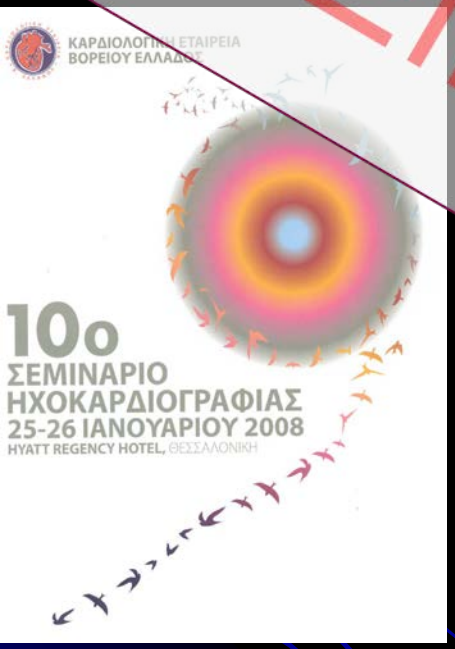
Υπερηχοκαρδιογραφική εκτίμηση της στεφανιαίας εφεδρείας ροής στην κλινική πράξη

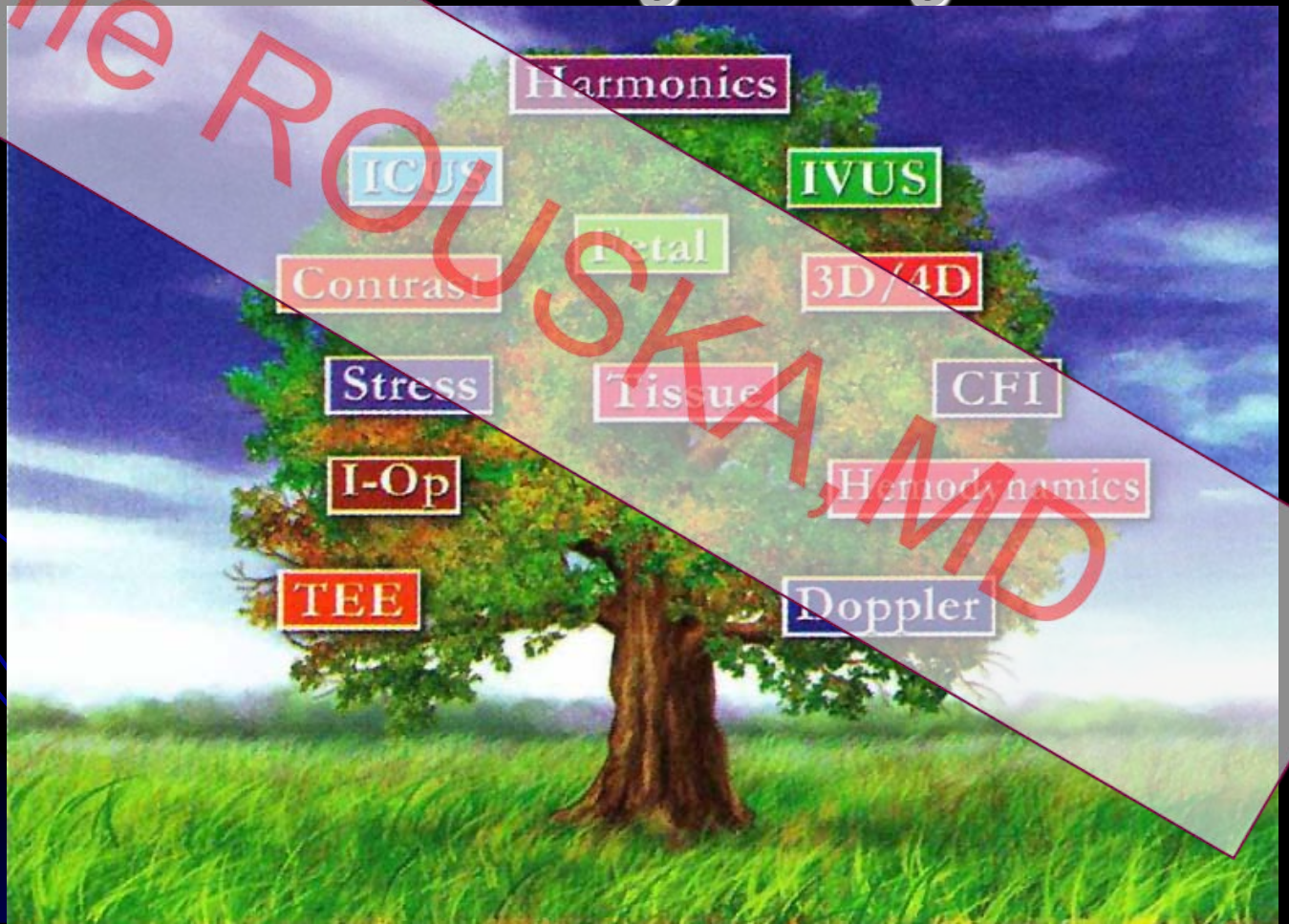


ΕΦΗ Γ. ΡΟΥΣΚΑ, *Καρδιολόγος*
BSE & EAE accredited in Echocardiography
Member of the European Committee for TOE
Επιμελήτρια Πανεπιστημιακής Καρδιολογικής Κλινικής Λάρισας

Nowadays…Echocardiography has become a mature tree that has numerous branches and is still growing!

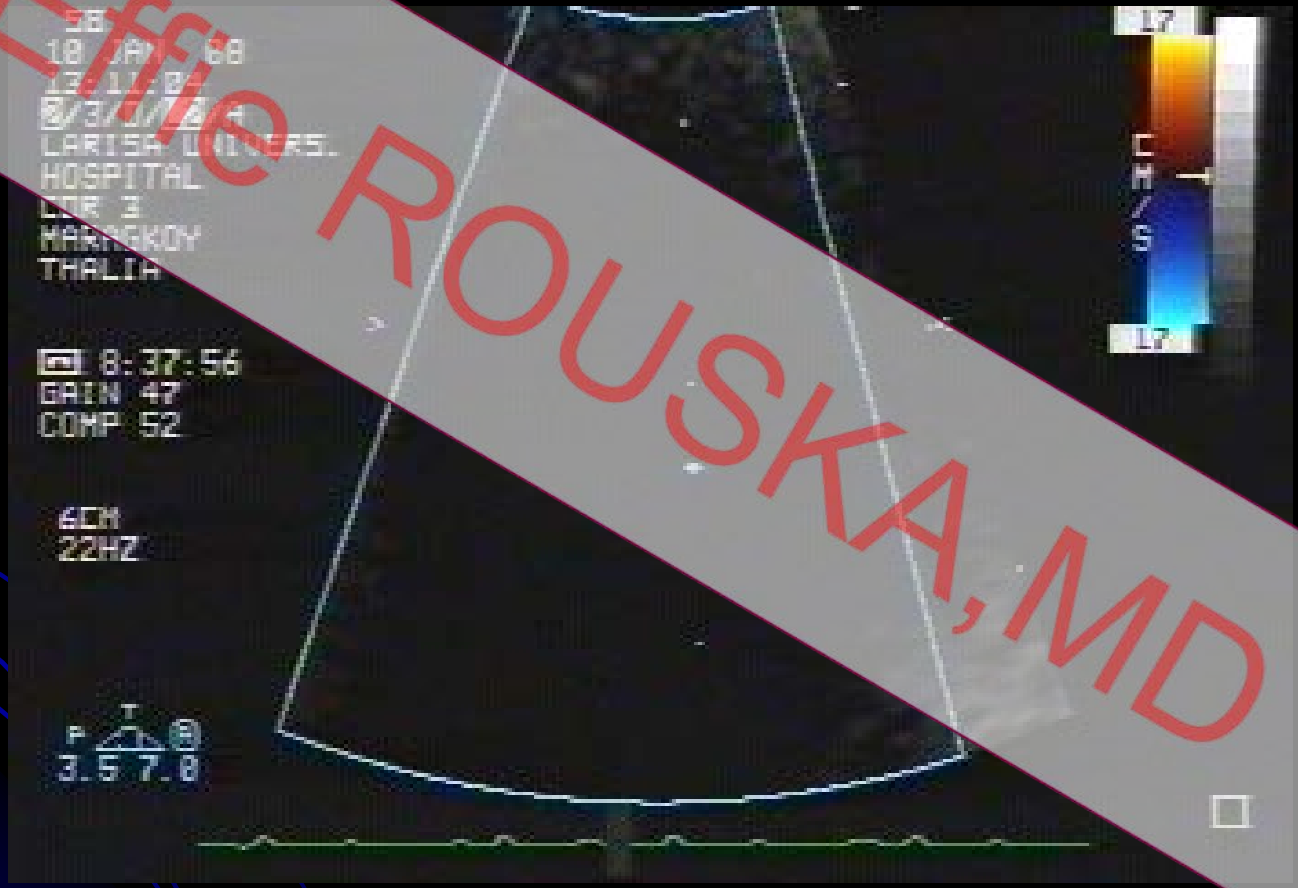
CFR

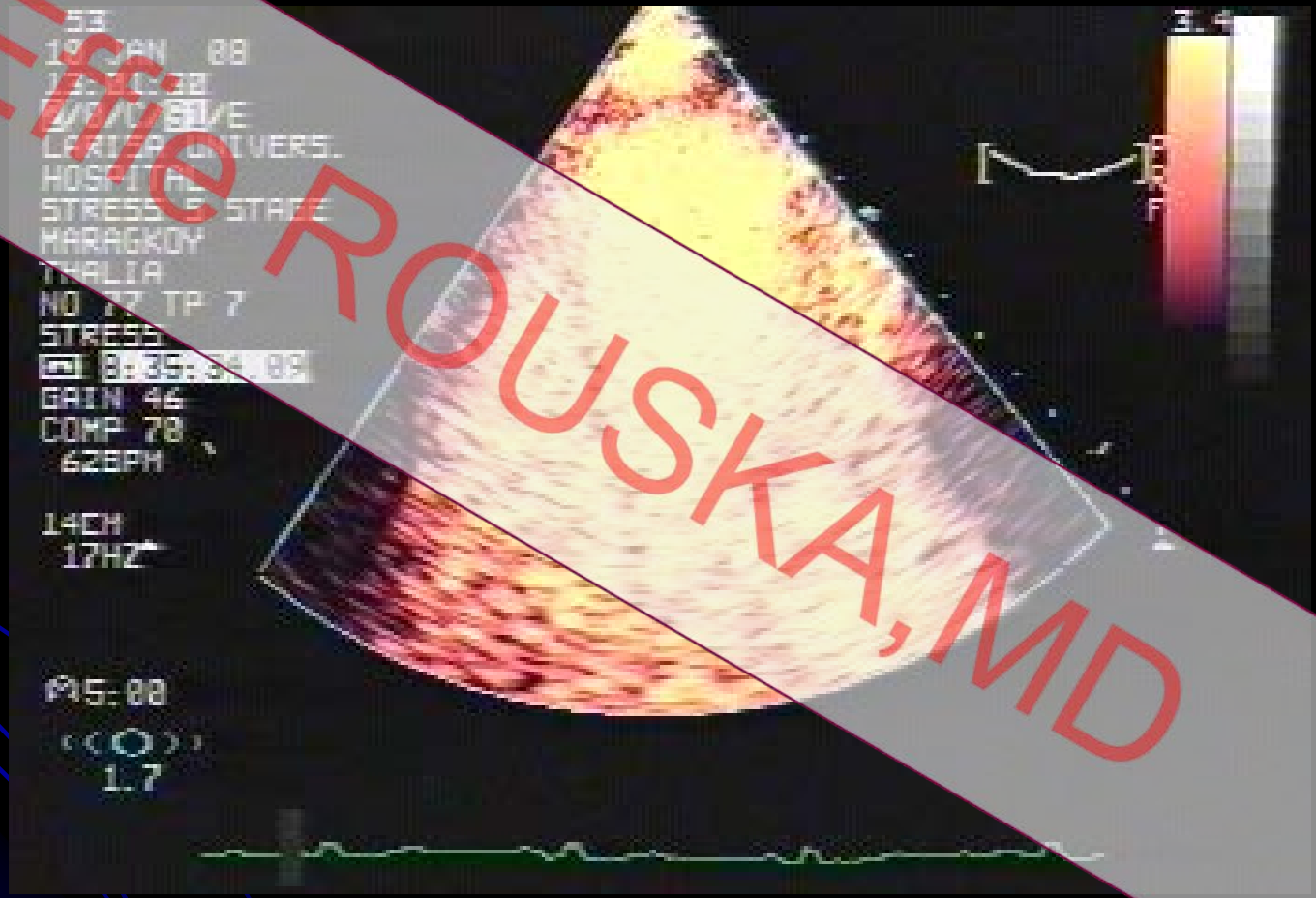
A new diagnostic power!



