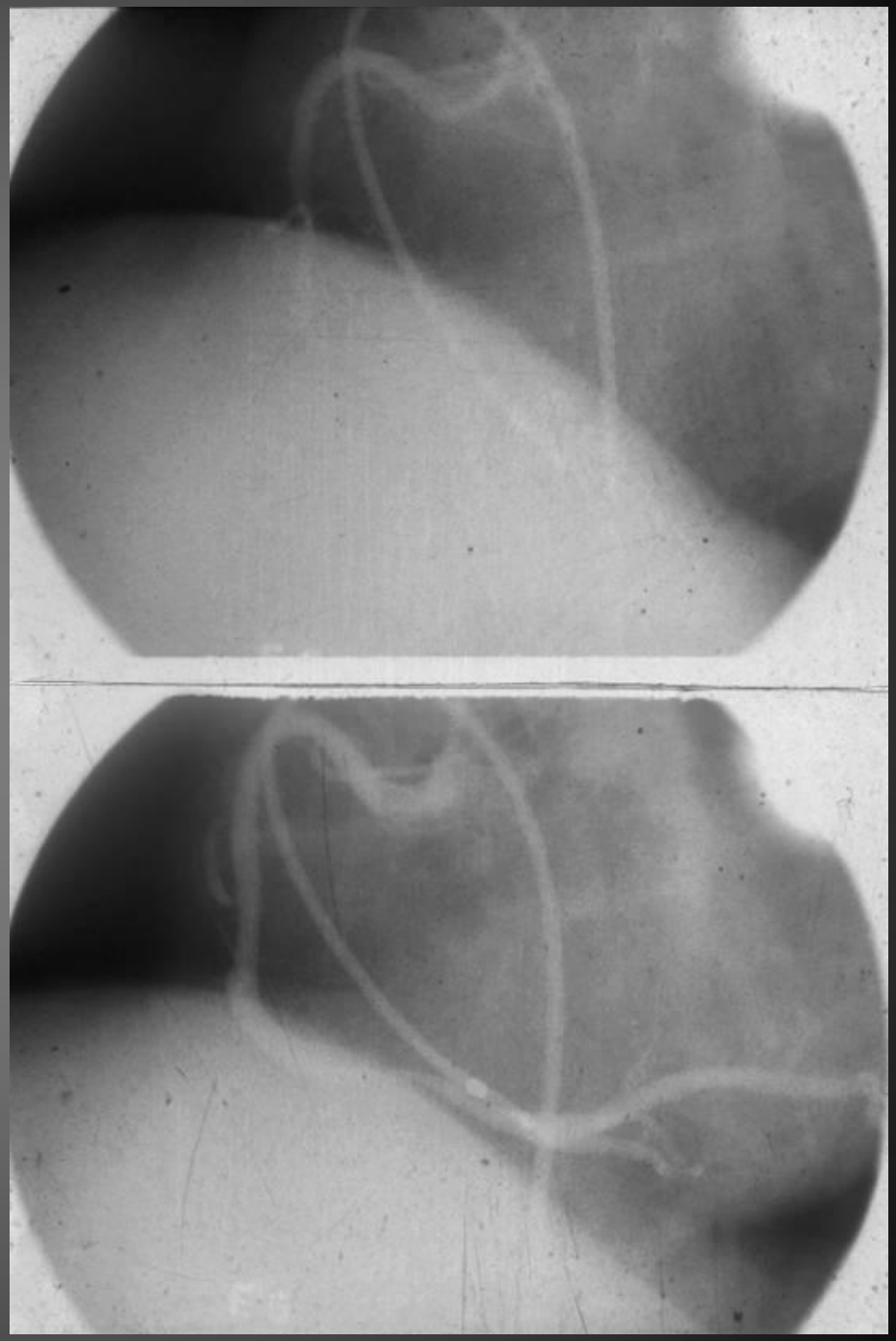
After EG:
RCA total occlusion

ECG after ICNG



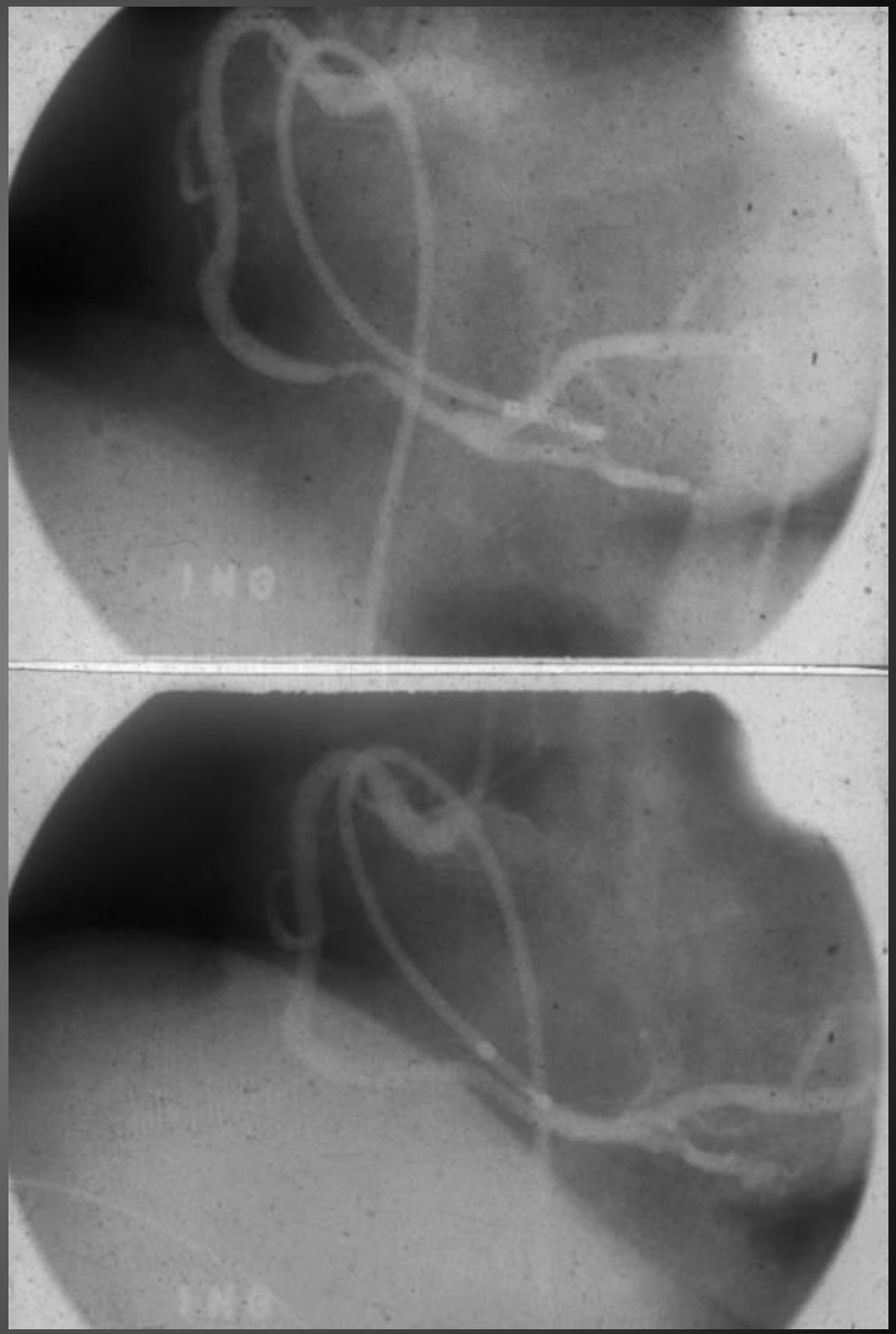
After provocation

After ICNG:
Fixed lesion in dRCA

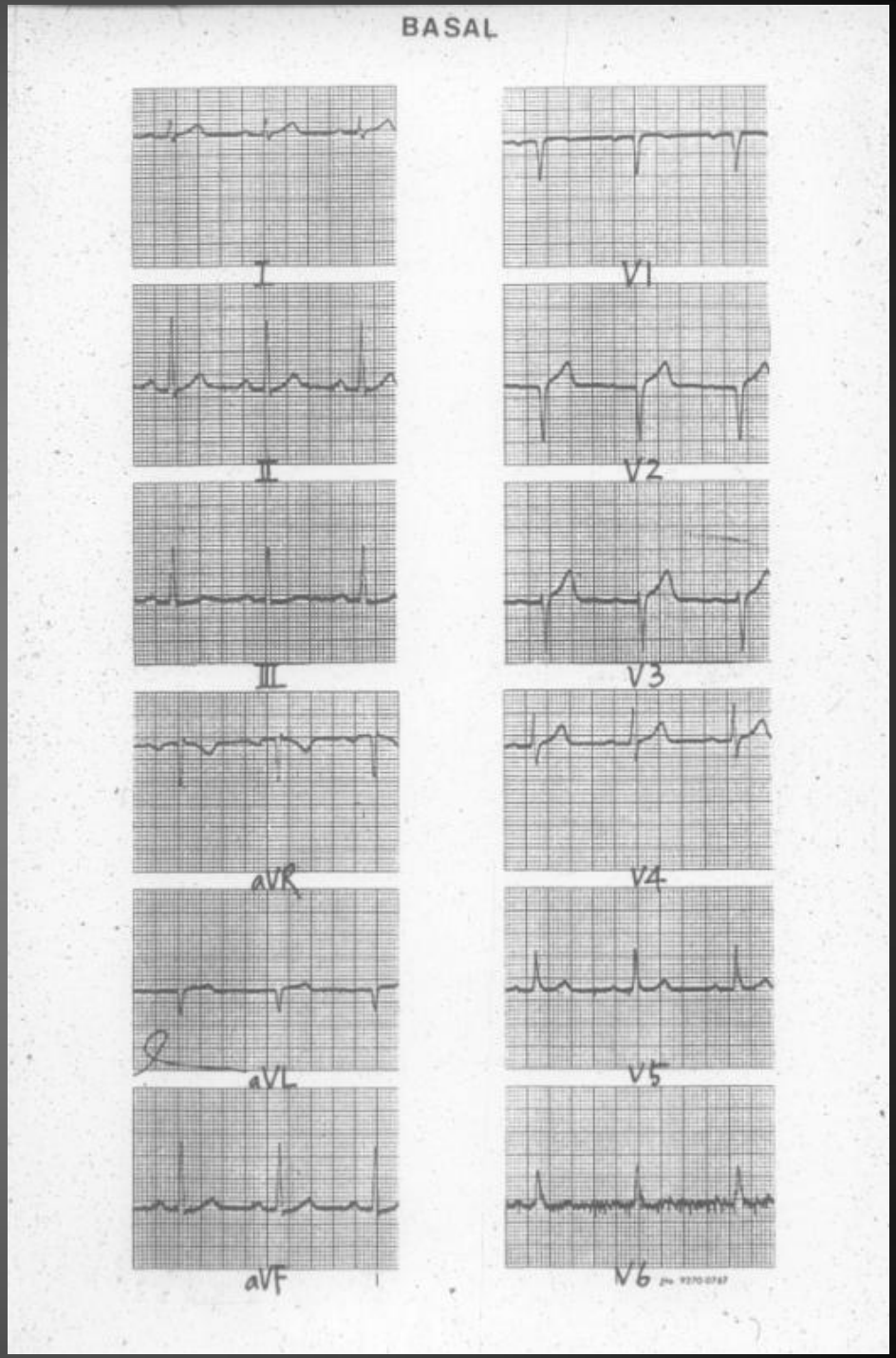


Fixed lesion in dRCA
(after ICNG)

