AMERICAN COLLEGE OF EMERGENCY PHYSICIANS
SCIENTIFIC ASSEMBLY
1999

Cardiology Exposés: An Interactive Point/Counterpoint Discussion of Angioplasty, Serum Markers of Ischemia, IIb/IIIa Inhibitors, and Chest Pain Centers

Considerable controversy exists regarding the initial diagnosis and treatment of myocardial ischemia and infarction. This two-hour course will use a point/counterpoint format to discuss several of these issues. Two lecturers will present opposing views on the topics of thrombolysis versus angioplasty, the use of new serum markers in the emergency department evaluation of chest pain, current indications for use of IIb/IIIa inhibitors, and the efficacy of chest pain centers. The audience will have time after each discussion to ask questions.

- Develop an informed opinion on the use of thrombolysis versus angioplasty, new serum markers of ischemia in the emergency department, IIb/IIIa inhibitors, and chest pain centers.

WE-122
Wednesday, October 13, 1999
8:00 AM - 9:55 AM
Room # N247
Las Vegas Convention Center

*Michael J Bresler, MD, FACEP
Honoraria: Genentech, Inc.

FACULTY

William K Mallon, MD, FACEP (Moderator)

Associate Professor/Director of Residency Training, Department of Emergency Medicine, Los Angeles/University of Southern California Medical Center, Los Angeles, California

*Michael J Bresler, MD, FACEP

Clinical Professor, Surgery, Division of Emergency Medicine, Stanford University School of Medicine, Palo Alto, California; Chief, Department of Emergency Medicine, Mills-Peninsula Hospitals, San Mateo, California

Mel Herbert, MBBS (MD) BMedSci, FACEP

Assistant Professor, Medicine, UCLA School of Medicine; Assistant Professor, Nursing, UCLA School of Nursing, Department of Emergency Medicine, Olive View-UCLA Medical Center, Sylmar, California

Cardiology Exposes: An Interactive Point/Counterpoint Discussion

- *Angioplasty vs. Thrombolysis for Acute Myocardial Infarction*
- *Serum Markers of Myocardial Ischemia*
- *Platelet Glycoprotein IIb/IIIa Inhibitors*
- *Chest Pain Centers*

Michael Jay Bresler, M.D., FACEP

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY vs. THROMBOLYTIC THERAPY FOR ACUTE MYOCARDIAL INFARCTION

The Problem

- Thrombolytic therapy (TBL) lyses the acute clot, but the underlying atheromatous lesion is still present.
- This can be addressed by either PTCA or CABG.

The Question

- Why not treat the clot and the atheroma at the same time with PTCA?

The Problem

- The complication rate is higher with immediate PTCA following successful pharmacologic thrombolysis, vs. delayed PTCA several months later after the vessel has healed.

Rogers WJ, et al. *Circulation* 1990;81:1457-1476 (TIMI 2).

The Question

- Why not skip the thrombolytic drug and go directly to PTCA?

The Answer ??

Several small studies yielded contradictory results.

Zijlstra F, et al. *N Engl J Med* 1993;328:680-684.
Gibbons RJ, et al. *N Engl J Med* 1993;328:685-691.

PAMI : Moderate size study: 395 patients treated within 12 hours of pain onset

Conclusion :

- Immediate PTCA reduced combined endpoint of nonfatal reinfarction or death.
- Lower rate of intracranial hemorrhage, with similar LV function.

Grines CL, et al. *N Engl J Med* 1993;328:673-679.

However:

- PAMI used the old 3 hr. regimen of tPA.
- PAMI did not show statistically significant lower mortality or statistically significant lower reinfarction with PTCA.
- Only when both mortality and reinfarction were combined did the difference reach statistical significance.
- PAMI demonstrated benefit from PTCA only in the subgroup > age 65. Pts. < 65 had no difference in either mortality or reinfarction.
- Time to treatment was superb in PAMI - and not attainable in most hospitals.

GUSTO IIb:

A larger study comparing t-PA with PTCA
1,138 patients within 12 hrs of symptom onset
1^0 endpoint -> *either* death, nonfatal reinfarction, *or* nonfatal disabling stroke at 30 days.

Result: 13.7% with t-PA & 9.6% with PTCA (p=0.033)

However:

- No statistically significant difference with any of the 3 components when considered individually, though the trends favored PTCA.
- And at 6 months, no difference for even the 1^o composite endpoint .

Authors' conclusion:

PTCA provides small-to-moderate, short-term advantage when it can be performed promptly at experienced centers.

GUSTO IIb investigators. *N Engl J Med* 1997;336:1621-1628

A Meta-Analysis

Review of 10 randomized trials comparing PTCA with various TBL drugs using various treatment regimens. The 10 studies were subgrouped according to the drug and regimen utilized.

Results:

PTCA superior to pharmacologic thrombolysis at 30 days in terms of:

- Death
- Death *or* nonfatal reinfarction
- Total stroke & hemorrhagic stroke

However:

- The standard 90-min. infusion of t-PA was utilized in only: 3 of the 10 trials, comprising 1,410 of the 2,606 patients, 1,138 of whom were the GUSTO IIb patients !
- Thus, of the 2,606 patients, only 272 were relevant to t-PA and not included in the GUSTO IIb results: one trial with 83 patients, the other with 189.

- For these 1,410 pts. treated with standard t-PA regimen, the odds ratios (95%CI) crossed one for death and for combined death or nonfatal reinfarction. (This was true even for the GUSTO IIb patients.)
- Mortality was lower for PTCA only for the entire population of 10 trials. *No* treatment subgroup alone demonstrated statistically significant mortality reduction with PTCA.
- Combined mortality or nonfatal reinfarction was significantly lower for PTCA in each subgroup, but the effect was much less in the standard t-PA subgroup.
- According to the authors:
  "None of the individual [10] trials has been large enough to evaluate adequately death or death and nonfatal reinfarction as a primary end point."