Normal CFR

Critically impaired CFR

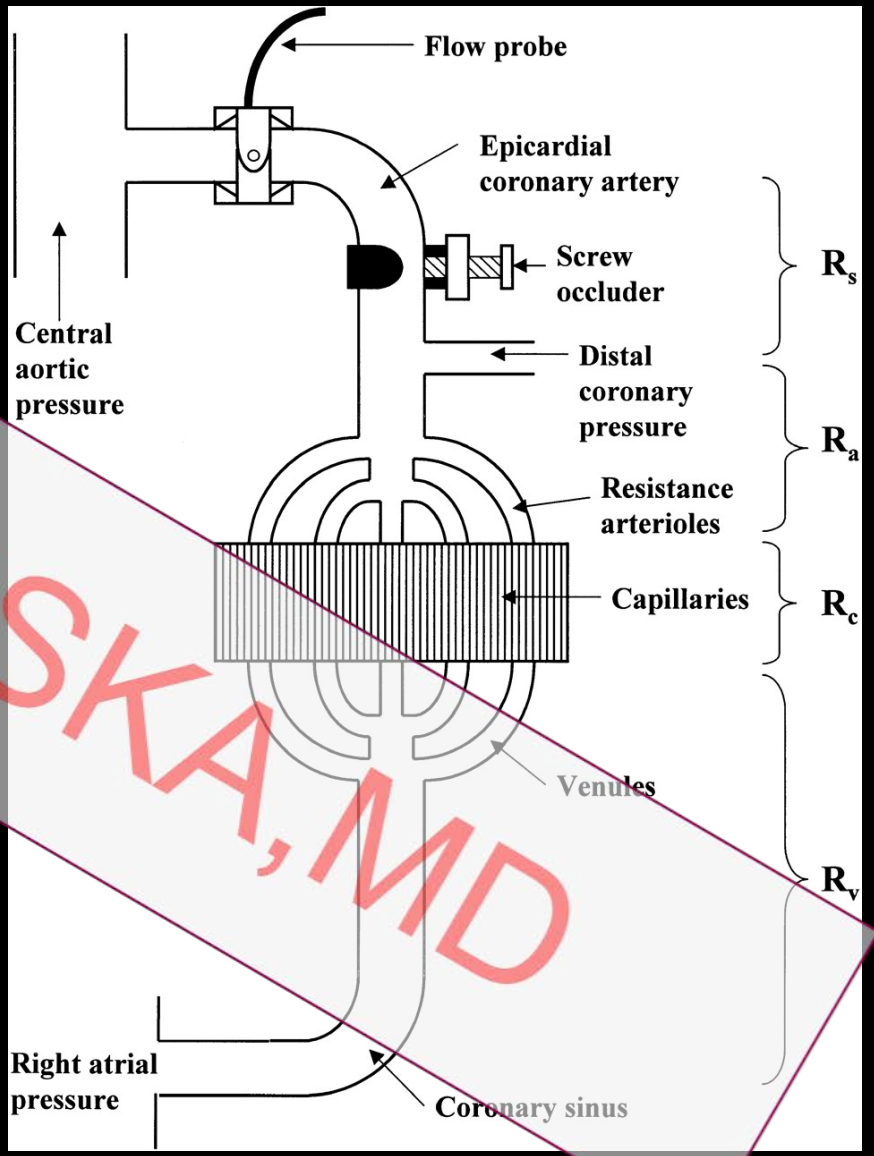




Effie ROUSKA, MD

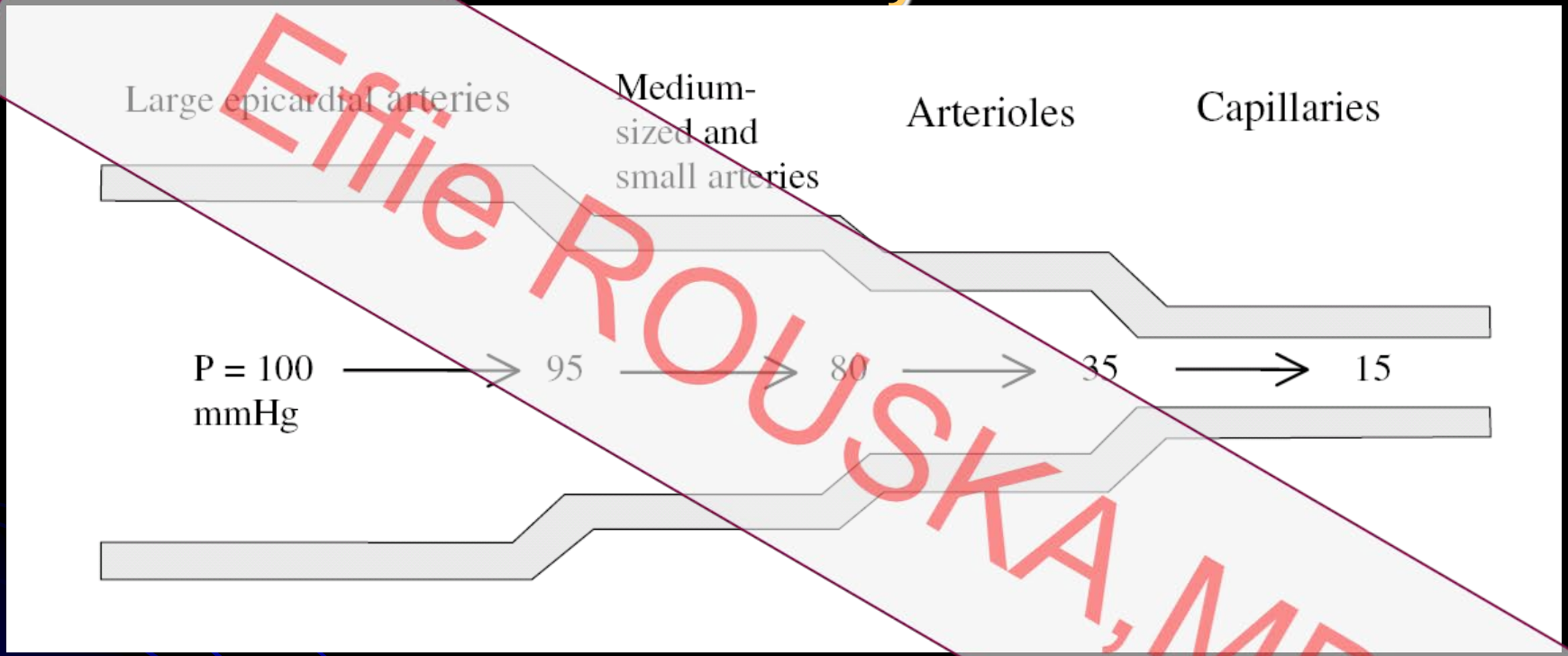
Coronary Circulation

The major Right and Left Coronary Arteries that serve the heart tissue are the first vessels to branch off the Ao. Thus the driving force for myocardial blood flow is the systemic arterial pressure. Most of the blood that flows through the myocardial tissue returns to the RA by way of the Coronary Sinus.



Jayaweera, A. R. et al. Am J Physiol Heart Circ Physiol 277: H2363-H2372 1999

Decrease of Coronary Perfusion Pressure and Distribution of Coronary Resistance in normal coronary arterial bed



	Large epicardial arteries	Medium-sized and small arteries		Arterioles	Capillaries
Diameter	>1000 μm	1000–100 μm.		100–10 μm	<10 μm
% of total resistance	5%		15–25% 400–100 μm	50–60%	20%
% length of coronary bed	5–10%	15–25%		60–75%	

Cardiovasc Ultrasound 2005;3:18-27

Active coronary autoregulation

- This means that within the autoregulatory range of perfusion pressure (usu. about 60-140mmHg), coronary blood flow is fairly constant, despite changes in arterial perfusion pressure.

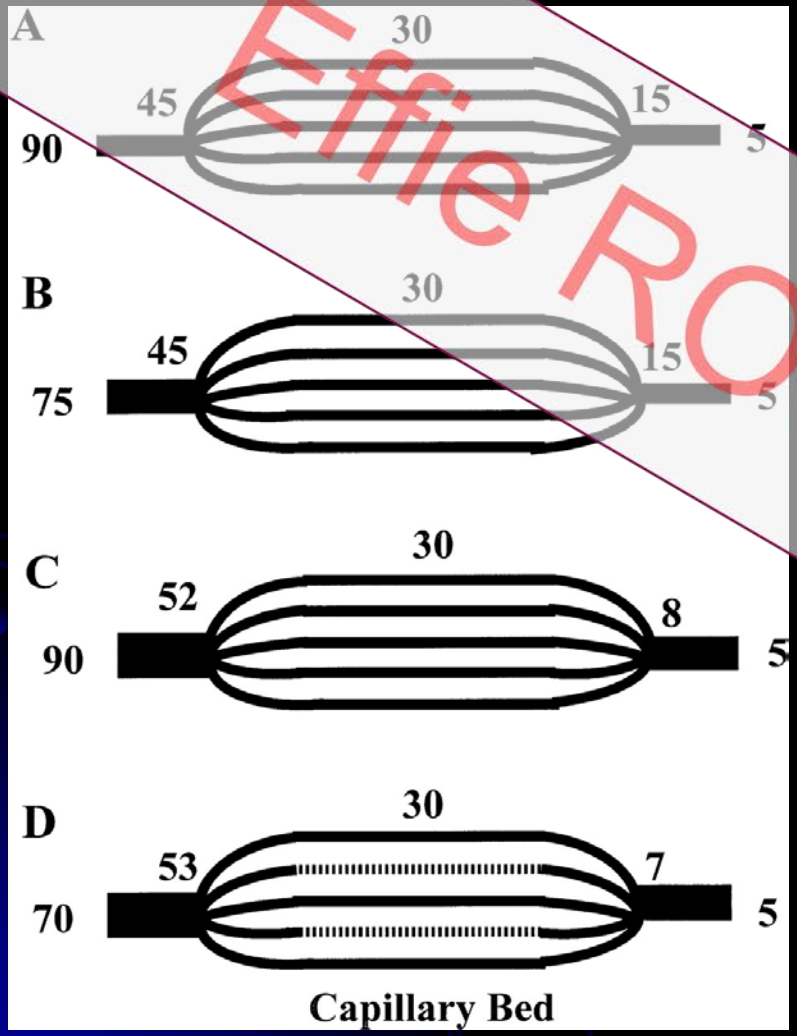
  Constant coronary flow is maintained

  until coronary blood pressure drops below 40-60mmHg

- The mechanisms responsible for the active change in vascular resistance that keeps coronary flow constant with change in perfusion pressure are poorly understood. (myogenic control and local metabolic control)

- Most of the resistance which opposes coronary blood flow, arises from resistance arterioles. The resistance is manifest by decreased coronary perfusion pressure.

Mechanisms of maintenance of constant capillary hydrostatic pressure



- At rest in absence of any stenosis
- At rest in presence of stenosis
- During hyperemia in absence of any stenosis
- During hyperemia in presence of stenosis

Jayaweera, A. R. et al. Am J Physiol Heart Circ Physiol 277: H2363-H2372 1999

Loss of Autoregulation

- Autoregulation is lost at pressures below approximately 60mmHg, and coronary blood flow becomes pressure-dependent

  (i.e.decreasing coronary perfusion pressure decreases coronary flow)

- Below the autoregulatory range, coronary vasodilator reserve is said to be exhausted.

- Vasodilator reserve is the difference between prevailing coronary flow and flow after maximal coronary artery dilatation.

- The loss of autoregulation at low coronary pressure is a critical element in producing angina pectoris.

Definition of CFR

- The difference between coronary blood flow corresponding to flow autoregulation plateau at rest and coronary blood flow after maximal vasodilatation is traditionally defined as CFR

- Calculated as the ratio of maximal(hyperemic)/resting CBF

- Up to now CFR has been evaluated invasively in the cath lab and in nuclear medicine through perfusion imaging. Only recently has CFR entered the Echo Lab, with the combination of CF assessed by Doppler and vasodilator stress.