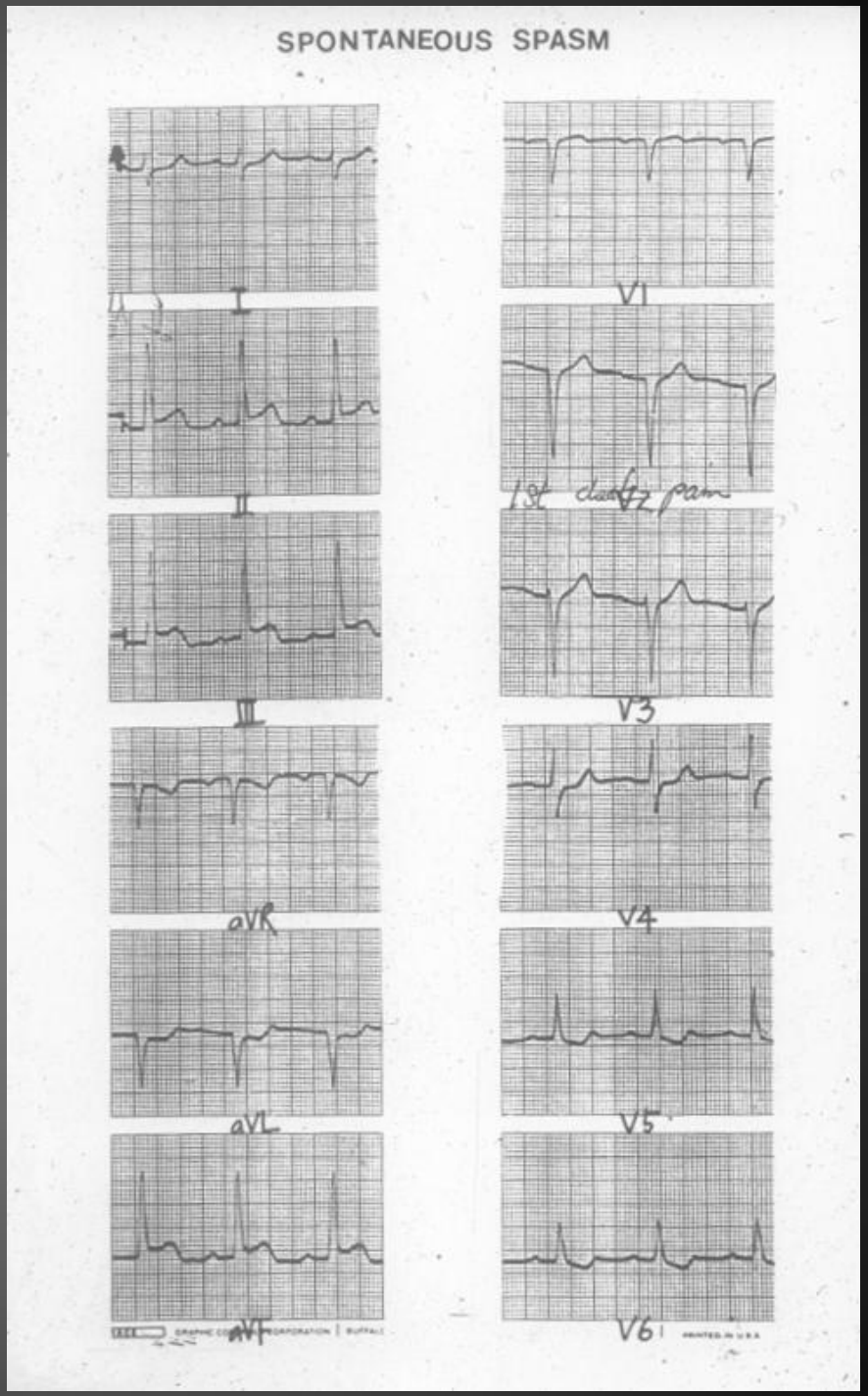
After PTCA



Baseline ECG

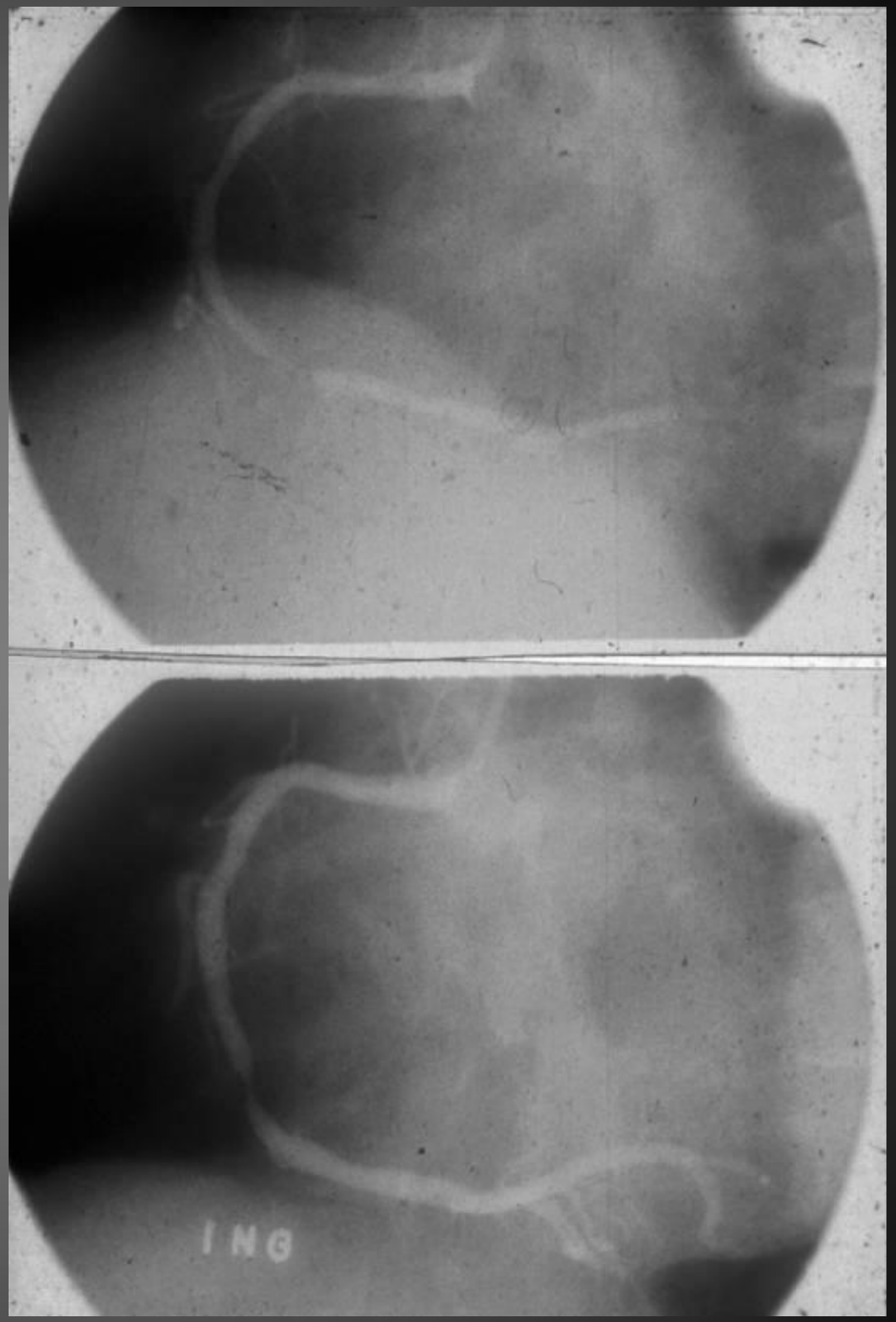


ECG during spontaneous spasm

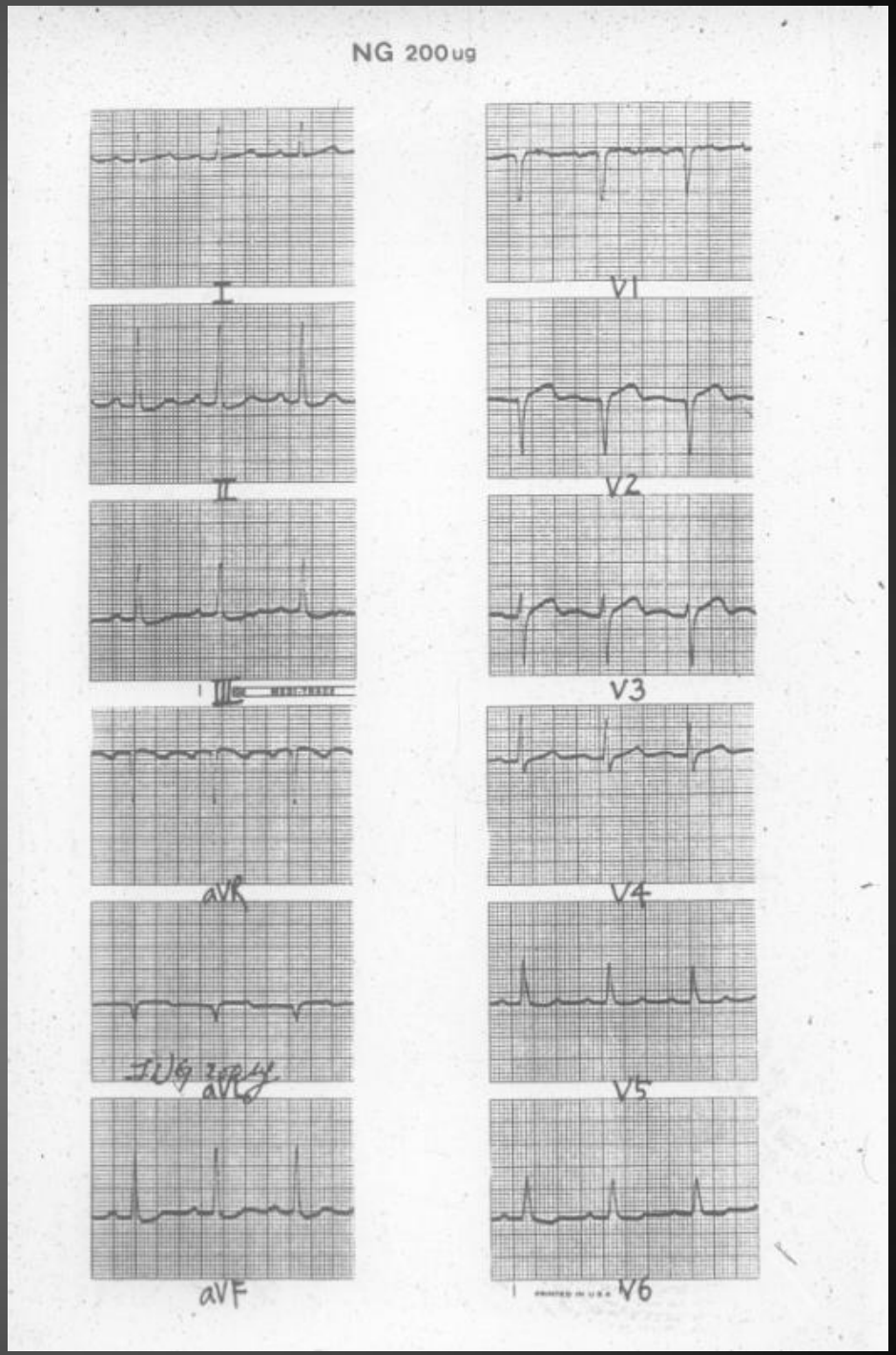


CAG during spontaneous spasm

After ICNG:
fixed lesion in dRCA

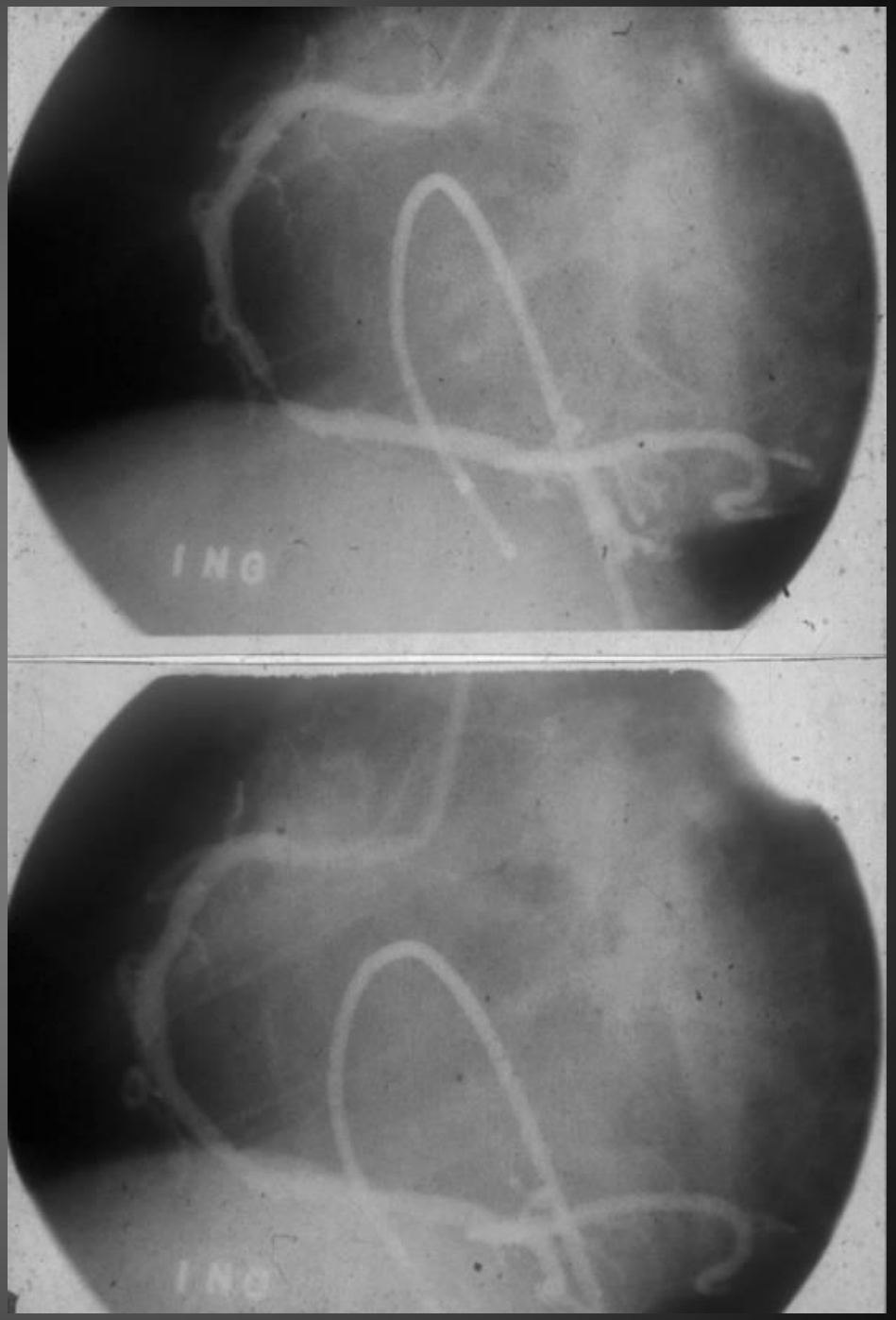


ECG after ICNG



Fixed lesion in dRCA
(after ICNG)

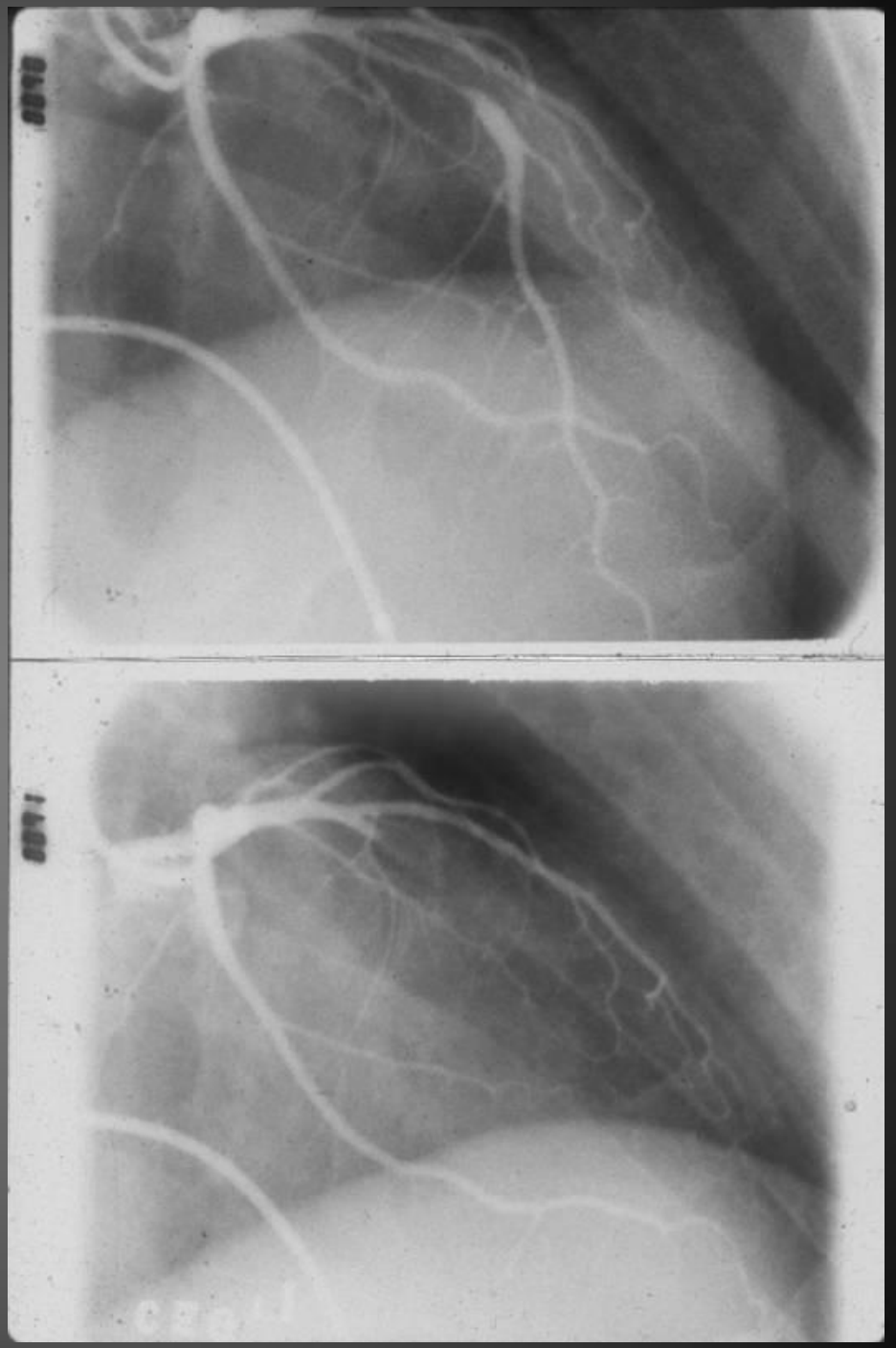
After PTCA



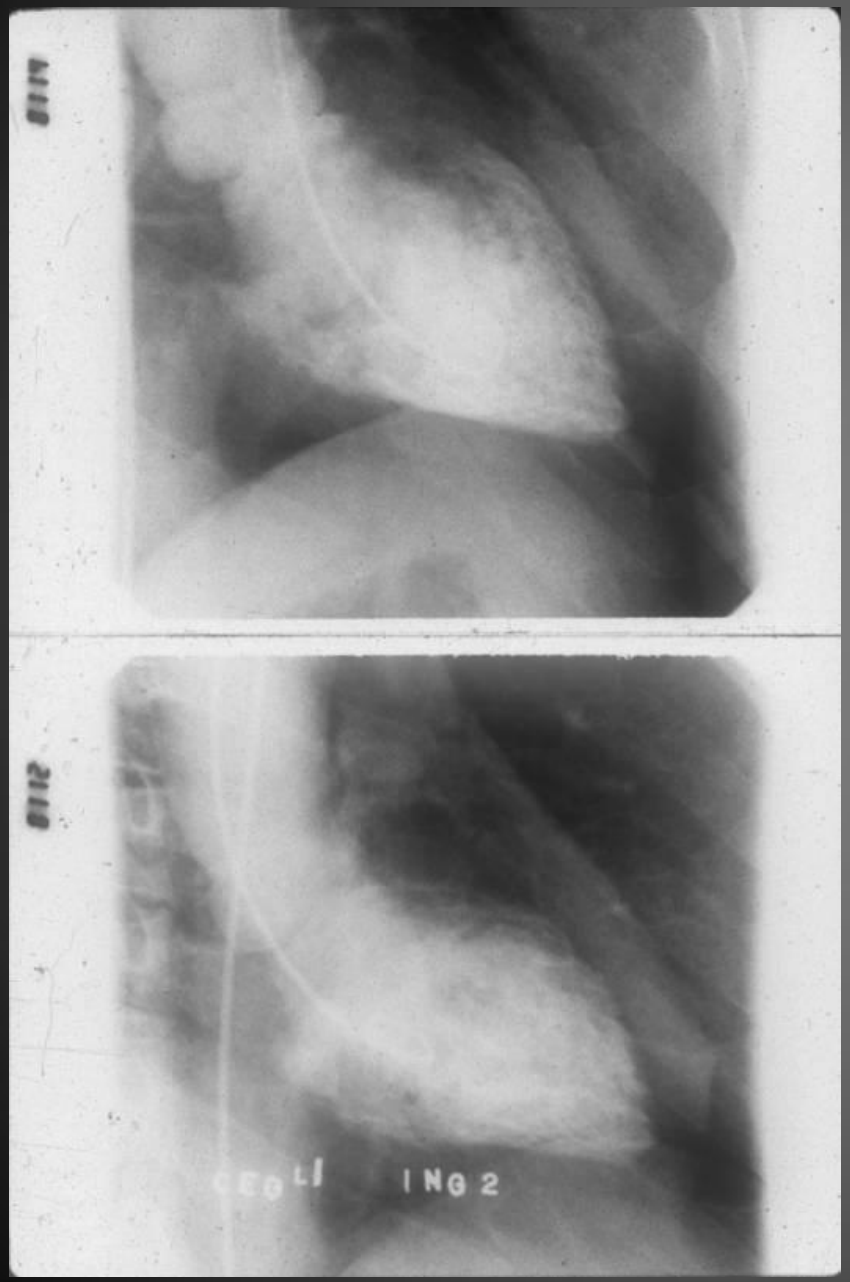
Recurrent coronary artery spasm leading to stunned myocardium

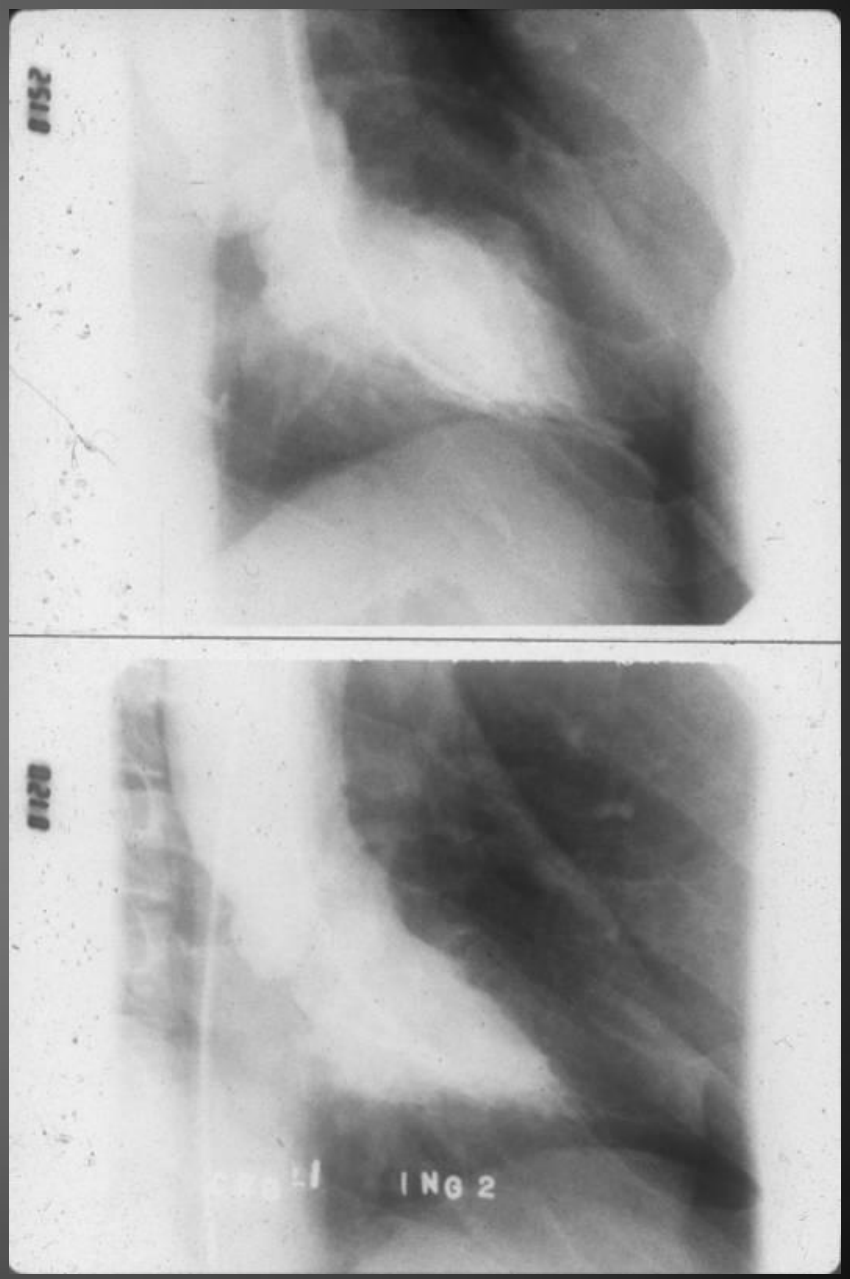
Baseline CAG

After EG provocation:
pLAD total occlusion



Stunned myocardium: relieved after ICNG





Introduction

Ventricular Asynergy without Myocardial Infarction

- Myocardial Stunning
- Myocardial Hibernation

Detection of Stunned Myocardium

- Perfusion - Contraction Mismatch
  - 99mTc- MIBI, PET, 201Tl scintigraphy
- Inotropic Reserve
  - Dobutamine infusion
  - Post-extrasystole potentiation
  - Nitroglycerin