Thus, it took a meta-analysis on 10 trials - each without statistical significance - to show a significant advantage of PTCA in terms of either mortality or combined endpoint of mortality or nonfatal reinfarction.

Weaver WD, Simes J, Betriu A, et al. *JAMA* 1997;278:2093-2098.

MITI Registry

However a very large study by Every et. al. yielded other results.
2,145 patients vs. 395 in PAMI and 1,138 in GUSTO IIb.

- Higher in-hospital stroke rate with TBL: 1.5 % vs. 0.7 %, but
- No difference in in-hospital mortality: 5.6 vs. 5.5 ($p = 0.93$)
- No association of TBL with long term (3 yr) mortality
  - even when hemorrhagic & other complications of TBL considered
- No difference in reinfarction rate: 4.3 % vs. 3.5 % ($p = 0.37$)
- Subgroup analysis: No significant difference in mortality during acute hospitalization or after 3 years in any of the following subgroups:
  - Patients eligible for TBL
  - Patients treated in high volume hospitals
  - Patients classified as high risk according to PAMI trial criteria
- Total cost was lower with TBL - both inhospital as well as after 3 years.
  - Mean total initial hospital costs: $16,838 vs. $19,702.
  - Mean total cumulative inpatient costs at 3 years: $22,163 vs. $25,459.

Conclusion: No advantage of PTCA over thrombolysis with either tPA or streptokinase.

Every NR, et al. *N Engl J Med* 1996;335:1253-60.

NRMI-2 REGISTRY

Very large analysis by Tiefenbrunn of 2nd National Registry of Myocardial Infarction data
>1,000 hospitals, 29,644 patients: 4,939 PTCA, 24,705 t-PA

In-hospital mortality was no different.

Stroke was of course more common with t-PA, esp. in elderly > 75.
But combined end-point of death or nonfatal stroke was the same, as was the rate of reinfarction
In-hospital mortality rate for PTCA was identical to that in GUSTO IIb, and mortality rate for t-PA was comparable to that in other trials using standard 90 min regimen with aspirin & IV heparin.

NRMI-2 Data: June 1994-Oct 1995.
Tiefenbrunn AJ, Chandara NC, French WJ, et al. *J Am Coll Cardiol* 1998;31:1240-1245.

Why are the results from the two large registries (MITI & NRMI-2) different from those of the smaller PAMI and GUSTO IIb studies?

The registry patients were not prospectively selected by investigators doing a study. The registry papers are retrospective analyses of patients treated in the real-world community of 19 Seattle hospitals (MITI) and over 1,000 U.S. hospitals (NRMI). There was no study artifact (Hawthorne effect). They reflect the "real world".

Does time matter?

6-week mortality rises with time to treatment from 1 to 4 hours.
Rogers WJ, et al. *Circulation* 1990;81:1457-1476. (TIMI-2)

30-day mortality rises with time to treatment from 0-2, through 2-4, to 4-6 hours
Topol EJ, et al. *N Engl J Med* 1994;33(4) and 331(10).(GUSTO)

Very early treatment within 70 minutes is associated with much lower mortality and infarct size and with higher ejection fraction, when compared with treatment begun between 70-180 minutes after symptom onset.

Weaver WE, et al. *JAMA* 1993. (MITI)

Time also matters with PTCA. Inhospital mortality rises as time to treatment increases from less than 2 hours, through 2-6 hours, to greater than 6 hours.
O'Keefe, et al. *Am J Cardiol.* 1989;64:1221-1230.

The "Real World" : from the National Registry of Myocardial Infarction

Times to PTCA

Non-transferred patients: Door to balloon = 115 min. (83,163) *
- half took longer than 115 (1 hr, 55 min)
- one quarter took longer than 163 (2 hrs, 43 min)

Transferred patients: First hospital door through transfer to balloon = 239 (4 hrs)

* Median time in minutes (25th, 75th percentiles)

NRMI 2 Data : June 1994-Dec. 1995. Patients with elevated ST segments or LBBB on ECG

Times to Thrombolytic Therapy

Non-transferred patients: 39 min. (25,60) *
Transferred patients:
Therapy initiated at 1st hospital = door to drug: 42
Therapy initiated at 2nd hospital = 160 (2 hrs, 40 min)
1st hospital door to 2nd hospital door = 110
2nd hospital door to drug = 50

* Median time in minutes (25th, 75th percentiles)

NRMI 2 Data : Oct. 1995 - Sep. 1996. Patients with elevated ST segments or LBBB on ECG
n = 93,22

Influence of time to PTCA from NRMI-2 data. n = 3,648

Mortality increased by nearly 50% if time > 2hrs vs. < 2hrs.
53% of pts presenting within 6 hrs of pain onset had door-to-balloon time >2 hrs
Cannon CP, et al, *J Am Coll Cardiol* 1996;27:Suppl A:61A. abstract. n = 3,648

When comparing times, the following must be considered:

Reperfusion occurs *during* the infusion with thrombolysis.
Many vessels open prior to the end of the 90 min. infusion.
Reperfusion with PTCA occurs only at the time of balloon *deflation*.

Advantages of PTCA

- Higher rate of reperfusion: 90 % vs. 75-85 % with tPA (55-60 % with SK)
- Higher chance of TIMI Grade 3 patency
- Single stage procedure: clot and plaque addressed at same time
- Greater efficacy with cardiogenic shock
- Fewer contra-indications

Disadvantages of PTCA

- TIME to balloon is greater than for thrombolysis
- 10% of vessels studied are not amenable to PTCA but might already have been reperfused with thrombolytic agents
- Fewer than 20% of US hospitals have angioplasty capability.
- Cardiac surgery standby is required for immediate treatment of coronary artery dissection or rupture, or for vessels not suitable for angioplasty
- Highly operator dependent
  A statistically significant decrease in major complications is seen in labs performing more than 400 procedures per year (Kimmel) *
- Cost +

* Kimmel SE, et al. *JAMA* 1995;274(14):1137-1142.
+ Every NR, et al. *N Engl J Med.* 1996;335:1253-1260.

