Coronary Syndromes

Clinical Aspect

G. Specchia
CORONARY SYNDROMES

CHRONIC CORONARY SYNDROMES
- Chronic Stable Angina / Silent Myocardial Ischemia
- Dilated Post-ischemic Cardiomyopathy
- Asymptomatic, non-ischemic Post-MI
- Patients who underwent revascularization procedures and are asymptomatic and non ischemic
- Syndrome X
- Vasospastic Angina (remission phase)

ACUTE CORONARY SYNDROMES
- Acute Myocardial Infarction (STEMI)
- NSTEMI - Unstable Angina
- Vasospastic Angina (active phase)
- Tako-Tsubo Syndrome
- Sudden Coronary Death
In US ~10.000.000 Pts with Chronic Stable Angina (out of 305.000.000 inh.)

10-20% > 65 years old

In Italy ~ 12.000.000 ≥ 65 years old
1.200.000-2.400.000 Pts with Chronic Stable Angina
ACS admitted to Hospital in three Regions of Northern Italy (Emilia Romagna, Lombardia and Friuli VG)

(IN-ACS OUTCOME- Registry)
The Most Important clinical difference between Acute and Chronic Coronary Syndromes is in the outcome
Mortality in pts with chronic stable angina on medical terapy

% x year

Framingham: 4
VA: 4.2
Europ Coll. Study: 2.5
Cardiac Event x Year pts with Chronic Stable Angina on Medical Therapy

- Death or fatal MI

Italian OD1 1982
COURAGE Trial 2007
In-Hospital Mortality of Pts with ACS admitted to Hospital in three Regions of Northern Italy (Emilia Romagna, Lombardia and Friuli VG)
Trials in Unstable Angina
Combined end-point on Placebo

- Essence
- Fraxis
- Miracle
- Paragon
- Azacs

1 mo  3 mo  16 we  1 mo  6 mo
Physiopathology

- Genetic Determinants
- Risk factors and endothelial dysfunction
- Atherosclerotic plaque
- Vessel remodelling
- Thrombosis
- Vasospasm and Vasoconstriction
- Aggressive Neo-intimal proliferation
- Intra-plaque bleeding
- Inflammation
- Mechanical wall stress
- Plaque rupture
The severity of coronary stenosis doesn’t correlate with subsequent coronary occlusion

Ellis S, JACC 1988
Ambrose JA, JACC 1988
Little WC, Circulation 1988
Hackett D, Europ. Heart J 1988
Berder V, Europ. Heart J 1991
Giaraud D, Europ Heart J 1991
Onset of pain in pts with Acute Myocardial Infarction

Specchia et Al, 1982
Clinical History of 103 pts with Unstable Angina

G. Specchia, Cardiologia 1982
• Progressive Narrowing of Coronary Lumen

• Acute Coronary Artery Occlusion

• Development of Collateral Circulation
Athero Process
Collateral Circulation
Plaque Instability
Coronary Occlusion
Small MI
Nothing
Unanswered questions

• Real correlations between known risk factors and presence/severity of CAD
• Identification of strong genetic determinants in the development of CAD
• The severity of stenosis or its functional consequences: the same information?
• Feasible methods to identify vulnerable plaques
• Which is the real trigger of inflammation and instability
Unanswered questions

• The frequent discrepancy between the time of reperfusion and severity of subsequent scar in pts with AMI: only due to amount of collateral circulation?
• Anginal syndromes in Pts without angiographic evidence of coronary disease
• Gender related characteristics of CAD
• Is CAD regression possible?
THE END
Today’s Problems in trans-catheter Revascularization

- CABG or STENTING for LM or 3-vessel disease?
- Opening chronic total occlusion?
- The best TIME for treating Ischemic Related Artery in ACS
- Antithrombotic therapy and Excess of Bleeding
- Late STENT Thrombosis, in particular with DES
- Keeping the success of revascularization with the Time
- Revascularization improves quality of life: does Revascularization prolong also survival?
- Is there a future for stem cells in pts with advanced coronary disease? in pts with LV disfunction?
Occurrence of ACS in pts with stable angina