Myocardial Stunning in Variant Angina

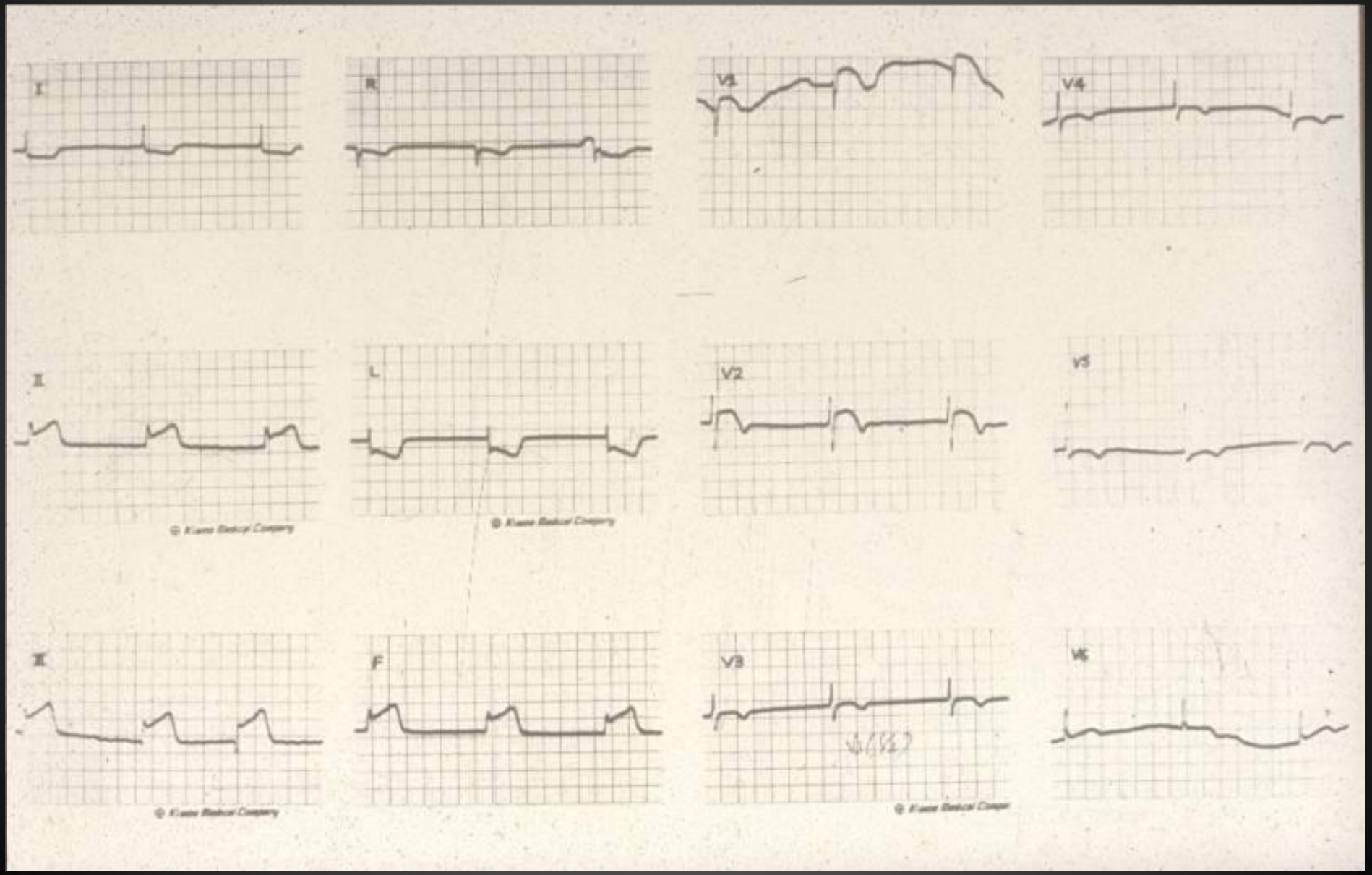
Takatsu F. et al (Am J Cardiol 1988; 58:647 - 649)

Mathias P. et al (Am Heart J 1987; 113:383 - 385)

Fournier C. et al (Am Heart J 1991; 121:593 - 595)

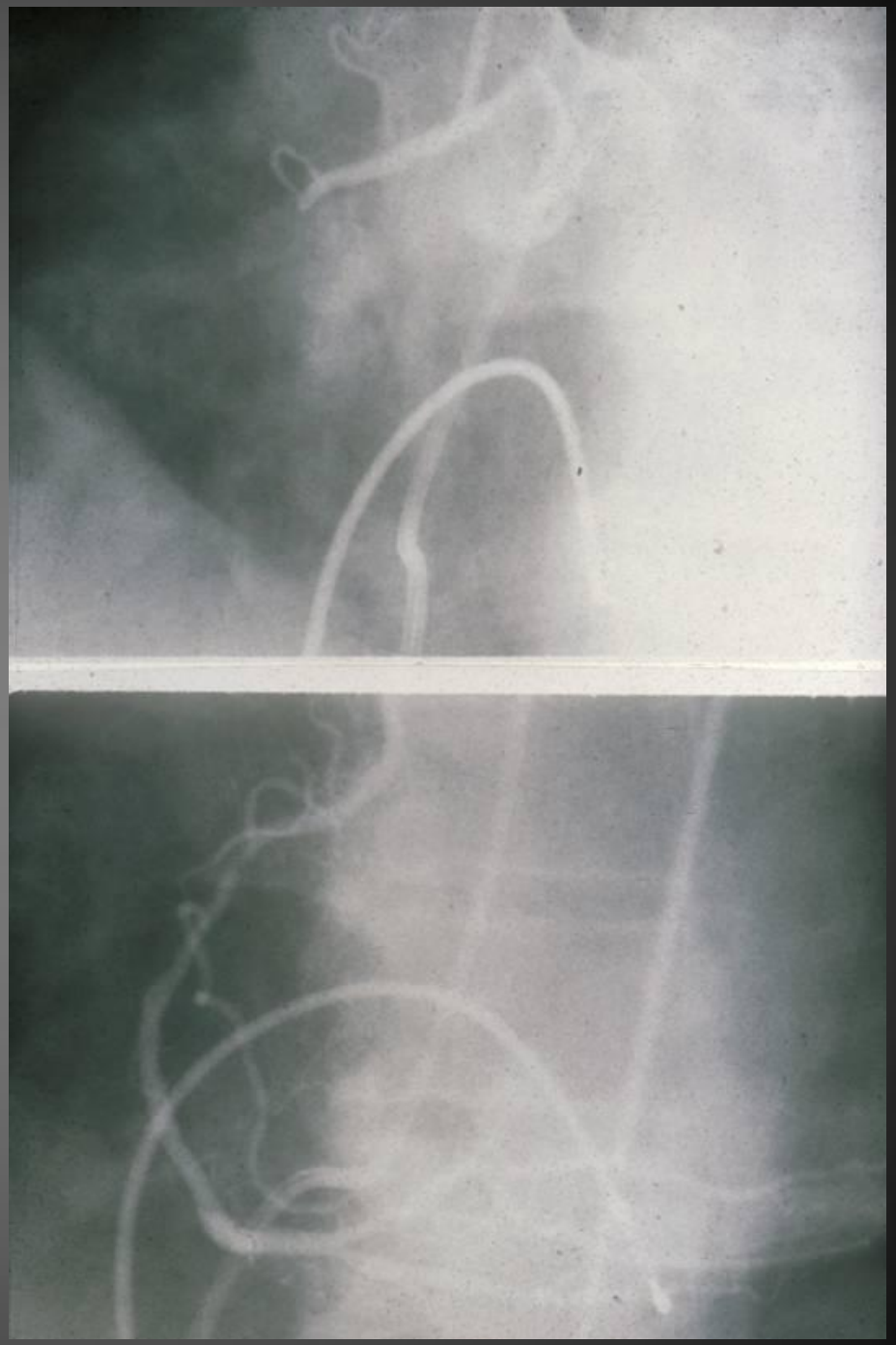
Recurrent spontaneous coronary artery spasm causing acute myocardial infarction

