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ELECTROCARDIOGRAPHIC RESPONSES TO MYOCARDIAL ISCHEMIA.

MECHANISMS AND SOURCES OF VARIABILITY

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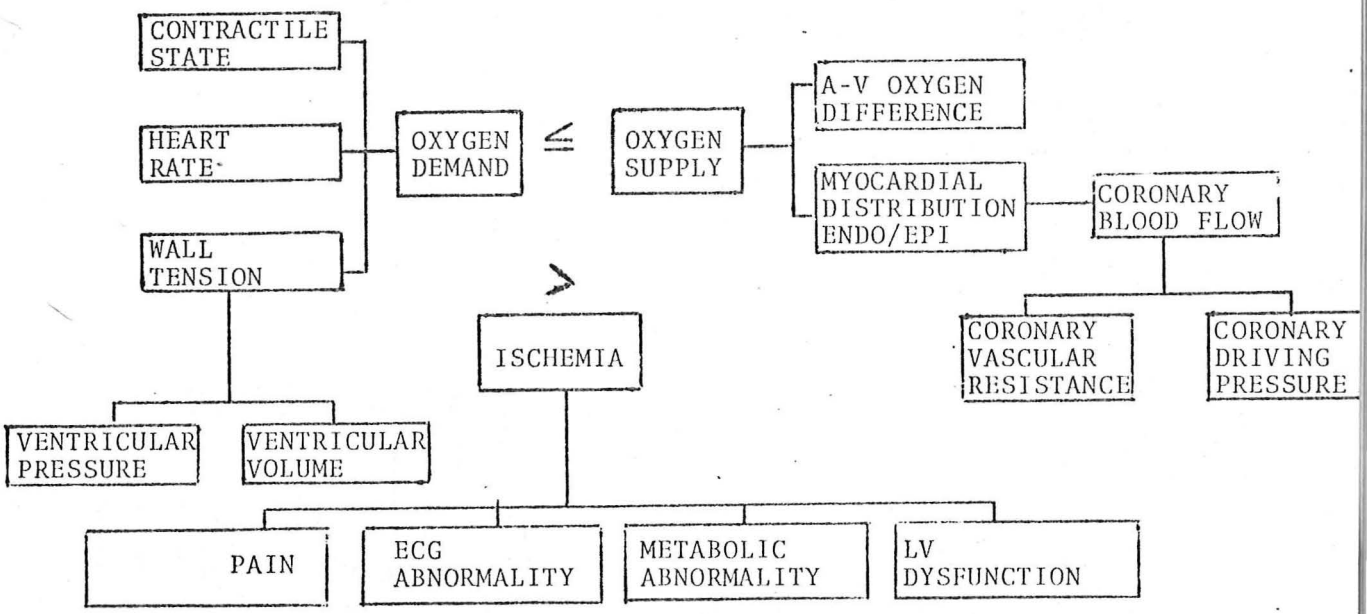
CONTENTS

Clinical electrocardiography is unquestionably an empirical branch of medicine. Diagnostic statements are primarily based on information derived from simple correlative clinical and pathological studies. The gap between clinical electrocardiography and basic electrophysiology and biophysics is still wide but it is being bridged. Myocardial ischemia provides an excellent example. This is an area in which recently a large amount of new data have become available relating to the interaction between anatomy and hemodynamic, metabolic, and electrical events. The discussion will focus on the various manifestations of transient ischemia.

I. PATHOPHYSIOLOGY OF MYOCARDIAL ISCHEMIA

Current concepts of the pathophysiology of myocardial ischemia are presented in diagrammatic form in Figure 1, modified after Ross (1971).

Figure 1



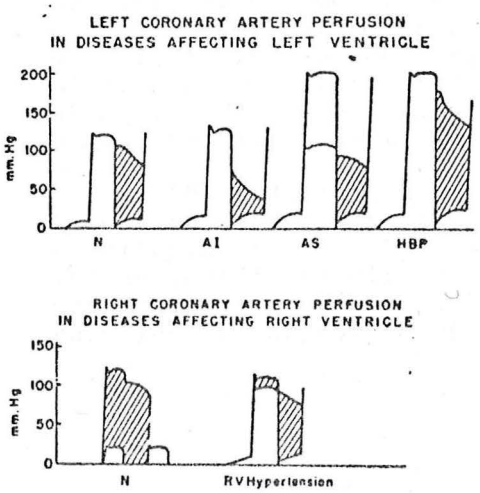
Determinants of Myocardial Oxygen Supply

The heart operates with a narrow margin of oxygen supply. Venous oxygen saturations of 30% with pO_2 in the range of 18 to 20 mm Hg are normally found only in the coronary veins and in blood leaving exercising skeletal muscle. However, skeletal muscle activity can be supported by anaerobic metabolic processes to a much greater extent than cardiac muscle activity. Any increase in myocardial oxygen demand must therefore primarily be satisfied by an increase in *coronary blood flow*. Average coronary blood flow at rest in normal subjects is about 70 ml/100 gm/min (HOLMBERG, 1967). Mean flow values as high as 280 ml/100 gm/min have been reported during heavy submaximal exercise in young normal subjects (KITAMURA *et al.*, 1972).

Coronary driving pressure and *coronary vascular resistance* are the two major determinants of coronary blood flow. The primary driving pressure is equal to the pressure gradient between the aorta and the right atrium for the bulk of the myocardium which is drained by the coronary sinus. In the free wall of the right ventricle and in part of the interventricular septum the driving pressure is equal to the pressure gradient between the aorta and the right ventricle. These areas are drained by veins bypassing the coronary sinus. The primary driving pressure is opposed by the intramural pressure. Intramyocardial tension is normally greater than the cavity pressure in all areas, highest in the subendocardium and gradually falling toward the epicardium. Tissue pressure effectively restricts left ventricular flow to diastole, but a significant proportion of right ventricular coronary flow normally occurs during systole.

The effect of various cardiac lesions on coronary driving pressure is illustrated in Figure 2 (GORLIN, 1970).

Figure 2



Above, pressure-time relationships in normal individuals *N* and in those with aortic insufficiency *AI*, aortic stenosis *AS*, or hypertension *HBP*. *Below*, pressure-time relationships in the normal subject *N* and in the subject with right ventricular *RV* hypertension. Hatched area, effective perfusion pressure-time relationship.

