MEDICAL GRAND ROUNDS

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UNSTABLE ANGINA PECTORIS - AN UPDATE

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I discussed unstable angina pectoris at these exercises almost nine years ago. I began my discussion with the following comments:

> "Unstable angina pectoris poses one of the most vexing issues currently facing the clinical cardiologist. This vexation can be attributed to a number of reasons, among them: the lack of a clear understanding of the pathophysiology and natural history of unstable angina, the lack of an ideal medical treatment, and the controversies over whether and which of these patients should have coronary artery bypass surgery as part of their treatment, and if so at what stage of their illness or recuperation."

I concluded with the formulation of tentative recommendations for management of the patient with unstable angina, "recognizing that changes will be necessary as further information becomes available."

Since then, much has changed. Our concepts of the pathophysiology have been substantially altered. We know more about the natural history. The suspicions of nine years ago that the clinical course was changing have been confirmed. New medical therapies have appeared and been tested. The role of coronary artery surgery on an emergency or semi-emergency basis has been clarified. Newer modes of therapy are on the horizon. Therefore, it seems timely to provide you with an update and a substantial revision of the tentative plan for management that I suggested in 1975.

HISTORICAL BACKGROUND, NOMENCLATURE, AND DEFINITION.

In his classic description of angina pectoris, (1, 2) Heberden alluded to unstable angina as he briefly mentioned non-exertional angina. Parry (3) mentioned it in 1979. But an appreciation of a syndrome intermediate to chronic stable angina pectoris on the one hand and myocardial infarction on the other was delayed by the long interval (until the early part of this century) between Heberden's description of angina and an appreciation of its pathophysiology (4) and the description of myocardial infarction (5, 6). Both of these pioneer descriptions of myocardial infarction also vaguely referred to what was probably unstable angina. However, attention was first drawn to unstable angina as a distinct entity in the 1930's, in the German literature (7-10) and in the United States by Sampson and Eliaser (11) and Feil (12). These latter two descriptions referred to this variety of pain as "precursor phenomena" and "preliminary pains of coronary thrombosis." Subsequently, this syndrome was described by a number of terms (13-20) (Table 1). Many of the terms connote that this unstable syndrome is a premonitory phase of acute myocardial infarction. But although a large fraction of patients with myocardial infarction experience a prodrome of unstable angina (11-12, 23-32); (table 2) most patients with unstable angina do not immediately progress to myocardial infarction. The term unstable angina was suggested by Dr. Noble Fowler (13) and is now almost universally accepted as the best coverall term into which the

TABLE 1

Some names applied to the syndrome intermediate between stable angina pectoris and myocardial infarction.

	Reference No.
Unstable angina pectoris	13
Intermediate coronary syndrome	14
Acute coronary insufficiency	15
Accelerated angina pectoris	
Acute atypical coronary artery insufficiency	16
Status anginosus	17
Slight coronary attacks	18
Coronary failure	19
Impending myocardial infarction	
Threatening myocardial infarction	
Pilot anginal attacks	20
Premonitary pain to coronary occlusion	
Precursor phenomena to coronary occlusion	11
Preliminary pains to coronary occlusion	12
Pre-thrombotic syndrome	
Pre-occlusive syndrome	
Pre-infarction angina	21
Crescendo angina	22

TABLE 2

Prodromes to Myocardial Infarction

			Ref.
50%	Feil	1937	12
48.1%	Sampson & Eliaser	1937	11
49%	Yater et al	1948	23
16%	Behrmann et al	1950	24
29%	Mounsey	1951	25
39%	Maurice et al	1955	26
39%	Vakil	1961	27
45%	Wood	1961	28
50%	Moss et al	1969	29
65%	Solomon et al	1969	30
84%	Hochberg	1971	31
60%	Fulton et al	1972	32

various subgroups of patients that are intermediate between stable angina and acute myocardial infarction can be grouped. While it is convenient to use this general term, the heterogeneity of patients presentations has made development of a universally acceptable definition difficult (33). The resulting heterogeneity of patients study groups confounds comparisons of natural history studies and intervention trials.

The specific subgroups which make up the syndrome of unstable angina in the broadest sense are:

1. New onset angina
2. Spontaneous angina at rest
3. Crescendo (accelerated, progressive) angina
4. Acute coronary insufficiency
5. Variant (Prinzmetal's) angina
6. Angina in the early post-myocardial infarction period.

Virtually all studies are composed of patients from one or more of these groups. Crescendo angina is deterioration of chronic exertional angina that was formerly stable in that it becomes more frequent, more easily provoked, more severe, longer in duration, or less readily relieved by rest and nitroglycerin. Some writers consider spontaneous angina at rest a part of the subgroup of crescendo angina. Acute coronary insufficiency is a bout of angina that lasts in excess of 15 minutes with poor or no relief by rest or nitroglycerin. Variant angina is angina at rest with transient ST-segment elevation on the ECG.

Of these six sub-groups, new onset angina is the most questionable one to include. There always has to be a first episode. New angina may appear following a certain provocation and then recur only following similar or greater provocation. Alternatively, new onset angina may develop that is crescendo in nature or that occurs at rest or with minimal provocation. Most writers have included only the latter type of new onset angina into the overall group of unstable angina.

Some investigators have included a requirement for transient ST-segment or T-wave abnormalities in the ECG. That is useful for an intervention trial to assure a more homogeneous (and higher-risk) study group. Such a requirement should not be made for the initial clinical diagnosis. By no means will all unstable angina patients demonstrate ST-segment or T-wave abnormalities at the time of admission (17, 26, 34-38); (table 3). In many cases ST and T changes may have occurred and resolved before the patient experienced pain or the ECG was obtained.

Further, to qualify as unstable angina, the presence of myocardial infarction must be confirmed.

For today's discussion, I will mainly omit variant angina and angina immediately following myocardial infarction. It is clear from a review of the available data that variant angina is due to transient spasm of an epicardial coronary artery. (39). For the most part, I think that variant angina deserves to be discussed as a separate entity.

TABLE 3

Unstable angina patients without ischemic ECG changes.

			Ref.
29%	Maurice et al	1955	26
48%	Nichol et al	1959	34
17%	Beamish & Storrie	1960	35
10%	Papp & Smith	1960	17
12%	Wood	1961	28
10%	Krauss et al	1972	36
17%	Gazes et al	1973	37
20%	Lopes et al	1973	38

TABLE 3A

Unstable angina in the absence of significant atheromatous disease.

				Ref.
25%	(54/216)	Proudfit et al	1966	58
19%	(15/79)	Scanlon et al	1973	54
5%	(1/19)	*Herman & Gorlin	1972	56
7%	(10/142)	Bertolasi et al	1974	43
10%	(29/182)	Alison et al	1975	59
10%	(3/31)	Donsky et al	1975	60

*All the patients in this group were "high risk" patients.

Angina immediately following myocardial infarction cannot be properly discussed without consideration of the infarction. Therefore, it too, I think, deserves separate discussion.

To reiterate, my comments today are directed to patients with: [1] chest discomfort that is consistent with myocardial ischemia; [2] the discomfort is unstable in that it is crescendo in nature, occurs spontaneously at rest, or exceeds 15 minutes in duration; [3] there is transient ST-segment depression or T-wave abnormalities or no ST-segment or T-wave changes on the ECG; and [4] there is no evidence for frank myocardial necrosis.

NATURAL HISTORY

The syndrome of unstable angina is worthy of discussion and study because of the observations that unstable angina denotes a change in the likelihood of development of myocardial infarction and cardiac death compared to patients with chronic stable coronary heart disease. A number of such observations from 1937 to the present are available. (Table 4). The differences among the studies in the selection of patients and treatment regimens complicate inter-study comparisons. Nevertheless, the results can be compared to the course of all patients with coronary heart disease at the time of the study to gain insight into the excess morbidity and mortality following destabilization of angina. It is interesting to divide the studies into those reported before and after 1970. Until the late 1960's, with the advent of beta-adrenergic blocker therapy and coronary bypass surgery, there was little to offer the patients but bedrest in the hospital and liberal sublingual and oral nitrate administration. Prior to 1970, the prognosis was ominous indeed. (16-17, 27-28, 35, 40-41); (table 5). About one-third of the patients experienced myocardial infarction and one-fifth died. Most of these coronary events (infarction or death) were in the first few months after destabilization.

Results of studies after 1970 have demonstrated a tendency toward a lower incidence of infarction and death compared to the pre-1970 data. Nevertheless, the incidence of a coronary event is still several multiples higher than expected from all patients with coronary heart disease in the same time period. As was true before 1970, the majority of coronary events occurred in the first few months after destabilization. The decline in the incidence of coronary deaths in patients with unstable angina may be similar to the incompletely understood decline in the overall coronary death rate that has occurred during the same period.