60 YO Male: Resting chest pain for 5 hours

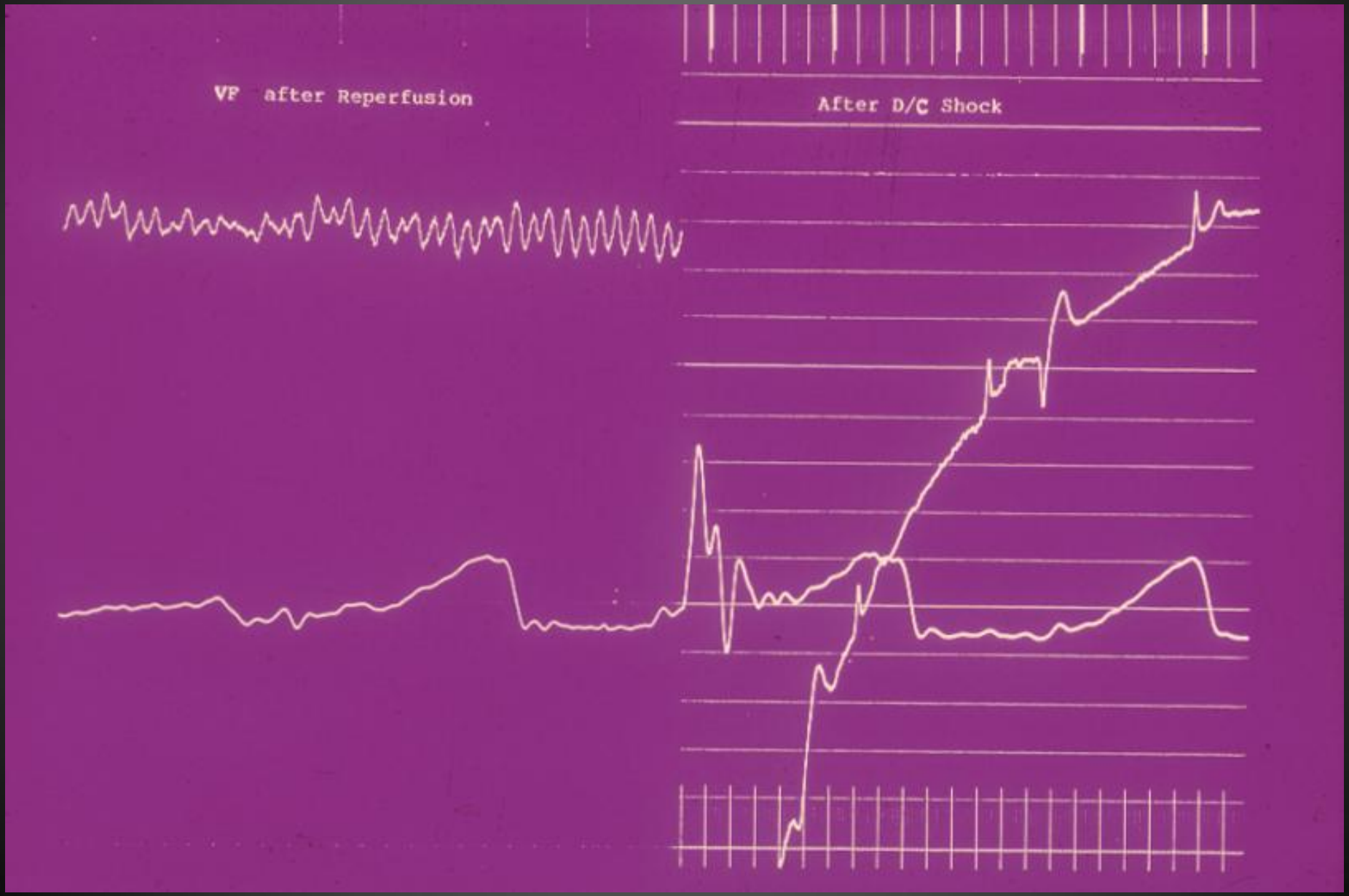


Baseline: RCA total occlusion

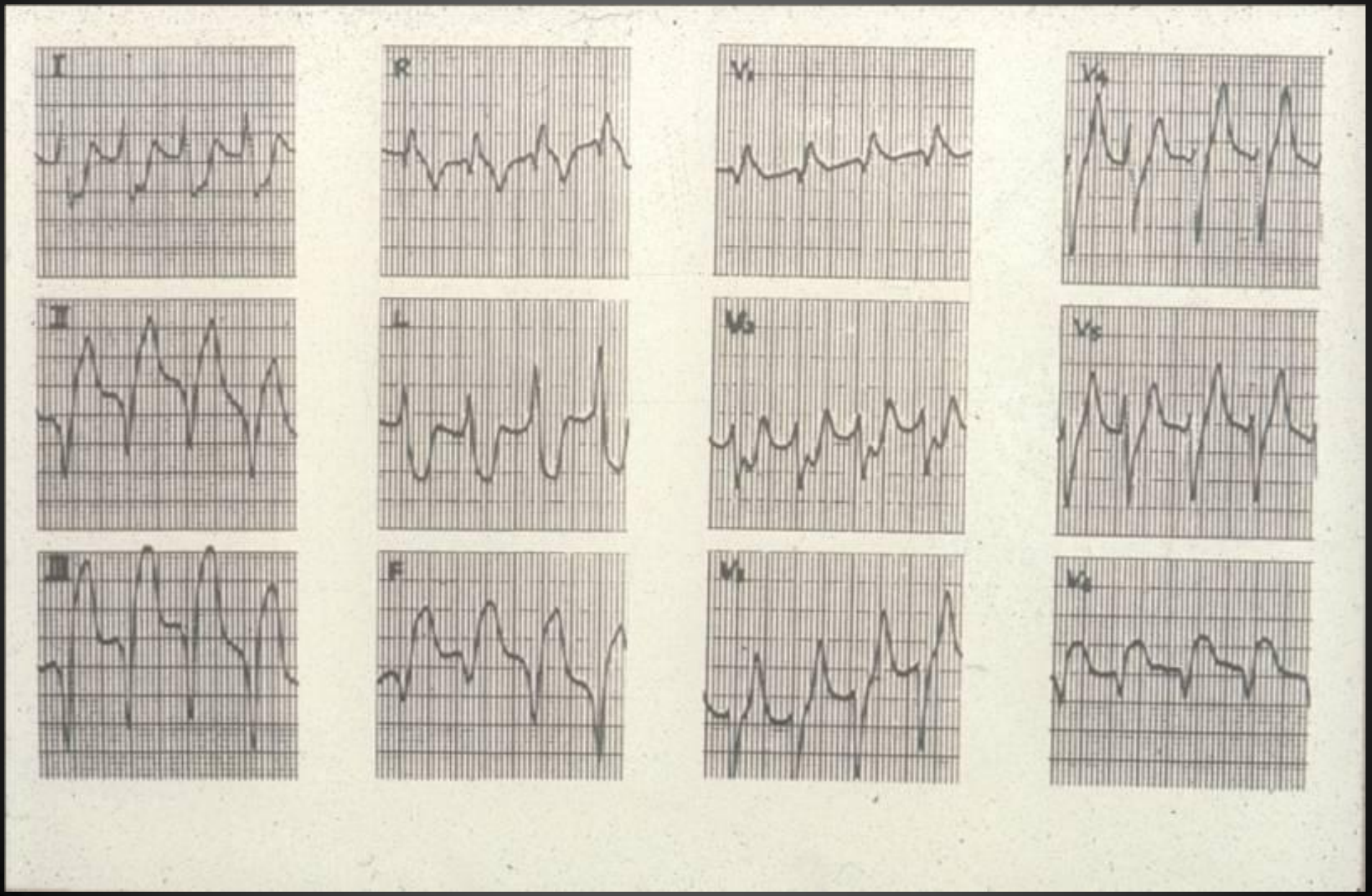
After IC NG



Reperfusion arrhythmia: Ventricular Fibrillation

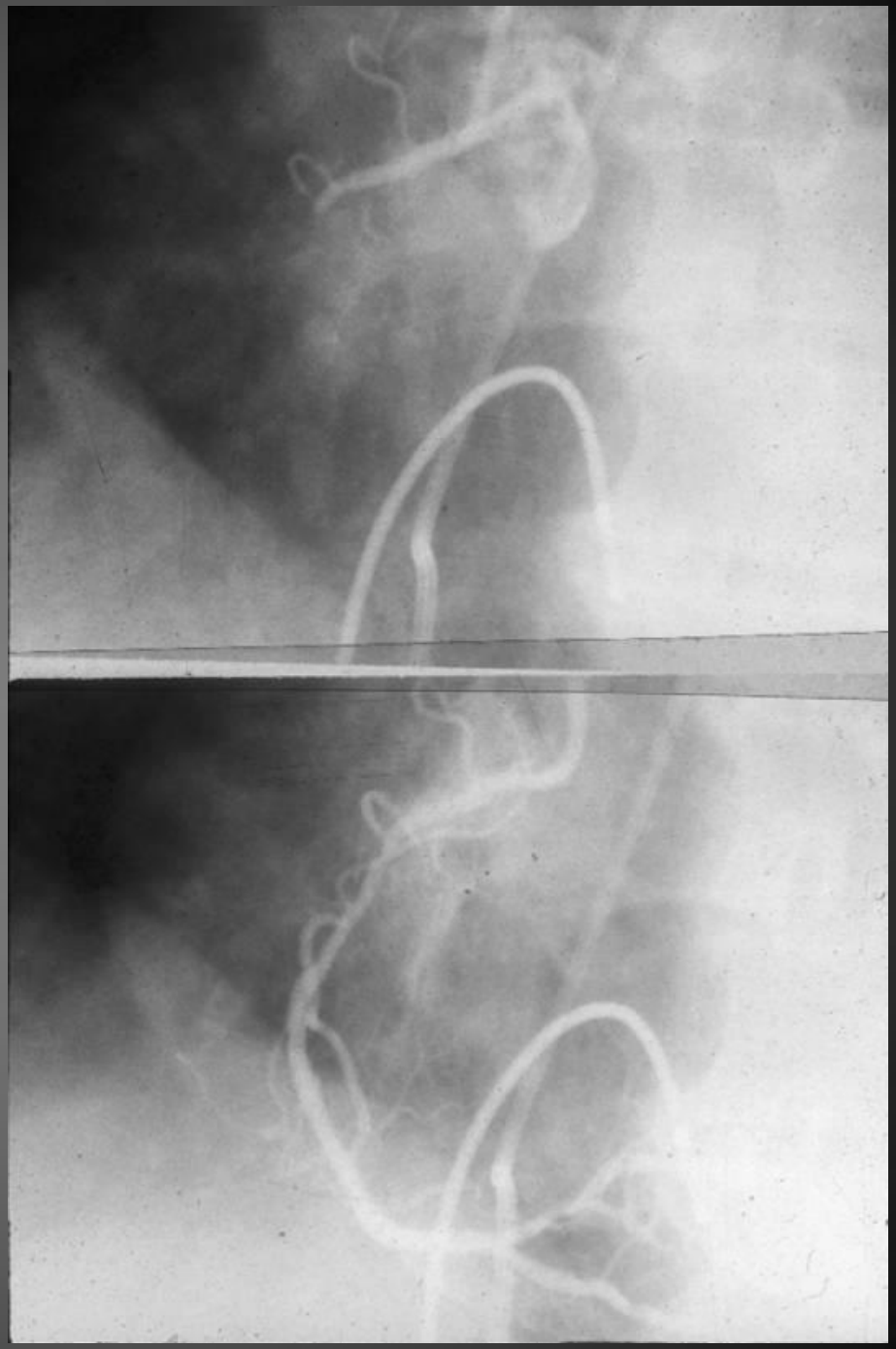


After defibrillation, ST elevation again



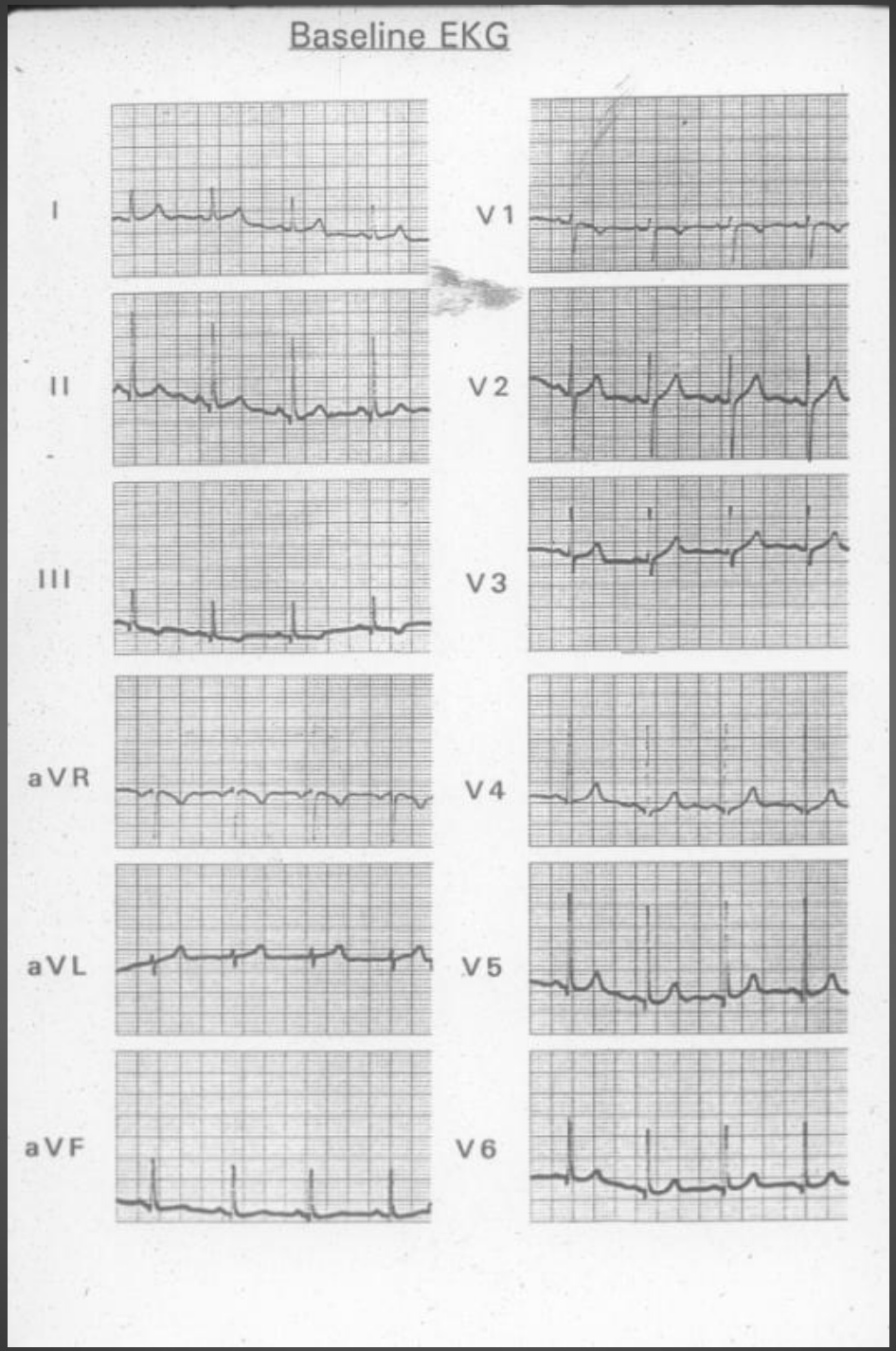
Re-occlusion of RCA prox

After IC NG again

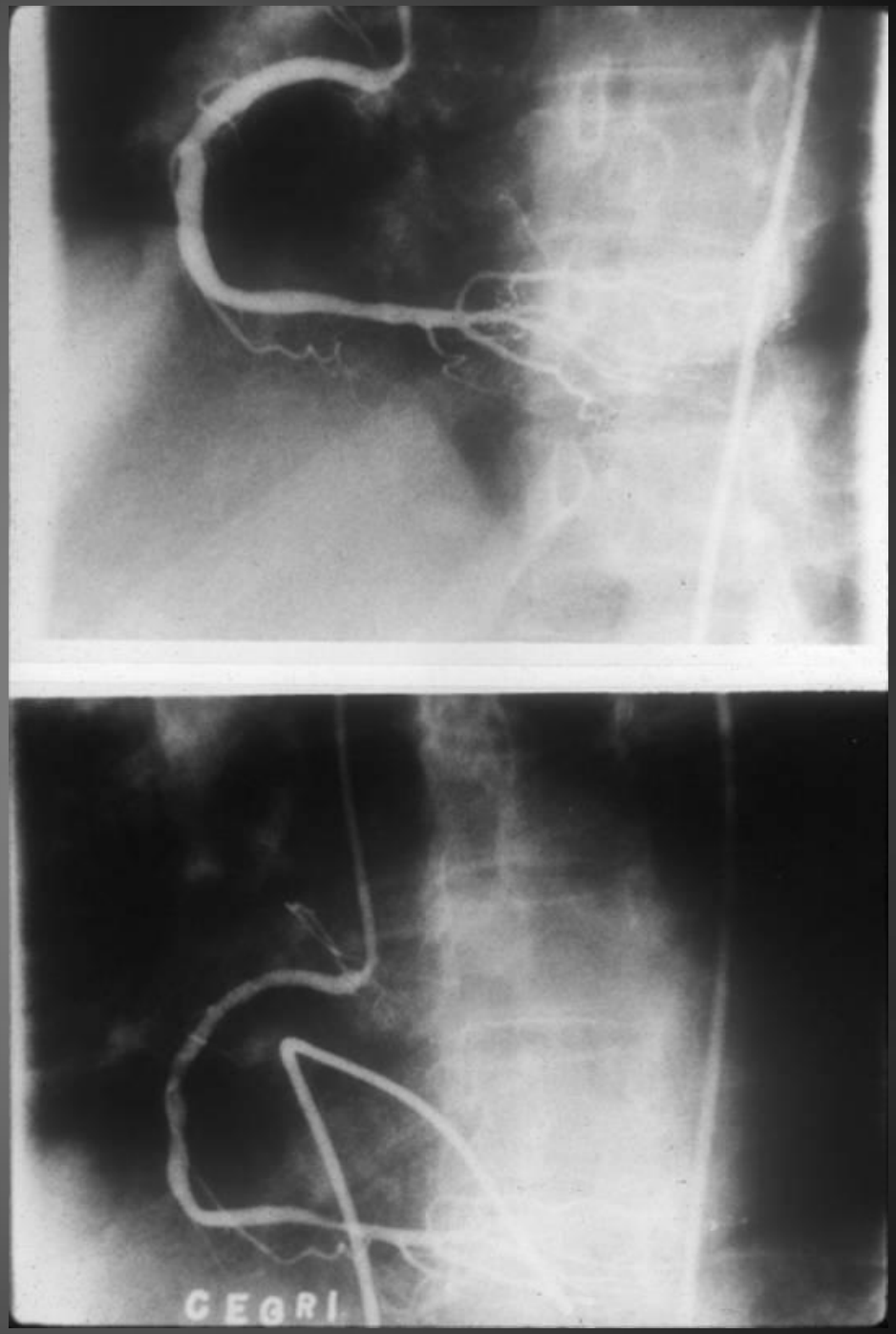


Intracoronary provocation with ergonovine

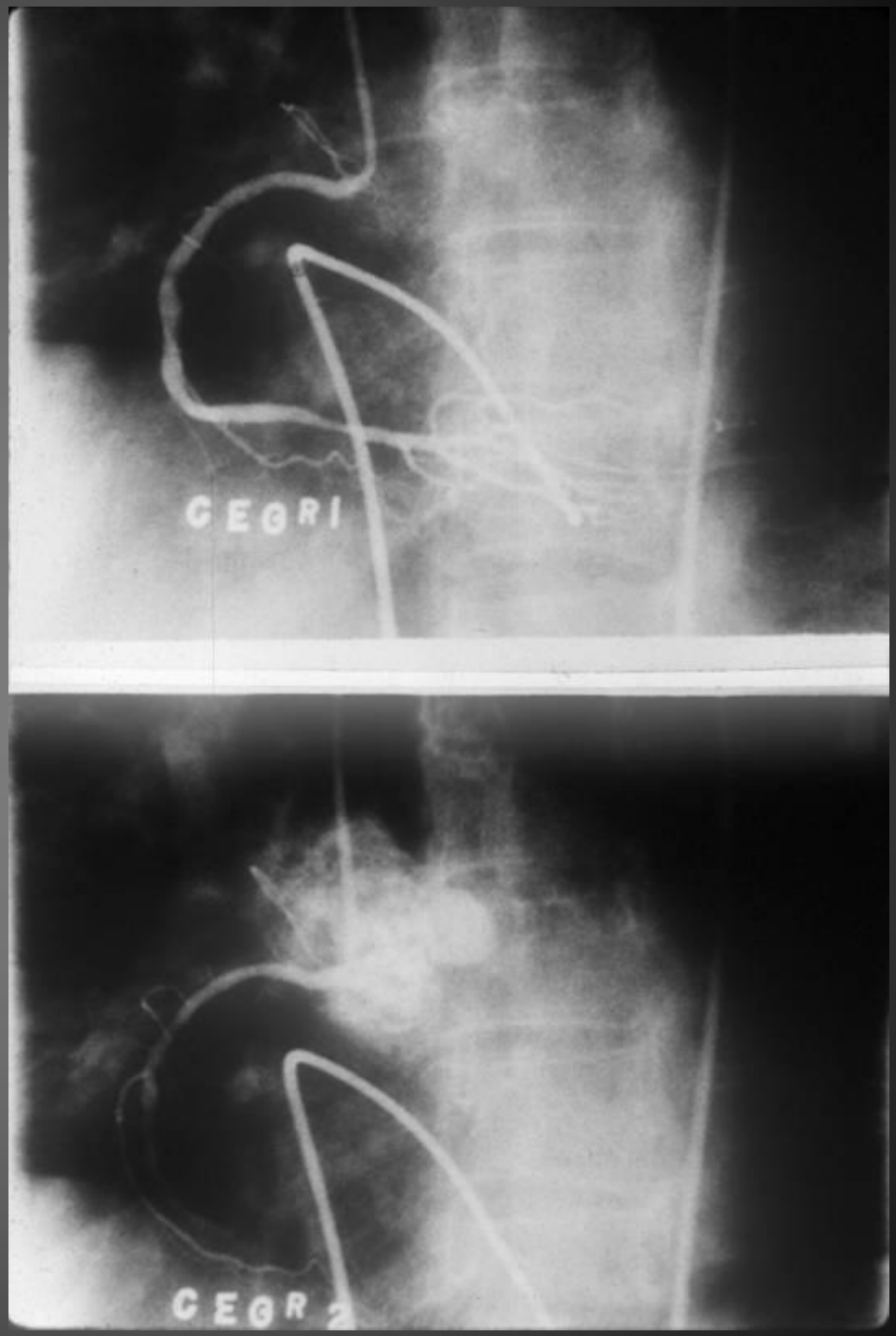
Baseline EKG