The systolic area of the left ventricular pressure curve may be taken as an index of myocardial work and myocardial oxygen demand. The pressure gradient over time is proportional to coronary flow if vascular resistance is held constant. It is readily appreciated from Figure 2 that arterial hypertension is self-correcting with a simultaneous increase of myocardial work and driving pressure while aortic stenosis represents a particularly unfavorable structure with an increase in work and oxygen demand associated with a decrease in driving pressure and flow. Aortic stenosis predisposes to myocardial ischemia also in the absence of any coronary disease. This is strikingly illustrated by the fact that children with critical aortic stenosis virtually without exception develop ischemic S-T abnormalities during heavy exercise (HALLORAN *et al.*, 1972).

Recent studies have emphasized that reduction in driving pressure is important also for right ventricular function. Severe right ventricular hypertension causes a striking decrease in myocardial flow at a time when right ventricular myocardial oxygen demand is maximal (FIXLER *et al.*, 1973).

Coronary vascular resistance is affected by vascular anatomical abnormalities and by neurohumoral mechanisms. Anatomical abnormalities primarily affect flow on large vessels and the main effects of vasoregulation are exerted on the arteriolar level.

Physical laws governing fluid flow in rigid tubing indicate that, for a given pressure gradient, flow is proportional to the 4th power of the radius (fluid flow = pressure gradient x radius^4 x π/ vessel length x viscosity x 8, Poiseulle's equation). This does not imply that a 50% reduction of the lumen diameter of a large coronary artery reduces regional myocardial flow to 1/16 of the original rate. Development of collaterals is a significant factor in chronic obstructive disease, and several factors lessen the impact of an acute obstruction. The arteriolar resistance is normally high in the coronary circulation and the cross section area of a major vessel has to be decreased by two-thirds before any significant pressure gradient develops under resting conditions. However, even a moderately severe lesion may seriously restrict coronary flow during exercise (GORLIN, 1970). Data from experimental studies in dogs indicate that acute but gradual narrowing of a coronary artery produces progressive functional abnormalities at a time when the degree of constriction has reached one-fourth of the initial diameter (SAYEN *et al.*, 1958).

A 50% reduction of lumen diameter (corresponding to a 75% reduction of cross sectional area) has been generally accepted as a criterior for significant angiographic abnormality, *i.e.*, a lesion that is likely to produce clinical manifestations of myocardial ischemia (PROUDFIT *et al.*, 1968), but even less severe lesions appear to be associated with a small increase in

coronary morbidity and mortality (BRUSCHKE *et al.*, 1973).

α-adrenergic stimulation (norepinephrine) and pitressin cause vasoconstriction, and β-adrenergic stimulation (isoproterenol) causes vasodilatation. Vasoconstrictor effects are often transient and modified by a competing dilator stimulus activated by hypoxia and causing arteriolar dilatation (GORLIN, 1970). The exact role of humoral vasodilatation in ischemia, mediated by adenosine and bradykinin (ROSS, 1971) remains to be defined.

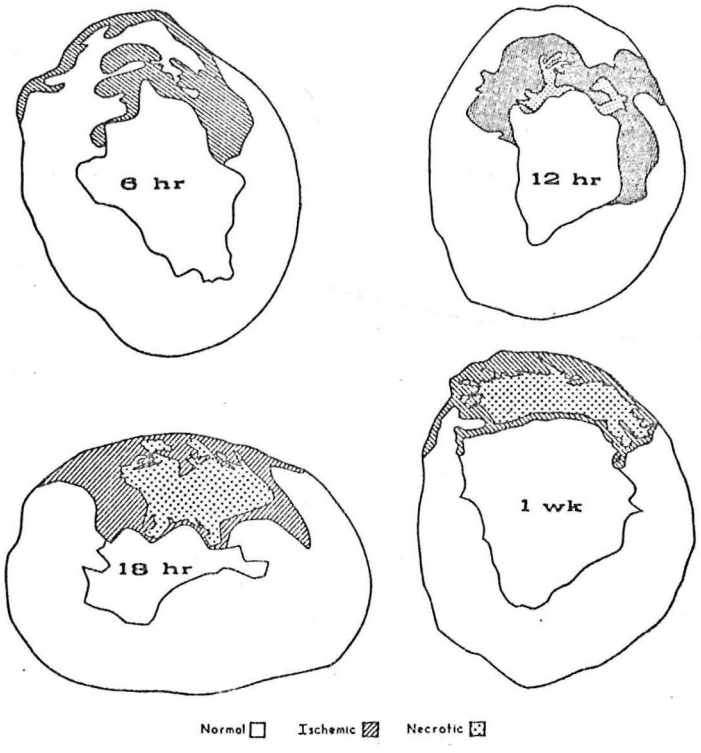
Recent studies have already demonstrated that there are important regional differences with respect to the *myocardial distribution of coronary blood flow*. The subendocardial layers of the myocardium normally function at a lower oxygen tension than the subepicardial layers. Subendocardial pO_2 values of 10 to 20 mm Hg with a transmural gradient of 8 to 13 mm Hg have been obtained with polarographic techniques (MOSS, 1968; WINBURY, 1971). Normal values for the blood flow ratio endo/epicardium are partially conflicting and tend to vary with the measurement method. Flow measurements using extravascular clearance of radioactive tracers generally show a flow ratio of less than 1 under normal conditions while intravascular methods such as the radioactive microsphere technique show resting flow ratios equal to or slightly above 1. A slightly higher subendocardial flow is still consistent with the transmural pO_2 gradient, since it has been estimated that the energy expenditure of subendocardial fibers is 1.5 - 2 times higher than that of subepicardial fibers (WINBURY *et al.*, 1971). Thus, the endocardial margin between adequate oxygen supply and ischemia is narrow even under normal resting conditions.

Recent studies have demonstrated that tachycardia causes a redistribution of blood flow in the normal heart with a decreased endocardial/epicardial flow ratio (NEILL *et al.*, 1973). There is abundant evidence indicating that the endocardium is much more vulnerable to flow reduction than the epicardium. Myocardial infarctions occurring in patients with significant coronary artery disease but without complete occlusions are generally subendocardial (EDWARDS, 1971). Measurements of blood flow after experimental coronary occlusion generally indicate a more severe ischemia in the subendocardial layers (BECKER *et al.*, 1971; FORMAN *et al.*, 1973).