Certainly, comparison of the morbidity and mortality of selected patients with unstable angina pectoris with national and international mortality and morbidity data is not entirely satisfactory. Careful analyses of the morbidity and mortality of well-matched, concurrently followed patients with stable and unstable angina are very sparse. However, two studies from Stanford, one retrospective (38), the other prospective (49), found that the long-term outlook for patients who were admitted to the CCU with unstable angina was as bad as for the patients who were admitted for documented myocardial infarction.

TABLE 4

Myocardial Infarction and Mortality Complicating Unstable Angina

Paper	Ref.	#Patients Before 1970	MI	Mortality	Follow-up
Littman & Barr, 1952	16	29	4%	7%	in-hospital
Cutts et al, 1957	40	69	26%	20%	<1 to >6 yrs
Beamish & Storrie, 1960	35	100	42%	24%	7wk - 6mos.
Papp & Smith, 1960	17	20	50%	50%	1 - 12 yrs
Vakil, 1961	41	251	36%	1%	3 mos
Wood, 1961	28	150	9%	12%	3 mos
Vakil, 1964	27	360	41%	16%	3 mos
		After 1970			
Fulton et al, 1972					
Duncan et al, 1976	32,42				
Total		251	16%	4%	6 mos
Hospitalized		87	12%	N.S.	in-hospital
Krauss et al, 1972	36	100	15%	22%	$\bar{x}$ 20 mos
Gazes et al, 1973	37				
Total		140	21%	18%	1 yr
"High Risk"		54	35%	43%	1 yr
Lopes, et al, 1974	38	170	N.S.	15%	$\bar{x}$ 17.9 mos
Skjaeggestad, 1973	52	132	13%	5%	2 mos
Bertolasi, et al, 1974&1976†	44-45				
"Intermediate Syndrome"		24	8%	21%	in-hospital
"Progressive Angina"		27	0%	4%	
Total		51	4%	12%	
"Intermediate Syndrome"		24	38%	46%	$\bar{x}$ 32 mos
"Progressive Angina"		27	7%	7%	
Total		51	22%	25%	
Heng, et al, 1976	45	158	13%	4%	in-hospital
Hultgren et al, 1977†	48	66	6%*	5%	1 month
		66	17%*	21%	$\bar{x}$ 23 months
Allison, et al, 1978	47	188	6%	4%	in-hospital
NHLBI, 1978†	46	147	8%	3%	in-hospital
		147	22%	9%	$\bar{x}$ 30 months
Schroeder, et al, 1980	49	88	8%*	19%	$\bar{x}$ 28 mos.
Mulcahy, et al, 1981	50	100	9%*	4%	28 days
		100	12%*	12%	1 year
Lewis, et al, 1983†	51	641	8%	3%	12 weeks

* Non-fatal MI only
† Results of control group for an intervention study

The only reasonable conclusion from the available data is that unstable angina still signals a period of heightened risk for myocardial infarction and death and the heightened risk is greatest with the onset of destabilization but persists for several months.

PATHOPHYSIOLOGY

There is nothing unique in the coronary anatomy of patients with unstable angina that is sufficient to explain the syndrome. Proudfit and his colleagues at the Cleveland Clinic (53) reported on the distribution of coronary arterial lesions of 627 patients with clinically presumed or suspected coronary heart disease. One hundred and seventy patients had unstable angina. The distribution of lesions in these patients was similar to that encountered in patients with stable angina pectoris. A larger number of arteriographic and pathologic studies from many institutions since then have supported Proudfit's observations. Inadequate collateral vessel formation has been suggested as a cause (54-55) but has not been confirmed by others (33, 56-57). A particularly vexing phenomenon is that at least 10% of patients with the clinical diagnosis of unstable angina have no hemodynamically significant coronary arterial narrowings by atherosclerotic plaques. (43, 54, 56, 58-60); (Tab. 3A).

There are some data suggestive that the time of unstable angina is associated with an accelerated rate of coronary artery narrowing. Neill and his associates (61) and Rafflenbeul and his co-workers (62) noted that there was a high rate of progression of critical coronary stenoses, but not of hemodynamically significant, but sub-critical ones. In a more recent report from Montreal, both critical and sub-critical coronary narrowings progressed during the period of unstable angina (63).

But what has completely changed our concepts of the pathophysiology of unstable angina pectoris is the recognition, over the last decade, that with rare exception, destabilization of angina owes to dynamic coronary stenoses, that is transient, usually reversible limitations in coronary blood flow. Until the early 1970's, it was generally believed that destabilization of angina was due to the development of spontaneous elevations in myocardial oxygen demand (minor elevations in heart rate, blood pressure, or cardiac contractility) that outstripped the limited coronary reserve to increase flow because of fixed, critical stenoses. Data from a variety of sources now refute that thesis.

Hemodynamic Investigations

In 1966, Newman and Roughgarden reviewed the literature on heart rate and blood pressure in patients with spontaneous angina at rest and concluded that most of these episodes were associated with tachycardia or hypertension or both (64). But because the hemodynamic measurements were made after the onset of pain, they recognized that a cause-effect relationship was not proved. Subsequently Roughgarden studied the temporal

relationship of hemodynamic changes to spontaneous angina in 10 patients with constant ECG and blood pressure monitoring (65). Indirect indices of myocardial oxygen demand ($\dot{M}VO_2$) rose before the onset of angina. These results supported the demand-side theory, if one accepts the thesis that the hemodynamic changes caused the ischemia. Hidden in that paper was an interesting observation. Two patients later underwent exercise testing and did not experience angina until a much higher pulse-pressure produce (heart rate x systolic blood pressure) was attained. That suggested that those two patients had a greater coronary reserve when their symptoms were stable than when their symptoms were unstable; that is, their coronary blood flow was transiently limited during the episode of spontaneous angina. Furthermore, other observations had shown that there were cardiac-initiated reflexes that resulted in systemic hypertension or tachycardia. (66-70). Therefore, it still remained uncertain if the ischemia with spontaneous angina at rest caused or was the result of the hemodynamic changes.

The findings of the two patients in Roughgarden's study mentioned earlier have been enlarged upon in four investigations. Berndt and his colleagues compared the double product and the triple product [heart rate x systolic blood pressure x ejection time (an index of cardiac contractility)] during spontaneous angina at rest with angina provoked by pacing-induced tachycardia. (71). The values during tachycardia induced angina were consistently and significantly higher than the values during spontaneous angina at rest. My colleagues and I in Dallas (72) and Uthurralt and his colleagues in Maseri's lab (73) compared hemodynamic variables that determine $\dot{M}VO_2$ in patients with spontaneous versus exercise induced angina. The values during exercise-induced ischemia were consistently and significantly higher than the values obtained during spontaneous angina at rest. (Fig 1). Finally Figueras and Cinca in Spain compared hemodynamic variables in patients during spontaneous angina vs. angina induced by hypertension from methoxamine infusion. (74). The hemodynamic values were higher during hypertension-induced ischemia than with spontaneous angina (Fig. 2).

If spontaneous angina were induced by hemodynamic changes, one would expect the hemodynamic variables at the threshold of episodes of ischemia to be similar, as they are with exertional angina. This has not been the case. Considerable differences in hemodynamic variables from one episode of spontaneous angina to another were noted initially by Roughgarden (65) and subsequently by Rosland (75) and Figueras et al (76).

Guazzi and his colleagues in Italy studied seven patients with spontaneous angina at rest with indwelling catheters in the pulmonary artery and left ventricle as well as monitoring the ECG and blood pressure (77). They obtained measurements for 44 bouts of spontaneous angina. Changes in heart rate, blood pressure, and the rate of rise of left ventricular pressure always followed ECG changes of ischemia. Figueras and his colleagues at Cedars Sinai in Los Angeles studied 11 patients with spontaneous angina with continuous recording of the ECG, blood pressure, and pulmonary artery pressure (76). Blood pressure and heart rate changes always followed ECG changes of ischemia. In contrast to

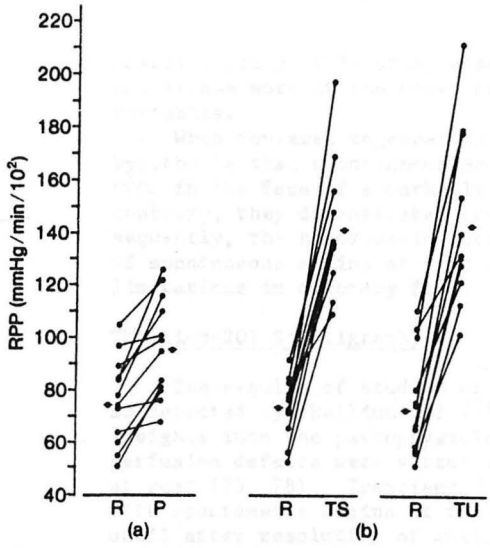

FIG. 1 The rate-pressure product (RPP) for each patient during unstable angina pectoris and at supine and upright exercise following restabilization of angina with medical therapy. RPP during (a) unstable angina is plotted (solid circles) for each patient during a pain-free interval at rest (R) and just prior to pain (P). For those patients with more than one episode of spontaneous angina, only the data from the first episode are plotted. (b) During stable angina, RPP is plotted (solid circles) for each patient at rest before exercise (R) and at termination of supine exercise (TS) and upright exercise (TU). Mean values are shown in open circles.