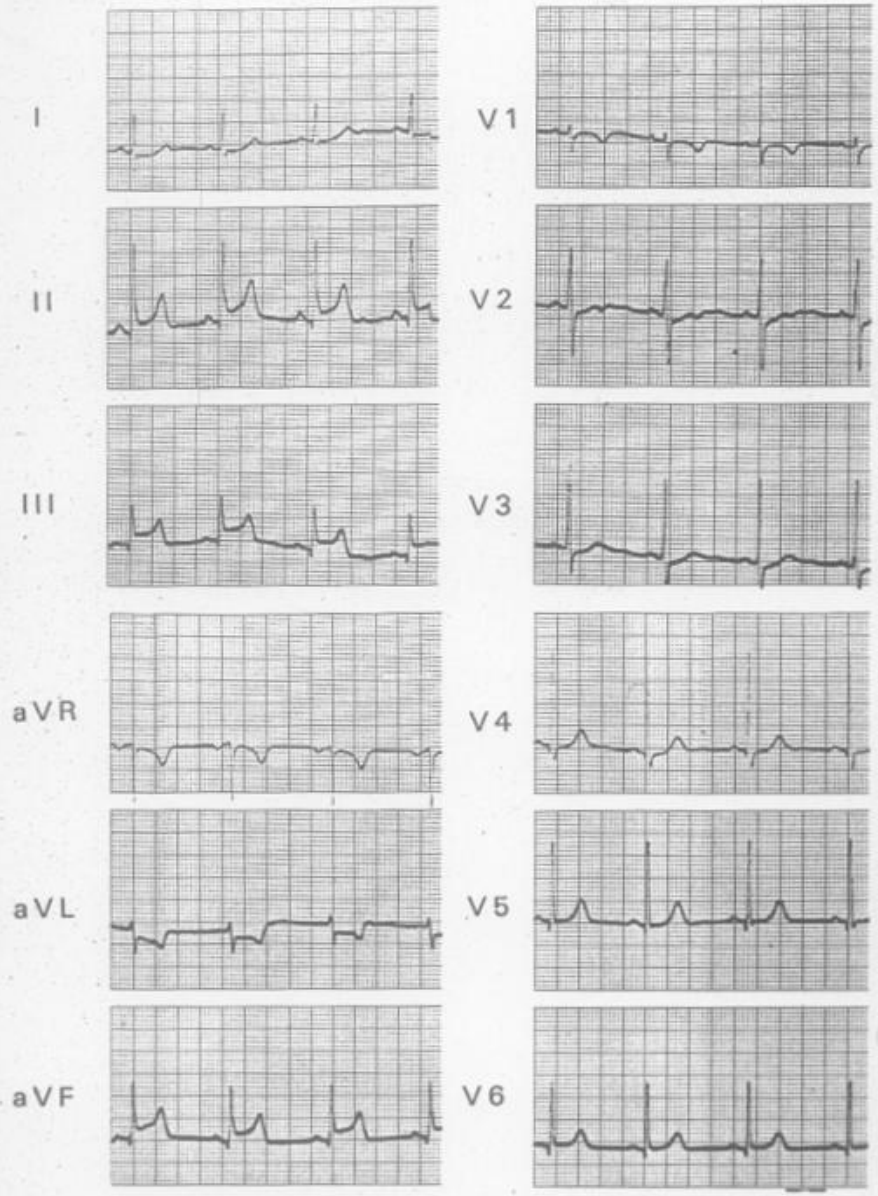
After 1st provocation dose



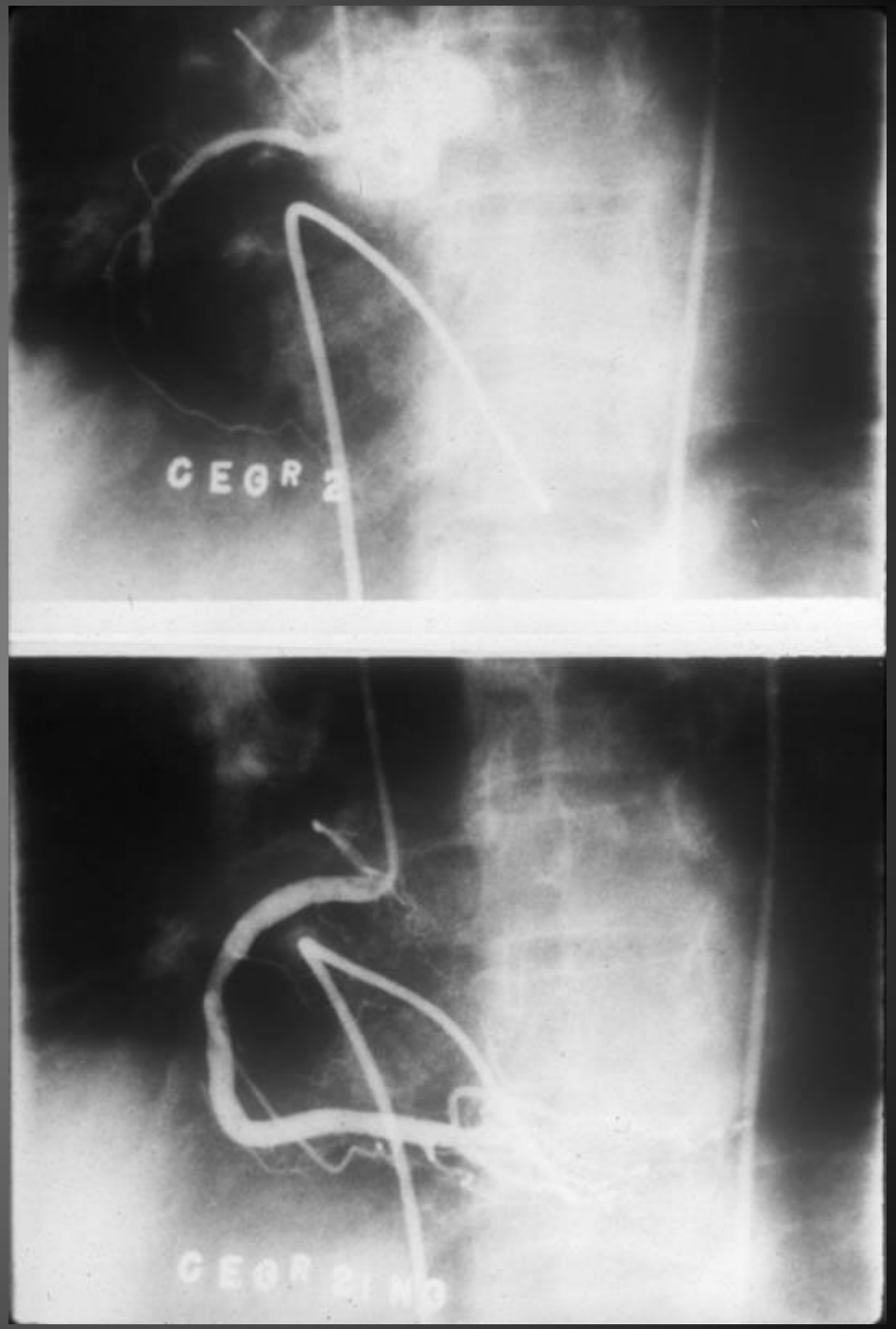
After 2nd provocation dose



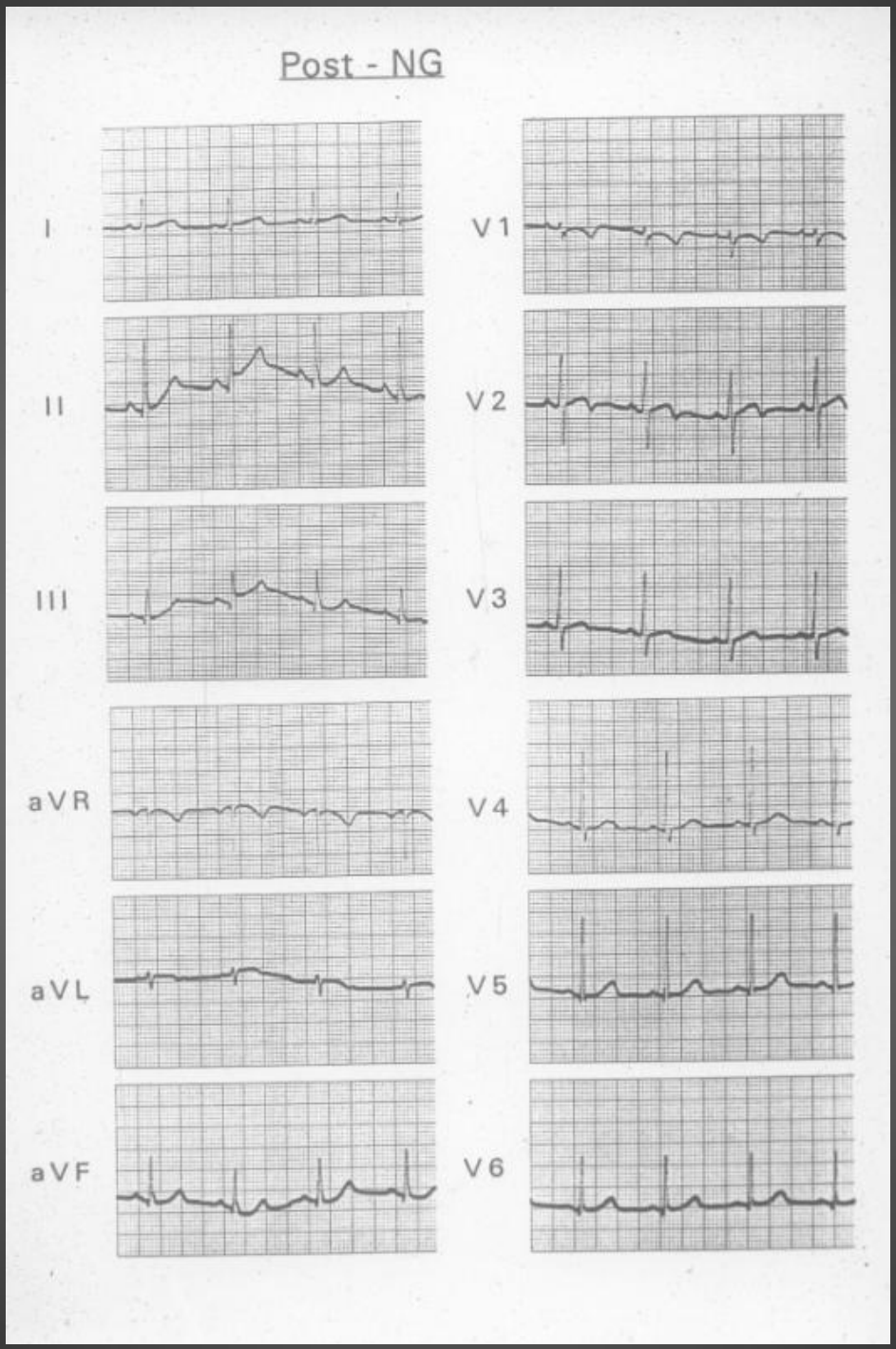
IC Ergonovine



Relieved by IC NG

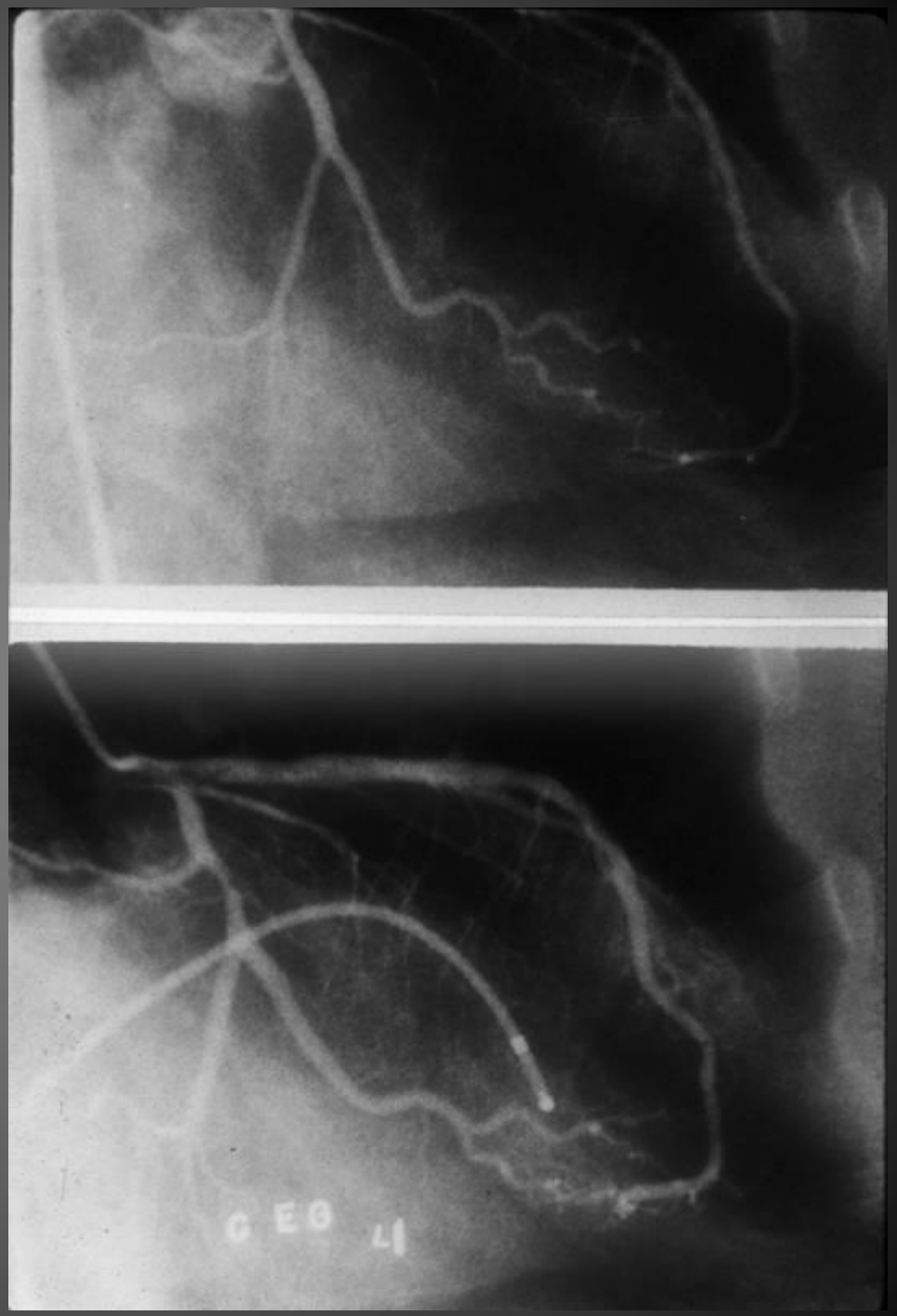


Post - NG

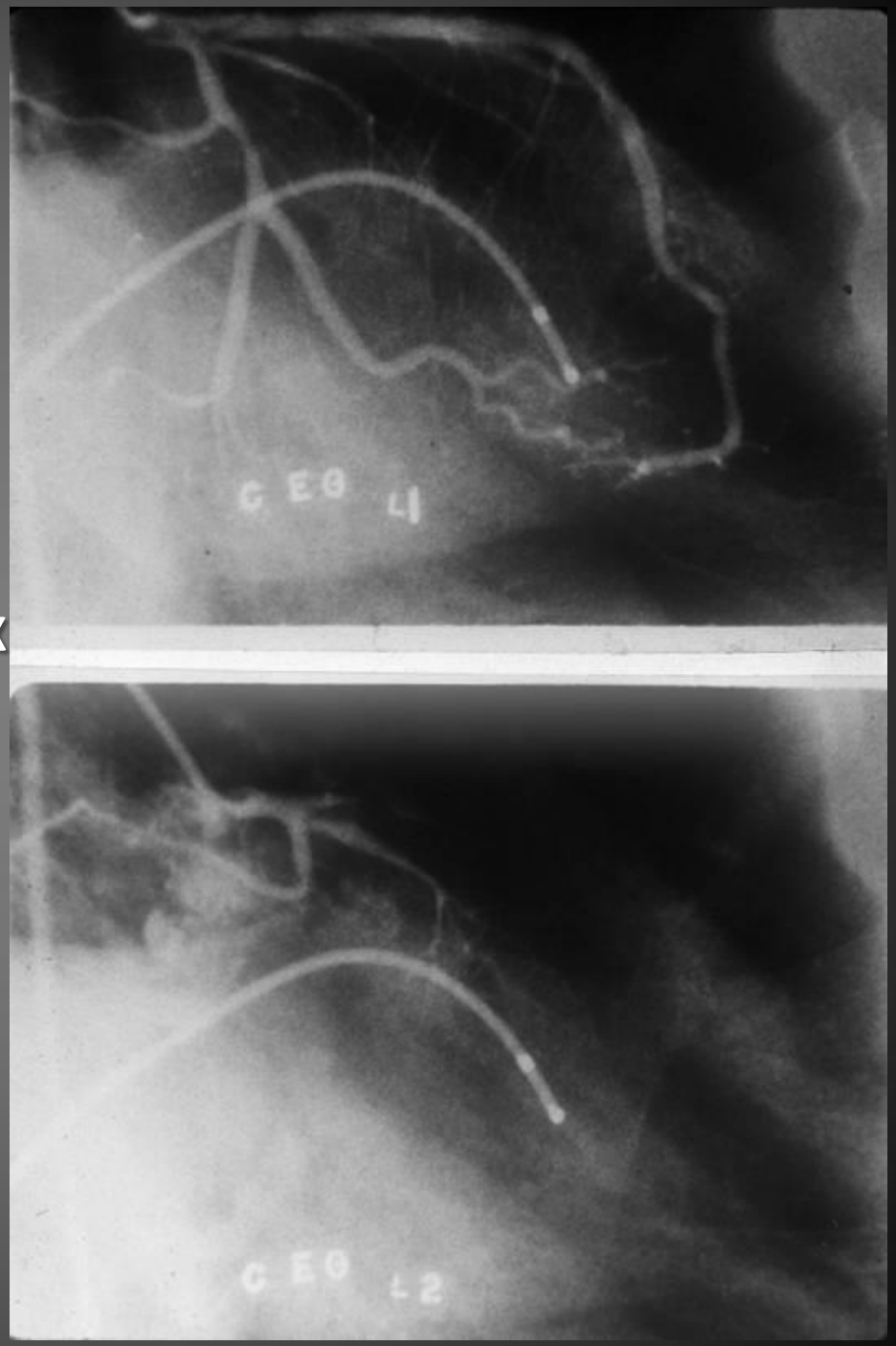


Intracoronary provocation with ergonovine

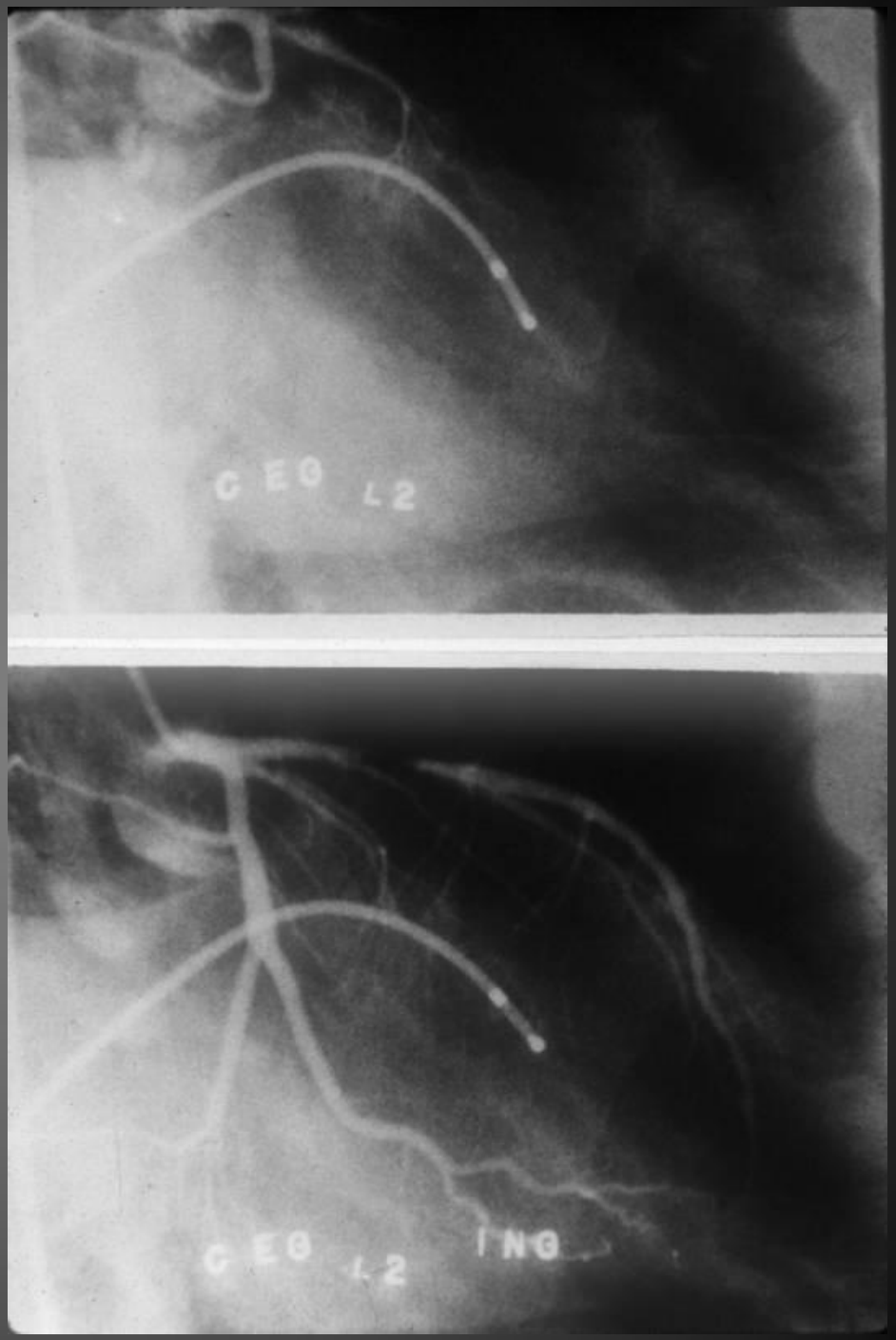
Minimal response after 1st provocation dose



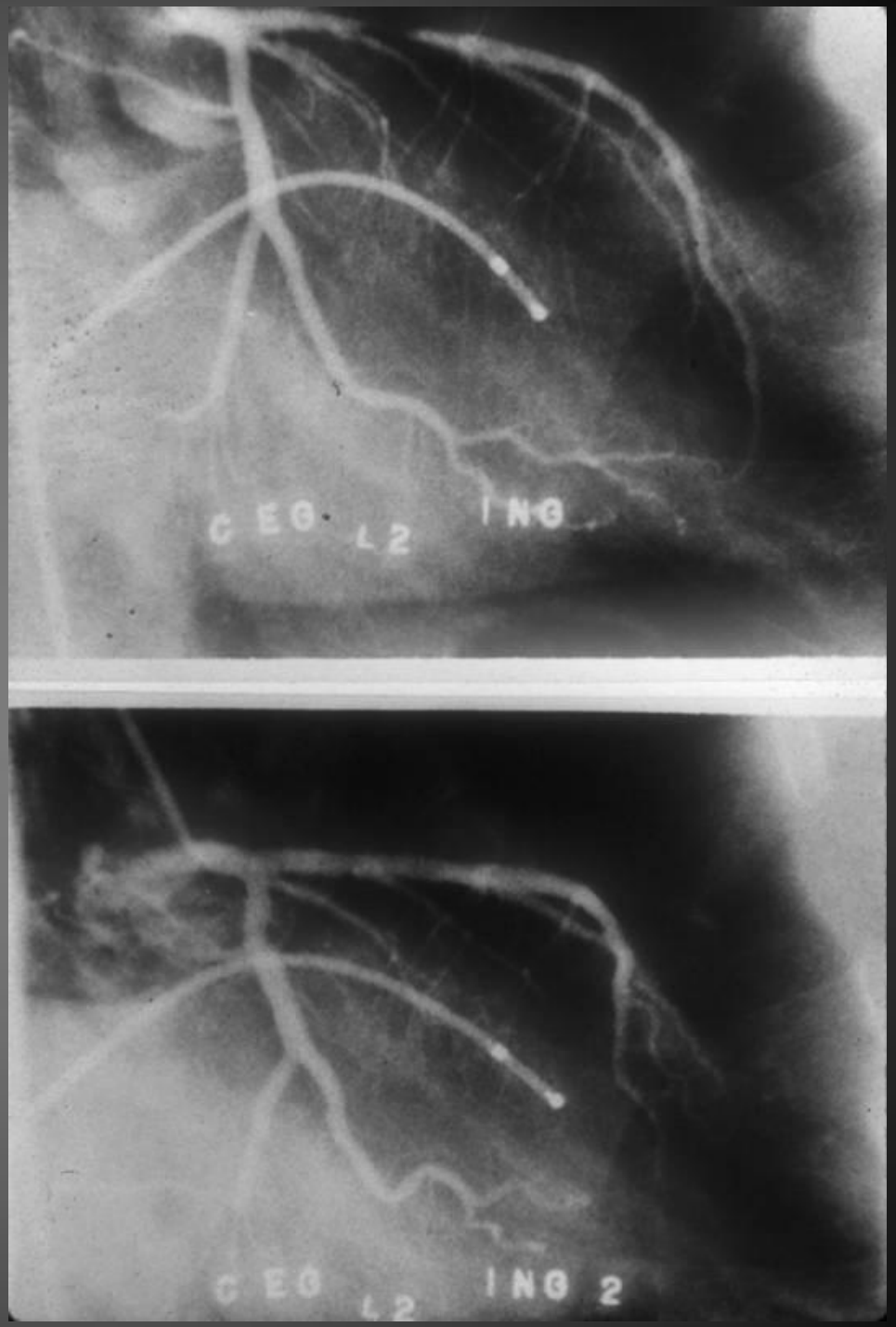
Total occlusion of LAD and LCx after 2nd provocation dose