Heterogenicity of coronary blood flow is an important characteristic of coronary artery disease. Pathological studies demonstrate a patchy irregular distribution of the necrotic and ischemic areas in myocardial infarction. This is the case also in experimental myocardial infarction after sudden and complete occlusion

of a major artery (Figure 3)(COX *et al.*, 1968).

Figure 3



Diagrammatic representation of the relative sizes of 3 morphologic zones of myocardium at varying intervals after coronary artery ligation.

Measurements of total coronary flow using nitrous oxide or krypton or xenon desaturation techniques under basal conditions have often failed to demonstrate any significant differences between patients with coronary lesions and normal subjects (KLOCKE AND WITTENBERG, 1969). This may be explained by arteriolar dilatation sufficient to compensate for major arterial obstruction resulting in a normal flow at rest. More likely, the normal flow in patients with significant arterial disease is an artifact due to the insensitivity of commonly employed methods to flow from underperfused areas. The heterogenicity of flow can be demonstrated also by analysis of mixed coronary sinus blood provided sensitive techniques are utilized. Clearance techniques based on direct myocardial or coronary arterial injection of the indicator substance have demonstrated monoexponential disappearance curves in normal hearts and two or more components in the presence of coronary artery obstructions (HORWITZ *et al.*, 1971). Failure to

sense slow components results in a falsely high average coronary flow (KOCKE AND WITTENBERG, 1969).

Similar considerations also apply to measurements of arteriovenous oxygen and lactate differences across the coronary bed (HERMAN *et al.*, 1967). Measurements of arterial-coronary sinus oxygen differences appear to be a more sensitive indicator of abnormality than coronary flow (HOLMBERG, 1967).

The complexity of coronary blood flow patterns is further illustrated by the response to vasoactive agents. There is evidence to suggest that nitroglycerin may improve subendocardial perfusion in the normal heart (WINBURY *et al.*, 1971) and the perfusion of chronically ischemic areas (HORWITZ *et al.*, 1971). However, nitroglycerin may in acute experimental coronary occlusion divert flow from vulnerable subendocardial regions (FORMAN *et al.*, 1973). Marked autoregulatory vasodilatation may in this experimental setting render the subendocardial vessels insensitive to nitroglycerin. Reduction of vascular subepicardial resistance after administration of nitroglycerin would in the absence of collateral distribution result in a steal of blood from deep to superficial myocardium. The coronary steal syndrome may have some clinical significance. Angina pectoris is occasionally precipitated by nitroglycerin (ROWE, 1970). Findings consistent with coronary steal during administration of isoproterenol have also been reported (BAKER *et al.*, 1969).

The last determinant of myocardial oxygen supply is the amount of oxygen that may be extracted from a given amount of arterial blood. The A-V oxygen difference is determined by a) *the oxygen content of arterial blood*, and b) *the tissues' ability to extract oxygen*. Under controlled experimental conditions, abnormalities of left ventricular function become apparent when the hematocrit is reduced below 24 - 31% (CASE *et al.*, 1955). It is impossible to estimate critical levels that would apply to a clinical situation. Presence of coronary arterial lesions, the effect of increased myocardial work and oxygen demand, and changes in coronary driving pressure modify the impact of any given reduction on oxygen content.

The clinical importance of changes in oxygen availability as determined by shifts in the dissociation curve of oxyhemoglobin is incompletely understood. As will be discussed later, the possibility that abnormal oxyhemoglobin dissociation characteristics may explain the syndrome of angina pectoris with normal coronary arteriograms is now considered remote, but there is some evidence that acute myocardial ischemia may affect the dissociation curve. Acute myocardial infarction causes a rightward shift in the oxyhemoglobin dissociation curve (KOSTUK *et al.*, 1973). The acute rightward shift has also been demonstrated in

patients with angina pectoris during atrial pacing. An increase in p_{50} (pO_2 at a saturation of 50%) was apparent only in coronary sinus samples but not in peripheral blood (SKAPPEL *et al.*, 1970).

Myocardial Oxygen Demand

Figure 4

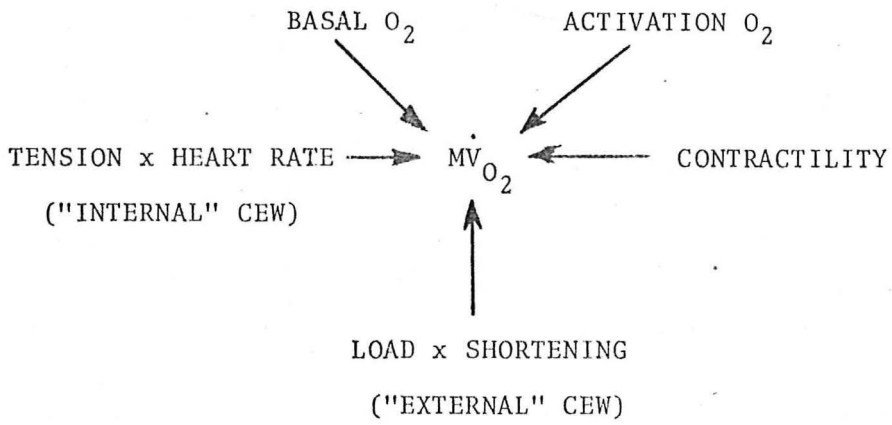


Figure 4 presents a more complete diagram of the determinants of myocardial oxygen demand (SONNENBLICK *et al.*, 1968) than the overview in Figure 1. *Activation energy* accounts for less than 1% of the total. *Basal metabolic rate* of the heart is less than 20% of the oxygen consumption of the beating heart on the intact resting subject. The major factors are internal contractile element work, *tension development*, *heart rate*, and *contractile state*. The *wall tension* varies with cavitary pressure, ventricular volume, and ventricular wall thickness. Tension is roughly proportional to the product of intracavitary pressure and to the square of the radius (the La Place relation), and inversely related to wall thickness. Tension *development* is much more important than the time tension is *maintained*. Release of all intraventricular pressure midway through systole reduces myocardial oxygen consumption by less than 10%. External contractile element work, the product of load and shortening, requires relatively little energy utilization in excess of the demand of tension de-

velopment or internal work. An increase of myocardial external work obtained by increasing pressure requires much more oxygen than an equally large increase due to an increase in the amount of fiber shortening, *i.e.*, an increase in stroke volume.