Gould revisited: 30 years later

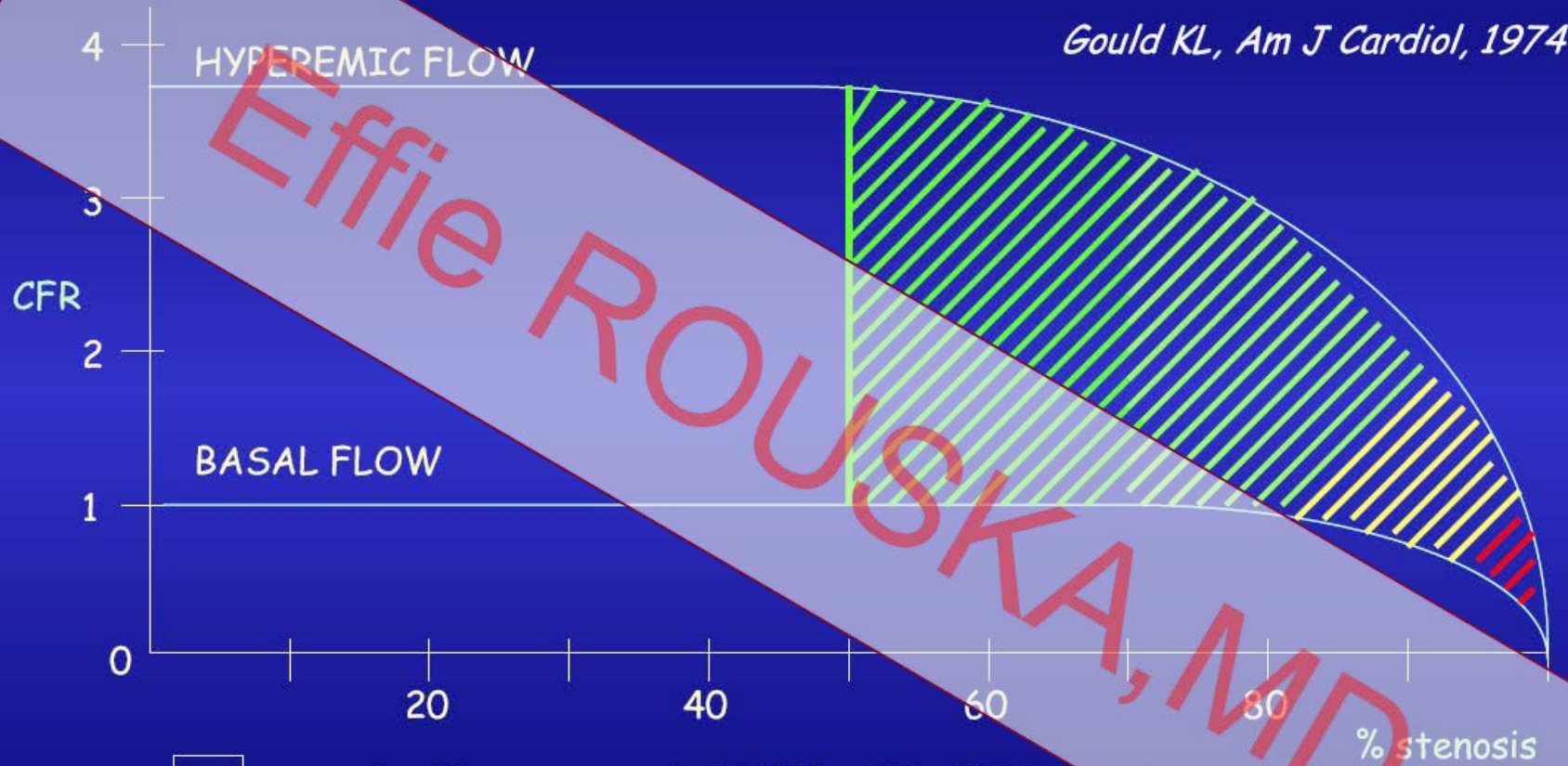
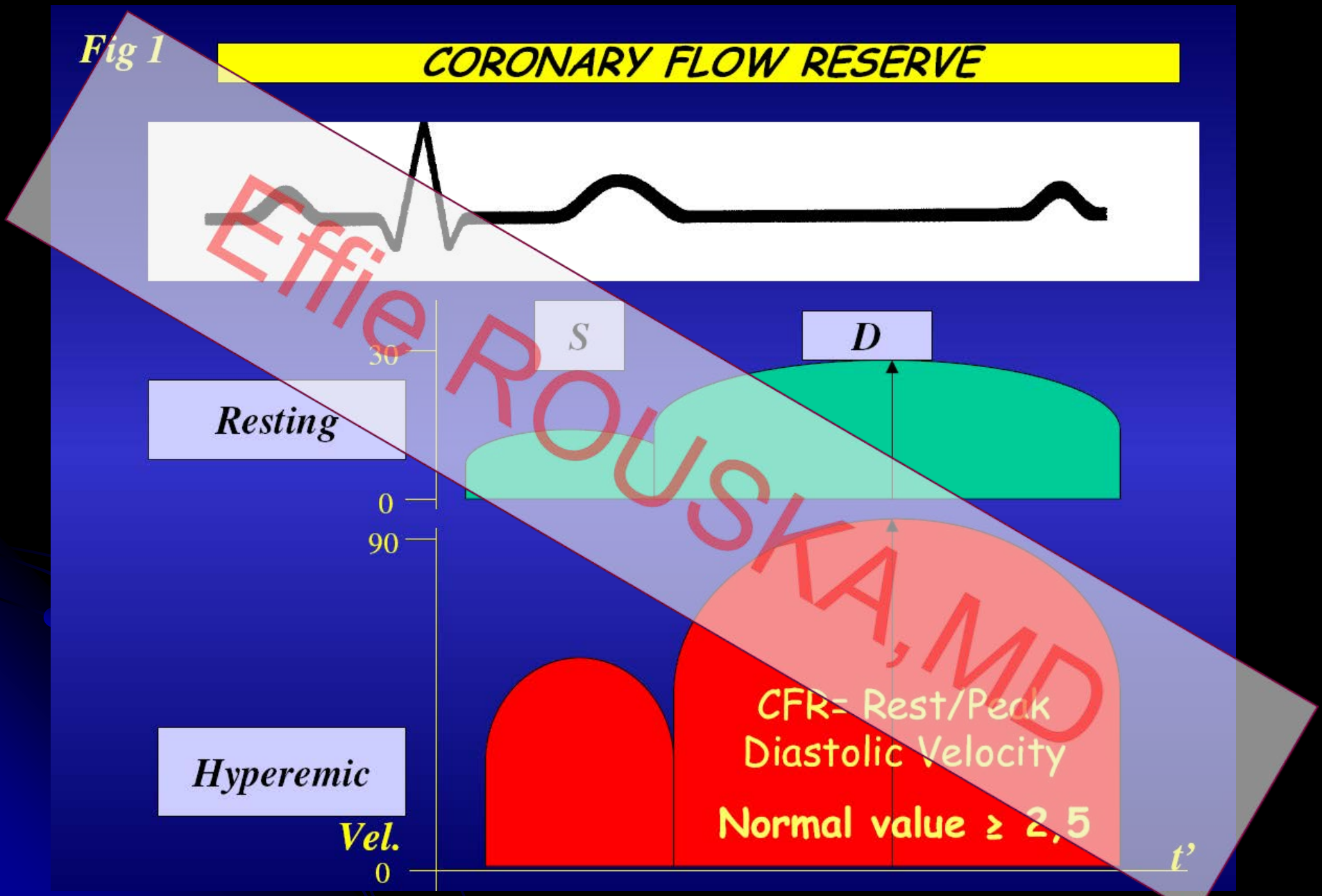


Fig 2

Fig 1



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CFR

- Normally coronary blood flow can increase approximately 4-6 fold to meet increasing myocardial oxygen demands.

  This effect is mediated by vasodilation at the arteriolar bed, which reduces vascular resistance, thereby augmenting flow.

- CFR represents the capacity of the coronary circulation to dilate following an increase in myocardial metabolic demands.

- It is an important index of the severity of epicardial coronary stenosis, or, in the absence of stenosis, of the integrity of the microvascular circulation.

Applications of Echo CFR testing

- To detect disease in the LAD (Reliable tool for evaluating patients with proximal LAD stenosis of intermediate severity)

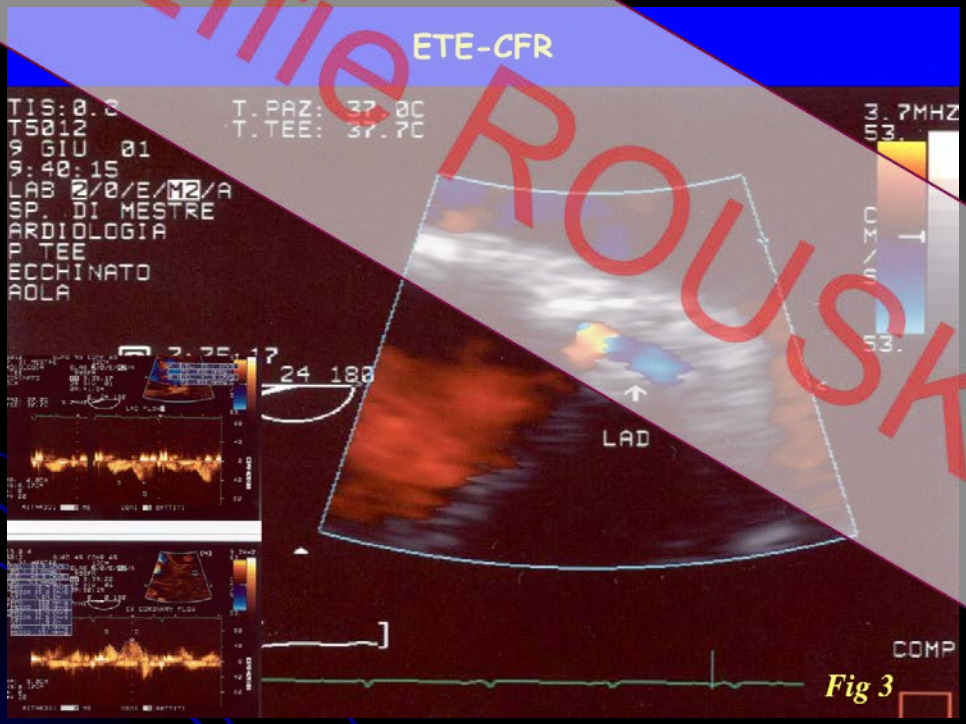
  Sensitivity 78%-92%

  Specificity 85%-93%
- To study coronary restenosis after PCI
- To identify IMA grafts patency
- To assess endothelial function
- To detect microvascular disease

  (pts with atypical chest pain, syndrome X, LVH, HTN,DM, hyperchlesterolemia,smokers)

CF signal on LAD

- First made possible by TEE – Circ 1991,83 Hutchinson SJ (Visualization of Left Main and bifurcation of LAD and Cx))



- Only more recently increase in clinical interest due to the development of the TTE method

Technical Aspects

- Technological factors which allowed the totally noninvasive TTE imaging of mid-distal LAD
  - second harmonic imaging
  - high frequency transducers(3.5-12MHz)
  - availability of contrast agents

- Machine settings(Nyquist limit, gains, filters,depth, angle incidence, sample volume etc)

- Training (Imaging pitfalls)

- Criteria valid for peripheral arteries

  Local maximal flow velocity>1.5m/s is an accurate sign of stenosis

Feasibility of measuring CFR

Table 1 Feasibility of measuring coronary flow reserve by transthoracic Doppler echocardiography

Author	Year	No	Method	Feasibility (%)
Ross[2]	1990	37	M-mode	85
Caiati[3]	1999	138	Harmonic, contrast	88
Hozumi[6]	1998	53	High frequency	77
Takeuchi[10]	2001	144	High frequency, contrast	90
Pizzuto[4]	2001	77	High frequency	96
Ruscazio[5]	2002	53	Harmonic, contrast	100

Imaging pitfalls

- Pericardial fluid (esp in PLAX)

  (max velocities in the pericardium will be present during systole rather than diastole)
- Thoracic Arteries

  (predominantly systolic flow)
- Small mediastinal veins and veins accompanying the IMA and the pericardial phrenic artery

  (significant respiratory variation and an almost continuous syst-diast flow pattern at very low velocities)