228 pts with stable angina on medical therapy
120 ± 9 months follow up

28 pts with ACS (12%)
Invasive vs. Conservative Strategies in UA/NSTEMI

- TIMI IIIB 1 year (p = 0.42)
- VANQWISH 1 year (p = 0.025)
- MATE 2 years (p = 0.6)
- FRISC II 1 year (p = 0.005)
- TACTICS-TIMI 18 6 months (p = 0.0498)
- VINO 6 months (p < 0.001)
- RITA-3 1 year (p < 0.007)
- ICTUS 1 year nonfatal MI (p = 0.005) death (p = 0.97)

UA = unstable angina; NSTEMI = Non-ST-elevation myocardial infarction
Today’s Problems in Surgery

- Ventricular Remodelling associated or not with CABG
- Surgery in pts on Clopidogrel IIb/IIIa long infusion?
ISCHEMIC VALVE DISEASE

Clinical Aspects

G.Specchia
Ischemic Mitral Regurgitation

- Mitral Insufficiency as a result of myocardial infarction or ischemia (papillary muscles damage and/or changes in left ventricular geometry and remodeling)
- By definition Mitral Leaflets are normal.
Ischemic Mitral Regurgitation Prevalence

- Increasing Survival in Ischemic Heart Disease → Increasing number of pts with IMR
- 15-50% of pts with AMI develop systolic murmur or ECHO findings of MR
- 10-20% of pts with chronic symptomatic CAD have MR, often moderate (~7%) or severe (~4%)
Ischemic Mitral Regurgitation

• ACUTE IMR: papillary muscle rupture (rare 1-5% of death in AMI) with mitral leaflets prolapse;
  • Annular dilatation
  • Discoordination of normal syncronous papillary muscle contraction: infarcted Papillary Muscle elongation while uninfarcted Papillary Muscle contracts earlier and vigorously

• CHRONIC IMR: Left Ventricle Remodeling, Annular dilatation, Papillary Muscle fibrosis and atrophy, with leaflet tethering and restriction of leaflet motion
  • Mitral Valve prolapse (Rare, probably antedate)
Mechanism of Functional MR

Normal Mitral Valve

- LV
- Papillary Muscle
- Chordae
- Mitral Annulus
- AO
- LA

Functional Mitral Regurgitation

- LV (Ischemic LV Distortion)
- Papillary Muscle Displacement
- Tethered Chordae
- Restricted Leaflet Closure
- Annular dilation
- AO
- MR
Ischemic Mitral Regurgitation
Clinical Presentation

- **ACUTE IMR:** Acute MI (more often Inferior Acute MI due to the fact that the blood supply to the PM papillary muscle depends on one CA) associated with Hemodinamic instability, Pulmonary Edema and Cardiogenic Shock. High Mortality Rate
- Olosystolic or mid-late systolic murmur
- ECG: Inferior MI, but often non specific changes (BBB, T wave changes)
- ECHO: Normal Left atrium associated with MR
- Often sub-endocardial infarction in autopsy series
- DD: Post-MI V Septum defect, Chordal Rupture without MI
Ischemic Mitral Regurgitation
Clinical Presentation

• CHRONIC IMR: Clinical findings depend from:
  • The occurrence and severity of myocardial ischemia
  • The degree of valvular insufficiency
  • The severity of left ventricular dysfunction
  • The response to physical effort
Apical Four-Chamber View Showing Color-Flow Doppler and Proximal Flow-Convergence Fegion at Rest and During Exercise in a Patient with a Large Exercise-Induced Increase in MR