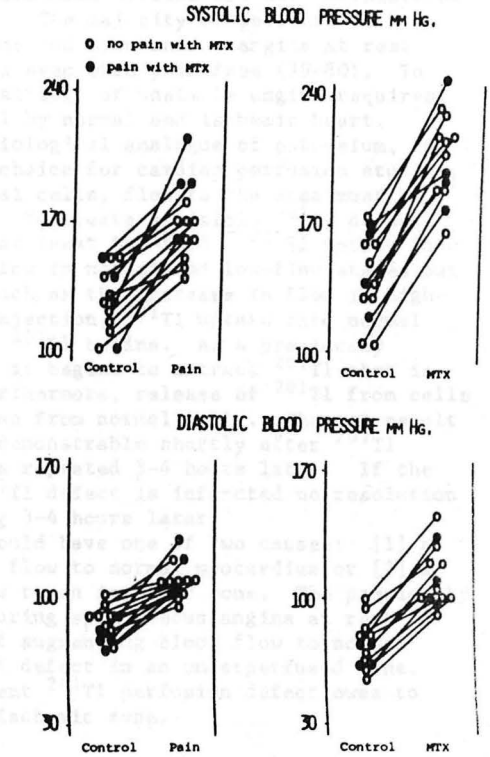

FIGURE 2. *Changes in systolic and diastolic blood pressure during spontaneous angina (left panels) and during the methoxamine (MTX) test (right panels). The higher increases in blood pressure during the drug administration than during spontaneous angina are apparent.*

Guazzi's study, this study also showed a slight drop in blood pressure and stroke work at the onset of ECG changes followed by a rise in these variables.

When reviewed together these hemodynamic data do not support the hypothesis that spontaneous angina at rest is brought on by a raised $\dot{M}VO_2$ in the face of a markedly limited coronary flow reserve. On the contrary, they demonstrated considerable coronary flow reserve. Consequently, the hemodynamic data support the hypothesis that the episodes of spontaneous angina at rest were brought on by sudden, transient limitations in coronary flow.

Thallium-201 Scintigraphy

The results of studies of transient myocardial perfusion defects as detected by thallium-201 (^{201}Tl) scintigraphy also give us some insights into the pathophysiology of unstable angina. Transient ^{201}Tl perfusion defects were virtually always found during spontaneous angina at rest (73, 78). Transient ^{201}Tl defects were found in 25% of patients with spontaneous angina at rest when the radionuclide was not administered until after resolution of angina (79). The majority of patients with accelerated exertional anginal syndrome and spontaneous angina at rest have transient ^{201}Tl perfusion defects even when pain-free (79-80). To relate these findings to the pathophysiology of unstable angina requires a brief explanation of uptake of ^{201}Tl by normal and ischemic heart.

Thallium-201, a radioactive physiological analogue of potassium, is the current nuclear imaging agent of choice for cardiac perfusion studies. For normal ^{201}Tl uptake into myocardial cells, flow to the area must be normal and the cells must be healthy. To create a visible ^{201}Tl defect, myocardial concentration must differ at least two-fold. ^{201}Tl uptake into myocardial cells is proportional to flow in normal and low-flow states but increases by only about one-half as much as the increase in flow in high-flow states. Within ten minutes of injection, ^{201}Tl uptake into normal myocardium is complete and release of ^{201}Tl begins. As a previously ischemic zone of myocardium recovers, it begins to extract ^{201}Tl that is being released from normal heart. Furthermore, release of ^{201}Tl from cells recovering from ischemia is slower than from normal cells. The net result is that the perfusion defect that is demonstrable shortly after ^{201}Tl injection has resolved when imaging is repeated 3-4 hours later. If the zone of myocardium with an initial ^{201}Tl defect is infarcted no resolution of the defect will appear upon imaging 3-4 hours later.

Thallium-201 perfusion defects could have one of two causes: [1] a two-fold or greater increase in blood flow to normal myocardium or [2] a 50% or greater reduction in blood flow to an ischemic zone. The previously mentioned hemodynamic data obtained during spontaneous angina at rest failed to show any stimulus capable of augmenting blood flow to normal myocardium sufficient to cause a ^{201}Tl defect in an underperfused zone. Therefore, we can infer that a transient ^{201}Tl perfusion defect owes to a transient reduction in flow to the ischemic zone.

But what about the transient ^{201}Tl defects observed in unstable angina patients when ^{201}Tl was injected in a pain-free interval? Animal experimentation has demonstrated that prolonged ischemia may cause abnormalities in myocardial contractility and biochemistry that require hours or even days to full resolve (81-83). This has been referred to as "stunned myocardium" (84). Drs. Nixon, Narahara, Hillert, and Brown, and I demonstrated transient abnormalities of contraction in patients with unstable angina when studied in a pain-free state (85-86) and suggested that this may be a clinical example of stunned myocardium. Accordingly, it is conceivable that such stunned myocardium may take up and release ^{201}Tl similarly to myocardium in a zone of transient hypoperfusion (79).

Possible causes of transient limitations in coronary blood flow.

The observations supporting transient limitations in coronary blood flow as the pathophysiologic basis of unstable angina leads to the obvious next question - what is responsible for these dynamic stenoses? The relationship of coronary blood flow and coronary narrowing have been well-established. There is little decrease in coronary blood flow until the diameter of the artery is reduced by one-half which corresponds to a 75% narrowing of the cross-sectional area of the artery (Fig. 3). From that point to a diameter narrowing of about 85% coronary flow drops sharply with each increment of coronary narrowing. Transient abnormalities of coronary vasomotion (even within the normal range of dilation and constriction), or transient platelet aggregates or thrombus at the site of an atheromatous plaque could lead to a dynamic stenosis superimposed upon the fixed stenosis.

Abnormalities of Coronary Vasomotion

Dr. Myron Prinzmetal's hypothesis (87-88) that variant angina pectoris owed to focal coronary spasm and total or near total occlusion in a major epicardial vessel usually at or near an atherosclerotic plaque has been proved to be correct. Abnormalities of coronary vasomotion in patients with unstable angina without ST-segment elevation may appear in: [1] incomplete focal spasm of a major coronary artery; [2] diffuse narrowing of a large epicardial vessel with diminished run-off; [3] complete spasm of a small coronary artery branch; or [4] spasm of collateral vessels supplying an ischemic zone (89-90). But can abnormalities of coronary vasomotion of this magnitude diminish coronary flow sufficiently to cause myocardial ischemia? The sparse data that are available suggest that the answer is yes. Doubtless the first such documentation is in a paper published by Dr. Richard Gorlin 19 years ago. He fortuitously recorded a marked reduction in coronary sinus blood flow 30 seconds before and during an episode of spontaneous angina at rest (142). One of the patients with the diagnosis