Protocol for assessing CFR

- Adenosine i.v. at a dose of 140mcg/kg/min
- Peak changes after 40-50secs
- Plasma half-life is less than 10secs
- Hyperpnea can degrade the image quality (end-expiratory breathhold maneuver)
- Antagonists of adenosine(xanthine derivatives) should be withdrawn for at least 24hrs before testing
- If contrast is necessary, separate i.v. line

Comparison between adenosine and dipyridamole characteristics

	Adenosine	Dipyridamole
Duration of action	30 sec	30 min
Time to max. Effect	30–55 sec	6–16 min
Advantage	Short action, short-lasting adverse effects	prolonged action allow to assess CFR and wall motion abnormalities during the same examination
Disadvantage	Frequent- hyperventilation Rare – bradycardia, AV block, hypotension, flushing, headache,	possibility of antidote-resistance prolonged ischemia, hypotension, flushing, headache, hyperventilation,

Cardiovasc Ultrasound 2005;3:18-27

Other drugs : Acetylcholine, Papaverine and Dobutamine

Antidotes to Dipyridamole and Adenosine : Methylxanthines

I.V. agents used to test CFR

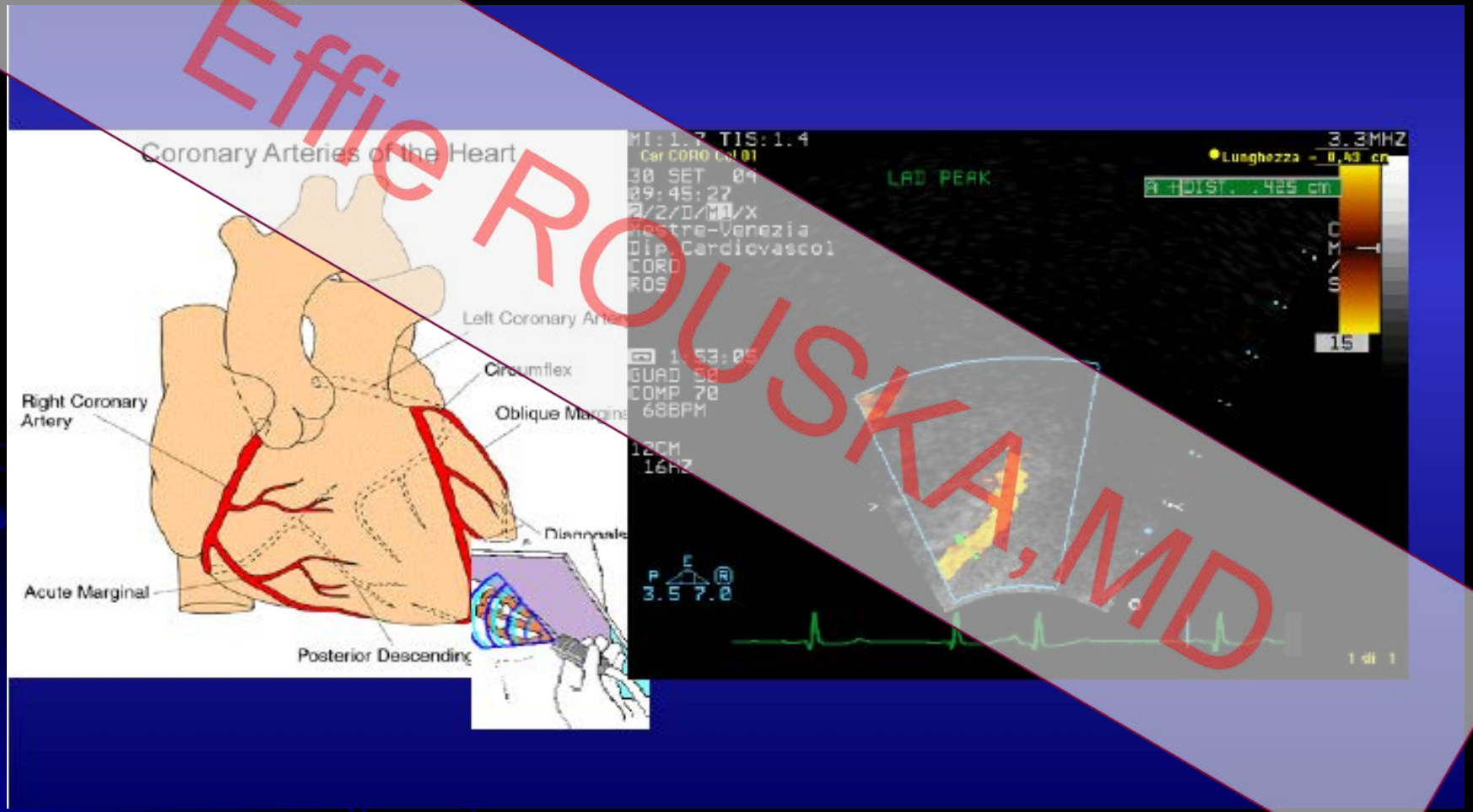
Table 1 Intravenous agents used to test coronary flow reserve using echocardiography

Agent	Doses	Normal CFR values	Advantages	Disadvantages
Adenosine	140 μg/kg/min	>2.0–5.0	• 30–55 s to effect • 30 s duration after discontinuation • Allows simultaneous evaluation of regional function	• Hyperventilation • Bradyarrhythmia • Headache
Dipyridamole	0.56–0.84 mg/kg	>2.0		• 30 min duration • 6–16 min to maximum effect
Dobutamine	5 μg/kg/min increased at 3–5 min intervals to a maximum dose of 40 μg/kg/min	>2.0–3.0	• Allows simultaneous evaluation of regional function	• Less hyperemic response • Changes in heart rate and contractility • Difficult to obtain the same images at peak stress

CFR, Coronary flow reserve.