Incompletely relieved by 1st IC NG



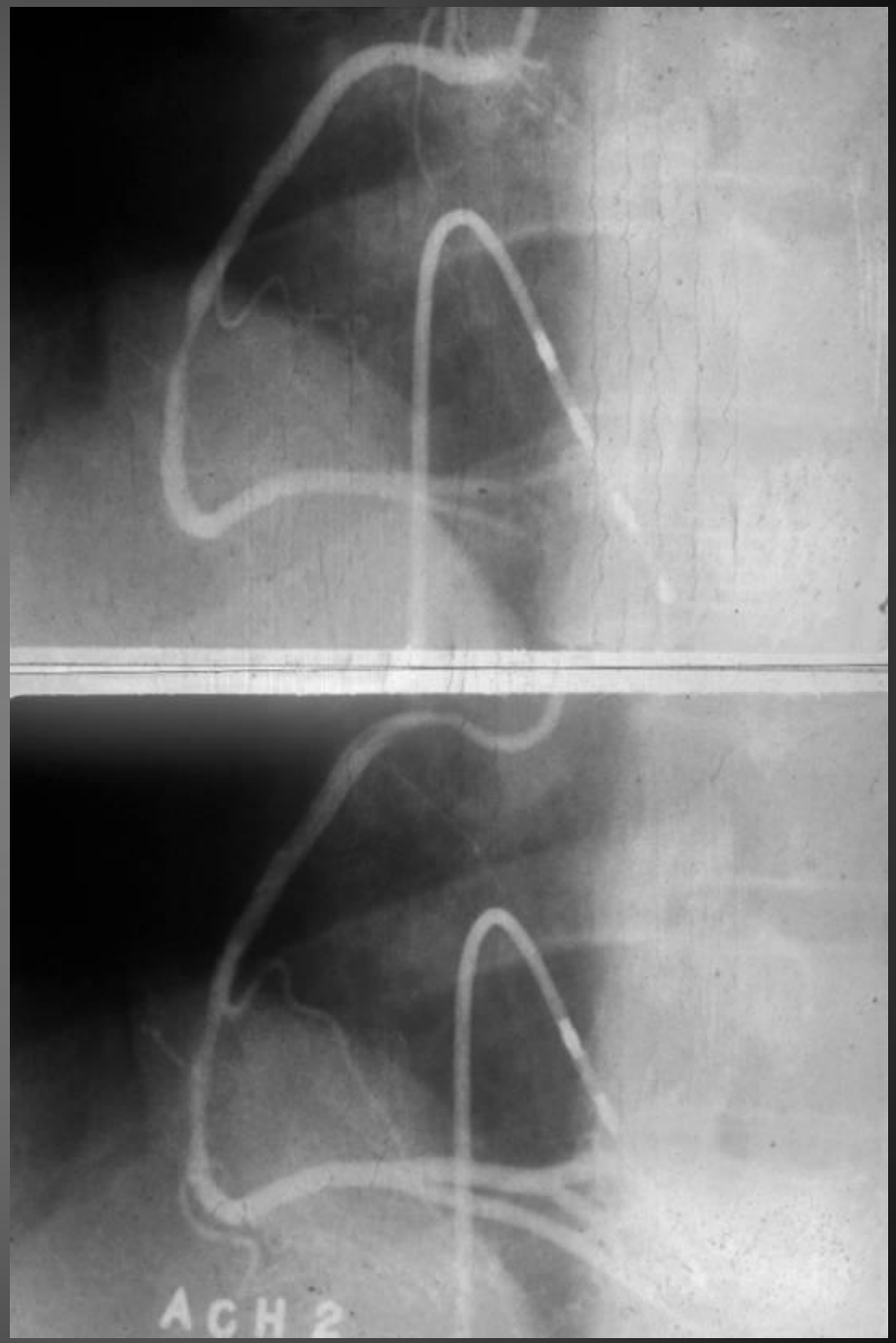
Completely relieved by 2nd IC NG



Nonspecific response to Ach

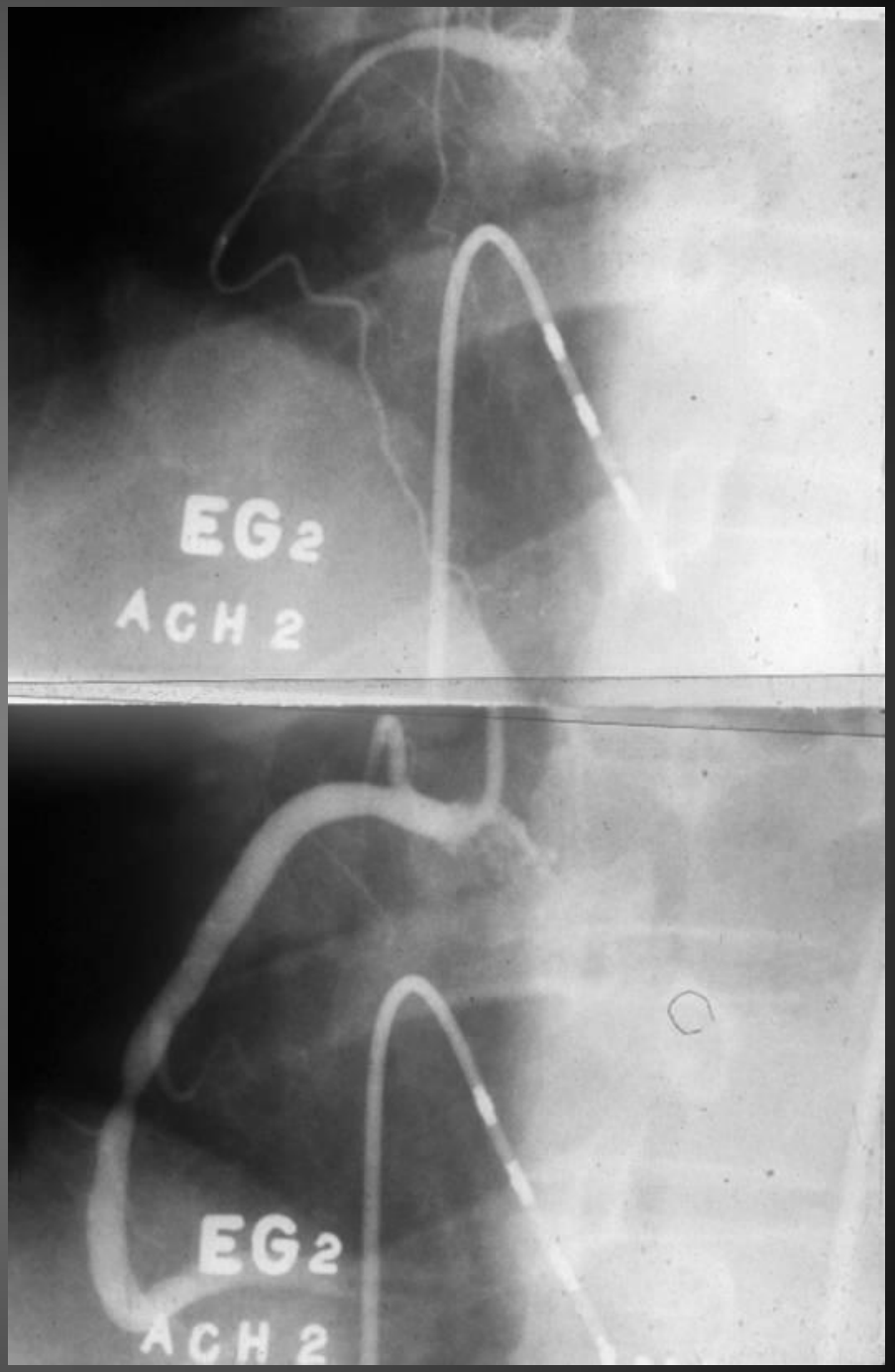
→ Provocation using ergonovine

Nonspecific response to Ach provocation

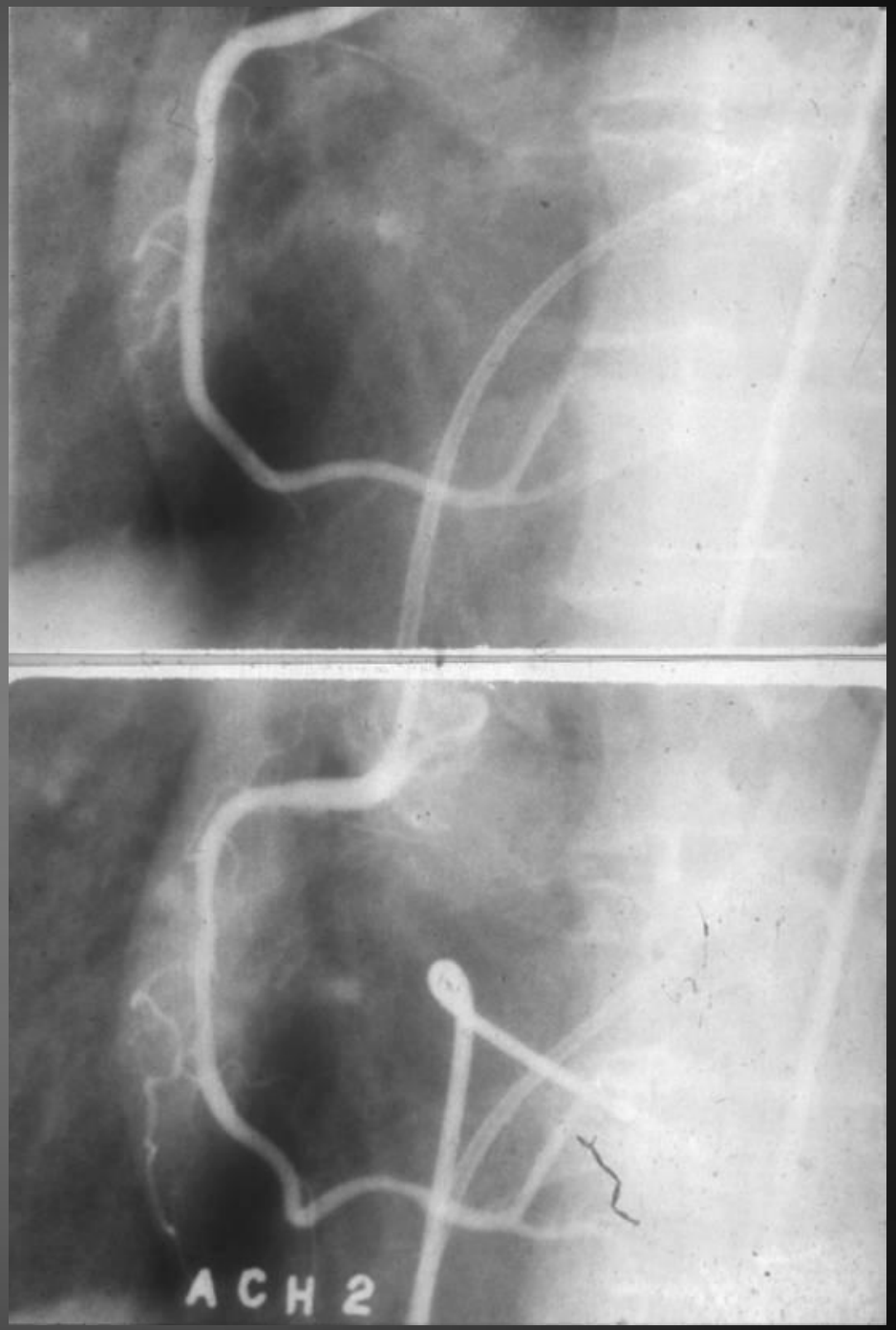


Total occlusion after ergonovine

Relieved by ICNG

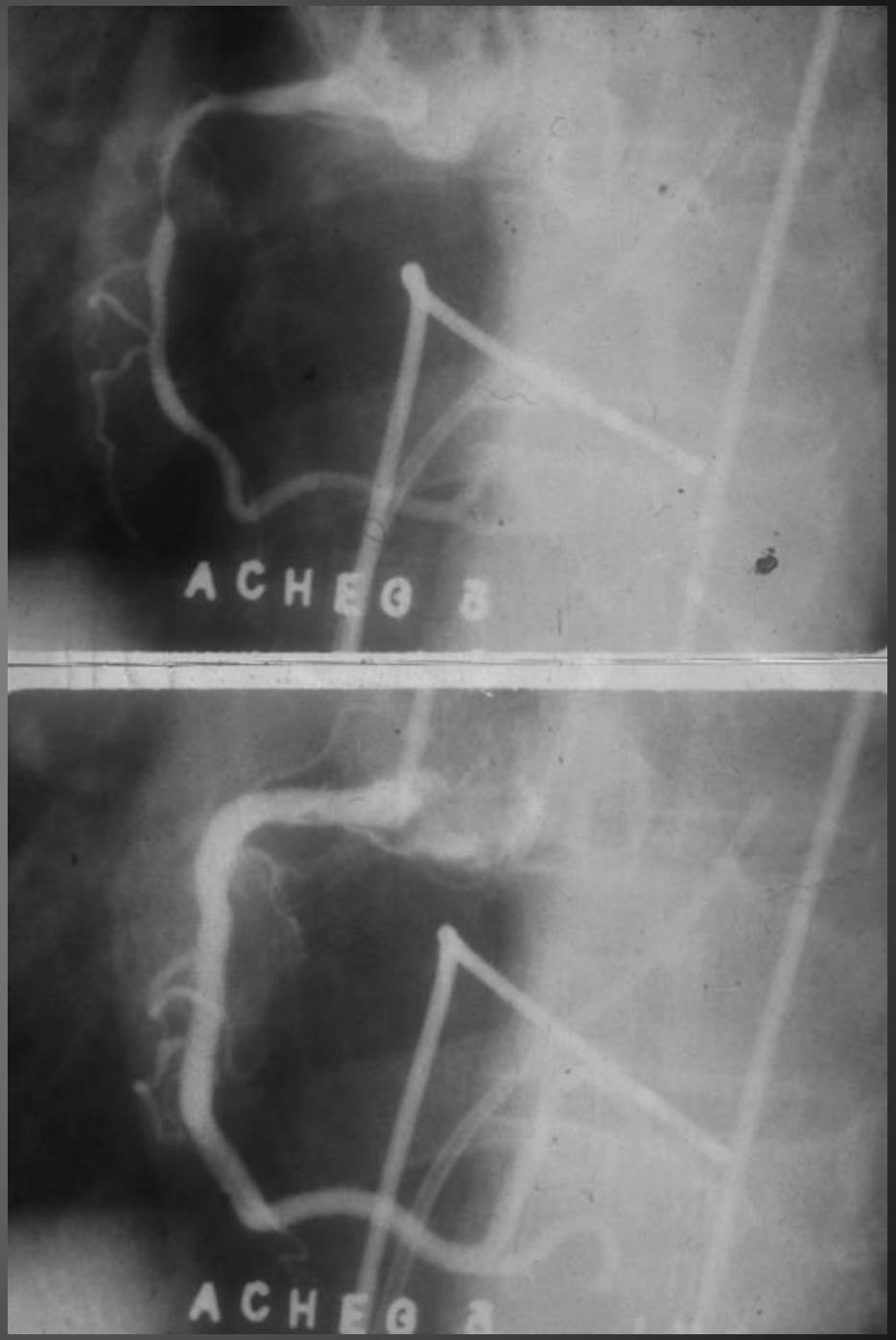


Nonspecific response to Ach provocation



Specific response after ergonovine

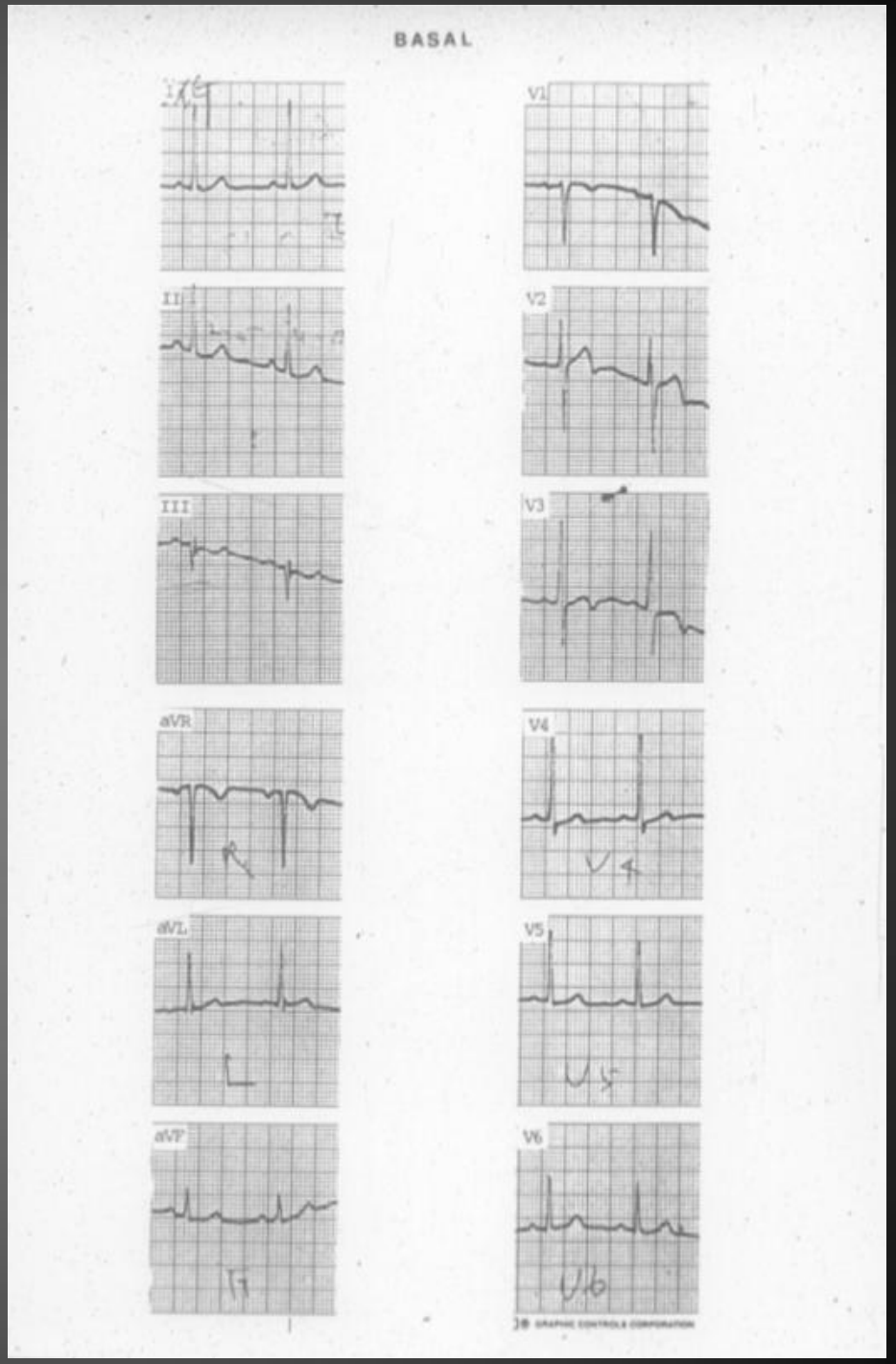
Relieved by ICNG