Contractile state is a major determinant of myocardial oxygen demand but this is not readily appreciated in the clinical situation, *e.g.*, after administration of digitalis in heart failure. An increase in the velocity of fiber shortening requiring an increase in energy utilization is often counterbalanced by a decrease in ventricular volume and wall tension.

Quantitative estimates of myocardial oxygen consumption are desirable in many clinical situations, *e.g.*, for objective evaluation of the effect of various therapeutic interventions in patients with coronary disease on the threshold of myocardial ischemia. Wall tension and contractile state cannot be properly evaluated without measurements of ventricular volume, unobtainable in most clinical situations. KATZ and FEINBERG (1958) demonstrated a close correlation between myocardial oxygen consumption and the product of heart rate and mean systolic blood pressure. SARNOFF *et al.* (1958), introduced the tension-time index, *i.e.*, the area under the left ventricular (or aortic) pressure curve times heart rate, as an estimate of myocardial oxygen demand.

The simple product of heart rate times systolic blood pressure or the triple product heart rate times systolic blood pressure times ejection time has been used in clinical studies (B. ROBINSON, 1967). The validity of the simple product heart rate times systolic blood pressure as an index of myocardial oxygen demand has been supported by recent direct measurements of myocardial oxygen uptake in normal subjects at rest and during exercise (KITAMURA *et al.*, 1971). Angina and ischemic ECG abnormalities occur at a reproducible level of the heart rate times blood pressure product (ROBINSON, 1967; BLOMQVIST AND ATKINS, 1971; SMOKLER *et al.*, 1973). However, interventions that have significant effects on contractility and ventricular volume invalidate the index as demonstrated in Table 1. The apparent threshold level of myocardial ischemia is falsely low, most likely due to an increase in ventricular volume, following administration of β-blocking agents.

Table 1

Effect of Placebo and Beta-adrenergic Blockade on the Threshold of Exercise-induced Ischemia

	MEAN VALUES DURING EXERCISE			
	HEART RATE	BLOOD PRESSURE	HR x SBP	WORK LOAD AT ANGINA
No Drug	110	156/92	173	339
Placebo	108	158/88	173	344
Propranolol	86	147/86	127	436

Interaction Between Determinants of Myocardial Oxygen Demand and Supply

Recent extensive studies on the effect of various interventions designed to modify infarct size after acute coronary occlusion (MAROKO *et al*, 1972; BRAUNWALD AND MAROKO, 1973; EPSTEIN, 1973) have demonstrated that many agents currently employed in the treatment of ischemic heart disease affect multiple determinants of myocardial oxygen supply, frequently in a manner that mixes beneficial and detrimental effects. The bidirectional effects on determinants of myocardial oxygen demand (contractile state and ventricular volume) that are exerted by digitalis and β-blocking agents have been outlined. It was noted that the effects of nitroglycerin on regional myocardial flow may be unfavorable, but the most important clinical effects of nitroglycerin are due to a reduction in arterial blood pressure, venous return, and ventricular volume. These effects are large enough to offset an increase in heart rate and a decrease in coronary driving pressure to cause a net decrease in myocardial oxygen demand.

II. CLINICAL ASPECTS OF TRANSIENT MYOCARDIAL ISCHEMIA

The clinical concept of angina pectoris has been strongly influenced by the classical study by BLUMGART, SCHLESINGER, and DAVIS (1940). Correlations made between the clinical histories and the pathologic anatomy of the coronary arteries indicated that in the absence of hypertension and/or valvular disease, the patient suffering from angina pectoris is likely to have extensive arterial disease with complete occlusion of at least one of the major coronary arteries and possibly of two or three major coronary arteries. These findings were later confirmed in a much larger series published by ZOLL, WESSLER, and BLUMGART (1951), but ZOLL *et al.* also noted that some patients may have angina due to narrowing of the coronary arteries without complete occlusion.

The modern equivalent of the studies by BLUMGART *et al.* (1940) and ZOLL *et al.* (1951) are the extensive surveys of the results of coronary angiography that have been published from the Cleveland Clinic. Correlations between clinical and angiographic findings, as they appear in a study of 1,000 cases by PROUDFIT *et al.* (1966), are reproduced in Tables 2 and 3.

Table 2

Correlation of Clinical Diagnosis with Arteriographic Findings in 1,000 Patients

Clinical diagnosis	No. of patients	% correlation	Arteriographic evidence
Normal	68	95.6	No significant obstruction
Probably normal	201	80.6	
Atypical angina pectoris	141	64.5	Significant obstruction
Angina pectoris, class I, II, or III	207	93.7	
Angina pectoris, class IV	173	87.3	
Rest pain only	42	78.6	
Coronary failure	174	78.7	
Myocardial infarction	176	98.9	
Possible myocardial infarction	50	74.0	
Congestive failure	63	87.3	
Other*	37	—	

*Embolus, pericarditis, arrhythmias, abnormal electrocardiograms, abnormal roentgenograms, and xanthoma tuberosum.

Table 3

Distribution of Patients Related to Extent of Arterial Obstruction and to Clinical Diagnosis

Clinical diagnosis	Extent of maximal obstruction					Total no. of patients
	None or slight (0-30%)	Moderate (30-50%)	Severe (50-90%)	Subtotal (90% +)	Total	
	No. of patients					
Normal	65	2	1	0	0	68
Probably normal	163	13	13	5	7	201
Atypical angina pectoris	50	9	34	17	31	141
Angina pectoris, class I, II, or III	13	3	45	36	110	207
Angina pectoris, class IV	22	5	30	34	82	173
Rest pain only	9	4	11	10	8	42
Coronary failure	37	4	27	35	71	174
Myocardial infarction	2	0	28	43	103	176
Possible myocardial infarction	13	3	4	6	24	50
Congestive failure	8	2	7	16	30	63

The more closely the patient's chest pain pattern resembled classical effort angina, the higher was the incidence of major arterial lesions. It should be noted that a significant fraction of the patients with the most severe form of angina (Functional Class IV, pain at rest only, and coronary failure) had negative coronary angiography. A later study of 723 patients, limited to men less than 40 years old, produced similar findings (WELCH *et al.*, 1970).

The series from Cleveland Clinic demonstrate that a large number of patients (37% of the total) with chest pain characteristics sufficiently close to those of angina pectoris to warrant coronary angiography have no demonstrable coronary disease. Extensive experience over the past 10 years with coronary angiography, supplemented by hemodynamic and metabolic studies, has modified the assertion that angina pectoris always is associated with severe coronary artery disease.