JASE 2004;17:704-7

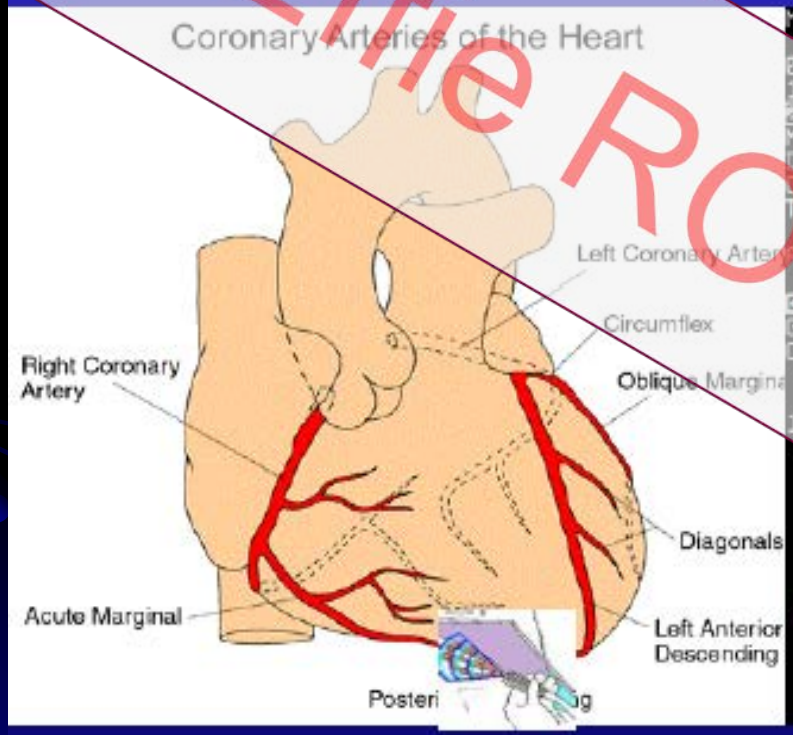
Mid-distal tract of LAD

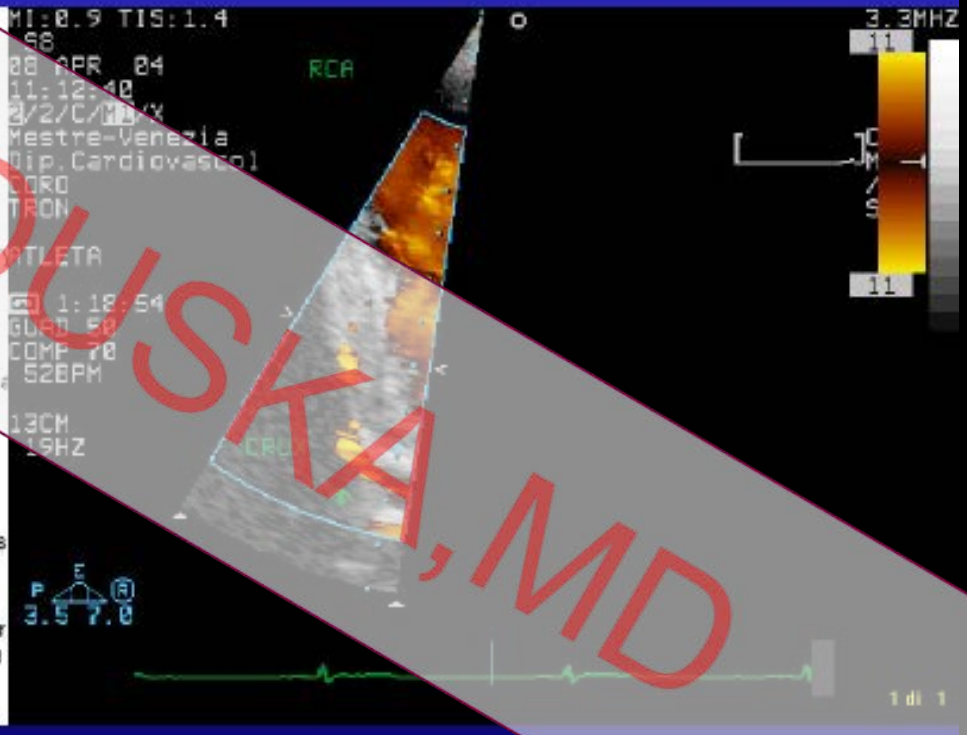


Feasibility of imaging

Distal LAD >90%

RCA and PDA

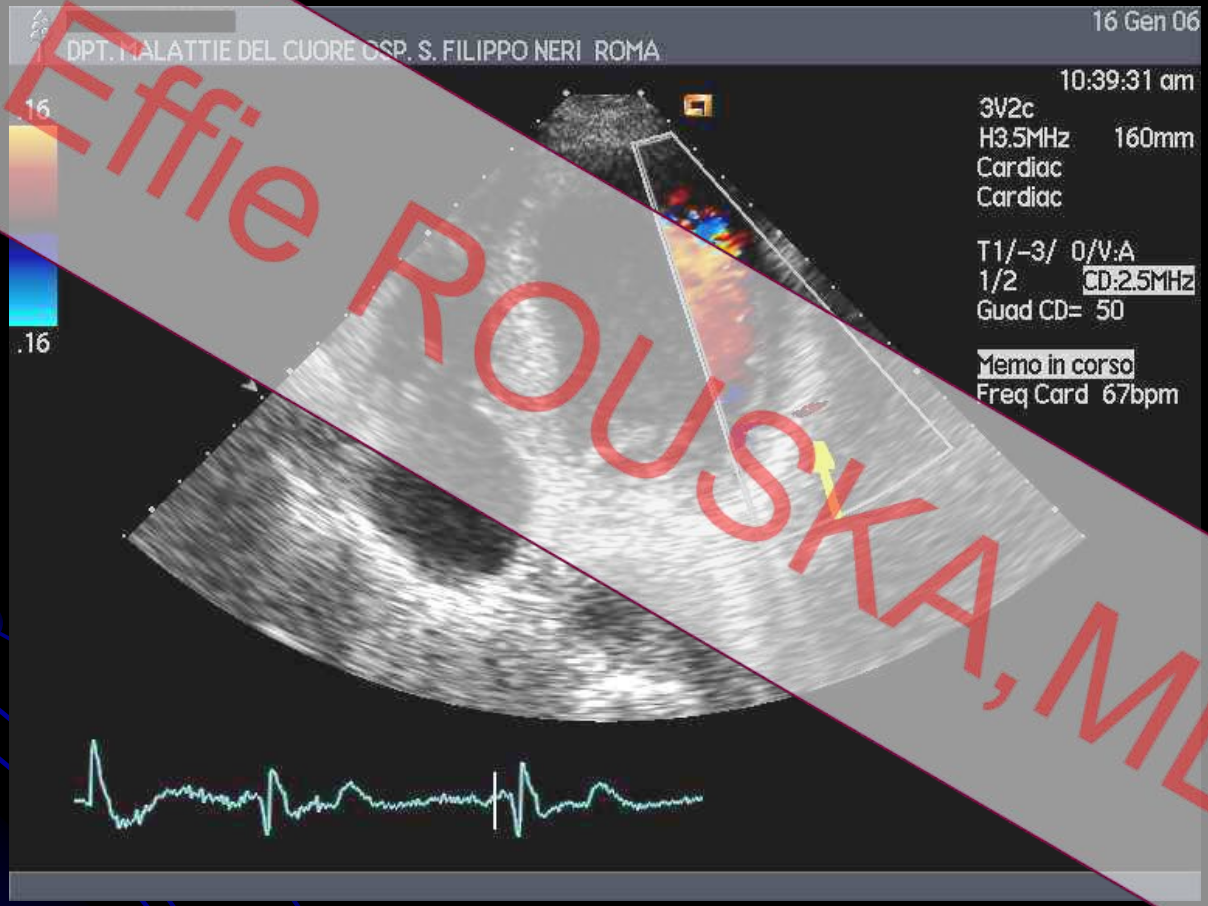




Feasibility of imaging

PDA >75%

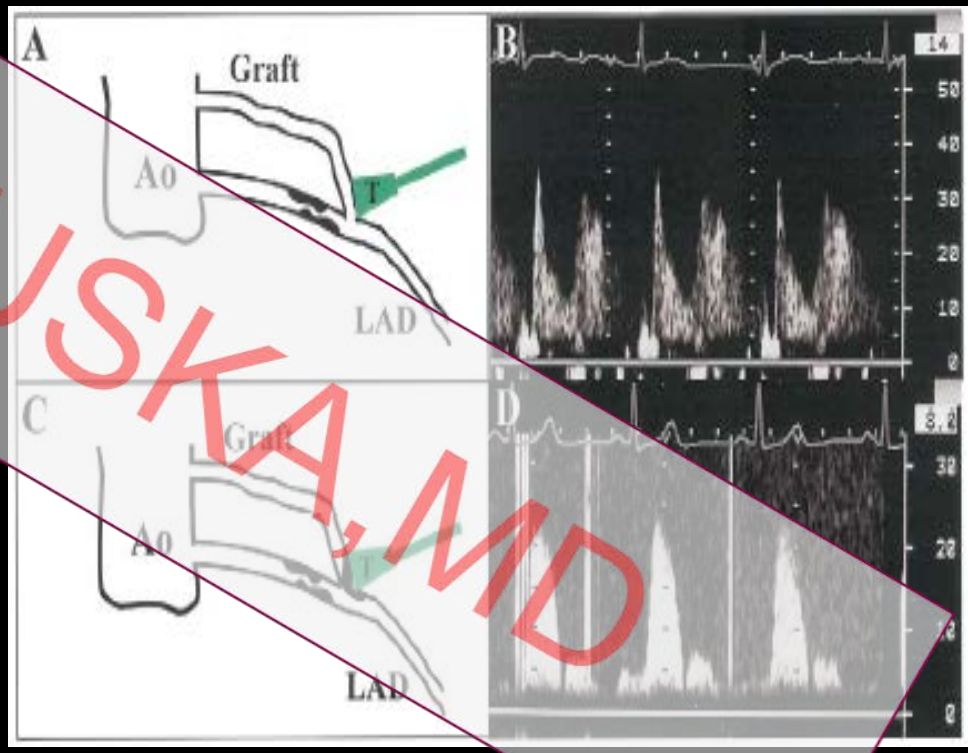
Cx



Feasibility of imaging
LCX >40%

LIMA

- Low left PLAX window
- In the native IMA flow is dominant systolic
- Patent IMA grafts show a gradual transition in the flow pattern from predominant systolic velocity proximally (at the origin from the subclavian artery) to the predominant diastolic velocity distally (proximal to the anastomosis with the native coronary artery)
- When IMA graft develops stenosis, low velocity profiles are recorded during diastole with an increase in the systolic component



JASE 2004;17:178-85

Feasibility of imaging
LIMA 70-95%

Criteria for normal reference values

- Coronary flow velocities
- Duration of diastolic and systolic flow (HR)
- Coronary flow patterns
- Rapid diastolic Deceleration Slope

  (integrity of the distal coronary bed / myocardial viability)
- Retrograde Flow

  (presence of collateral flow)
- Flow Damping (velocity< 13cm/s)
- Lower limit of normal CFR is > 2.5 (3.0)

Ho-Joong Youn: JASE 2004;17:178-85

Results on CFR in different pathologies

	Number	Male/Female	Mean age(years)	CFR
Normal patients	76	47/29	39 ± 12	3,32 ± 0,3
Syndrome X	97	24/73	57 ± 17	2,27 ± 0,3
LAD (≥ 70%)	223	171/152	63 ± 16	1,38 ± 0,2
LAD (<70%)	128	84/44	62 ± 16	2,2 ± 0,24
Hypertensive pts	323	72/251	56 ± 17	2,46 ± 0,44
DC	48	29/19	64 ± 12	1,94 ± 0,24
HCM	44	35/9	53 ± 11	2,21 ± 0,23
Aortic stenosis	22	6/14	74 ± 13	2,18 ± 0,34
Aortic insufficiency	12	5/7	68 ± 12	2,57 ± 0,40
PCI- LAD (>3 mo.)	72	51/21	61 ± 16	2,52 ± 0,45
Graft-IMA (>3 mo.)	56	41/15	64 ± 14	2,60 ± 0,38
Post-AMI (>3 mo.)	93	69/24	68 ± 17	1,98 ± 0,41
Athletes	41	41	34 ± 12	4,5 ± 0,45

LAD = Left anterior descending coronary artery; Syndrome X = microvasculature dysfunction; DC = Dilated cardiomyopathy; HCM = Hypertrophic cardiomyopathy; PCI-LAD = after LAD angioplasty (>3 months); Graft-IMA = By-pass with internal mammary artery on LAD; Post-Ami = after anterior myocardial infarction not revascularized.

It is important to underline the fact that different pathologies can give the same values in terms of CFR

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Factors limiting CFR

1. Increase of resting coronary blood flow due to increased myocardial oxygen demand as a result of:

- tachycardia
- increased myocardial contractility
- myocardial hypertrophy

2. Decrease of maximal (hyperemic) coronary blood flow:

- epicardial coronary artery stenosis
- decrease mean aortic pressure = coronary perfusion pressure e.g. aortic insufficiency, exaggerate response to vasodilator agent
- wall thickening (remodeling) of resistance arterioles
- reduced density of arterioles
- cardiomyocyte hypertrophy
- perivascular fibrosis
- interstitial fibrosis
- endothelial dysfunction
- increased blood viscosity: policythemia, macroglobulinemia
- elevated LV diastolic pressure increasing extravascular compressive forces and resistance (particularly in subendocardial layer).

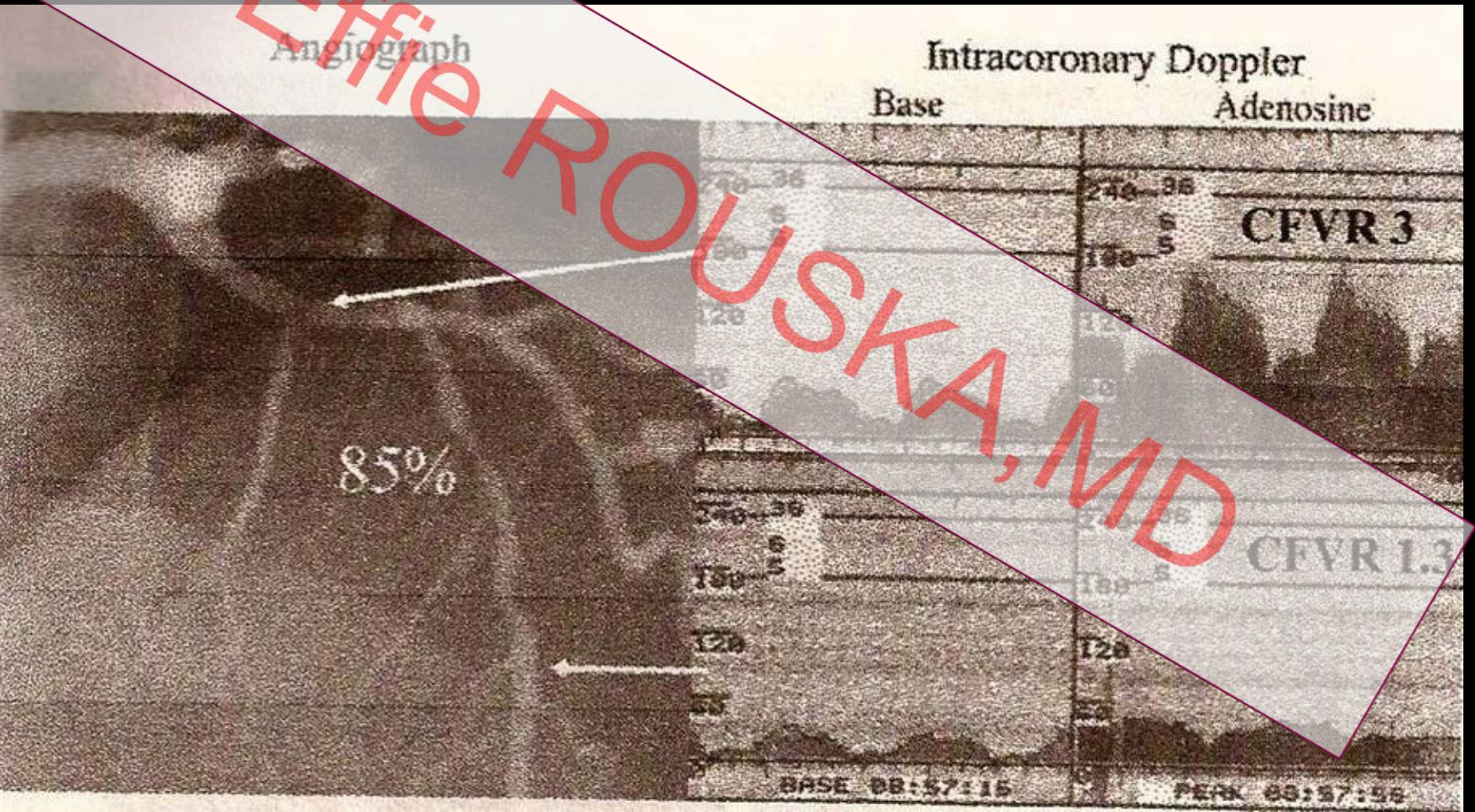
3. Shift to the right in the pressure-flow relation through maximally dilated vessels due to an increase in zero flow pressure line:

- increased left ventricular diastolic pressure
- tachycardia
- myocardial hypertrophy

JASE 2004;17:6

Cardiovasc Ultrasound 2005;3:18-27

CFR correlates well with invasive measurements



Accuracy of CFR to detect LAD disease

- Sensitivity: 78-92%
- Specificity: 85-93%

Diagnostic value of 2D Echo and CFR

	Sensitivity	CI 95%	Specificity	CI 95%	Accuracy	CI 95%
2D Echo	74%	64–84%	91%	87–96%	86%	82–91%
Coronary Flow Reserve (cut-off = 2)	89%	81–96%	77%	71–84%	81%	76–86%
Coronary Flow Reserve (cut-off = 1,9)	81%	72–90%	84%	79–90%	83%	79–88%
Coronary Flow Reserve (cut-off = 1,8)	69%	58–79%	90%	85–95%	83%	79–88%
Coronary Flow Reserve (cut-off = 1,7)	63%	52–74%	97%	94–99%	86%	82–91%
Coronary Flow Reserve (cut-off = 1,6)	50%	38–61%	100%	-	85%	80–89%
Coronary Flow Reserve (cut-off = 1,5)	30%	19–41%	100%	-	79%	73–84%
2D Echo / CFR cut-off = 1,9	90%	81–98%	94%	91–98%	93%	89–97%

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Accuracy of TTE analysis of CFR

- The gold standard for measurement of CFR is the intracoronary Doppler guidewire.
- Increasing interest in noninvasive imaging modalities has led to the use of MRI, PET, TOE and more recently TTE
- Validation of these modalities against the gold standard of intracoronary Doppler has been undertaken infrequently, particularly in the case of TTE.
  (Paper from Cambridge (Parworth Hospital) 2002)

Hildick-Smith D : JASE 2002;15:984-90

Practical Advantages of transthoracic CFR over other Imaging Modalities (e.g. MRI, PET)

- No radiation exposure
- Non invasive
- Good diagnostic performance
- Excellent clinical utility / reliable
- Widely available / accessible
- Safe
- Low cost
- Minimal pt discomfort

Limitations of using CFR as a stand-alone diagnosic criterion

- In most of the cases only LAD is sampled
- CFR cannot distinguish between microvascular and macrovascular CAD
- The flow information is relatively unaffected by concomitant antianginal therapy, which markedly reduces the sensitivity of of ischaemia-dependent regional WMA and does not influence CFR or does so only to a limited extent.