Time Delays with PTCA

While many of the actions to be taken are similar for thrombolytic therapy and for PTCA, the latter requires a number of additionaltime-consuming actions.

- The cath team must be assembled

- The patient transported to the lab (or transferred to another hospital, re-evaluated, and then transported to the lab)

- The infarct artery catheterized
- An angiogram performed
- The balloon inflated
- The balloon deflated.

Only after all of this has been accomplished, does reperfusion occur.

Advantages of pharmacologic thrombolytic therapy

- TIME: door to treatment of 30-60 min
- Availability: every hospital

Disadvantages of pharmacologic thrombolytic therapy

- Hemorrhagic risk, especially stroke
- Lower rate of reperfusion
- Lower rate of TIMI Grade 3 patency
- Angiography & often PTCA or CABG must be performed at later date

Conclusions

1. PTCA is more effective (especially in cardiogenic shock) and safer (especially with age >75) than pharmacologic thrombolytic therapy - *if performed rapidly.*

2. Thrombolysis occurs during the drug infusion but must await balloon inflation/deflation with PTCA.

3. In the “real world”, PTCA is usually not available.

4. Even when f PTCA is available, time delays are very frquently excessive, in which case pharmacologic thrombolysis is superior.

How much time is acceptable ?????

Initiate thrombolytic therapy within 30-60 minutes of ED arrival.

Alternatively, begin PTCA within 60-90 minutes of ED arrival.

If inter-hospital transfer, initiate thrombolytic therapy prior to transfer unless total time from first hospital arrival to PTCA is < 90 minutes

Balloon inflation/deflation should be achieved by the time the thombolytic infusion would have been completed.

T I M E M A T T E R S

THROMBOLYTIC DRUG *PLUS* ANGIOPLASTY

tPA Followed by PTCA

The advantage of thrombolytic drugs is speed.
The disadvantage is lower patency rate, both partial & complete (TIMI grades 2 & 3).

The advantage of PTCA is higher patency, especial complete (TIMI 3).
The disadvantage is time delay.

Why not combine both?

> Because TIMI and other studies showed no advantage - and a higher complication rate - for *immediate* PTCA following successful thrombolysis.

What about immediate PTCA if thrombolytic therapy is unsuccessful or achieves only partial patency?

Plasminogen Activator Angioplasty Compatibility Trial (PACT)

606 patients at 10 centers: half received 50 mg bolus of tPA, half placebo bolus.

All underwent immediate angiography.

> If TIMI 3 flow -> 2nd 50 mg bolus of tPA given.
> If TIMI 0,1, or 2 flow -> immediate angioplasty

Follow-up: angiogram at 5-7 days & exercise tolerance test at 6 weeks.

Results

Time to treatment (hours):

Pain to bolus Rx:	2.7
Bolus to Angiogram	0.85
Angiogram to PTCA	0.95

Time to achieve TIMI 3 patency (minutes):

tPA	51
PTCA	93

Patency on cath lab arrival (%)

	TIMI 3	TIMI 2	Total
tPA	28	33	61
Placebo	20	15	35

All comparisons $p < 0.001$
Note that only 1/2 the usual dose of tPA was given.

Final patency on leaving cath lab

	TIMI 3	TIMI 2	Total
tPA	79	17	96
Placebo	78	16	94

No difference in any adverse event, including major bleeding or stroke.

LV function: Global ejection fraction, regional motion, & # of pathologic cords:

All measurements significantly Improved if TIMI 3 achieved by time of cath lab arrival.
If TIMI 3 patency achieved only after PTCA, still better result than if not. ($p < 0.001$ for all measurements above)

Time delay: Global ejection fraction & number of pathologic cords:

Both measurements significantly worse if > 1 hour delay in achieving TIMI 3 flow between cath lab arrival and PTCA. ($p < 0.03$ & 0.05)

Limitations of trial:
Dosing of tPA might not be optimal.
Trial environment may be different than in average hospital.
Newer technologies not specifically accounted for (stenting, IIb/IIIa platelet inhibitors, etc.)

Conclusion from preliminary PACT data:

"Treatment with a 50 mg bolus of tPA produced a significant infarct artery patency rate achieved even prior to cath lab arrival.

"The technical success of PTCA was not diminished by pre-angioplasty thrombolytic therapy.

"There was no increase in complications associated with bolus tPA administration."

Reference

Lundergan CF, Reiner JS, Coyne KS, et al. Effect of delay of successful reperfusion on ventricular function ountomce; The case for prior thrombolytic therapy with PTCA in acute myocardial infarction. *Circulation* 1998;89:1-281. Abstract. (Full article to be published summer 1999.)

SERUM MARKERS IN THE DIAGNOSIS OF MYOCARDIAL INFARCTION & ISCHEMIA

Myocardial damage causes leakage of intracellular enzymes into the general circulation. Unfortunately, this takes time. Serum enzyme levels are thus often normal early in the course of acute MI (AMI), thereby lowering sensitivity.

Many of these enzymes are also found in other tissues, thus lowering specificity.

The ideal enzyme would maximize both sensitivity and specificity, be rapidly measurable - and most importantly for use in the ED - rise rapidly after onset of symptoms.

A number of cardiac enzymes are available,
and some of them can be assayed by different methods.

SGOT & LDH

These were among the first enzymes to be measured. They are not specific for cardiac muscle and have been replaced by the enzymes below.

TOTAL CK (creatine kinase)

- **formerly called CPK (creatine phosphokinase)**

Total CK has been replaced by its isoenzymes, which are more sensitive & specific.

CK-MB

Total CK and CK-MB may not begin to rise in peripheral blood until 4-8 hours after onset of MI (though sometimes earlier). They peak in 12-20 hours.

The isoenzyme CK-MB is more specific than total CK, is ultimately very sensitive by 14 hours, and has been considered the gold standard for diagnosing MI.

However, neither total CK nor the MB isoenzyme is sufficiently sensitive during the ED phase of care.