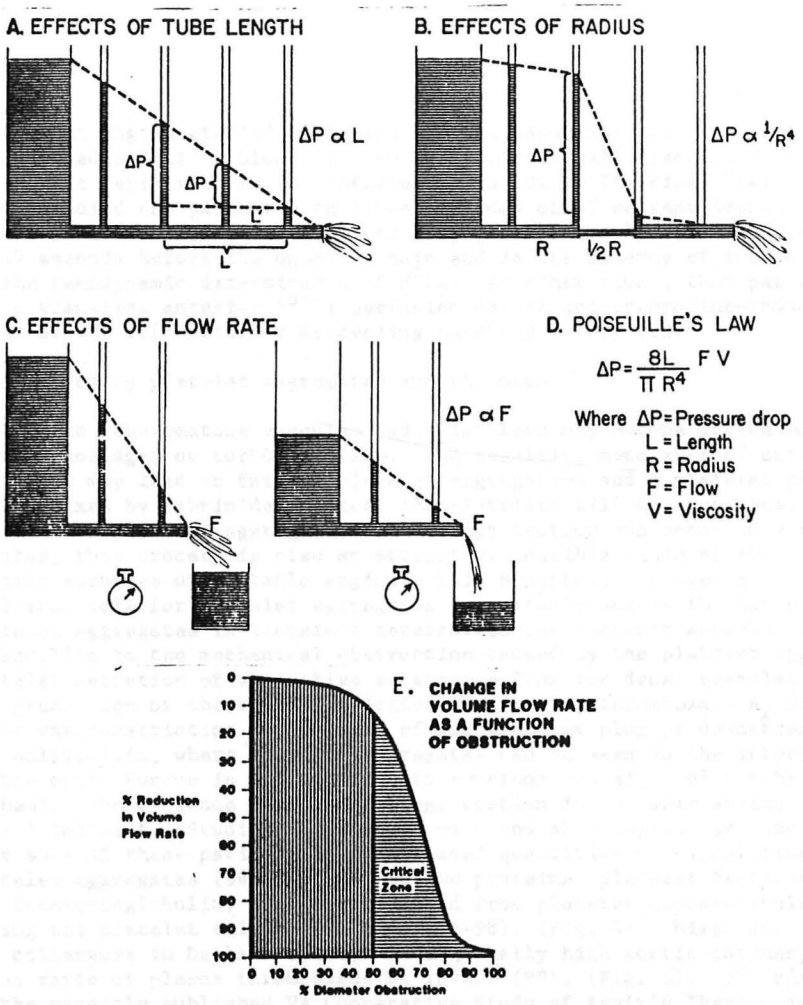

Figure 3. The concept of dynamic coronary stenoses is based upon the relationships of pressure and volume flow rate through a vessel to the radius of the vessel as expressed by Poiseuille's Law [D]. The drop in pressure (ΔP) during laminar flow of a homogeneous fluid through a rigid tube of constant caliber is directly proportional to the length of the tube, [A]. Under the same conditions, the drop in pressure is also inversely proportional to the reciprocal of the radius raised to the fourth ($1/R^4$) power and is directly proportional to the volume flow (F) through the tube [B] and to the viscosity (V) of the fluid. With all other variables constant, coronary volume flow rate changes little until the diameter is narrowed to 50% (75% cross-sectional narrowing). From this degree of diameter narrowing to about 85%, flow falls linearly with respect to increments in diameter obstruction. In this critical zone, any transient increment in coronary obstruction (vascular tone, platelet plug, thrombus) will lead to a corresponding transient decrement in coronary volume flow rate [E]. (Figure modified from Rushmer, RF. Cardiovascular Dynamics. 4th edition. W.B. Saunders. 1976.)

of variant angina studied by Pepine and his associates in Gainesville experienced a fall in blood flow to the inferior wall associated with ST segment depression in the inferior leads (92). The Pisa, Italy group studied one patient with three episodes of ST-segment depression in the anterior leads. Coronary sinus pO_2 consistently fell an average of 37 seconds before the onset of pain and in the absence of increases in the hemodynamic determinants of $M\dot{V}O_2$. At other times, that patient had a transient anterior ^{201}Tl perfusion defect and ergonovine-induced spasm of the left anterior descending coronary artery (93).

Intra-coronary platelet aggregates and thrombus

In an atheromatous vascular bed, platelets may become activated by exposed collagen or turbulent flow. The resulting monolayer of activated platelets may lead to further platelet aggregation and a platelet plug. Unless fixed by fibrin deposition, the platelets will disaggregate. Inasmuch as platelet aggregation and disaggregation can occur in a few minutes, this process is also an attractive possible cause of the dynamic stenoses of unstable angina. This hypothesis creates an analagous role for platelet aggregates in unstable angina to that of platelet aggregates in transient cerebrovascular ischemic attacks (TIA's). In addition to the mechanical obstruction caused by the platelet aggregate, platelet secretion of vasoactive substances from the dense granules and production of the vasoconstrictive prostanoid, thromboxane A_2 might favor vasoconstriction at the site of the platelet plug or downstream. But unlike TIAs, where platelet aggregates can be seen in the arteries of the optic fundus in relationship to symptoms and signs of cerebral ischemia, the evidence for platelet aggregation in unstable angina is all indirect. Studies of patients with unstable angina have shown that some of these patients have increased quantities of circulating platelet aggregates (94, 95), and of two proteins, platelet factor-4 and β-thromboglobulin, that are released from platelet alpha-granules during the platelet release reaction (95-98). (Fig. 4) Hirsh and his colleagues in Dallas reported an abnormally high aortic:coronary sinus ratio of plasma thromboxane B_2 levels (99). (Fig. 5). The results of the recently published VA Cooperative Study of Aspirin Therapy in Unstable Angina provide additional although also indirect, evidence favoring enhanced platelet reactivity in the coronary bed as a factor in transient reductions in coronary flow (51).

A striking possible animal laboratory parallel to transient platelet aggregation as a cause for the transient reductions in coronary blood flow comes from animal experiments begun by Folts (100) and extended upon in other labs, including Dr. Willerson's. It has been found that partially occluded dog arteries undergo cyclic reductions in flow, that these reductions are due to platelet aggregates and that agents that prevent platelet aggregation and thromboxane A_2 production blocked these cyclic reductions in coronary flow. These experiments were discussed at these exercises by Dr. Willerson (Medical Grand Rounds, January 19, 1984) so I will not dwell upon them here further.

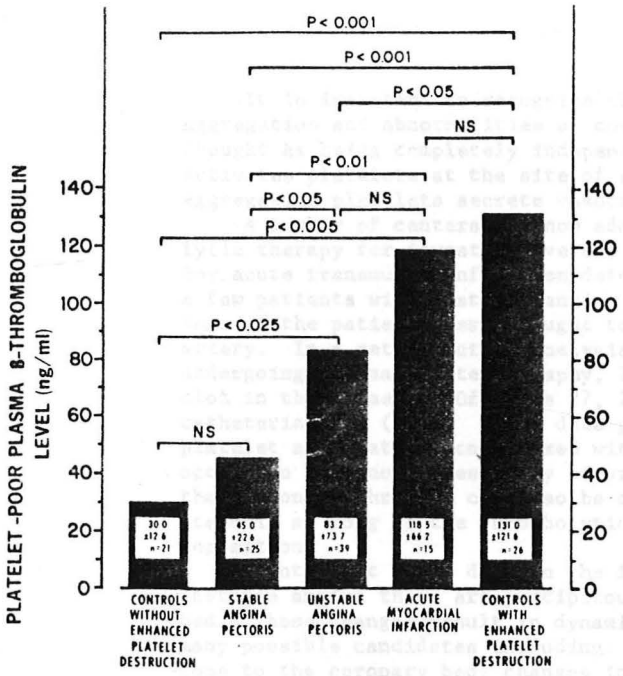

FIGURE 4. Beta thromboglobulin levels in platelet-poor plasma in the five study groups. The insert in each bar shows the mean ± standard deviation and the number (n) of persons in each group. The probability (P) values for the differences among the mean values of the groups are shown on the appropriate connecting lines. NS = not significant.

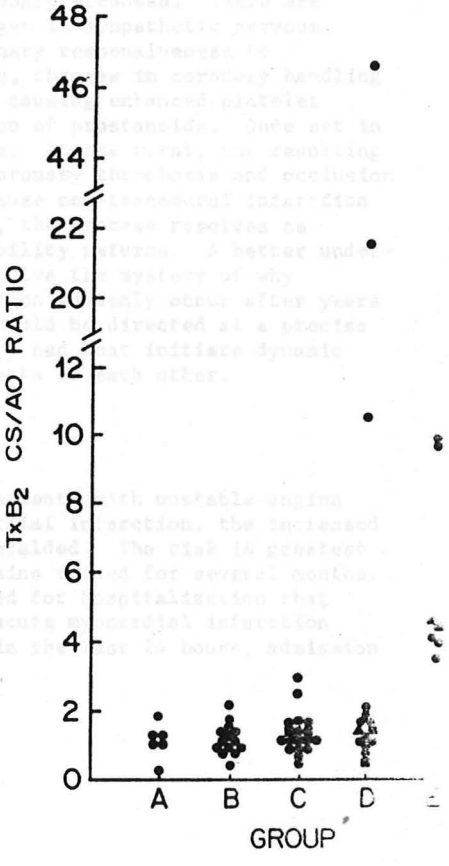

Fig. 5. Ratios of Thromboxane B_2(TxB_2) in Coronary Sinus and in Ascending Aorta (CS/AO) in the Five Groups of Patients.
Each point represents the data from one point. Squares identify patients who received a cyclooxygenase inhibitor within five days of study, and triangles patients with coronary arterial spasm. In Groups A (valvular and congenital nonischemic heart disease), B (chest pain syndrome without ischemic heart disease, and C (ischemic heart disease without chest pain for at least 96 hours), all patients had TxB_2CS/AO ratios of 3.1 or lower. Group D (ischemic heart disease with chest pain 24 to 96 hours before study) had a bimodal distribution: 12 patients had low TxB_2CS/AO ratios, whereas 3 had very high ratios. Group E (ischemic heart disease and chest pain within 24 hours before study) had TxB_2CS/AO ratios (range, 3.5 to 9.9) that were higher than those of Groups A, B, and C ($P < 0.05$).