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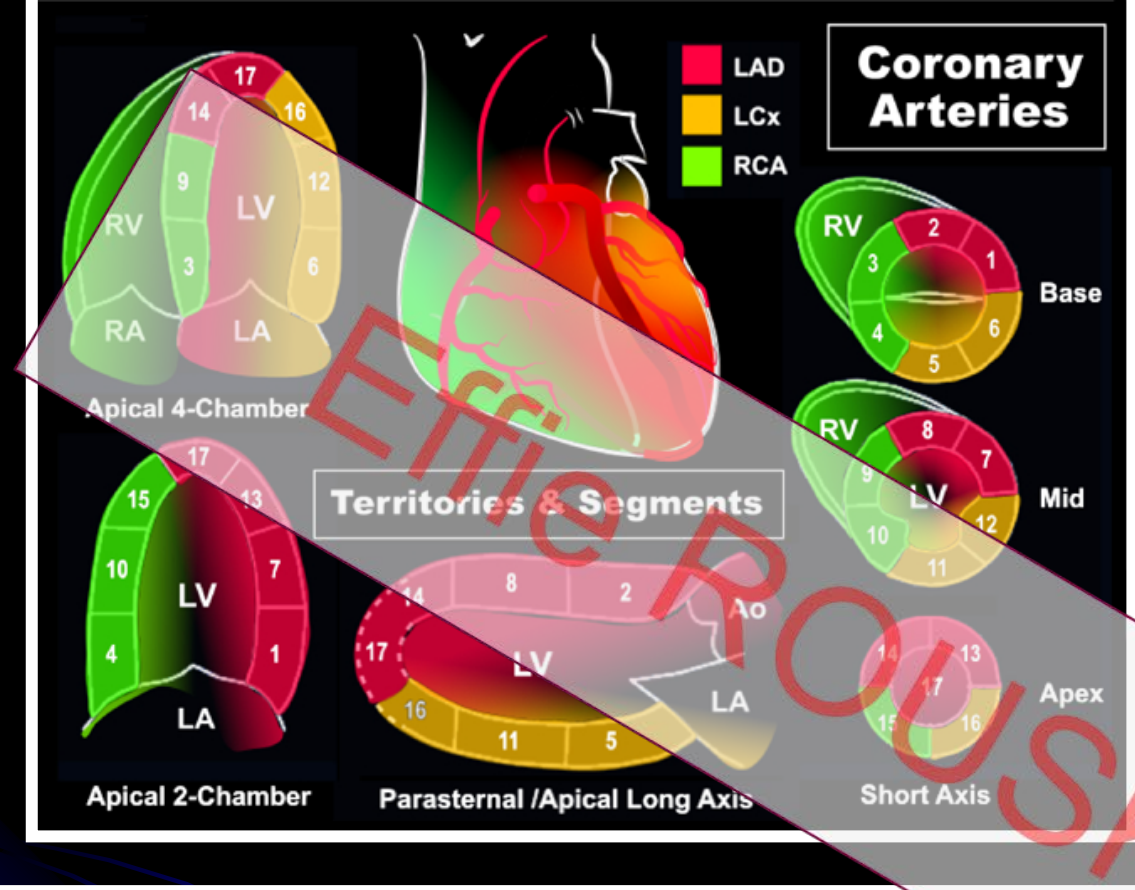
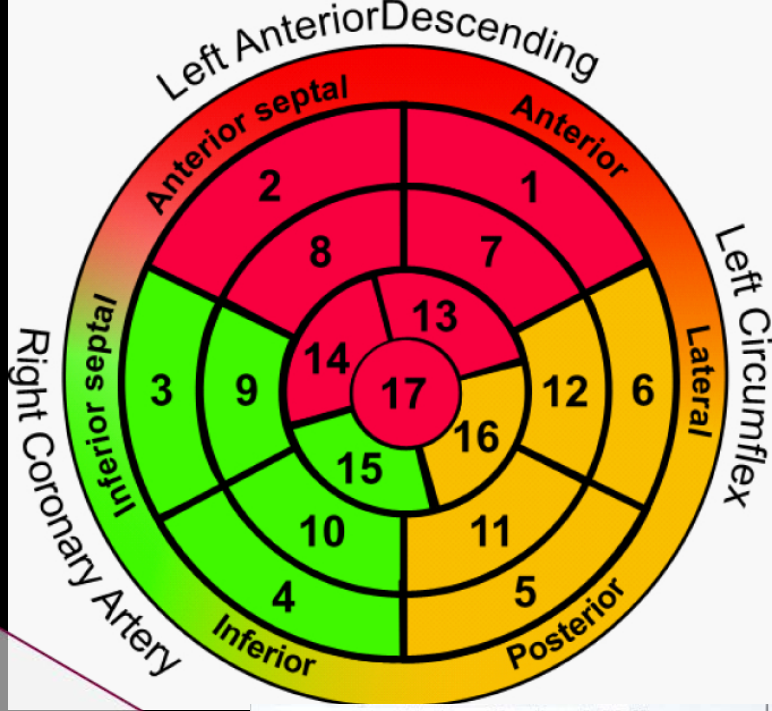
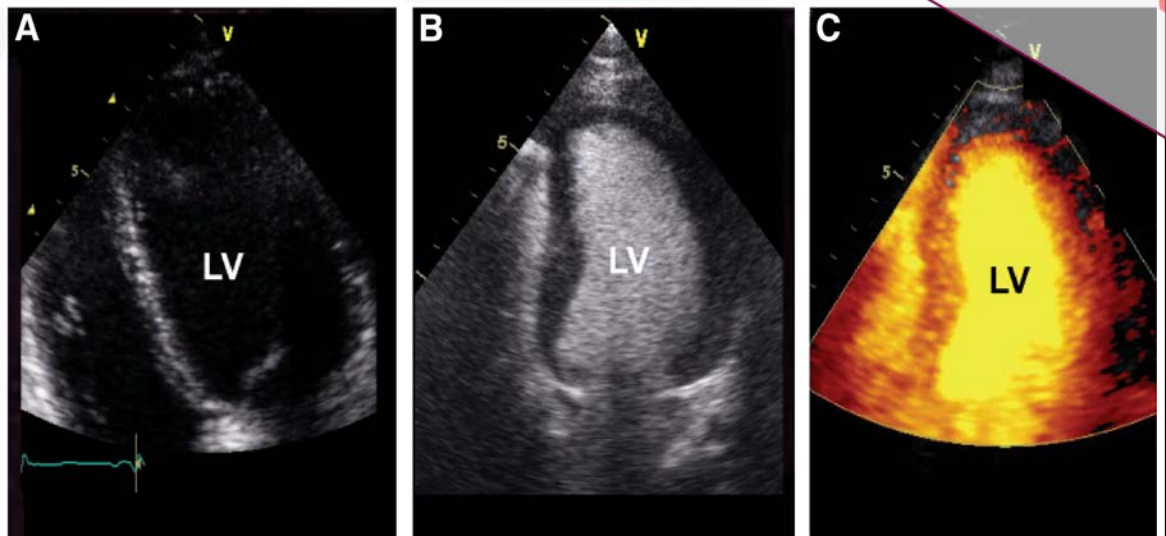
Echocardiography in IHD

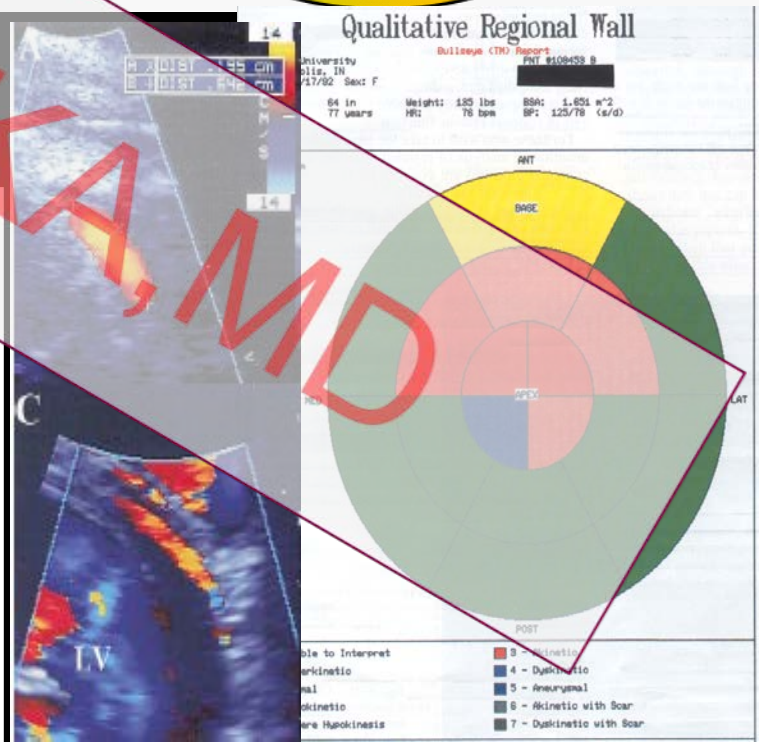
- Assessment of **regional** systolic function (Stress echo)
- Contrast echo for
  -LV opacification
  -Myocardial perfusion
- CFR

Combining all in one ??









Contrast – Enhanced DSE

- Which is the better method in detecting significant LAD stenosis during contrast-enhanced DSE? CFR or WM assessment?

- Studies demonstrated in a large series of unselected patients that both methods have an equivalent diagnostic accuracy in detecting significant LAD stenosis

Takeuchi,M: JASE 2003;614-21

CFR in stress-echo lab

This technological novelty is changing the practice of stress echo for 3 main reasons:

- Adds in the same sitting
  high specificity *(regional wall motion)* and
  high sensitivity (*CFR*) / flow–function relationship

- The technicalities of CFR shift the balance of stress choice in favour of Vasodilators/ more robust hyperemic stress and easier to perform with dual imaging

- CFR adds a quantitative support to the exquisitely qualitative assessment of wall motion analysis

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Protocol of Dipyridamole Stress Echocardiography