A recently developed immunochemical method for determining CK-MB <u>mass</u> has shown increased sensitivity - and shorter laboratory time - compared with the older electrophoretic or column chromatography methods for determining CK-MB <u>activity</u>.

A single CK-MB mass determination is still not sufficiently sensitive to R/O MI in the ED, but rapid turnaround time makes serial testing in the ED feasible.

By 3 hours after ED presentation, serial CK-MB mass testing has a sensitivity of 80% and as specificity of 94%. (1)

False negatives do occur with muscle damage and renal failure, but measurement of CK-MB index (ratio of CK-MB / total CK) improves specificity.

Sensitivity of CK-MB mass is still not sufficient to R/O MI in the ED.

CK-MB ISOFORMS

The CK-MB isoenzyme consists of several subforms (isoforms): $CK\text{-}MB_1$ and $CK\text{-}MB_2$.
$CK\text{-}MB_2$, normally in the cytosol, is released into the bloodstream after myocardial damage, where it is eventually converted to $CK\text{-}MB_1$.

$CK\text{-}MB_2 > 1$ or a ratio of $MB_2 / MB > 1.5$, indicates AMI.
This ratio changes before CK-MB begins to rise, and thus allows earlier detection.

In one study, sensitivity for AMI was 8% by 2 hours of symptom onset, 56% by 4 hours, and 96% by 6 hours. Specificity at 6 hours was also 96%. (2)

However, this study compared isoforms to the older activity assay for CK-MB, rather than the more sensitive and more specific CK-MB mass assay.

Nevertheless, the sensitivity of CK-MB isoform is not sufficient for EM practice.

MYOGLOBIN

An oxygen-binding heme protein, myoglobin is present in all skeletal muscle, and is released into the bloodstream with any muscle damage. It is thus not very specific for cardiac injury.

However, it is released earlier than the other markers, and is thus particularly sensitive during the early hours of AMI.

The serum level of myoglobin may begin to rise as early as 1-2 hours after symptom onset, peaking in 6-9 hours, and normalizing in 24-36 hours. (3,4)

Sensitivity has been measured at 62% on ED arrival, and 100% 3 hours later, with specificity of 80% 3 hours after ED arrival.

TROPONINS I & T

The contractile complex of muscle contains 3 subunits of troponin: C, I, & T. All occur in both cardiac and skeletal muscle, but subforms of T and I are more specific to cardiac muscle (cTnI & cTnT).

Small amounts of cardiac troponin reside in the cytosol and may be released into the bloodstream with ischemia.

Most of the troponin however is structurally bound as part of the contractile apparatus. With infarction, large amounts of troponin are released from the degenerating myofibrils. (5,6)

Like CK-MB, troponins I & T begin to rise about 4-6 hours post symptom onset. But their levels remain elevated up to 5 days (cTnI) or 10 days (cTnT), unlike CK-MB mass, which returns to normal after 48 hours. (5,6)

cTnI is more cardiospecific than for cTnT, but both are very specific. While cTnT may be elevated in renal failure or skeletal muscle injury, cTnI is specific for cardiac events.

Rapid bedside tests using monoclonal antibodies are now available for both cTnI & cTnT.

One study of patients with chest pain <u>without ST segment elevation</u> tested both on ED arrival and 4 hours or more hours later (at least 6 hours post symptom onset). [AMI was defined by >2 x nl total CK with elevated CK-MB at 24 hours.] (7)

Sensitivity (%) by 6 hours after symptom onset

	<u>cTroponin I</u>	<u>cTroponin T</u>
Myocardial Infarction	100	94
Unstable angina	36	70

Sensitivity of cTnT would be higher if patients with ST elevation were included. Elevated troponin was a strong predictor of cardiac events by 30 days.

Elevated troponins are a strong predictor of adverse cardiac events occurring within the ensuing 1-6 months (death, MI, CHF) (8-13)

Elevated troponin with normal CK-MB thus probably indicates microscopic infarction rather than unstable angina. Risk statification based on troponin may suggest vigorous treatment, including heparin, glycoprotein IIb/IIIa inhibitors, angioplasty, stenting, and *possibly* (if proven effective) thrombolytic therapy despite normal CK-MB and nondiagnostic ST segments.

While troponins are very useful because of their specificity and their *eventual* sensitivity, nevertheless in the early hours, they are less sensitive than myoglobin. Thus as with the other tests, troponins are not the ultimate answer for diagnosis of AMI in the ED.

EXPERIMENTAL MARKERS

Elevated C-reactive protein has been found in unstable angina patients with negative troponin T, and has been associated with unfavorable outcome. (14)

The presence of serum malondialdehyde-modified low density liproprotein (MDA) may reflect plaque instabilty. MDA detection with negative troponin may be a marker for unstable angina. Both would be present with AMI. (15)

CONCLUSIONS

No single negative enzyme study is sufficient to rule out AMI in the early hours during the ED phase of care.

New assays for CK-MB mass offer greater sensitivity and specificity compared with the older activity assays.

CK-MB isoform M_2 and the ratio of M_2 / M_1 are also more sensitive and more specific than older CK-MB assays, but they are difficult to perform and no more helpful during the early hours of AMI.

Myoglobin is the most sensitive test early in the course of AMI, but it lacks specificity.

Troponins T & I (especially I) are the most specific tests and can be performed at the bedside. They may become the new gold standard for diagnosing myocardial necrosis. But they rise no faster than CK-MB.

In conclusion, no single test - and no combination of tests - is sufficiently reliable to exclude AMI during the first 6 hours. A combination of myoglobin for sensitivity and troponin I for specificity may be the best test available at this time.

REFERENCES

1. Gibler WB, Young GP, Hedges KR, et al. Acute myocardial infarction in chest pain patients with non-diagnostic ECG's: serial CK-MB sampling in the emergency department. *Ann Emerg Med* 1992;21(5):504-512.

2. Puleo PR, Meyer D, Wathen C. Use of a rapid assay of subforms of creatine kinase MB to diagnose or rule out acute myocardial infarction. *N Engl J Med* 1994;331:561-566.