It is important to recognize that intra-coronary platelet aggregation and abnormalities of coronary vasomotion need not be thought as being completely independent. Coronary spasm probably activates platelets at the site of spasm (101). As already noted, aggregating platelets secrete vasoconstrictors.

A number of centers are now administering intracoronary thrombolytic therapy for investigative and clinical purposes principally for acute transmural infarction detected very early after onset. But a few patients with unstable angina have been included (102-104). Some of the patients were thought to have thrombus in a coronary artery. In a retrospective analysis of 300 consecutive patients undergoing coronary arteriography, 27 were judged to have demonstrable clot in the vessels. Of those 27, 24 had unstable angina prior to catheterization (105). These data provide evidence that even when platelet aggregates become fixed with fibrin, progression to complete occlusion does not necessarily occur. It seems reasonable to assume that coronary thrombus can also be considered as a cause for dynamic stenosis as long as the thrombolytic rate exceeds the rate of thrombus deposition.

I interpret these data in the following way. With the onset of unstable angina there are precipitous changes in or to the coronary bed. These changes result in dynamic coronary stenoses. There are many possible candidates including: changes in sympathetic nervous tone to the coronary bed, changes in coronary responsiveness to vasoactive substances and sympathetic tone, changes in coronary handling of Ca^{+2}, anatomical changes in the vessel causing enhanced platelet reactivity, and changes in local production of prostanoids. Once set in motion the process becomes a vicious cycle. At the worst, the resulting ischemia causes sudden cardiac death or coronary thrombosis and occlusion occurs. Prolonged dynamic stenoses may cause non-transmural infarction without coronary thrombosis. At the best, the process resolves as mysteriously as it began and clinical stability returns. A better understanding of these events should help to solve the mystery of why coronary thrombosis and myocardial infarction suddenly occur after years of atherosclerosis. Work to the future should be directed at a precise understanding of the events in the coronary bed that initiate dynamic stenoses and the relationship of these events to each other.

TREATMENT

The major goal of the treatment of patients with unstable angina pectoris is to prevent the death or myocardial infarction, the increased risk of which the unstable syndrome has heralded. The risk is greatest immediately after destabilization but remains raised for several months. The patient with unstable angina has a need for hospitalization that probably is as great as the patient with acute myocardial infarction (38, 39). If the patient has had angina in the last 24 hours, admission

to an intensive care unit is the most prudent course. Quiet bed-rest is crucial and in years past, as the only treatment available, was often sufficient to restabilize the patient. Myocardial infarction should be searched for with ECG, enzymatic, and scintigraphic studies. Any precipitating causes such as tachyarrhythmias, heart failure, fever, thyrotoxicosis, hypoxia, severe hypertension, and anemia, etc. should be sought for and corrected when present.

Drug Treatment

Many patients will be admitted to the hospital already receiving antiangina drug therapy. Unless that regimen appears to have paradoxically worsened symptoms, it should be continued. The major paradoxical response of concern is with beta-adrenergic blockers. A fraction of patients with variant angina pectoris appear to have worsened coronary vasospasm when administered beta-blockers (or other sympatholytic agents (106). The data implicating abnormal coronary tone as a cause of unstable angina certainly at least raises the possibility of a similar paradoxical worsening in unstable angina as in variant angina. But having given the warning, it must be said that such paradoxical worsening in unstable angina pectoris is rare. A paradoxical worsening may also occur if unacceptable bradycardia, tachycardia, hypotension, or worsened heart failure have accompanied use of nitrates (hypotension, bradycardia, heart failure), or calcium blockers (hypotension, bradycardia, tachycardia, heart failure) alone or in combination. In this case, the agent(s) responsible for the lowered coronary perfusion pressure or raised $M\dot{V}O_2$ that will result must be sought out and corrected.

Drug therapy has a dual role for the patient with unstable angina: [1] to quickly restabilize the anginal syndrome; and [2] as part of long-term therapy to provide a satisfactory quality of life after re-stabilization has been achieved. Our current understanding of the pathophysiologic basis for destabilization of angina and a better understanding of the ways that nitrates, beta-adrenergic blockers, and calcium blockers prevent myocardial ischemia allows construction of rational drug therapy.

Nitrates

Nitrates have a dual mechanism of action in coronary heart disease. They increase venous capacitance and thereby decrease cardiac preload and $M\dot{V}O_2$. They are potent dilators of the large coronary arteries and at high doses of coronary arterioles. The controversies about the efficacy of orally administered nitrates have been settled. Oral agents are effective if they are given in high enough doses frequently enough. Tolerance to the venous capacitance effects appears to be minimal. It is unknown whether tolerance to the coronary vasodilating properties occurs with long-term administration. Long-acting nitrates can be administered through the buccal mucosa, by mouth, or transcutaneously (107).

Their coronary vasodilating properties, our long familiarity (108) with nitrates, and the ease of their administration make nitrates the first choice in the initial management of unstable angina. Fairly high doses will usually be required and the dose should be adjusted upward rapidly until either headaches, orthostatic hypotension or complete relief of symptoms is achieved. Cutaneous administration, with ointment or transcutaneous patches, are particularly well-suited. Absorption is fairly reliable, moderately large doses can be administered, and nitrate levels fall to low levels within about 30 minutes of removal from the skin, in the event administration must be stopped abruptly. For the patient with frequent episodes at the time of admission or for the patient who does not come under control easily with conventional nitrate administration, intravenous nitroglycerin is the most practical choice for achieving prompt, high, and consistent nitrate levels (109). Nitrate levels fall quickly after the infusion is stopped. In the last few years nitroglycerin for intravenous administration and special intravenous tubing for its administration have been marketed, thus eliminating the necessity of crushing and dissolving nitroglycerin tablets and sterilizing the solution with a millipore filter every 8 hours. It is important to use glass bottles and specially prepared i.v. tubing. Standard plastic i.v. solution bags and infusion sets absorb large quantities of nitroglycerin. Even glass bottles and the special infusion sets absorb some of the nitroglycerin. As well, nitroglycerin is inherently unstable. These factors should be taken into account if the effects of an infusion appear to wane with time.

Beta-adrenergic blockers

When the beta-adrenergic blockers were introduced into clinical use almost 20 years ago, the mechanism of unstable angina was still considered to be transient elevation of MVO_2, in the face of severely limited coronary reserve. Beta-blockers which are effective for classical angina by preventing increases in MVO_2 brought about by increased sympathetic tone or circulating catecholamines, were naturally employed, at first cautiously, and then quite widely.

By most accounts (110-111) the results with beta-blocker therapy were highly successful, but the accounts were largely anecdotal. In light of our current understanding of the pathophysiology of unstable angina, we need to question the rationale of beta-blocker therapy as first-line treatment in the management of the patient with unstable angina and no history of exertional angina. Beta-blockers do not increase coronary blood flow or lyse coronary spasm. Indeed in rare patients, beta-blocker may decrease coronary flow as discussed above. Three small randomized prospective trials reported favorable results with beta-blocker therapy. Mizgala and his associates at the Montreal Heart Institute (112) randomly assigned 68 patients with unstable angina (progressive angina, acute coronary insufficiency, and postinfarction unstable angina) to placebo or propranolol therapy. The total incidence of acute events (death, MI, recurrent unstable angina) was significantly lower ($p < 0.05$) in the propranolol group during follow-up, which was an average of 19 months long.

Norris and coworkers in the United Kingdom (113) studied 43 patients with threatened infarction randomly assigned to propranolol or to a control group. (Threatened infarction is a term used by several groups of investigators for patients suspected to have infarction, but whose initial ECG and enzymes are not diagnostic. This classification not only includes patients with acute coronary insufficiency, but also patients in an early stage of evolving MI.) Significantly fewer ($p < 0.005$) patients developed abnormal Q waves and creatine kinase release was considerably ($p < 0.1$) lower in the propranolol group.

In a controlled (non-placebo) trial of early intervention with atenolol in 400 patients with suspected MI, Yusuf and Sleight and their associates (114-115) found that 143 of the 400 patients had threatened infarction. Patients were randomly assigned to atenolol treatment or no beta-blocker for 10 days. Significantly ($p < 0.01$) fewer of the atenolol than control patients progressed to MI (by their ECG and enzyme criteria).