Three subgroups of patients with angina pectoris will be examined: Classical angina pectoris, Prinzmetal's or Variant angina, and Angina with normal coronary arteriogram. The common demonimator is chest pain involving at least some part of the sternum and described as visceral in character, *e.g.*, tightness, squeezing, constriction (FRIESINGER *et al.*, 1970). Characteristics relating to myocardial oxygen supply and myocardial oxygen demand separate the groups.

Classical Angina Pectoris

Significant coronary arterial lesions curtailing oxygen supply are, as a rule, present in classical angina. Pain and ECG abnormalities are precipitated by an increased myocardial oxygen demand. Exercise capacity is markedly restricted when spontaneous anginal pain at rest becomes a major problem.

Age and Sex

Men less than 60 years old accounted for 70% of the total in the series of patients with coronary angiography published by PROUDFIT *et al.* (1966). Only 21% of their patients were women, of which two-thirds had no significant arterial lesions. A similar distribution has been reported by FRIESINGER *et al.* (1970).

Data from the Framingham study of a general population sample (KANNEL AND FEINLEIB, 1972) suggests that uncomplicated effort angina is equally common in both sexes. The total incidence of angina was almost twice as high among Framingham men; but 47% of the angina cases in men were preceded or followed by a myocardial

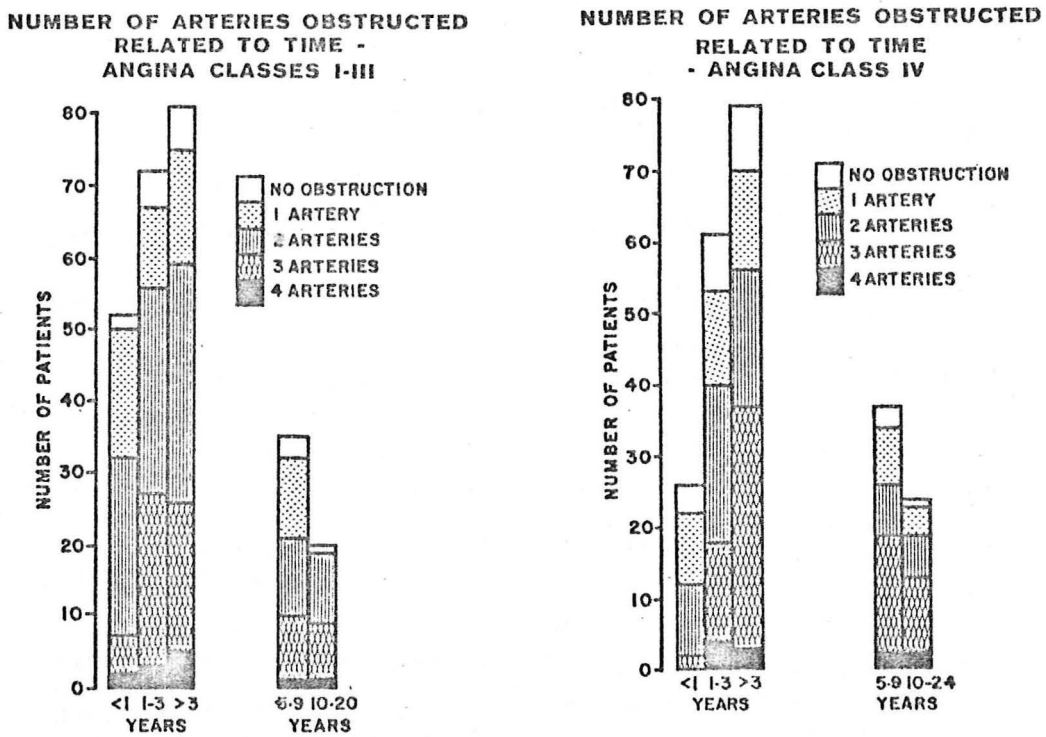
infarct versus only 15% in women.

Angiographic Data

Figure 5 illustrates the extent of coronary arterial lesions in patients with classical angina (PROUDFIT *et al.*, 1968). FRIESINGER *et al.* (1970) reported a higher proportion of patients with no or minimal lesions (14%).

Figure 5

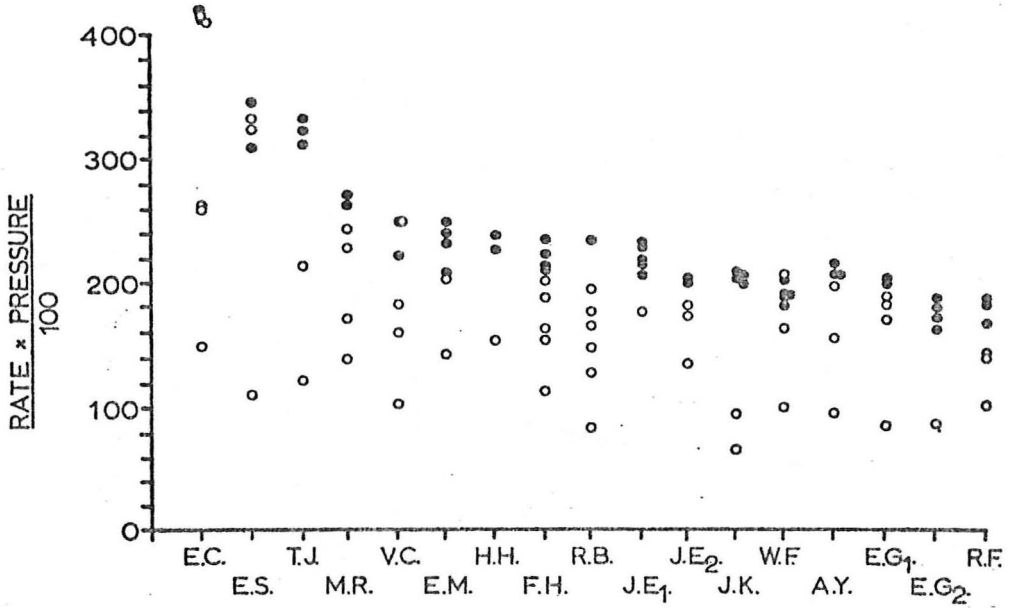
(PROUDFIT *et al.*, 1968)



Precipitating Events

The basic feature of the history in classical angina pectoris is the relation between chest pain and effort. The history correlates well with hemodynamic changes preceding the onset of angina and other manifestations of ischemia. The well-defined and reproducible threshold of myocardial ischemia is illustrated in Figure 6 (From ROBINSON, 1967).