3. Vaidya HC. Myoglobin. *Laboratory Medicine* 1992;23(5):306-310.

4. Ohman EM, Casey C, Bengston JE, et al. Early detection of acute myocardial infarction. Additional diagnostic information from serum concentration of myoglobin in patients without ST elevation. *Br Heart J* 1990;63:335-338.

5. Adams JE III, Abendschein DR, Jaffe AS. Biochemical markers of myocardial injury: Is MB creatine kinase the choice for the 1990's? *Circulation* 1993;88(2):750-763.

6. Katus HA, Scheffold T, Remppisa A, et al. Proteins of the troponin complex. *Laboratory Medicine* 1992;23(5):311-317.

7. Hamm CW, Goldmann BU, Heeschen C, et al. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med* 1997;337:1648-1653.

8. Hamm CW. "Cardiac-specific troponins in acute coronary syndromes". In Braunwald E. Heart Disease. Update 3. W.B. Saunders 1997.

9. Hamm CW, Ravkilde J, Gerhardt W, et al. The prognostic value of serum troponin T in unstable angnia. *N Engl J Med* 1992;327:146-150.

10. Lindahl B, Venge P, Wallentin L for the FRISC Study Group: Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. *Circulation* 1996;93:1651-1657.

11. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;335:1342-1349.

12. Lindahl B, Andren B, Ohlsson J, et al. Risk stratification in unstable coronary artery disease. Additive value of troponin T determinations and pre-discharge exercise tests. *Eur Heat J* 1997;18:762-770.

13. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratificatin in acute myocardial ischemia. *N Engl J Med* 1996;335:1333-1341.

14. Liuzzo G, Biasucci LM, Gallimore R, et al. The prognostic value of C-reactive protein and serum amyloid: a protein in severeunstable angina. *N Engl J Med* 1994;331:417-424.

15. Holvoet P, Collen D, Van de Werf F. Malondialdehyde-modified LDL as a marker of acute coronary syndromes. *JAMA* 1999;281(18):1718-1721.

PLATELET GLYCOPROTEIN IIb/IIIa INHIBITORS

Pathophysiology

Myocardial infarction is thought generally to occur when a tear in the intimal lining of the vessel exposes underlying collagen, which is thrombogenic. Platelets are attracted to the site and activated -> platelet adhesion -> platelet plugging.

This process triggers the coagulation cascade -> -> thrombin activation -> fibrin clot around a platelet core.

Treatment thus should address both the platelet plug and the fibrin clot.

Thrombolytic agents (STK, tPA, rPA, etc.) attack the fibrin clot already formed. However, fibrin dissolution actually -> increased production of thrombin, a potent platelet agonist. Moreover, activated platelets release large amounts of plasminogen activator inhibitor -> interference with both natural, as well as pharmacologic, plasminogen activators.

Glycoprotein IIb/IIIa inhibitors address the platelet problem by directly attacking the plug already formed, as well as by inhibiting additional platelet aggregation, thereby reducing recurrent thrombosis.

How do these agents work?

Platelet activation ->

- change in platelet shape from smooth to spiculated -> increased surface area for thrombin generation.
- change in conformation of 50,000 Glycoprotein IIb/IIIa receptors on surface of each platelet, converting them from ligand-unreceptive to ligand-receptive state.
- binding of fibrinogen and other ligands to GP IIb/IIIa receptors -> chains of platelets linked together by fibrinogen, forming large plugs (platelet aggregation).
- other ligands bind the platelet plugs to the endothelial surface.

Platelet inhibition

Aspirin and ticlopidine (Ticlid™) interfere with platelet aggregation indirectly and incompletely

GP IIb/IIIa inhibitors block aggregation directly at the endpoint by binding to the ligand receptor sites, thereby preventing them from binding fibrinogen.

Laboratory ADP-induced platelet aggregation is inhibited 10% by aspirin, 30% by ticlopidine and clopidogrel, and 80% by GP IIb/IIIa inhibitors. (1)

Classes of GP IIb/IIIa Inhibitors

Monoclonal antibody: Parenteral agents which bind irreversibly to platelets
abciximab (ReoPro™)
Peptide and peptidomimetic inhibitors: Parenteral agents which bind reversibly
eptifibatide (Integrilin™) tirofiban (Aggrastat™), lamifiban, klerval
Oral agents: Competitive inhibitors
xemilofiban, orbofiban, sibrafiban, fradifiban

Potential Uses for GP IIb/IIIa inhibitors

GP IIb/IIIa inhibitors would theoretically be useful whenever there is damage to the endothelium and/or thrombosis:

- mechanical angioplasty with or without stenting, either elective or emergent, with or without infarction
- unstable angina
- myocardial infarction with thrombolytic agents

Heparin and aspirin would theoretically also be used.

GP IIb/IIIa Inhibitors and Angioplasty

EPIC trial: Abciximab vs. placebo (n=2099)
35% reduction at 30 days in composite of death, MI, or urgent need for revascularization. (2) Continued advantage at 6 months and 3 years. (3)

EPILOG trial: Abciximab with either standard or low dose heparin vs. heparin alone (n=2792)
56% reduction at 30 days in death, MI, or urgent revascularization.
With low dose heparin, no increase in major bleeding. (4)

CAPTURE trial: Abciximab vs. placebo. All received heparin & ASA. (n=1265)
29% reduction at 30 days in death, MI, or urgent revascularization. (5)

Trials with other GP IIb/IIIa inhibitors have yielded mixed results, some showing benefit, others only non-statistically significant trends (6), others no benefit .