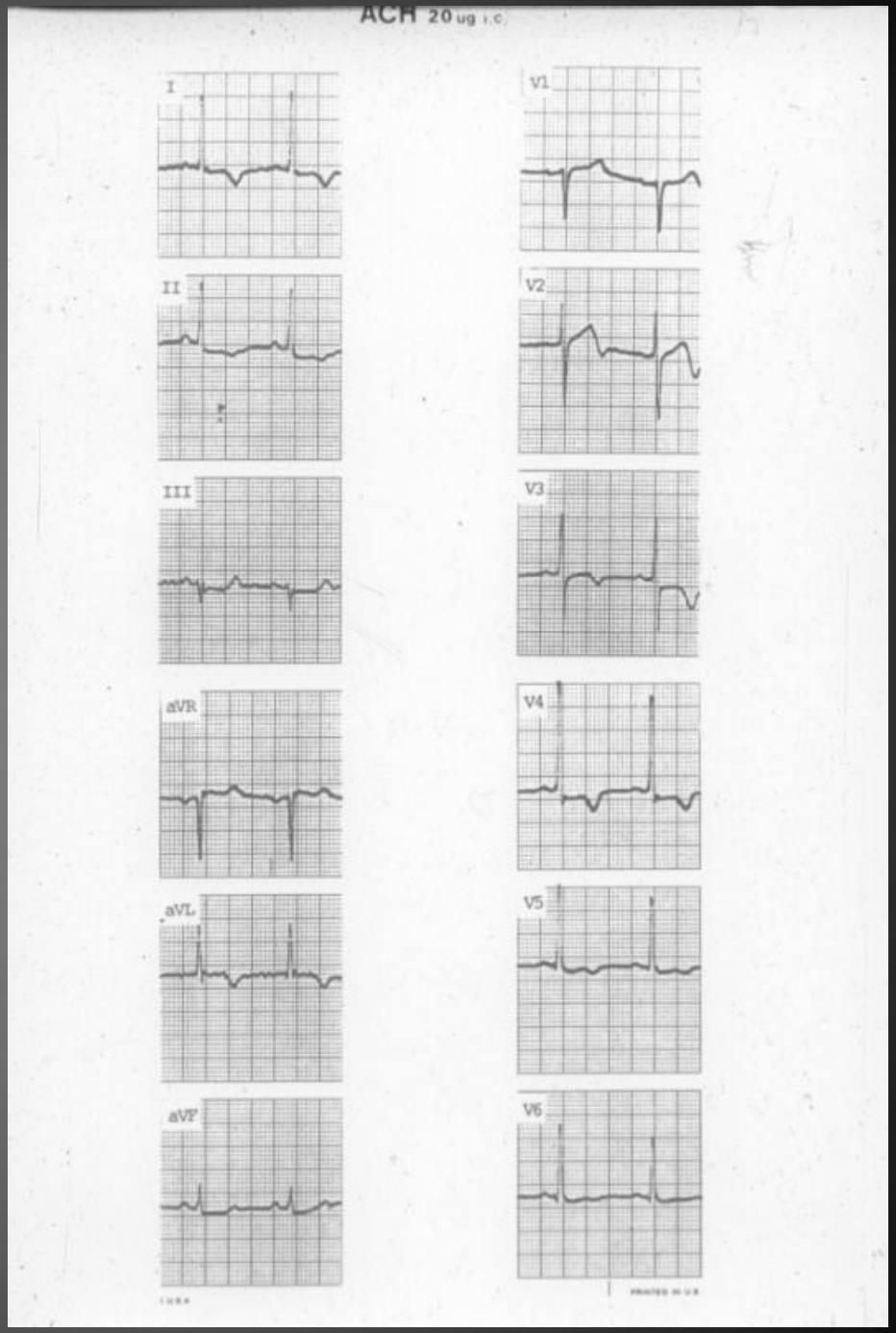
Significant spasm

without significant ECG change

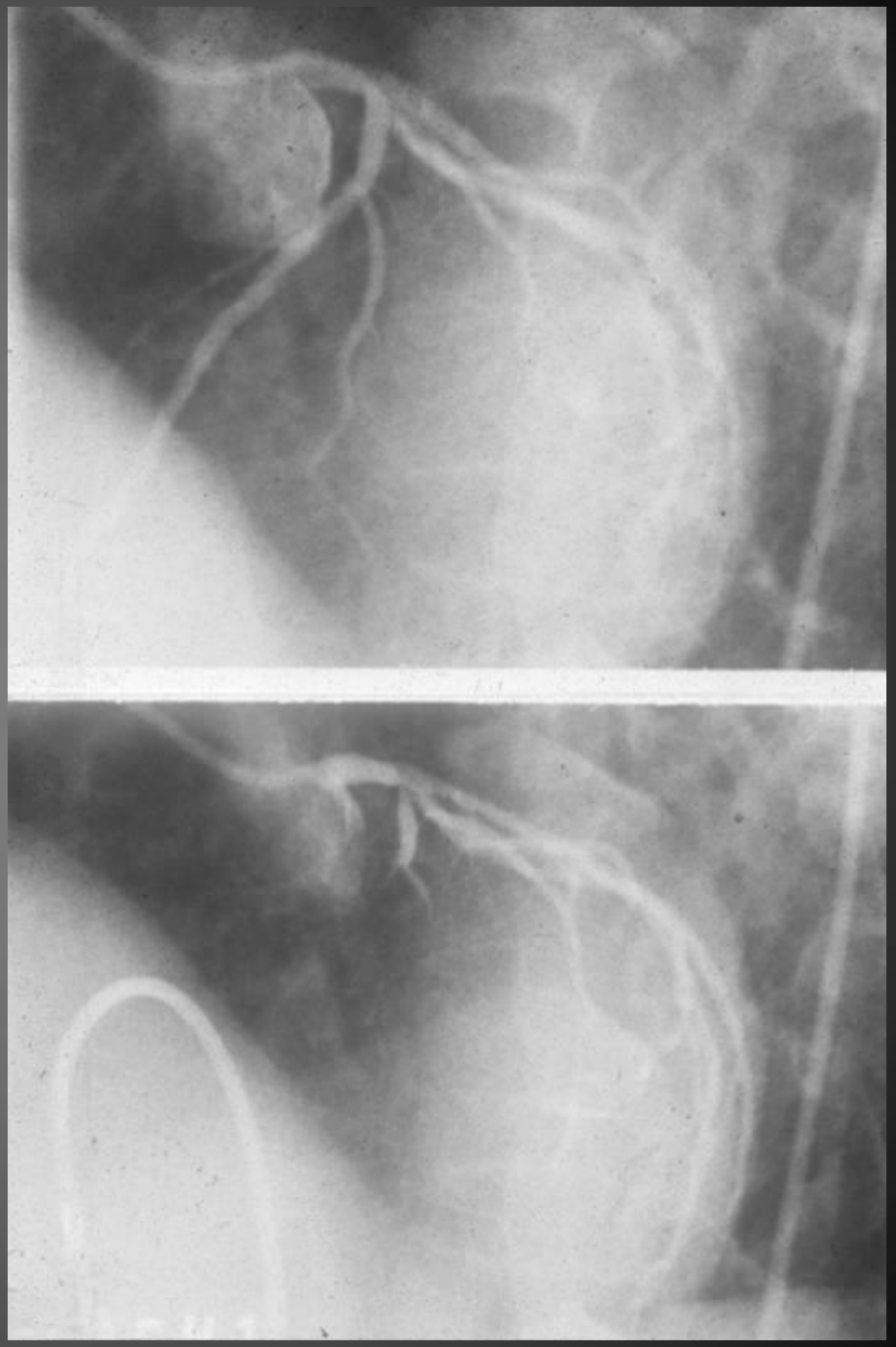
Baseline ECG



ECG after Ach provocation



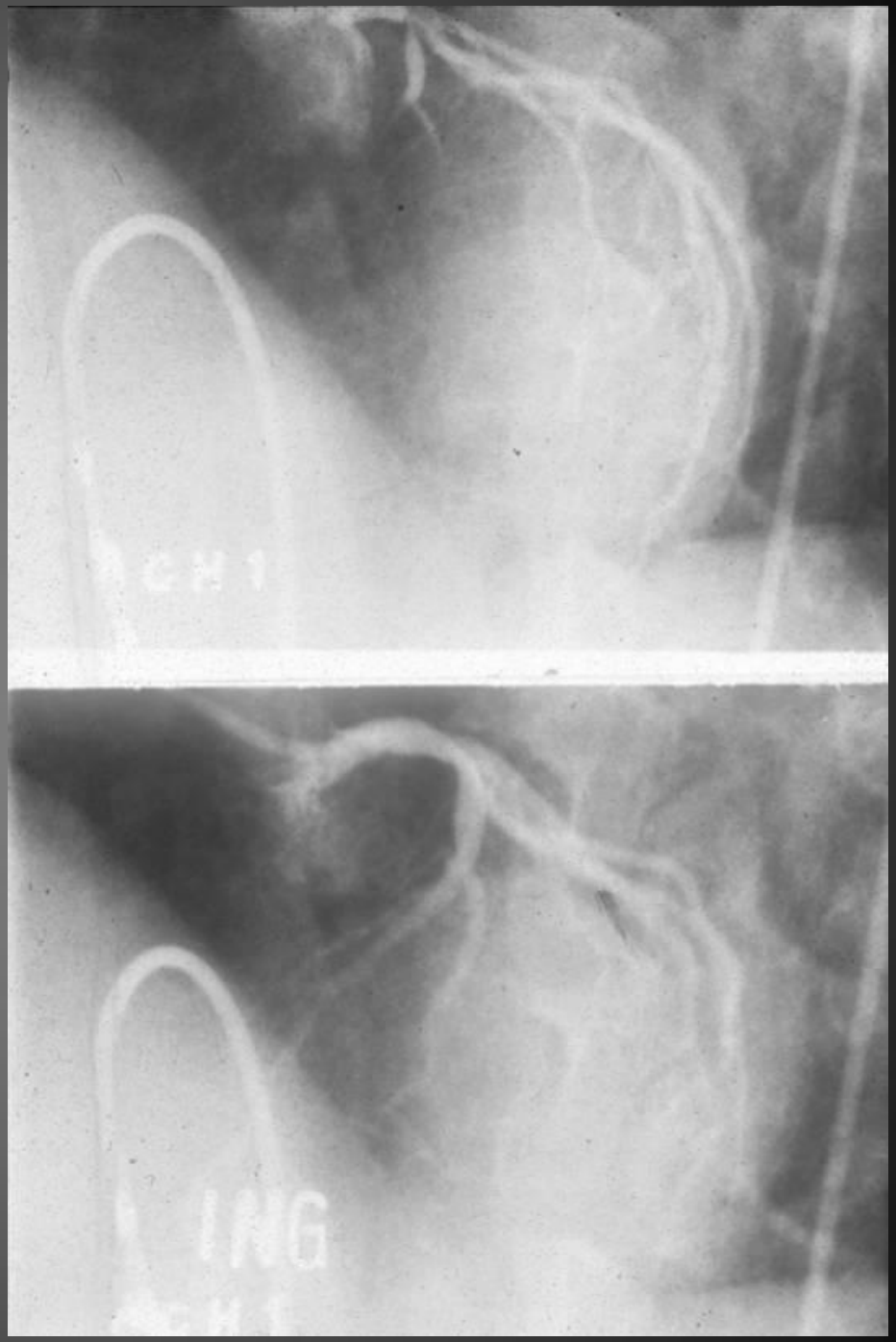
Baseline CAG:



After Ach:
LAD total occlusion

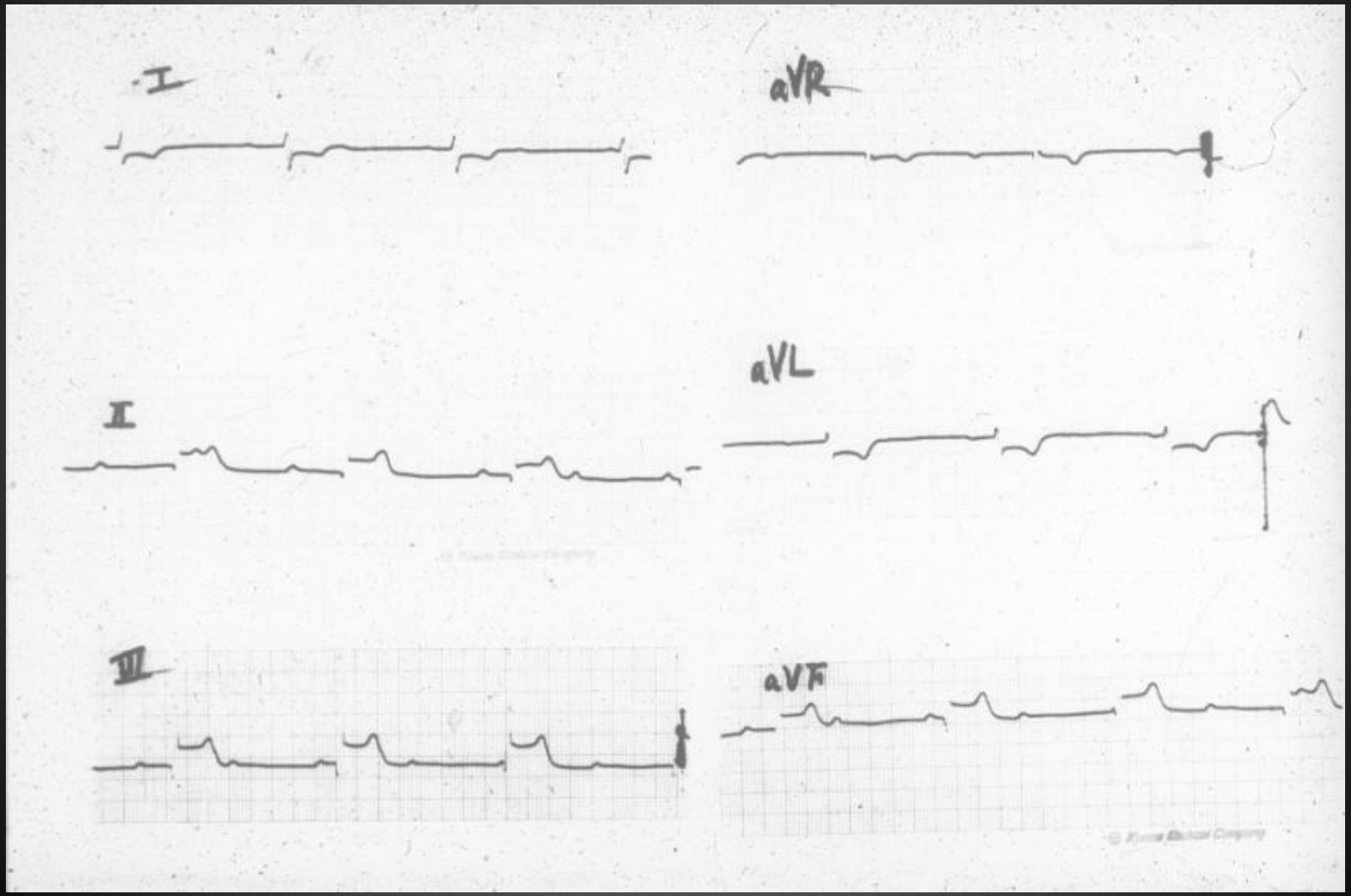
After Ach:
LAD total occlusion

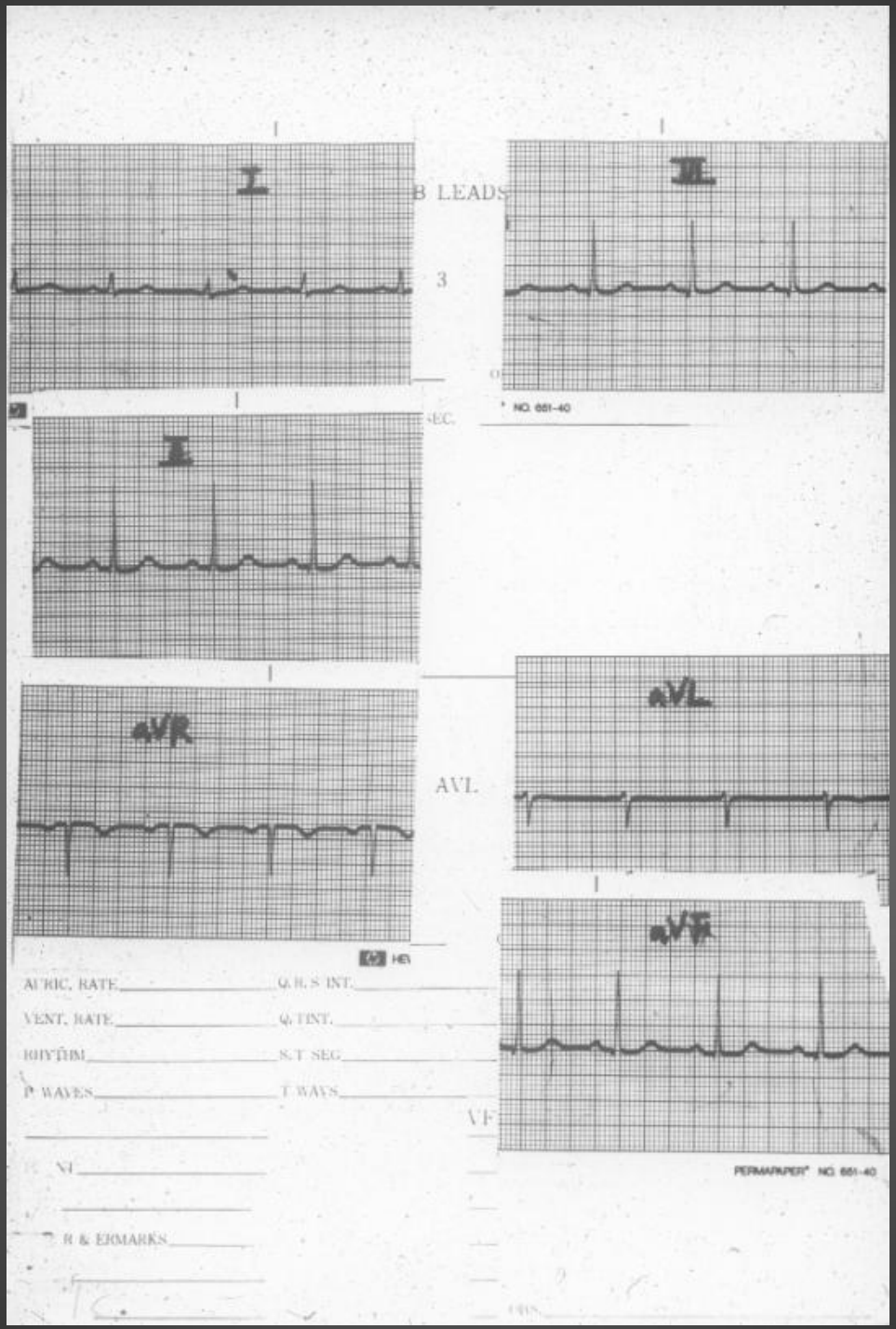
After ICNG



Complete AV block due to coronary artery spasm

Patient was recommended to have PM implantation in an outside hospital d/t documented complete AV block