Figure 6



Rate-pressure product achieved during each period of stress in 15 patients. Closed circles denote episodes in which pain occurred and open circles those in which there was no pain.

ROUGHGARDEN (1966) and LITTLER *et al.* (1973) have studied patients with effort angina as well as spontaneous attacks. Spontaneous attacks are virtually without exception preceded by increases in heart rate and blood pressure to levels corresponding to those precipitating angina during effort.

Pain Characteristics

The original description of angina pain by HEBERDEN (1772 and 1804) is still valid.

> "But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris.
>
> "They who are afflicted with it, are seized while they are walking, (more especially if it be up hill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes.

"In all other aspects, the patients are, at the beginning of this disorder, perfectly well, and in particular have no shortness of breath, from which it is totally different. The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of the os sterni, and often more inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm. The pulse is, at least sometimes, not disturbed by this pain, as I have had opportunities of observing by feeling the pulse during the paroxysm. Males are most liable to this disease, especially such as have past their fiftieth year."

Electrocardiographic Findings

Fifty to 70% of all patients with effort angina and no prior infarction have a normal ECG at rest (MATTINGLY *et al.*, 1958). The proportion of normal resting ECG's is lower among patients selected on basis of angina and abnormal coronary angiogram, *e.g.*, 50% or less (ROITMAN *et al.*, 1970; ELLIOTT, W.C. AND GORLIN, R., 1966).

The likelihood of the ECG at rest being normal decreases with increasing arterial involvement, but a normal ECG at rest may be present also in 4 to 16% of patients with severe triple vessel disease (MARTINEZ-RIOS *et al.*, BENCHIMOL *et al.*, 1973).

Our own experience (Table 4) suggests that S-T abnormalities at rest are associated with 3-vessel disease. Similar data have been reported by LIKOFF *et al.* (1965).

Table 4

ECG at Rest

Per Cent Patients with 1, 2 and 3 Vessel Disease

	1	2	3	
ST and T Normal	29	65	6	(N = 17)
ST Normal, T Abnormal	-	64	36	(N = 11)
ST Abnormal	18	9	73	(N = 11)

$x^2 = 17.73$; $p < 0.01$

The first report on the ECG during angina was published by BOUSFIELD (1918), but the findings were atypical, a right bundle branch block with T wave abnormalities. The classical ECG patterns during angina, transient horizontal depression of the S-T segment with or without inversion of the T wave was first described by FEIL AND SIEGEL (1928)(Figure 7).

Figure 7 - (1) and (2)

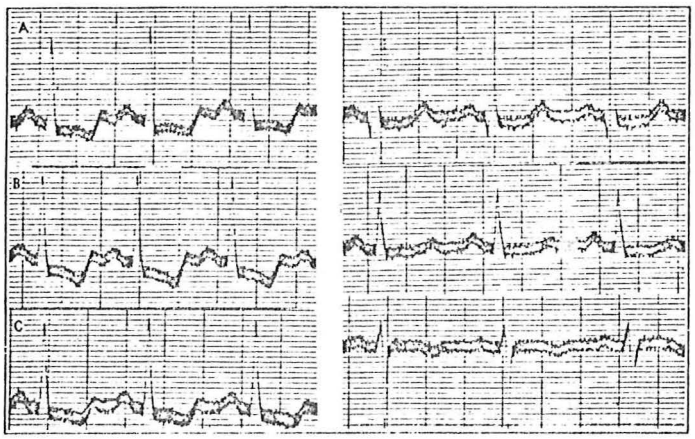


FIG. 1.—Electrocardiogram of J. M. (Lead II) taken (*A*) (*B*) during severe paroxysm of pain; (*C*) as pain was subsiding (October 30, 1926).

FIG. 2.—Electrocardiogram of J. M. (Leads I, II, III) taken after pain had subsided (five minutes after FIG. 1). (October 30, 1926.)

WOOD AND WOLFERTH (1931) and SCHERF AND GOLDHAMMER (1933) demonstrated that the ECG abnormalities that were present during a spontaneous attack of angina also could be precipitated by exercise.

Only slowly did exercise testing gain acceptance as a standard clinical tool in the study of patients with angina pectoris. The standard Master's test has now largely been replaced by individualized multilevel tests. The rationale for this change has previously been discussed in detail (BLOMQVIST, 1972). Electrocardiographic and general aspects of exercise testing have recently been reviewed by several authors (BLACKBURN, 1969: BRUCE AND HORNSTEN, 1969; GOLDBERG *et al.*, 1970; ROITMAN *et al.*, 1970; REDWOOD AND EPSTEIN, 1972, FRIESINGER AND SMITH, 1972).

S-T segment depression of 1 mm or more, horizontal, or downsloping, and lasting for $\geq$ 0.08 sec is now generally accepted as

suggestive evidence of ischemia. Transient arrhythmias, conduction defects, and T wave abnormalities frequently occur, but are nonspecific abnormalities. Table 5 (from DETRY, 1973) shows the correlation between ECG response and cardiogram in three different series and Table 6 correlates pain characteristics, ECG response, and coronary angiography.

Table 5

Correlation between coronary arteriography and ischemic ST segment depression ⩾ 1 mm in near-maximal exercise testing of patients with typical or atypical chest pain.

Source	Number of cases	C + E +	C + E —	C — E +	C — E —	Sensitivity %	Specificity %
Mason et al. (1967)	84	38	11	4	31	78	89
Kassebaum et al. (1968)	68	18	18	1	31	50	97
Roitman et al. (1970)	46	24	6	2	14	80	87
TOTAL	188	80	25	7	76	76	92

C + indicates the presence of coronary stenosis ⩾ to 50 % of the lumen of at least one coronary vessel and C — the absence of such finding.

E + and E — refer to the presence or the absence of ischemic ST segment depression ⩾ 1 mm during or after exercise.

Table 6

Correlation between clinical history, electrocardiographic response to near-maximal exercise and coronary arteriographic data in 152 patients (adapted from Mason et al., 1967, and Kassebaum et al., 1968).