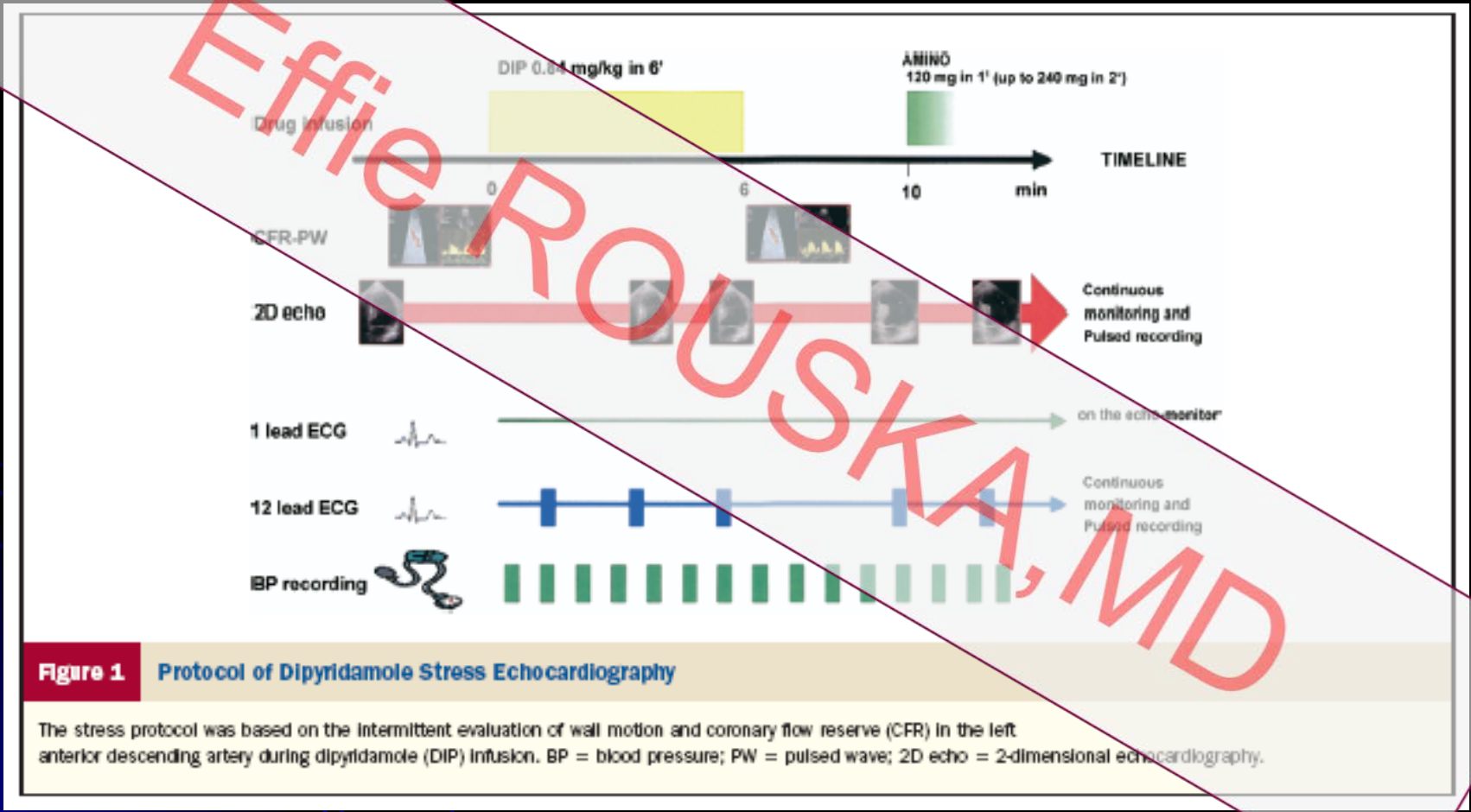
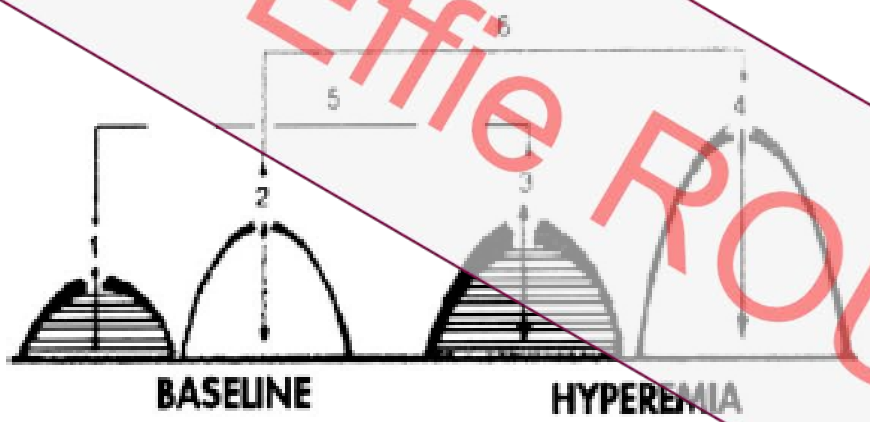


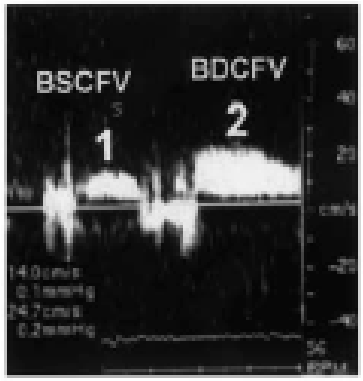
Figure 1 **Protocol of Dipyridamole Stress Echocardiography**

The stress protocol was based on the intermittent evaluation of wall motion and coronary flow reserve (CFR) in the left anterior descending artery during dipyridamole (DIP) infusion. BP = blood pressure; PW = pulsed wave; 2D echo = 2-dimensional echocardiography.

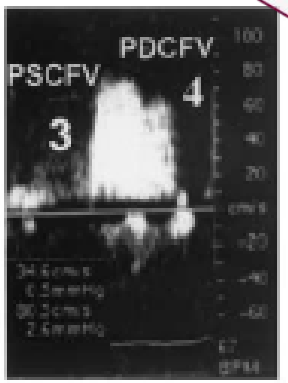
Cortigiani L.:JACC 2007; 50:14

CFR in Dip-SE





BASAL



DIPYRIDAMOLE

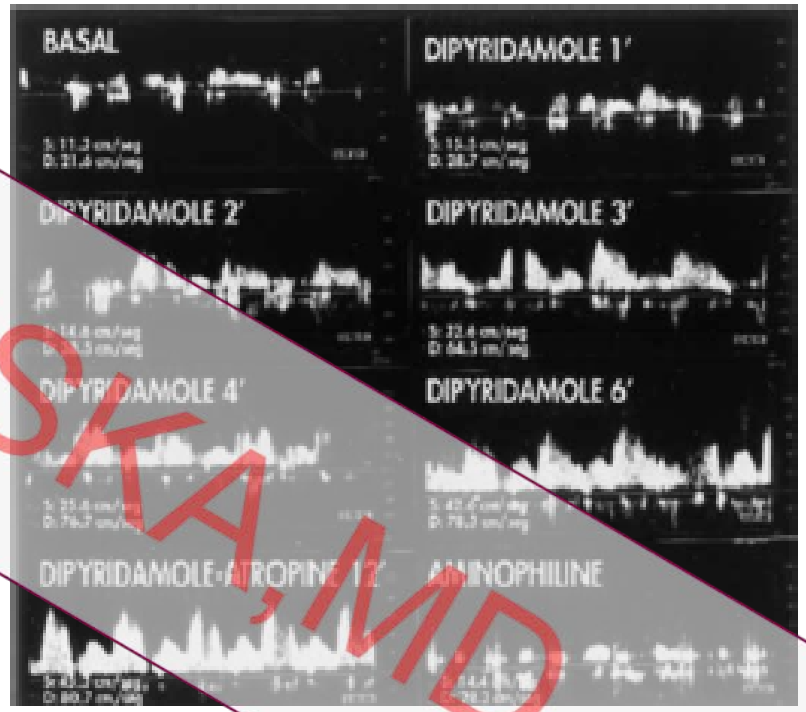


Figure 4 Temporal sampling of coronary flow reserve (CFR) by transthoracic echocardiography. There is progressive, stepwise increase in CFR peaking after high dose and immediately reversed on aminophylline administra-

Lowenstein J.:JASE 2003; 16:607-13

CFR in Dob-SE

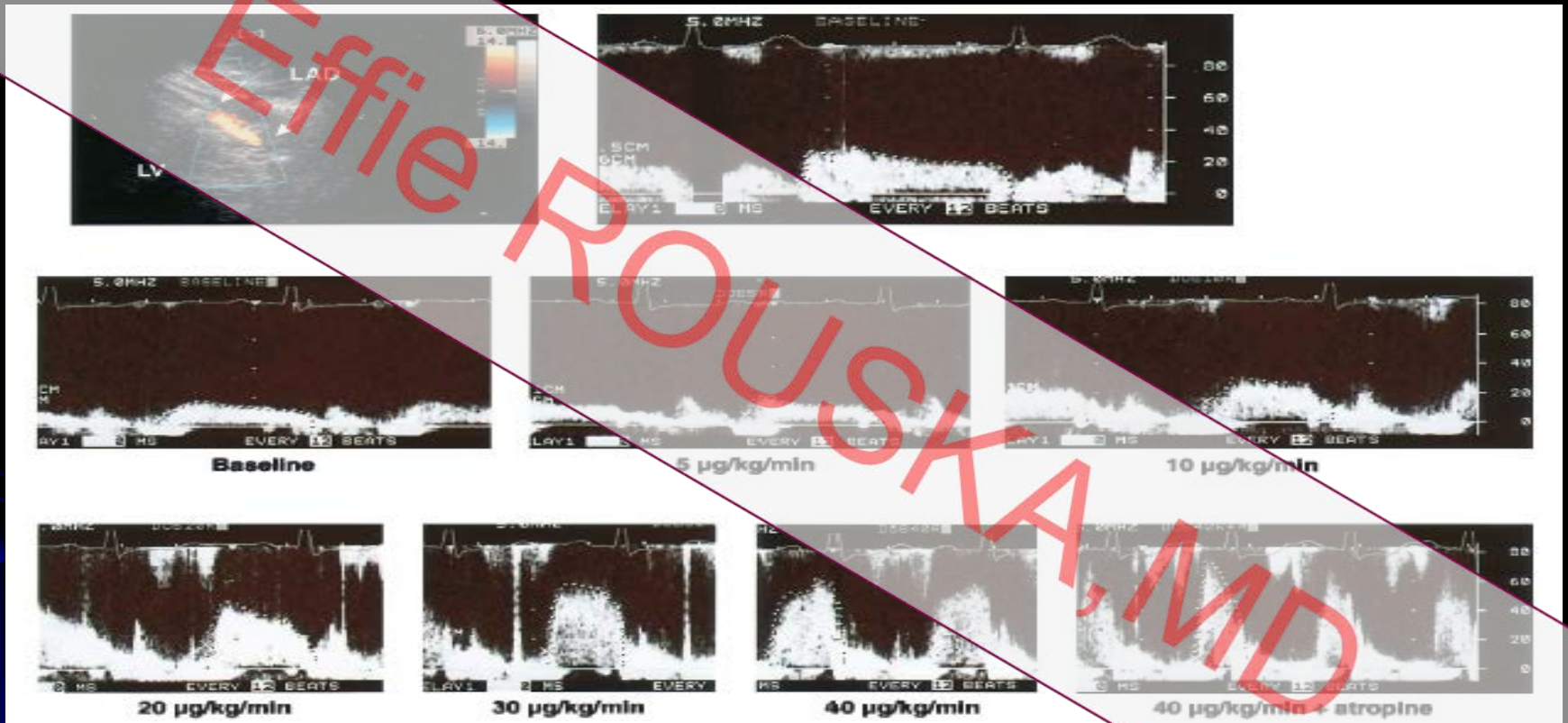


Figure 1. Color Doppler flow mapping of modified low parasternal long-axis view (**top left**) and spectral Doppler tracing (top right) in distal left anterior descending coronary artery (LAD) after contrast enhancement. Color-coded blood flow in the LAD is clearly seen (**arrow**). Spectral Doppler shows biphasic coronary flow with predominance of diastolic component. **Middle and lower panels** show an example of another patient with normal response. After infusion of dobutamine, coronary flow velocity gradually increased. Baseline diastolic mean velocity was 17.2 cm/s, and flow velocity increased to 54.4 cm/s after injection of atropine; thus, coronary flow velocity ratio peak is 3.16. Speed of recording 100 mm/s, velocity scale 80 cm/s. LV = left ventricle.