But there are also negative data. Telford and Wilson conducted a double-blind, placebo controlled trial in 214 patients of placebo, heparin, atenolol, or heparin and propranolol. They found no protective effects of atenolol (116).

Thus, while not unequivocally proved, beta-blocker therapy probably provides a protective effect for the patient with unstable angina similar to that reported recently for patients with MI.

Treatment with beta blocker is certainly rational for the unstable angina patient with a history of exertional angina.

Calcium-blockers

Three calcium blockers have been introduced into clinical use in the United States in the last few years. While these drugs, nifedipine, diltiazem, and verapamil differ in their potency for peripheral vasodilation, and decreased inotropic, chronotropic, and dromotropic effects on the heart, all three improve blood flow to ischemic myocardium at rest and and exercise and are effective in preventing coronary spasm (117). The timing of their introduction was such that several critical analyses of their role in the treatment of unstable angina have been undertaken.

Three cross-over studies (118-120) demonstrated a significant reduction of episodes of ischemia (angina and ST-segment deviation) with verapamil therapy compared to placebo. One of these studies (118) was a three-way study including propranolol, which was significantly better than placebo, but was significantly inferior to verapamil.

A randomized trial of diltiazem versus propranolol (121) in decreasing the frequency of pain showed that the calcium-blocker was significantly better than the beta-blocker.

Five uncontrolled studies (122-126) of the addition of nifedipine to the regimen of patients who had failed conventional treatment with nitrates and β-blockers all reported successes in large fractions of their cases. A randomized, placebo-controlled trial of the addition of nifedipine to conventional nitrate and β-blocker therapy was performed

at Johns Hopkins (127) in 138 patients. The combined incidence of death, MI, and need for by-pass surgery was significantly higher ($p=0.03$) in the placebo group. A randomized multi-center trial for 14 days in 126 patients of conventional (β-blocker and nitrate) versus nifedipine therapy (128), however, failed to demonstrate significant differences in the frequency of episodes of ischemia or in progression to MI. However, in this study, propranolol administration was continued if it had been previously given, regardless of treatment assignment. In those 67 patients, addition of nifedipine was significantly ($p=0.026$) better than an increase in conventional therapy. On the other hand, for the 59 patients not receiving propranolol before, initiation of nifedipine alone (which tended to increase heart rate) was significantly ($p< 0.001$) worse than conventional therapy. In a companion study, a randomized double-blind, placebo-controlled trial, the same group (129) did not demonstrate prevention of progression to infarct when patients with threatened MI were treated with nifedipine.

Thus, in summary, calcium blockers have generally been shown to decrease the number of episodes of ischemia in unstable angina. Further, the evidence is strong that they are superior to beta-blockers in this regard as long as deleterious hemodynamic effects, such as tachycardia, are blocked. The best effects may be achieved when calcium blockers are combined with nitrates and beta-blockers in a three-drug regimen (that is carefully chosen so as to avoid unwanted hemodynamic side-effects).

Anti-thrombotic drug therapy

Several trials of anticoagulation were performed in the 1960s (27-28, 130-132). The results were contradictory. By the standards that we apply to clinical trials today, they are flawed. In the early 1970s, the role of coronary thrombosis in the cause of MI had come under question and interest in using anticoagulation for "pre-infarctional" states waned accordingly. Later in the 1970s, however, it became clear that most patients with transmural (Q-wave) infarcts and about one-half the patients with non-transmural (non Q-wave) infarcts have pre-MI coronary thrombosis (133). Furthermore, the recognition that unstable angina is due to transient reductions in coronary blood flow which might be a pre-emble to coronary thrombosis puts anticoagulation on a firmer theoretical footing. Interest in anti-thrombotic therapy has risen accordingly.

Recently, two studies with heparin treatment have been reported. The first, from North Ireland, was the previously mentioned randomized, double-blind, placebo controlled trial in 214 patients of i.v. heparin for 7 days followed by warfarin for 8 weeks, atenolol, or both drugs (116). The study was comprised of three groups: crescendo angina, acute myocardial insufficiency, and non-transmural infarctions. Unfortunately the data were not presented in a way to allow separation of the group with infarction from the two groups with unstable angina. Nevertheless, heparin therapy was associated with a statistically significant ($p=0.024$) reduction in progression to transmural infarction. The second study was an uncontrolled

study comprised of 42 patients, 25 with unstable angina and 17 with acute infarction who received long-term therapy with daily subcutaneous heparin (134). The mortality of these patients was reported to be lower than the age and sex matched death rate for the general American population.

But in the coronary arteries, especially atherosclerotic coronaries, it is more likely that platelet aggregation leads to coronary thrombosis than stimulation of the clotting cascade. The growing evidence for enhanced platelet activation in patients with coronary disease and the suggestions that anti-platelet therapy with aspirin might be protective against death and acute myocardial infarction in patients with coronary heart disease led to initiation of a trial with aspirin in men with unstable angina in the mid-1970s. The results were reported last summer (51). Administration of 325 mg of aspirin once a day begun within 51 hours of hospital admission and for 12 weeks thereafter led to a statistically significant halving of the death and infarction rates compared to placebo-treated control patients. (fig 6, table 5). At about the same time as this trial started, several trials with anti-platelet agents were begun in survivors of MI. With a few exceptions, these trials showed a trend toward reduced reinfarction and death, but the changes were not great enought to achieve statistical significance (135). There are several possible explanations for the greater effects demonstrated with unstable angina than with survivors of MI. The first is the dose of aspirin. The unstable angina study choose a dose of 325 mg per day because it was known when that trial started that that dose caused near-maximal inhibition of *in vitro* platelet aggregation. The post-MI studies with one exception, administered aspirin in divided doses, totalling about a gram a day. In recent years, we have learned that low (40-80 mg) or intermediate (325 mg) dose aspirin given once a day (or less frequently) provides marked suppression of platelet thromboxane A_2 production, but may not totally suppress vascular production of the vasodilatory, anti-platelet aggregatory prostanoid, prostacyclin I_2 (136). Aspirin in higher doses administered several times a day, however, probably blocks prostacyclin production near-maximally. A second possible reason is that the unstable angina patients were studied at a time of maximal risk, when intervention with a platelet inhibitor had the greatest chance of exhibiting a protective effect. In contrast, many of the patients with MI were entered into the study protocols months or years after MI, a time of less risk and a time when enhanced platelet activity is probably less important.

Aspirin therapy was not, however, associated with a reduction in the frequency of angina or a reduction in the frequency of recurrent unstable angina.

There are too few data available now to attempt comparison of the protective effects of specific thromboxane synthetase inhibitors or thromboxane receptor antagonists with heparin and aspirin.

In summary, recent re-examinations of anti-thrombotic therapy, especially anti-platelet therapy with aspirin, demonstrate protection from progression to infarct and death, but unlike beta-blocker, calcium-blocker, and nitrate therapy, no diminution in the frequency or severity of angina.

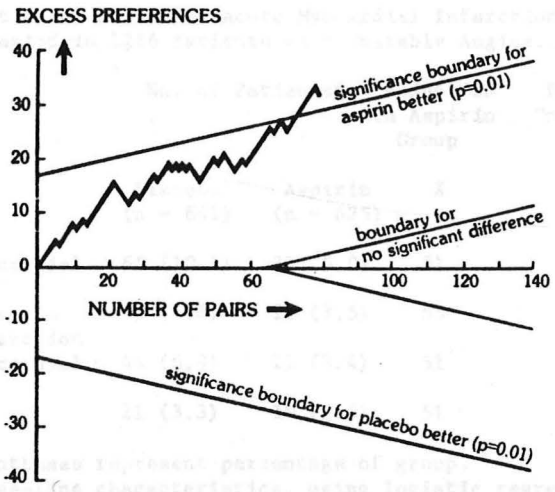

Figure 6. Sequential Analysis for the Combined End Point Death or Acute Myocardial Infarction in Patients with Unstable Angina. This is a sequential plan (Table 3.2 from Armitage[25]) with a two-sided overall significance level of 0.01. Each patient receiving aspirin is paired with a patient receiving placebo on the basis of entry date. The abscissa represents the number of pairs in which a preference occurred (within a pair, the patient receiving one treatment died or had an acute myocardial infarction, whereas the other did not). The ordinate represents the direction of the preference (plot moves up one unit if preference is in favor of aspirin, down one unit if preference is in favor of placebo). If the sample path had crossed either boundary for no significant difference, we would have had 95 per cent confidence that the reduction in the event rate is not as large as 50 per cent. The significance boundary was crossed on the 75th pair when there were +29 excess preferences (52 preferences in favor of aspirin and 23 in favor of placebo). This ensured that the difference between the treatment groups for the end point death or acute myocardial infarction was significant at the 0.01 level even after we allowed for multiple tests during the trial.