Classification of the patients		Coronary arteriography **	
Typical angina pectoris	ECG response to exercise *	C +	C —
+	+	48	1
+	—	20	11
—	+	8	4
—	—	9	51

* Positive (+) ECG response to exercise refers to ST segment depression ⩾ 1 mm.

** C + and C — (see legend of table 5).

A recent study by Doctor PANSEGRAU at St. Paul Hospital (to be published) demonstrates that it is possible to obtain in unselected series of patients a sensitivity and specificity comparable to that reported by ROITMAN *et al.* (1970) in a selected group of patients with normal ECG at rest. Doctor PANSEGRAU employs a 15-lead system and special measurement techniques.

It is evident that present methods and criteria for evaluation of ischemic S-T abnormality result in a relatively high number of false negatives at an acceptable level of false positives in unselected series. However, the likelihood of significant arterial changes is high among patients with typical angina and S-T abnormality and low among patients with neither. There is considerable disagreement between the ECG response and angiography among patients with atypical pain.

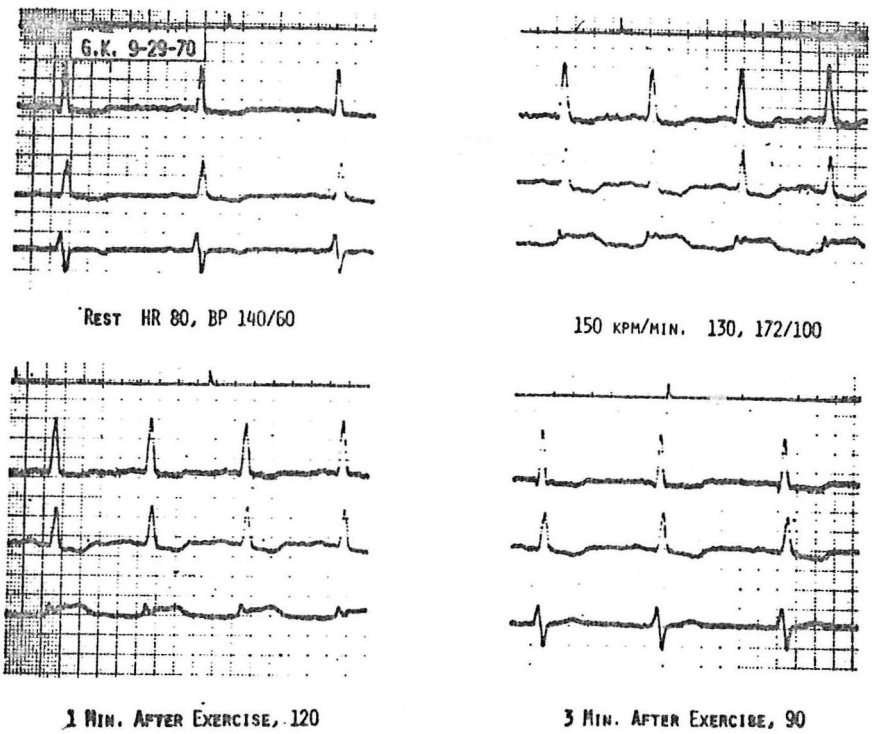
The data presented in Tables 5 and 6 are based on predominantly male series. The rate of S-T depression classified as ischemic according to common criteria is high among asymptomatic middle-aged women (ASTRAND, 1965). Recent studies correlating the exercise ECG and coronary angiography also indicate that low sensitivity or false negatives is the main problem in men and low specificity or false positives the problem in women (HYLAND, Baylor University Hospital Staff Meeting, 1973).

A firm clinical diagnosis of ischemic heart disease with or without abnormal ECG at rest was not too long ago considered a contraindication against exercise testing. Current use of exercise testing in this group of patients as a means of determining physical work capacity has demonstrated a highly variable ECG response. Exercise frequently precipitates S-T elevation of the type otherwise associated with acute transmural myocardial infarction or Prinzmetal's angina (BELLET *et al.*, 1962; SODERHOLM *et al.*, 1962). FORTUIN AND FRIESINGER (1970) published a series of 12 patients with S-T segment elevation in the exercise ECG. A total of 5 patients had ECG evidence of previous myocardial infarction. More striking 11/12 patients had angiographic evidence of total or near-total coronary artery occlusions at sites corresponding to the distribution of S-T elevation.

Figure 8 shows the ECG in a patient studied in our laboratory. He had classical effort angina, had had no myocardial infarction, and never had pain at rest. Angiography demonstrated a near complete occlusion of his anterior descending artery.

Figure 8

Exercise-Induced S-T Elevation in a Patient With Effort Angina



Each panel shows Frank leads X, Y and Z, approximately the equivalents of standard leads I, aVF, and V_2.

The close correlation between the spatial distribution of the S-T elevation and the anatomical localization of the arterial lesion is in sharp contrast to the findings in patients with S-T depression. HERMAN *et al.* (1967) reported a definite correlation between the S-T pattern and anatomic and metabolic abnormalities, but several other observers have largely been unable to confirm their findings (ARESKOG *et al.*, 1967; KASSEBAUM *et al.*, 1968; ASCOOP *et al.*, 1971).

ATTERHÖG *et al.* (1971) have demonstrated that S-T elevation is the most common response to exercise during the early recovery phase among patients with a recent anterior myocardial infarction. Significant S-T elevation was found in 10/12 patients during submaximal work (heart rate 100-120 beats/min) three weeks after onset of symptoms. The magnitude and prevalence of S-T elevation diminished gradually over the ensuing 12-18 months; occasional patients converted from S-T elevation to S-T depression.

Figure 9 summarizes the ECG response to exercise in an unselected series of patients with significant coronary disease who recently were studied in our laboratory. ST&T abnormalities were defined by computer measurement and comparison with a normal control group (BLOMQVIST *et al.*, 1973).