GP IIb/IIIa Inhibitors and Stenting

EPISTENT trial: Abciximab vs. placebo. All received ASA & heparin. (n=2399)
With stenting: 51% reduction at 30 days in death, MI, or urgent revascularization
With PTCA alone: 36% reduction (7)

GP IIb/IIIa Inhibitors and Unstable Angina or Non-Q-Wave MI

PRISM trial: tirofiban vs. heparin. All received ASA (n=3231)
36% reduction at 48 hours in composite of death, MI, or refractory ischemia. (8)

PRISM-PLUS trial: tirofiban + heparin vs. heparin alone. All received aspirin. (n=1915)
34% 7-day, and 27% 30-day, reduction in composite of death, MI, or refractory ischemia. (9)

PURSUIT trial: eptifibatide vs. placebo. (n=10,948, 28 countries)
8.35% 4-day, and 9% 30 day, reduction in composite endpoint of death or nonfatal AMI. (10)

GP IIb/IIIa Inhibitors and Myocardial Infarction

As described above, the platelet inhibitors are effective additions to angioplasty in treating acute MI.

Are they useful and safe in conjunction with thrombolytics?

A number of small studies with several agents suggest an additive benefit from combination therapy [TAMI 8 (11), IMPACT-AMI (12), PARADIGM (13)].

TIMI-14 trial: On-going study, but preliminary data are particularly interesting. (14)
1^0 endpoint: 90 minute TIMI grade 3 patency
4 groups:
tPA alone
Abciximab alone
Abciximab + tPA in various doses
Abciximab + SK in various doses
All groups received aspirin and heparin:
tPA alone group: standard dose heparin: 70 U/kg, then 15 U/hr
All abciximab groups: reduced dose: 60 U/kg, then 7 U/hr
Eligibility: ST segment elevation MI within 12 hrs of symptom onset.

Regimen	tPA	Abciximab	SK + Abciximab		tPA + Abciximab	
Abciximab	-	+	+	+	+	+
SK (U x 10^3)	-	-	500	750	-	-
tPA (mg)	100	-	-	-	20	35
TIMI 3 flow	60%	31%	42%	37%	55%	71%
Major Bleed (%)	5	6	6	8	6	0

Conclusion: Combination of abciximab and low dose tPA (plus ASA & heparin) produces a higher rates of TIMI grade 3 patency at 90 minutes than standard dose tPA (plus ASA & heparin) without increased bleeding. Abciximab alone and SK alone (with heparin & ASA) are less effective than either tPA or the combination of tPA + abciximab. [Other doses of SK and tPA are being tested.]

Cautions in the Use of GP IIb/IIIa Inhibitors

The monoclonal antibody abciximab (ReoPro™) binds very tightly to the IIb/IIIa receptor -> prolonged effect - which may be beneficial or harmful.
Unwanted hemorrhage cannot be reversed by merely stopping the drug, though platelet transfusion will help.

The peptide and peptidomimetic inhibitors such as tirofiban (Aggristat™) and eptifibatide (Integrilin™) bind more loosely and have short half-lives.
While stopping the drug may reverse bleeding within a few hours, constant infusion is necessary for continuing effect.

The oral agents have long half-lives, but hemorrhage may thus also be prolonged. They can be dialyzed, however.

Standard dose of heparin combined with GP IIb/IIIa agents does cause unacceptable bleeding. (2,4) Lower dose heparin does not. (4,6,15,16)

Bleeding is increased in the elderly and those with lower weight.

Future Considerations

Evidence suggests that acutely thrombosed coronary arteries may remain susceptible to reocclusion for some time, perhaps for months. Oral GP IIb/IIIa inhibitors may have role in this regard. (17, 18)

The different agents bind differently to other platelet surface integrins besides IIb/IIIa; some are nonspecific (abciximab) and others are more specific. The various advantages & disadvantages need to be elucidated. (16)

Conclusions

Glycoprotein IIb/IIIa inhibitors are effective in preventing reocclusion following PTCA.

They appear to be effective and safe when combined with low dose heparin in treating unstable angina and non-Q-wave MI.

They are also probably effective and safe when combined with a low dose of a thrombolytic, aspirin, and low dose heparin, in treating ST segment elevation MI.

The main concern is hemorrhage.

It would also be easier if any of these agents could be pronounced in the English language.....

REFERENCES

1. Coller BS, Folts JD, Scutter LE, Smith SR. Antithrombotic effect of a monoclonal antibody to the platelet glycoprotein IIb/IIIa receptor in an experimental model. *Blood* 1986;68:783-786.

2. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high risk angioplasty. *N Engl J Med* 1994;330:956-961.

3. Topol EJ, Ferguson JJ, Weisman HG, et al. Long-term protection from myocardial ischemic events after brief integrin ß3 blockade with percutaneous coronary intervention. *JAMA* 1997;278:479-484.

4. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;336:1689-1696.

5. The CAPTURE Investigators. Randomized placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: The CAPTURE study. *Lancet* 1997;349:1429-1435.

6. The RESTORE Investigators. The effects of platelet Glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation* 1997;96:1445-1453.

7. Topol EJ. The EPISTENT trial, presented at the American College of Cardiology Scientific Sessions, March 1998.

8. Platelet Receptor Inhibition In Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998 338:1498-1505.

9. Platelet Receptor Inhibition In Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N. Engl J Med* 1998;338:1448-1497.

10. PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIbIIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998;339:436-443.

11. Kleiman NS, Ohman EM, Calif RM, et al. Profound inhibition of platelet aggregation with monoclonal antibody 7E3 Fab after thrombolytic therapy: Results of the Thrombolysis and Angioplasty in myocardial Infarction (TAMI 8) pilot study. *J Am Coll Cardiol* 1993;22:381-389.

12. Ohman EM, Kleiman NS, Gachioch G, et al. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with integrilin in acute myocardial infarction: Results of a randomized, placebo-controled, dose-ranging trial. *Circulation* 1997:95:846-854.

13. PARADIGM Investigators. Combining thrombolysis with the platelet glycoprotein IIb/IIIa inhibitor lamifiban: Results of the Platelet Aggregation Receptor Antagonist Dose Investigation and Reprefusion Gain in Myocardial Infarction (PARADIGM) trial. *J Am Coll Cardiol* 1998;32:2003-210.