TABLE 5

ASPIRIN THERAPY FOR UNSTABLE ANGINA

Frequency Distribution of Death and Acute Myocardial Infarction during the 12-Week Study Period in 1266 Patients with Unstable Angina.

Event	No. of Patients*		Reduction In Aspirin Group	P Value Unadjusted	P Value Adjusted†
	Placebo (n = 641)	Aspirin (n = 625)	%		
Death or acute myocardial infarction	65 (10.1)	31 (5.0)	51	0.0005	0.0002
Fatal or nonfatal acute myocardial infarction	50 (7.8)	22 (3.5)	55	0.001	0.0003
Nonfatal acute myocardial infarction	44 (6.9)	21 (3.4)	51	0.005	0.002
Death	21 (3.3)	10 (1.6)	51	0.054	0.059

* Figures in parentheses represent percentage of group.
† Adjusted for base-line characteristics, using logistic regression model.

TABLE 6

EMERGENCY SURGERY FOR UNSTABLE ANGINA

Study	Reference	No. of Patients	Follow-up
NIH	46, 142-143	288	30 mos.
Parkland	Pugh, et al, 145	27	18 mos.
Portland VAMC	Selden, et al, 144	40	4 mos.
Buenos Aires	Bertolassi, et al, 43-44	113	32 mos.

Therapy with vasodilatory and anti-platelet prostaglandins

A small number of patients in several centers have been treated with intravenous infusion of prostaglandin I_2 (prostacyclin) (137-138) or prostaglandin E_1 with reports of benefit in some but not all patients (139). These prostaglandins dilate the coronary arteries and inhibit platelet aggregation. They also dilate peripheral vessels and, thus, may cause deleterious hypotension and reflex tachycardia. A multi-center double-blind, placebo-controlled trial of intravenous prostacyclin therapy was begun recently. The patients in this trial are also treated with anti-anginal agents and may be treated with anti-platelet agents if the patient's physician so chooses. No major protective or deleterious effect of intravenous prostacyclin is apparent so far in this trial.

Revascularization Therapy

Since my last discussion of unstable angina, the proper role of surgery in the unstable angina patients has been greatly clarified. Soon after the introduction of coronary bypass surgery, emergency revascularization surgery for unstable angina was undertaken in a number of centers. What could be more natural in impending infarction than to try to bypass the offending stenosis emergently? At the last discussion, I reviewed scores of non-concurrent, non-controlled and non-randomized clinical trials. These trials showed clearly that the incidence and severity of angina was reduced in survivors of surgery, but the results of prevention of infarction and death were very unclear. Furthermore, reports from centers with excellent surgical facilities showed that emergency surgery imposed a mortality rate several-fold higher than operation on patients comparable except for stable symptoms (140-141). Fortunately, since then, four randomized trials of urgent coronary bypass surgery plus medical therapy vs medical therapy alone have reported their results (43-44, 46, 142-145). One additional trial is still underway. Fortunately, the similarities in the results exceed the differences, so that a reasonable synthesis of the role of urgent surgery is possible. The studies are identified in table 6. The NHLBI, Portland VA, and Parkland studies used similar definitions of unstable angina and randomized patients after coronary arteriography. The Buenos Aires study randomized patients before coronary arteriography and divided their patients into two groups, the intermediate syndrome and those with progressive angina. Those with progressive angina had accelerated (crescendo) angina. Classification into the intermediate syndrome was based upon somewhat complicated criteria. Among the major criteria were prolonged recurrent rest pain and normal cardiac enzyme level of 50% above basal level. Thus the group in the intermediate syndrome presumably included some patients with small amounts of myocardial necrosis who would have been excluded from the other three studies.

The incidence of MI during initial hospitalization is shown in table 7. The results are uniform. Urgent surgery did not prevent myocardial infarction. Indeed the surgical groups had an infarction rate during initial hospitalization that was 2 or 3 times the medical groups. Virtually all of the surgical group infarcts were perioperative.

TABLE 7

EMERGENCY SURGERY FOR UNSTABLE ANGINA

Myocardial Infarction During Initial Hospitalization

	No. of Patients	Medical	Surgical
NIH	288	12/147 (8%)	24/141 (17%)
Parkland	27	0/14 (0%)	2/13 (15%)
Portland VAMC	40	0/19 (0%)	3/21 (14%)
Buenos Aires			
Intermediate	52	2/24 (8%)	4/28 (14%)
Progressive	61	0/27 (0%)	4/34 (12%)
Totals	468	14/231 (6%)	37/237 (16%)

TABLE 8

EMERGENCY SURGERY FOR UNSTABLE ANGINA

Mortality During Initial Hospitalization.

	No. of Patients	Medical	Surgical
NIH	288	4/147 (3%)	7/141 (5%)
Parkland	27	0/14 (0%)	1/13 (8%)
Portland VAMC	40	0/19 (0%)	1/21 (5%)
Buenos Aires			
Intermediate	52	5/24 (21%)	3/28 (11%)
Progressive	61	1/27 (4%)	3/34 (9%)
Totals	468	10/231 (4%)	15/237 (6%)

The incidences of death during initial hospitalization are shown in table 8. Only one of the differences between medical and surgically treated groups, the intermediate syndrome patients of the Buenos Aires study were statistically significant. Total mortality and infarction rates for all of these four studies are shown in table 9. The follow-up averaged 30 months in the Parkland study, four months in the Portland VA study, and 32 months in the Buenos Aires. During long-term follow-up, more patients in the medical groups sustained MI than in the surgical group so that the incidence of MI was no longer different. Again, the only significant difference between medical and surgical patients groups was within the intermediate syndrome group in the Buenos Aires study. In an attempt to resolve this discrepancy, Conti and Curry reanalyzed the outcomes of patients in the NIH study and redefined their patients using the definition of the intermediate syndrome of the Buenos Aires study (146). Of these, 131 were randomized to medicine and 128 to surgery. There were 11 deaths in both groups of patients (8% for medical therapy and 9% for surgical therapy). Thus they were unable to confirm the results with this particular subset of patients in the Buenos Aires study.

The frequency of class III-IV angina at any time during follow-up in the medial and surgical groups at long-term follow was, however, quite different (Table 10). About one-third of the medical group in the NIH study experienced severe enough angina to warrant cross-over to surgical therapy during long-term follow-up. A very interesting insight was provided by that group. Their surgical mortality was considerably lower than for the patients who underwent urgent coronary revascularization (46). That finding has been confirmed by others (147-148).

From the results of these four trials, the following recommendations regarding the role of surgery can be made:

1) There is no basis for emergency surgery to prevent MI or death.
2) The vast majority of patients can be stabilized, at least initially, with aggressive drug therapy.
3) One-third or more of the patients will experience limiting angina during long-term follow-up and will require elective surgery, which can be carried out with less risk than when performed urgently during the unstable state.

Percutaneous Transluminal Coronary Angioplasty (PTCA)

Percutaneous transluminal balloon angioplasty has now been performed on the coronary vessels of several thousand patients with coronary heart disease (Dr. David Hillis will review PCTA at Medical Grand Rounds on June 21, 1984.) Most of those patients have undergone PTCA for the management of chronic exertional angina but some patients with unstable angina have undergone PTCA. As was the case with bypass surgery, the rate of complications has been reported to be higher for patients with unstable angina (149). Not unexpectedly, it appears likely that a period of intensive medical therapy in order to allow elective PTCA will, like bypass surgery, allow angioplasty with complications no more frequently than with stable angina (150-151).

TABLE 9

EMERGENCY SURGERY FOR UNSTABLE ANGINA

Total Mortality and Myocardial Infarction Rate

Average Duration of Follow-up	No. of Patients	Death		Myocardial Infarction	
		Medical	Surgical	Medical	Surgical
30 mo NIH	288	13/147 (9%)	14/141 (10%)	32/147 (22%)	43/141 (30%)
18 mo Parkland	27	1/14 (7%)	1/13 (8%)	1/14 (0%)	3/13 (23%)
4 mo Portland VAMC	40	0/19 (0%)	1/21 (5%)	2/19 (11%)	3/21 (14%)
32 mo Buenos Aires					
Intermediate	52	11/24 (46%)	3/28 (11%)	9/24 (38%)	4/28 (14%)
Progressive	61	2/27 (7%)	3/34 (9%)	2/27 (7%)	4/34 (12%)
Totals	468	24/231 (12%)	22/237 (9%)	45/231 (19%)	57/237 (24%)

TABLE 10

EMERGENCY SURGERY FOR UNSTABLE ANGINA

Follow-up of Functional Classes III and IV

Average Duration of Follow-up	Medical (%)	Surgical (%)
30 mo NIH	45	15
18 mo Parkland	38	0
4 mo Portland VAMC	63	4.7
32 mo Buenos Aires		
Intermediate	16.6	3.5
Progressive	18.5	0

The current indications for PTCA for the patient recovering from unstable angina are the same as for stable exertional angina. Briefly, the ideal patients have the following characteristics:

1) They are candidates for bypass surgery.
2) They have one-vessel coronary narrowing in a proximal segment. (The order of preference is anterior descending > right > circumflex).
3) The stenoses are short, concentric, non-calcified, and are not in an area prone to undergo spasm.