Rest

Exercise

$r = 0.55 \text{ cm}$

$r = 1.11 \text{ cm}$
Kaplan-Meier Curves of Cardiovascular Survival in Patients with (n=141) and without (n=586) MR (multivariate P=0.0022)
# Impact of Mitral Regurgitation (MR) on Long-term Survival After Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th></th>
<th>No MR</th>
<th>Mild (MR Grade 1)</th>
<th>Moderate (MR Grade 2)</th>
<th>Severe (MR Grade 3-4)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year actuarial survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>92.3%</td>
<td>84.5%</td>
<td>74.6%</td>
<td>68.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF ≤40%</td>
<td>75.7%</td>
<td>66.9%</td>
<td>53.7%</td>
<td>46.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF &gt;40%</td>
<td>93.5%</td>
<td>89.6%</td>
<td>82.2%</td>
<td>86.5%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction

Ellis SG, AmJCardiol 2002
F Grigioni et Al, JACC 2004
Events (Death or CHF)

F Grigioni et al, JACC 2005
ERØ, mm²

- ≥20
- 1-19
- 0

P<0.0001

Events: CHF or Cardia Death

Years

F Grigioni et Al, JACC 2004
Multivariate predictors of one-year mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Intervals</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild mitral regurgitation</td>
<td>2.40</td>
<td>1.31 - 4.42</td>
<td>0.005</td>
</tr>
<tr>
<td>Moderate or severe mitral regurgitation</td>
<td>2.82</td>
<td>1.34 - 5.92</td>
<td>0.006</td>
</tr>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.00 - 1.06</td>
<td>0.031</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.59</td>
<td>0.95 - 2.68</td>
<td>0.080</td>
</tr>
<tr>
<td>Killip class &gt; 1</td>
<td>1.75</td>
<td>0.96 - 3.14</td>
<td>0.060</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.65</td>
<td>0.97 - 2.81</td>
<td>0.064</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.53</td>
<td>0.30 - 0.94</td>
<td>0.031</td>
</tr>
<tr>
<td>Three vessel disease</td>
<td>1.85</td>
<td>1.07 - 3.19</td>
<td>0.028</td>
</tr>
<tr>
<td>Creatinine clearance &lt; 60</td>
<td>2.26</td>
<td>1.19 - 4.30</td>
<td>0.013</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.94</td>
<td>0.92 - 0.96</td>
<td>0.001</td>
</tr>
</tbody>
</table>

• In AMI acute MR can cause early death (1-5% of deaths).
• MR represent a frequent complication in survivors after AMI. Early after MI 15-50% of pts show systolic murmur, which in many pts disappears by the time.
• In pts who undergo PPCI ~ 20% have MR which persists after the acute phase, in others MR may develop later.
• Pathological changes that lead to acute or chronic IMR are multiple, involving LV remodelling, annular dilatation, papillary muscle displacement, dysfunction or rupture, chordal thetering, leaflet prolapse or restriction
• Lysis and PPCI did not change significantly the frequency of post-MI MR. In fact the improved survival in pts with AMI has resulted in increasing number of pts with post-MI chronic MR and subsequent LV dysfunction and HF.
• Post-MI pts with MR have a poorer prognosis in comparison with post-MI pts without MR
• Waiting for an effective and applicable, catheter-based percutaneous approach, surgery (urgent or elective) represents in most of the cases of IMR the only therapeutic strategy available today
END
Trials in ACS (UA or NSTEMI)
Combined end-point in Conservative Arms
One-year survival stratified by the severity of baseline mitral regurgitation

Impact of randomization to stenting versus balloon angioplasty (pooled regardless of abciximab administration), and to abciximab versus no abciximab (pooled regardless of stent use) on one-year mortality as a function of the severity of baseline mitral regurgitation

All subjects: $r^2 = 0.10$, n.s.  
Group 1: $r^2 = 0.33$, $P < 0.01$

All subjects: $r^2 = 0.64$, $P < 0.001$  
Group 1: $r^2 = 0.59$, $P < 0.001$
Changes in tenting area (cm²)

Changes in ERO (mm²)