14. Antman E, Giugliano R, McCabe, et al. Abciximab (ReoPro) potentiates thrombolysis in ST elevation infarction: Results of TIMI-14 trial. *J Am Coll Cardiol* 1998;31(suppl A):191A.

15. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. *Lance*t 1997;349:1422-1428.

16. Lefkovits, MB, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. *N Engl J Med* 1998;332:1553-1559.

17. Harrington RA, Moliterno DJ, Dewby K, et al. Amplification of clinical benefit at six months with glycoprotein IIbIIIa inhibitor lamifiban in patints with non ST-segment elevation acute coronary syndromes. *Circulation* 1997;96(suppl 1):1-473. Abstract.

18. Cannon CP, McCabe CH, Borzak S, et al. A randomized trial of an oral platelet glycoprotein IIb/IIIa antagonist, sibrafiban, in patients after an acute coronary syndrome: Results of the TIMI-12 trial. *Circulation* 1998;97:340-349.

Good review article:

Gibler WB, Wilcox RG, Bode C., et al. Prospective use of glycoprotein IIb/IIIa receptor blockers in the emergency department setting. *Ann Emerg Med* 1998;32:712-722.

CHEST PAIN CENTERS

- A Contrarian Point of View -

The Concept

Low-intermediate risk patients
- If admitted to inpatient service -> safer but increased cost
  - Workup over 3 days?
- If discharged home -> cheaper but increased risk
  - Workup over 3 weeks?

Solution? ED based chest pain center
- As safe as admission
- Cheaper than admission
- Allows preventative intervention

Many studies support establishment of emergency department based chest pain centers (CPC's). (1-8)

Most frequently cited advantage is "cost".

> 3 million patients hospitalized per year for chest pain
2/3 ultimately found not to have acute cardiac event (4,9,10)
Cost estimated to be $3 billion just for those found free of acute cardiac event (5)

Cost for ED CPC care estimated to be only 20-50% of cost for CCU admission
Estimated savings for ED CPU evaluation vs. CCU admission range from $450 - $2,600/pt (2,6,8,11-14)

One estimate is savings of $1 billion for every 10% of CCU admissions converted to CPC (2)

So what's not to like??

Essential components of a chest pain center
- Safety
- Cost effectiveness
- Treatment of acute event
- Prevention of future events

The crucial questions to be addressed regarding evaluation of chest pain are:
- *Where?*
  - *What?*
    - *When?*
      - *Who? and Why?????*

Where? Can monitor and test cardiac status anywhere - ED or "upstairs". Location is irrelevant.

What? Serial ECG's, continuous ST monitoring, stress testing, et al.

When? Within 24 hours.

Who? ED nurses or cardiology nurses. Both competent.
Emergency physicians or cardiologists. Both competent (?)
But who's more "expensive" - esp. to hospital ???

Why? To decrease cost - the most frequently cited advantage of ED CPC
To attract patients - never cited as a reason for ED CPC !
To decrease inappropriate discharge from ED -
usually mentioned somewhere in the articles.....

NOTE: Nothing in the essential components implies a greographic necessity.

Inpatient "chest pain center"

Cost
- 24 hour monitored beds are expensive - major cost is personnel
  - Critical care nurses with high RN/patient ratio
- Cardiologists drive Mercedes. Will hospital pay them???

Reimbursement
- Hospital
  - Inpatient reimbursement often less than outpatient
    - Global inpatient charge
    - DRG
    - Capitation
    - Procedures bundled with overall admission
- Cardiologists
  - Same factors
    - Global inpatient charge
    - Capitation
    - Less reimbursement than same procedure in their private office

Soution? Dump on the E.D.!

Emergency Department Chest Pain Center ("Heart ER")

Cost

If ED is expanded to accomodate CPU

Start-up construction cost
Additional 24 hour RN staffing
But how can hospital save money if staffing is at same level as inpatient unit?? ED based CPC is pointless unless total hospital staffing is reduced. (4)

If ED is NOT expanded to accomodate CPU

No increased RN staffing/salary - just incresased work!
No increased bed cost - already 24 hr beds "available"
Often empty at night
ED overcrowding not a hospital concern
ED bodies generate revenue per hour!
Emergency physicians are cheap
- either fee-for-service or already salaried
Even if hospital supplements EP income,
EP's drive Toyotas; cardiologists drive Mercedes.....

Reimbursement

Hospital
Separate charge for "outpatient" care - better rate of $$
No DRG
Outpatient services usually not capitated
Outpatient procedures -> where the $$ are !!

Emergency Physicians
A different story
Usually "maxed out" with Level 5 charge anyway
Reimbursement for "observation" or "prolonged attendance" highly problematic - great in theory only
Questionable payment for procedures
May be capitated or fixed fee per visit
Often salaried
Often already overburdened with patients
(Chest pain ED's not usually placed in quiet facilities)

Cost Analysis - Another Look

Most cost studies do not consider factors which *increase* cost:

Construction & equipment costs for outfitting the CPC if ED facility is expanded to accomodate CPC

Cost of care for patients admitted to the CPC who would have been discharged home from the ED (15)

One study estimated $389 million to $3.9 billion in *increased* national cost for CPC's (16)

Moreover, most articles claiming to evaluate *cost* actually compare *charges*. (8,13,14)
Hospital may charge less for ED CPU - but are the costs really less?

And most studies do not consider the added cost for patients evaluated in the CPC who would have been discharged from the ED, only a small proportion of whom prove to have an acute cardiac event.

Some studies do consider actual *cost* , as well as increased expense of CPC evaluation of patients who otherwise would have been discharged from the ED.

Registry study of 8 CPC's compared with 5 previously published studies. (7)
23,407 pts presenting to the ED with chest pain (5.3% of ED pts)
2,314 fewer pts were admitted to the hopital
Savings = $4,093,466
But 2,250 more pts who would have been discharged underwent r/o MI evaluation
Additional cost = $1,219,500
Net savings = $2,873,966 (4,093,466 - 1,219,500)
Net savings for 4,564 pts whose workup was altered = $630/pt

Another article used true cost and found a net mean savings of only $567/ pt. (5)
Mean length of stay in the ED CPC was 33.1 hrs. vs. 44.8 of admitted pts.