Intra-aortic Balloon Pump (Circulatory Assistance)

Of the various circulatory assistance devices that have been developed, only the intra-aortic balloon pump has had a lasting impact. This device can be inserted operatively or percutaneously into the descending thoracic aorta. The balloon, containing about 30 ml of gas, alternately rapidly deflates during early systole and inflates during early diastole thus lowering systolic and raising diastolic blood pressure. Theoretically, this should lower $M\dot{V}O_2$ and increase coronary blood flow.

Intra-aortic balloon pump assistance has been applied to patients with unstable angina with great success (152-153). In my experience it virtually always is successful in achieving restabilization of angina, even when all other measures have failed. The improvement owes chiefly to reduced $M\dot{V}O_2$ rather than increased coronary flow (154). The invasiveness of the procedure, its complication rate, and its expense limit its application to cases where drugs have failed and imminent revascularization is contemplated.

IDENTIFICATION OF HIGH-RISK PATIENTS

As with all of the clinical syndromes of myocardial ischemia, it is important to define high- and low-risk subgroups (for death, MI, and severe angina) in order to limit aggressive diagnostic procedures and therapeutic interventions to those who are the most likely to benefit. No entirely practical and highly sensitive and specific risk stratification technique has yet been forthcoming, but continued pain in the hospital and ST and T-wave abnormalities help to mark a high-risk group (37). Drs. Nixon, Lipscomb, Narahara, Hillert, Brown and I carried out a series of studies of patients at the VA that suggest that evaluations of left ventricular function and work capacity may be useful in risk stratification. Submaximal exercise (targeted to a heart rate of 120) performed a week after restabilization of symptoms was useful in an early determination of the risk of Class III/IV angina in the 3 months after hospital discharge (155). Abnormal elevation, at the time of hospital discharge, of the ratio of left ventricular end-diastolic volume to corrected mitral valve closure time LDD/PR(ECG) - AC (mitral valve ECHO) predicted a group at high risk for Class III/IV angina (156). This ratio has been found to be predictive of clinical course in several groups of patients with

coronary heart disease and is postulated to be a reflection of the left ventricular pressure/volume relationship. Studies with echocardiography (85) and gated blood-pool scintigraphy (86) showed that changes in left ventricular contractile function during initial hospitalization aids in predicting later class III/IV angina. Patients whose contractile performance improved during hospitalization had a much smaller likelihood of developing class III/IV angina than those whose contractile performance stayed the same or deteriorated. Johnson et al in a study performed in Dallas found that abnormal ST-segment motion found on continuous tape-recorded 2-channel ECG monitoring helped find high-risk subsets with variant angina, left main coronary artery stenoses, and patients with poor prognoses (157). Patients with the diagnosis of unstable angina established by ECG and routine enzyme determinations, but who have positive pyrophosphate cardiac scans (158) or raised CK-MB values (159) are also in a high-risk group.

A RECOMMENDED PLAN OF MANAGEMENT

The patient with discomfort consistent with myocardial ischemia in an unstable pattern with acute myocardial ischemia or crescendo angina should be hospitalized in a quiet environment with bedrest. If the patient's last episode of discomfort was within 24 hours of presentation, admission to an ICU is the most prudent course. Any precipitating factors should be sought out and corrected. The presence of myocardial necrosis should be looked for with appropriate serum enzyme, electrocardiographic, and scintigraphic studies. If evaluation in the first 12-24 hours for myocardial necrosis is negative, treatment for unstable angina should be started. During early evaluation and treatment, it is particularly important to look for evidence for left ventricular dysfunction (exam and chest x-ray), continued pain at bedrest, and transient ST-segment and T-wave changes of ischemia. These abnormalities can easily be ascertained at the bedside, especially if the patient is in an ICU, and help identify the high-risk patient. It is too expensive and impractical to recommend routine Holter ECG monitoring, gated blood-pool scintigraphy, and echocardiography for every patient. They can play an important role, however, in evaluating certain difficult cases and may be very useful in investigation in establishing subgroups with differing risk, etc.

If the patient has been receiving an anti-angina regimen, the possibility of paradoxic worsening should be considered and the offending drug should be discontinued or the dose altered. If the patient has not been receiving anti-anginal medicines or has received nitrates only, I favor initiating therapy with nitrates and a calcium blocker. The choice of calcium blocker rests upon the hemodynamic effects (heart rate, inotropic state, and blood pressure) that are desired or unwanted for a given patient. If nitrates and nifedipine are chosen, a careful watch for hypotension and a reflex tachycardia are prudent. The tachycardia should be prevented by addition of beta-blocker therapy. Doses of drugs should be increased frequently so that the desired effects are obtained within a few days. For patients who have previously been treated with

nitrates and calcium blockers, beta-blockers should be added.

Unless contraindicated, anti-thrombotic therapy should be started. Current data favor aspirin administration. If it is feared that early surgery will be required, some prefer heparin because of concerns about post-operative bleeding following aspirin therapy. Use of an anti-platelet agent such as sulfinpyrazone that exerts an anti-platelet effect only when the drug is present in the circulation and thus is quickly reversible is untested but, may be a rational alternative to aspirin in the patient who may require early surgery. While anti-thrombotic therapy will probably not contribute to diminishing angina, it should diminish the chance of progression to MI or death. The role of thrombolytic therapy will require further clarification in the future. The risks of emergency coronary arteriography to identify thrombus and the risks of streptokinase or urokinase are too great to allow routine recommendation of thrombolytic therapy with these agents, either into the coronary arteries or intravenously, for patients with unstable angina.

With such a treatment regimen, greater than 90% of patients will restabilize. Intravenous nitroglycerin is the logical next step for patients who are failures with conventional drug therapy. The majority of the remaining patients will stabilize with this intervention. For the few remaining failures, an intra-aortic balloon should be inserted if it is technically feasible and is successful in regaining clinical stability in almost all.

Coronary arteriography and revascularization with surgery or PTCA should be delayed if at all possible until the patient has been free of pain for at least 24 hours.

After clinical stability has been regained, the physician must plan for long-term management. A decision must be made regarding the desirability of coronary arteriography and revascularization. Patients who require i.v. nitroglycerin or an intra-aortic balloon pump for restabilization will obviously require early coronary arteriography and revascularization if feasible. There are differences of opinion about the role of routine elective coronary arteriography for the patients who restabilize with conventional hospital therapy. Some advocate elective coronary arteriography for all these patients in order to identify the 10-15% with insignificant or no coronary obstructions and the 10-15% of patients with >50% obstruction of the left main coronary artery. Others recommend delaying coronary arteriography until and unless class III/IV angina occurs. Until we have a non-invasive technique that is highly accurate for quantifying the extent of coronary heart disease this debate will continue.

Unfortunately, the extent of coronary disease as an isolated variable is only a weak predictor of subsequent class III/IV angina. We have found that submaximal exercise testing a week or more after restabilization to: (1) be very helpful in the prognostication of subsequent limiting angina, and (2) to not be unduly risky (155). It has not met with universal acceptance, however, because of concerns that it may contribute to another episode of unstable angina.

For the patient who restabilized with conventional therapy, the recommendations for bypass surgery are not greatly different than for patients with stable exertional angina, in my view. The major indications for surgery are the presence of left main coronary obstruction >50% and class III/IV angina in spite of good medical therapy. The possible role of bypass surgery for prolongation of life in some subsets of patients with 3-vessel disease and 2-vessel (with anterior descending involved) disease were discussed at these exercises a few months ago. (Dr. Kirk Lipscomb, Medical Grand Rounds, October 13, 1983). Routine recommendation for revascularization for all patients with unstable angina who are candidates for the procedure has its adherents (160), but I do not think that our current knowledge supports that stance. Future work in patients with unstable angina should be directed at deriving better techniques for early prediction of limiting angina. We know that about 1/3 of the patients who restabilize with medical therapy will require surgery within the first year of follow-up. They will experience considerable disability and incur much expense during that interval that could have been eliminated by earlier revascularization. On the other hand, it would be ideal to avoid risky and expensive invasive procedures for the nearly 2/3 of the patients who do very well after restabilization.

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