I
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Q-T INT.
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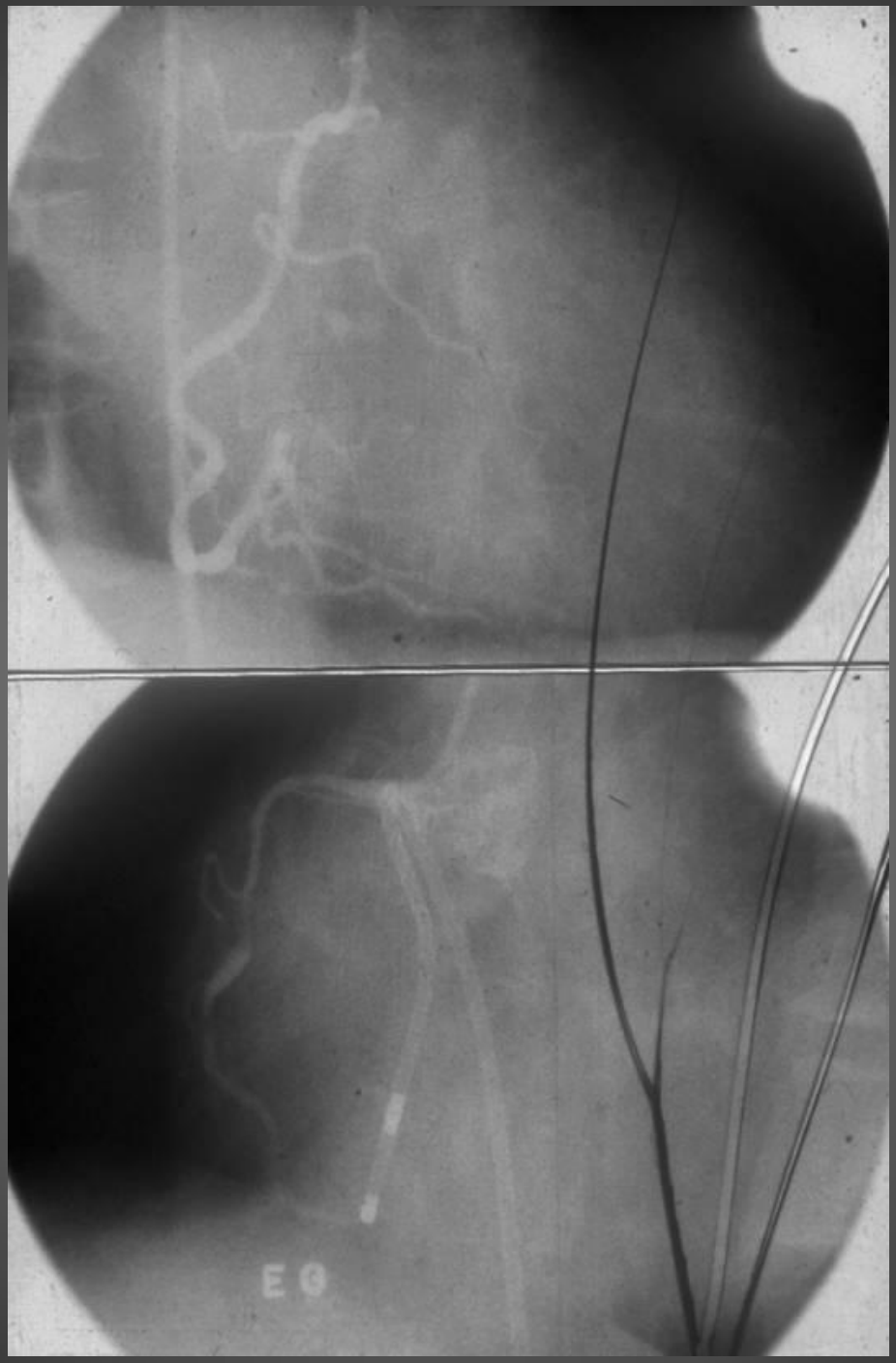
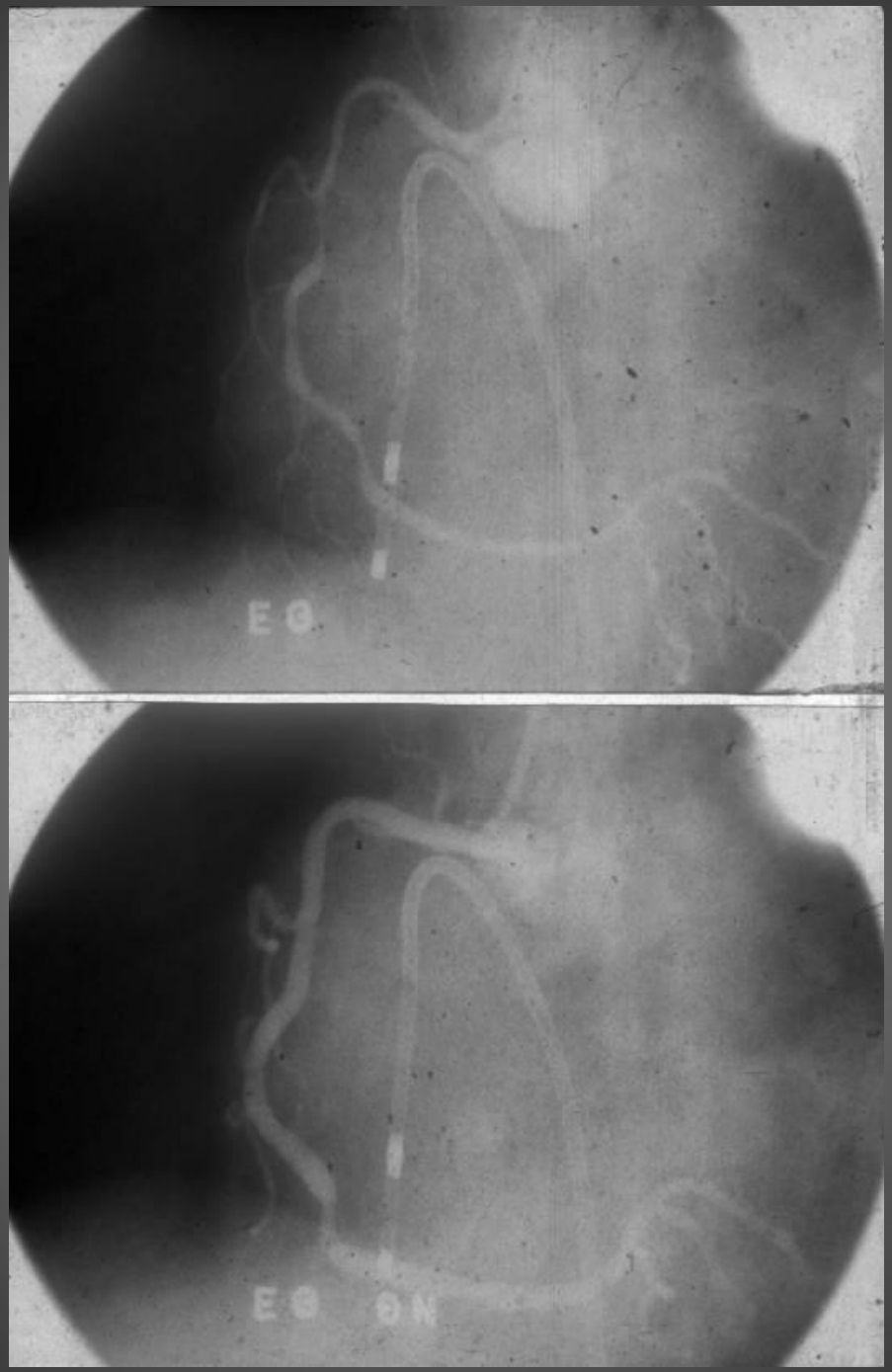
PERMAPAPER NO. 651-40


EG


EG
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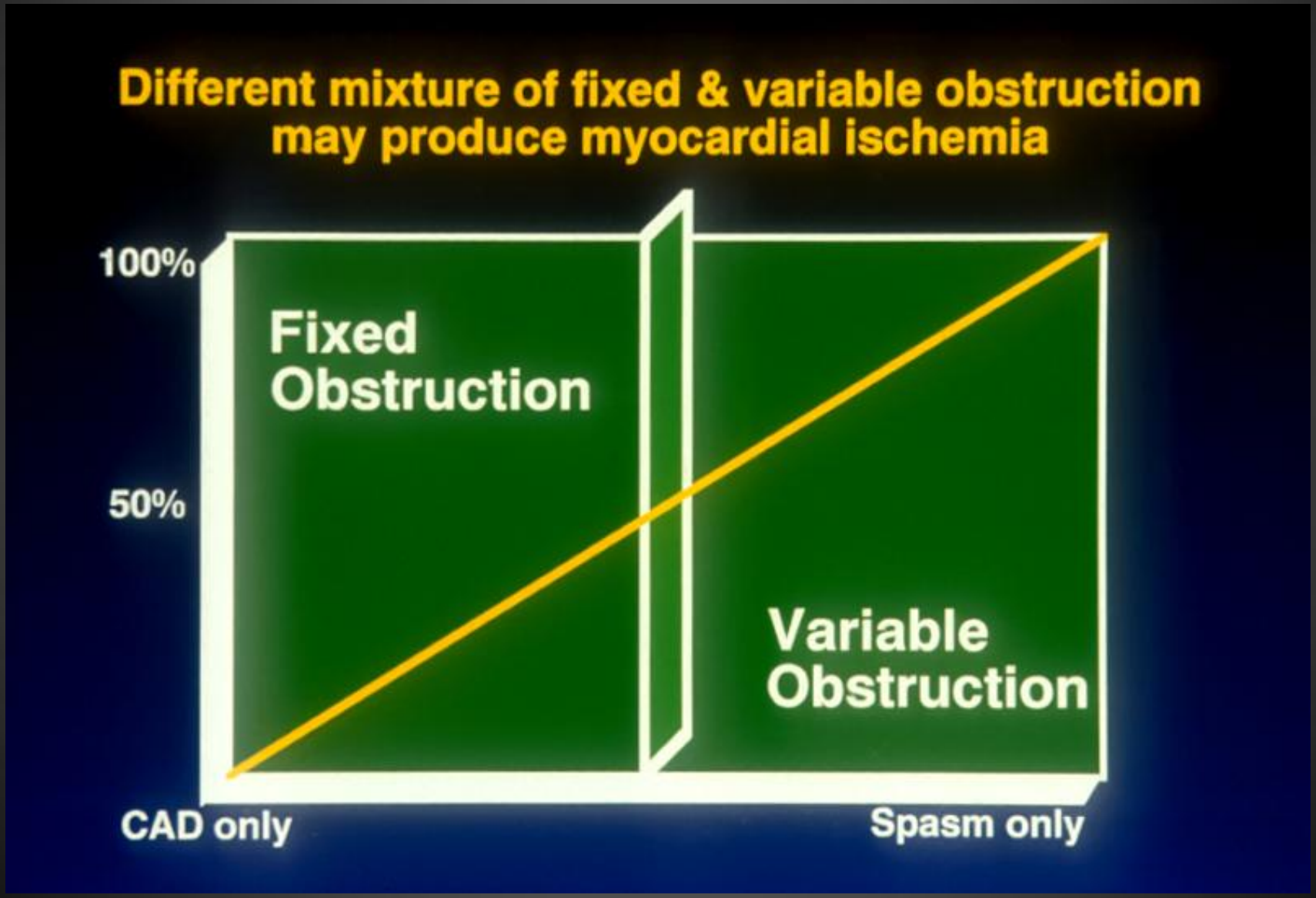
Lessons from

the SNUH Experience

Lesson 1: Coronary artery spasm may be one of the dynamic mechanisms of myocardial ischemia



Lesson 2: Coronary artery spasm can be a cause of AMI and sudden cardiac death

관동맥조영술상 관동맥 연축을 동반한 급성심근경색증*

서울대학교 의과대학 내과학교실

최동주 · 조명찬 · 김준수 · 김영권 · 김치정 · 손대원
이명묵 · 박영배 · 최윤식 · 서정돈 · 이영우

=Abstract=

Acute Myocardial Infarction with Coronary Artery Spasm on Coronary Angiogram

순환기. 1990;20(4):668-78.

Lesson 3: For provocation of coronary artery spasm, ergonovine IV or IC is the preferred method.

Ergonovine 관동맥내 투여를 이용한 관동맥 연축 유발검사 소견에 관한 연구*

서울대학교 의과대학 내과학교실

한규록 · 최동주 · 최영진 · 박선수 · 김용진 · 손대원
오병희 · 이명묵 · 박영배 · 최윤식 · 서정돈 · 이영우

= Abstract =

Intracoronary Ergonovine Provocation Test in Patients with Coronary Artery Spasm

순환기. 1994;24(1):53-9.

Provocation Test

1. Discontinue antianginal and antiplatlet agents
2. Baseline ECG and CAG
3. Pacemaker insertion
4. Provocation test

Ergonovine

Intravenous EG q 5 min
50,100,200 µg
Intracoronary EG q 5 min
10,10 µg for RCA
10,10,10 µg for LCA

Acetylcholine

Intracoronary ACH q 5 min
20,50,100 µg for LCA
20,50 µg for RCA

12 lead ECG and CAG at the time of chest pain or 2min after ECG or 1 and 2 min after ACH

5. Intracoronary nitroglycerin immediately after demonstration of spasm or at the end of the study

Acetylcholine Provocation Test

- Endothelial dysfunction
- Short duration of action
- Wide applicability
- Sinus arrest, atrial fibrillation
- Diffuse spasm

I.V. Ergonovine Provocation Test

- Conventional method
- Focal spasm
- Endothelial function ?
- Long duration of action
- Hypertension

Lesson 4: Genetics may play a role in coronary artery spasm

Genetics

Common adrenergic receptor polymorphisms as novel risk factors for vasospastic angina

Jin-Shik Park, MD, PhD,[a,b,1] Shu-Ying Zhang, MD, PhD,[a,b,1] Sang-Ho Jo, MD,[a,b] Jae-Bin Seo, MD,[a,b] Lian Li, BA,[a,b] Kyung-Woo Park, MD,[a,b] Byung-Hee Oh, MD, PhD,[a,b,c] Young-Bae Park, MD, PhD,[a,b,c] and Hyo-Soo Kim, MD, PhD[a,b,c] *Seoul, South Korea*

Park JS, Park YB et al. Am Heart J. 2006;151(4):864-9.

Association of adrenergic receptor polymorphisms with coronary artery spasm

Table III. Odds ratio and 95% CI for VA clinical parameters and AR genotypes in multiple logistic regression analysis

	OR	95% CI	P
α_{2C}Del322-325 allele carrier	5.132	2.094-12.578	.0003
β_2Gln27 homozygote	3.152	1.364-7.285	.0072
Smoking	4.902	2.105-11.416	.0002
Male sex	1.348	0.570-3.186	NS
Age (1 y)	1.089	1.046-1.135	<.0001
Diabetes	4.103	0.836-20.131	NS
Hypertension	0.434	0.184-1.024	NS
Dyslipidemia	1.869	0.541-6.457	NS

Park JS, Park YB et al. Am Heart J. 2006;151(4):864-9.

[현재진행중인 연구]
Scanning the whole genome
: GenomeWide Association Study

Variant Angina
(N=260)

Inclusion Criteria

1) EG/Ach-provocation test (+)
2) Spontaneous coronary spasm → relived with IC-NG
3) EG echocardiography (+)

From 5 educational centers in Korea

- 서울대병원
- 충남대병원
- 분당서울대병원
- 아산병원
- 보라매병원

Healthy Control
(N=780)

한국인유전체역학조사사업
(KoGES, Korean Genome and Epidemiology Study)
: 검진센터 기반 코호트 사업
(대도시 코호트)
: 건강검진을 통해 심혈관질환의 증거가 없는 대상자

1:3 matching with case patient

- Age
- Gender
- Smoking status

Genotyping (Affymetrix SNP array 6.0)

9개의 Candidate Gene 발견
→ Replication 단계 연구 진행

Chr	SNP ID	Position	Locus	Dominant allele	Gene symbol	GWAS		
						MAF	OR	P
3	rs12491866	11792421	3p25.2b	A	near C3orf31	0.39	0.6544	5.72E-05
4	rs11131966	181125591	4q34.3c	A		0.25	0.5616	1.65E-05
4	rs17045377	165847618	4q32.3b	G		0.16	1.787	1.88E-05
5	rs3811964	32805856	5p13.3b	T	NPR3	0.19	1.648	4.33E-05
6	rs9295100	159791920	6q25.3e	G		0.27	0.569	8.16E-06
6	rs699941	46634975	6p12.3e	T	CYP39A1	0.23	1.662	1.83E-05
9	rs10818642	123974865	9q33.2b	T	C9orf18	0.14	0.4874	2.33E-05
13	rs4329788	90406889	13q31.3a	G		0.19	0.5147	8.36E-06
18	rs8099415	3810765	18p11.31d	C	DLGAP1	0.45	1.568	2.72E-05

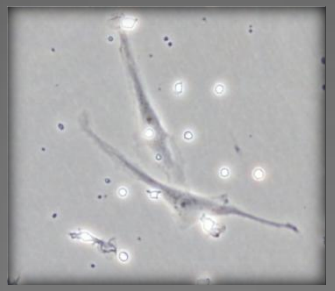
관상동맥 경련이 증명된 자매…
: 이들이 유전자와 세포는 뭐가 다를까???

이형성 협심증 환자들의 혈관세포: 수술하지 않는 한 얻을 수 없었음!

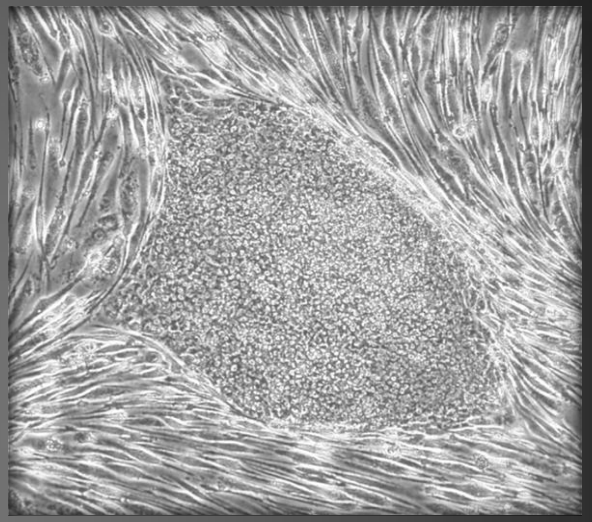
Blood

Only 10cc!

장 용 O F/55
장 선 O F/52

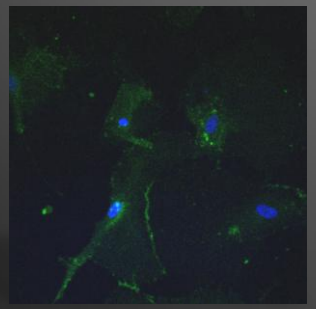


말초혈액줄기세포
(CiMS)

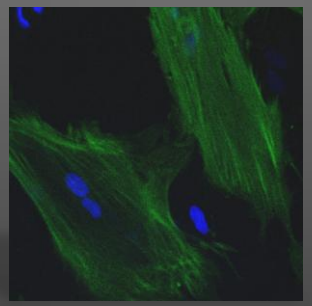


역분화만능줄기세포
(iPS)

내피세포



혈관평활근세포



Mechanism Study

Lesson 5: 약 종류뿐만 아니라 투여 시간과 방법도 중요

증상의 호발 시간대: 자정부터 아침 8시 사이 (특히 새벽 3-6시 사이)

1. Patient with fixed lesion and coronary artery spasm
   : 종일 혈관 확장 작용 필요 → 일정한 간격의 약제 투여가 중요
   (예. tid pc가 아니라 q 8hr or bid pc가 아니라 q 12hrs)

2. Patient without fixed lesion and coronary artery spasm:
   : 밤과 새벽시간대의 vasodilator coverage가 중요
   long acting nitrate 또는 CCB를 밤 10시 투여, 이것으로 불충분하면
   nitrate patch를 고려

Take Home Messages

1. **S**uspicion is the key to diagnosis!
2. **C**oronary artery spasm ≠ variant angina: important in conversion to UA, can cause AMI and even sudden cardiac death
3. **W**hen needed provocation is key. Ergonovine provocation (IC or IV) is the preferred method.
4. **G**enetics may play a role in coronary artery disease.
5. **T**ime and method of medication is important in treatment.

SNUH 서울대학교병원 SEOUL NATIONAL UNIVERSITY HOSPITAL

IRICT Innovative Research Institute for Cell Therapy

감사합니다