Takeuchi,M:JACC 2001; 38:117-23

Combining Stress Echo with Contrast and CFR

- Cut-off value of CFR is accepted to be <2.0 for predicting significant LAD stenosis of >75%
- CFR has a good correlation with perfusion
- WMSI normal=1
  CFR normal>2.5

  High negative predictive value for CAD
- WMSI normal=1
  CFR low<2

  Microcirculatory disorders / altered endothelial function

Different Coronary Anatomic and prognostic CFR Conditions

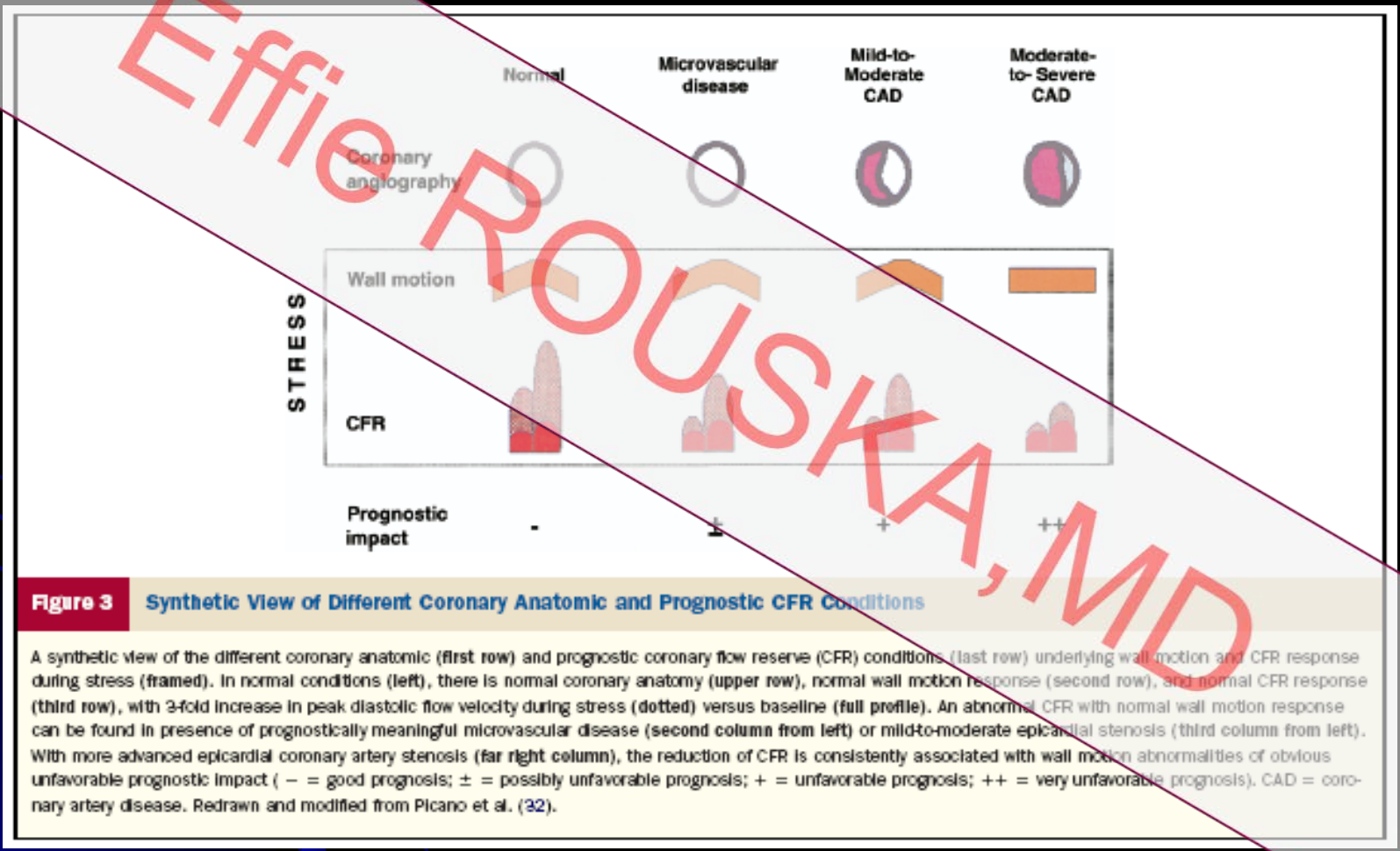


Figure 3 Synthetic View of Different Coronary Anatomic and Prognostic CFR Conditions

A synthetic view of the different coronary anatomic (first row) and prognostic coronary flow reserve (CFR) conditions (last row) underlying wall motion and CFR response during stress (framed). In normal conditions (left), there is normal coronary anatomy (upper row), normal wall motion response (second row), and normal CFR response (third row), with 3-fold increase in peak diastolic flow velocity during stress (dotted) versus baseline (full profile). An abnormal CFR with normal wall motion response can be found in presence of prognostically meaningful microvascular disease (second column from left) or mild-to-moderate epicardial stenosis (third column from left). With more advanced epicardial coronary artery stenosis (far right column), the reduction of CFR is consistently associated with wall motion abnormalities of obvious unfavorable prognostic impact (− = good prognosis; ± = possibly unfavorable prognosis; + = unfavorable prognosis; ++ = very unfavorable prognosis). CAD = coronary artery disease. Redrawn and modified from Picano et al. (32).

Cortigiani L.:JACC 2007; 50:14

Abnormal CFR with normal WM

Pathophysiology behind prognosis

- 1. Mild-Mod epicardial coronary artery stenosis (mirrored in stress induced perfusion defects)
- 2. Severe epicardial coronary artery stenosis in presence of effective anti-ischemic therapy
- 3. Severe microvascular disease in presence of patent epicardial coronary arteries

Rigo F: Am Heart J 2006;151:124

Meta-analysis on CFR and WMSI diagnostic value

	SENSITIVITY (%)		SPECIFICITY (%)		ACCURACY (%)	
	DIP-2D	Dip-2D + CFR	DIP-2D	Dip-2D +CFR	DIP	Dip-2D + CFR
Rigo et al, Am J Cardiol 2003	74	90	91	94	82	93
Lowenstein et al, JASE 2003	69	87	91	73	81	80
Nohtomi et al, JASE 2003	72	93	95	70	82	83
Chirillo et al, AJC 2004	67	93	91	93	71	93
Ascione et al, Int J cardiol 2004	51	83	96	98	78	94
	67 ± 9	90 ± 3	93 ± 2	86 ± 12	79 ± 5	89 ± 7

Cardiovasc Ultrasound 2005;3:8

CFR in stress-echo lab

- Represents the best choice in echo-lab evaluation of the flow-function relationship

  CFR adds information on WMAs which is of high diagnostic accuracy and strong prognostic power.

- CFR can be especially helpful for mid-mod stenosis (capable of reducing CFR, but to subischaemic levels)

- Identifies patients with microvascular disease

CFR with high-dose dipyridamole in pts with ACS

- In pts recovering after an ACS, analysis of the myocardial wall motion during DSE is widely accepted for risk-stratification, identifying those who need to have an angio *(decreasd sensitivity because of antianginal treatment)*

- CFR is feasible and safe adding information

Ascione L; 2005

CFR to assess dysfunction of coronary microcirculation

- HTN
- DM
- Hypercholesterolemia
- Syndrome X
- AoV Disease
- HOCM
- Idiopathic Dilated CMP

CFR to assess dysfunction of endothelial function

- Before and 5 hours after high and low fat meals
- Effects of passive smoking
- Effect of red wine

Has been shown to be of prognostic significance

- May be reversible!!

Pellikka P: JASE 2004;17,700-

CFR response to LAD stending and its value in predecting Coronary Restenosis

- Immediately after percutaneous intervention may not adequately reflect expected improvement in CFR because of transient ischaemia/ microvascular stunning
- Several days after the intervention may provide a more accurate information on coronary hemodynamics.
- For serial follow up of treated patients.
- Despite successful stenting CFR impairment occurs in a large proportion of pts (extent of atherosclerotic coronary disease)

Tsutsui J: JASE 2003;16,469-75

The prognostic impact of CFR in non-ischaemic dilated CMP

- Reduced CFR is a marker of impaired coronary microcirculation.
- The abnormal CFR in DCM is related to an increased incidence of cardiac mortality, independent of the degree of LV functional impairment and the evidence of overt HF
- Dip-SE
- Aggressive treatment

Rigo F: EHJ 2006;27,1319-23

Prognostic role of CFR

- In pts with CAD, without WMAs but impaired CFR, this is a negative predictor

Circulation 2004;110:511-7

- In pts who underwent PCI after AMI, impaired CFR is a negative predictor

Am J Cardiol 2003;90:522-6

- In pts with microvascular dysfunction such as Dilated CMP and HOCM impaired CFR is a negative predictor

(important guide to the efficient management)

JACC 2004;44:1627-33

Problems of CFR

- According to the model of Hoffman the highest CFR is that measurable in the subepicardial layer of myocardium

  (in humans only total reserve is determined)

  The reduction of global CFR from 4.0 to 2.0 could be associated with the loss of flow reserve in a part or all of the subendocardial layer of the myocardium.

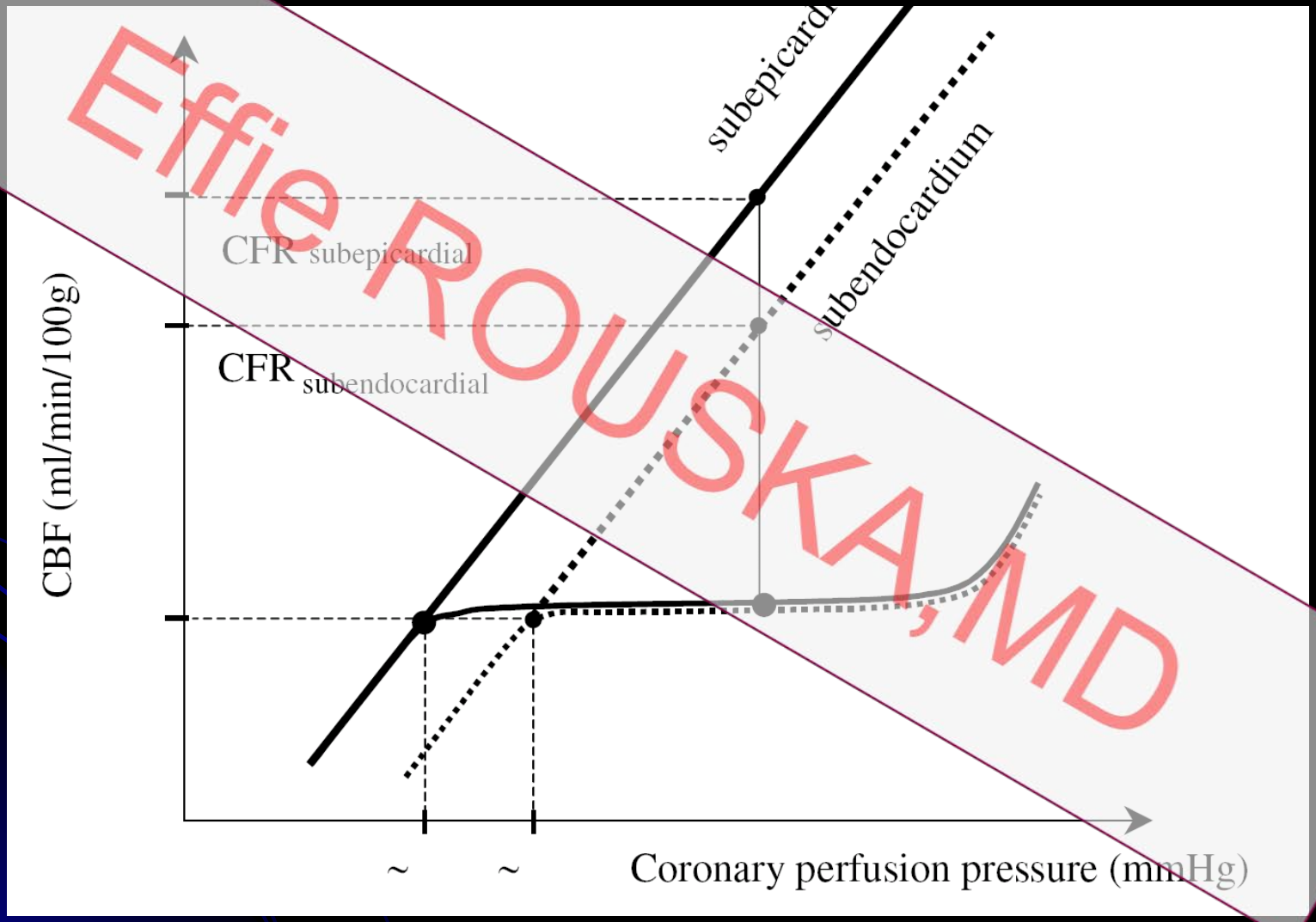
- Spatial Heterogeneity of CFR across the myocardial wall

  Small ischaemic regions??

- Maximal flow is achieved by giving either a maximal dose of vasodilator or by examining the peak reactive hyperemia- evidence provided that both these approaches are flawed.

Transmural Distribution of CFR

CFR subepicardial > CFR subendocardial



Cardiovasc Ultrasound 2005;3:18-27

New Horizons for CFR

- Relationship between DSE WMAs and CFR in Heart Transplant Pts without Angiographic CAD

- Regional Reserve esp in small subendocardial regions

- Determine what mechanisms govern maximal coronary vasodilation and how this can be evaluated and tested in humans

CONCLUSIONS

Prof. Grimm
Cleveland Clinic, USA
Oct 2007

"CFR is
an echocardiography examination
highly useful clinically and
cost-effective
in diagnosis and treatment
of IHD"

Life is short,
science is so long to learn,
opportunity is elusive,
experience is dangerous,
judgment is difficult

Hippocrates – Aphorisms (c.415BC)

Thank you