Neither article considered start-up costs.
The true <u>cost</u> savings is only about $600/pt. once the start-up costs have been met.

Conclusions regarding cost analysis

Most studies analyzed *charges* , not true *cost .*
Most studies do not factor in added expense of low risk patients admitted to ED CPC, who would have been discharged form the ED.
Most studies do not consider start-up costs.
Most (if not all) studies were conducted in hospitals which economically supported their ED based CPU.

Chest Pain Center in E.D. vs. "Upstairs" - Advantages & Disadvantages

Advantage to hospital

Great marketing ploy
Cost is less - *but only if total nursing FTE's are cut*
Charges - *and reimbursement* - are great!
Less risk than discharge from ED

Disadvantage to hospital

Huh?

Advantage to emergency physicians

Less risk than discharge

Disadvantage to emegency pysicians

More risk vs. admission
More work
Doubtful reimbursement

Advantage to patients

Some who might have been discharged with unstable angina might be diagnosed.

Disadvantage to patients

Some with unstable angina might be placed in inadequately staffed unit.

SUMMARY

Comprehensive monitoring and workup within 24 hours of intermediate risk patients, is definitely safe, cost-effective, and beneficial to everyone.

Location of such activity is irrelevant to the patient, but highly relevant to hospital, nurses, and physicians.

Such activity does not require a specific "unit", no matter where it is located. It is the activity that matters.

According to a 1995 survey, of 1,454 metropolitan hospitals who responded, 22.5% claimed to have ED based CPC's. Obviously, many such designations are merely marketing ploys. It is doubtful that even back then, nearly 1 out of 4 American hospitals had upgraded their ED's to adequately staff 24 hour cardiac units. (17)

According to an ACEP concensus panel publication - which supported ED based CPC's - "time studies have shown these observations patients require twice the amount of emergency physician services required by traditional ED patients. (18) Observations patients require additional nursing services as well. Thus, ED's that provide CPU services need additional staffing." (2)

CONCLUSION

Unless adequate resources are allocated to solve problems of staffing and reimbursement, emergency department based chest pain units are not appropriate.

REFERENCES

1. Gibler WB, Runyon JP, Levy RC, et al. A rapid diagnostic and treatment center for patients with chest pain in the emergency department. *Ann Emerg Med.* 1995 Jan;25(1):1-8.

2. Graff L, Joseph T, et al. American College of Emergency Physicians Information Paper: Chest pain units in emergency departments - a report from the short-term observation services section. *Am J Cardiol.* 1995 Nov;76:1036039.

3. Gibler WB: Chest pain units: Do they make sense now? *Ann Emerg Med* 1997 Jan;29:168-71.

4. Zalenski RJ, Rydman RJ, McCarren M, et al. Feasibility of a rapid diagnostic protocol for an emergency department chest pain unit. *Ann Emerg Med* 1997 Jan;29:99-108.

5. Roberts RR, Zalenski RJ, Mensah EK, et al. Costs of an emergency department-based accelerated diagnostic protocol vs hospitalization in patiens with chest pain: A randomized controlled trial. *JAMA* 1997 Nov 26;278(20):1670-6.

6. Mikhail MG, Smith FA, Britton GM, Frederiksen SM. Cost-effectiveness of mandatory stress testing in chest pain center patients. *Ann Emerg Med.* 1997 Jan;29(1):88-98.

7. Graff LG, Dallara J, Ross MA, et al. Impact on the care of the emergency department chest pain patient from the chest pain evauation registry (CHEPER) study. *Am J Cardiol* 1997 Sep 1;80(5):563-8.

8. Hoekstra JW, Gibler WB. Chest pain evaluation units: An idea whose time has come. *JAMA* 1997 Nov;278(20):1701-2.

9. Selker HD, GriffithJL, D'Agostino RB. A tool for judging coronary care unit admission appropriateness, valid for both real time and retrospective use: A time-insensitive predictive instrument (TIPI) for acute cardiac ischemia. A multicenter study. *Med Care* 1991;29:610-27.

10. Roberts R, Kleiman NS. Earlier diagnosis and treatment of acute myocardial infarction necessitates the need for a "new diagnostic mindset." *Circulation* 1994;89:872-81.

11. DeLeon AC, Farmer CA, King G, et al. Chest pain evaluation unit: A cost-effective approach for ruling out acute myocardial infarction. *South Med J* 1989;82:1083-9.

12. Gaspoz JM, Lee TH, Cook EF, et al. Outcome of patients who were admitted to a new short-stay unit to "rule out" myocardial infarction. *Am J Cardiol* 1991;68:145-9.

13. Hoekstra JW, Gibler WB, Levy RC, et al. Emergency department diagnosis of acute myocardial infarction and ischemia: A cost analysis. *Acad Emerg Med* 1994;1:103-110.

14. Gomez MA, Anderson JL, Daragounis LA, et al. An emergency department-based protocol for rapidly ruling out myocardial ischemia reduces hospital time and expense: Results of a randomized study (ROMIO). *J Am Coll Cardiol* 1996;28:25-33.

15. Stomel R, Grant R, Eagle KA. Lessons learned from a community hospital chest pain center. *Am J Cardiol*. 1999 Apr 1;83(7):1033-7.

16. Shesser R, Smith M. The chest pain emergency department and the outpatient chest pain evaluation center: Revolution or evolution? *Ann Emerg Med.* 1994 Feb;23(2):334-41.

17. Zalenski RJ, Rydman RJ, Ting S, et al. A national survey of emergency department chest pain centers in the United States. *Am J Cardiol* 1998 Jun 1;81:1305-9.

18. Graff LG, Wolf S, Dinwoodie R, et al. Emergency physician workload: A time study. *Ann Emerg Med* 1993;22:1156-63.