$\text{r} = 0.85$

P. Lamcellotti et Al, JACC2003
Cardiac Rupture
Clinical Aspect

G. Specchia
Left Ventricle Rupture

Infrequent complication (2-4%)

High Mortality (5-24% of all in-hospital deaths)
Left Ventricle Rupture
Clinical Characteristics

• Age > 55 years – Women vs Men
• First transmural MI
• Killip class I or II
• Persistent S-T elevation
• Persistent or Recurrent Chest Pain
• Sudden or Progressive Hypotension
• Sudden E-M Dissociation
Left Ventricle Rupture
Factors Facilitating

- Extension of MI
- Early MI Expansion
- Left Ventricle - Anterior MI – LAD area
- Delayed Hospital Admission
- Persistent Arterial Hypertension
- Agitation, Unusual effort, Cough, Repetitive vomiting
- Not on beta-blocker
- Left Ventricle Hypertrophy (conflicting data)
- Poor Collaterals
During the reperfusion era the frequency of acute cardiac rupture has declined. Left ventricular free wall rupture occurs in less than 2% of cases, Left ventricular septum or papillary muscle rupture in less than 1% of cases. Fibrinolytic therapy more than 14 hours after onset of symptoms represents a risk factor. The most important determinants in preventing rupture are successful early reperfusion. The highest risk is within the first 24 hours after MI.
1978–1989 (n = 149)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Pts with Rupture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1975/89</td>
<td>1990/95</td>
</tr>
<tr>
<td>Admission delay 24 h</td>
<td>81 (8%)</td>
<td>58 (38.9%)</td>
</tr>
<tr>
<td>In-hospital angina</td>
<td>120 (11.9%)</td>
<td>28/52 (53.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36/62 (58.1%)</td>
</tr>
</tbody>
</table>

JFigueras JACC 1998
In Hospital Deaths in AMI pts treated with thrombolysis

Mauri F et Al, G.It Cardiol 1987
Multivariable analysis of patients treated with Thrombolytic agents, experiencing cardiac rupture

RC Becker et Al, JACC 1999
Primary Angioplasty Versus Systemic Thrombolysis in Anterior Myocardial Infarction

Garcia E, Circulation 1999
Early Deaths due to Cardiac Rupture

- TIMI II 1992
- GUSTO 1994
- KHAN 1990
- BRODIE 1997

% early deaths due to cardiac rupture

Lysis
PPCI
% of Post-MI Angina in PTS with Septal, Free Wall or Papillary Rupture

Figueroas, JACC 1998
% of Patients with Cardiac Rupture and Nr of Vessel Diseased

Number of vessels (>70%)

Patients, %

- 1 vessel: FWR 77 (58), SR 67 (57), PMR 24 (46)
- 2 vessels: FWR 77 (38), SR 67 (33), PMR 24 (29)
- 3 vessels: FWR 77 (4), SR 67 (10), PMR 24 (25)

p<0.05

J Figueroas Jacc 1998
% of Pts with Cardiac Rupture and IRA

J Figueroas Jacc 1998
Left Ventricle Rupture
Clinical Presentation

• ACUTE: Acute Tamponade with Hypotension- Cardiogenic Shock - Electro-mechanical Dissociation

• SUB-ACUTE: Moderate to Severe Pericardial Effusion with or without Cardiac Tamponade and Hemodynamic Progressive Deterioration
Silent Subacute Free Wall Rupture

- No hemodynamic compromise
- Pericardial effusion identified on a routine ECHO
- Attribution to a peri- or post- MI pericarditis
- Initial healing by fibrin deposit and subsequent definite healing

- Delayed development of pseudo-aneurism
- Re-rupture, cardiac tamponade and Death
Cardiac Rupture in Pts treated with Thrombolytic Agents

F Mauri et Al, G. It. Cardiol 1987
Multivariable analysis of patients with non-rupture-related death

RC Becker et al, JACC 1999