Figure 9

STT Abnormalities at Rest and During Exercise in Patients With ASHD

Rest	No. of Patients	Exercise
Normal ST and T	17 — 4	No change
	13	Abnormal ST
	3	Normal ST Normal T
Normal ST	11 — 2	No Change
Abnormal T	6	Abnormal ST
	1	Normal ST Normal T
	2	ST Normal T Abnormal
ST Abnormal	11 — 8	No Change

The data once again demonstrate the variability of the ECG response among patients with documented coronary artery disease. The sensitivity was high among patients with normal ST-T at rest. Two of 4 patients with normal ECG's at rest and during exercise reached a normal maximal work load and had no angina. They may represent a group of patients with a true dissociation between anatomy and physiology rather than a falsely negative ECG response. Presence of ST or T abnormalities at rest decreased the likelihood of additional abnormalities appearing during exercise. Paradoxical T wave normalization is a common finding in patients with abnormal T waves at rest. Our series demonstrated that paradoxical normalization of S-T also occurs.

Attempts have been made to formulate simple criteria for abnormal exercise response among patients with abnormal ECG at rest (COHN *et al.*, 1971), but sensitivity and specificity are both low.

Hemodynamic and Metabolic Features

The technique of right heart catheterization was first applied to the study of angina by MÜLLER AND RORVIK (1958) and JOHNSON *et al.* (1959). Both groups recorded increased pulmonary artery and pulmonary capillary wedge pressures during angina and attributed these findings to transient left ventricular failure. Later studies have demonstrated a transient increase in left ventricular end-diastolic pressure and an abnormal left ventricular function curve during exercise-induced or spontaneous attacks of angina pectoris and during atrial pacing (PARKER *et al.*, 1966; ROSS, 1971; PARKER *et al.*, 1969).

Parker and associates reported a depressed left ventricular function curve and an abnormal decrease in left ventricular end-diastolic pressure (LVEDP) in 24 of 24 patients who developed angina during exercise. Elevation of LVEDP usually preceded the onset of pain. Others have found a more variable LVEDP response to exercise (COHEN *et al.*, 1965), but there is little doubt that angina pectoris in most patients is associated with an increase in LVEDP (ROSS, 1971).

To what extent a decreased myocardial compliance (or increased stiffness) contributes to the abnormal end-diastolic pressure is still an unsettled problem. The combined evidence from several studies suggests that a compliance change occurs during angina precipitated by atrial pacing (ROSS, 1971).

Patients with angina pectoris tend to have a wide arterial-coronary sinus oxygen difference as a sign of an increased myocardial oxygen extraction (HOLMBERG *et al.*, 1966). However, the relationship between significant ischemia (as indicated by angina) and increased oxygen extraction is tenuous (HELFANT *et al.*, 1970), presumably due to heterogeneous myocardial flow.

Myocardial lactate production appears to be a more sensitive metabolic marker. The heart normally extracts lactate. Angina induced by atrial pacing is associated with decreased lactate extraction in most patients and frank lactate production in one-half to two-thirds of patients with abnormal coronary arteries (HELFANT *et al.*, 1970; PARKER *et al.*, 1969), but lactate production also occurs during pacing in some patients with coronary disease without angina. Significant lactate production is usually associated with the development of S-T changes (PARKER *et al.*, 1969), but the correlation is not perfect. Temporal relationships during the development and resolution of ischemia rule out a causal relationship between lactate production, ECG abnormalities and also between pain and lactate production (PARKER *et al.*, 1969; HELFANT *et al.*, 1970). WILLERSON *et al.* (1973) have demonstrated a dissociation between lactate production and ECG abnormalities after experimental coronary occlusion.

Prinzmetal's Or Variant Angina Pectoris

More than a decade ago, Prinzmetal *et al.* (1959, 1960) delineated a previously unrecognized form of angina pectoris. Two major characteristics separate the variant from the classical form of angina pectoris. In variant angina, the *onset of pain is unrelated to exertion.* Pain frequently occurs at rest. *The S-T segments* are transiently and often remarkably *elevated during angina*, and there is reciprocal S-T depression. Ventricular arrhythmias and A-V blocks are frequently present during pain. Based on ECG features, subsequent development of myocardial infarction in the area corresponding to the S-T elevation, and a series of experimental studies (EKMEKCI *et al.*, 1961), Prinzmetal and his associates concluded that variant angina was caused by a severe reduction of flow in a major artery causing severe ischemia in a localized area as opposed to more widespread and less severe ischemia associated with S-T segment depression and classical angina pectoris. Arterial spasm was considered a likely factor.

Prinzmetal's angina has been considered quite rare until recently. MACALPIN *et al.* (1973) reviewed the literature and found a total of 95 cases, including Prinzmetal's original series, and added 20 patients of their own. The paper by MACALPIN *et al.* provides an excellent source of references to which the reader is referred.

Age and Sex: Clinical Data

The age and sex distribution of patients with Prinzmetal's angina is similar to that of patients with classical angina. Factors predisposing to atherosclerosis are frequently present. Autopsy studies have regularly demonstrated coronary atherosclerosis.

Angiographic Characteristics

MACALPIN *et al.* (1973) found significant abnormalities in 18 of 19 patients studied with coronary angiography. Fifteen patients conformed to the pattern originally observed by Prinzmetal and had a single stenotic lesion of a single major coronary artery. However, several case reports have now been published describing patients with all the characteristic features of Prinzmetal's angina but completely normal coronary arteries. CHENG *et al.* (1972) recently published a series of 5 patients, 4 of which had completely normal coronary angiograms. (For further references, see MACALPIN *et al.*, 1973).

Our own experience (DONSKY *et al.*, to be published) includes 6 patients with highly variable angiographic features. Two patients had no abnormalities, two had severe proximal stenosis of the left anterior descending artery, and one patient had complete occlusion of the right coronary artery and one patient had severe triple vessel disease.

Precipitating Events

Sophisticated hemodynamic studies by GUAZZI *et al.* (1970) during 38 attacks of Prinzmetal's angina in 5 patients, including direct measurement of arterial pressure, right atrial pressure, heart rate and cardiac output, completely failed to reveal any circulatory changes preceding the onset of ECG abnormalities and chest pain. MACALPIN *et al.* (1973) were also unable to demonstrate any hemodynamic changes heralding spontaneous attacks of pain. They performed a maximal exercise test in 18 patients, and 13 patients were able to achieve heart rates of 150 beats/min or greater. The exercise capacity was severely restricted only in one patient and the remainder had normal or near-normal physical work capacity. Anginal pain was produced by exercise at high work load levels in 6 patients. Isoproterenol stress in 4 patients failed to produce pain.

The combined evidence from arteriographic and physiological studies suggests that the degree of coronary occlusion is variable. The exercise data presented by MACALPIN *et al.* are consistent with a fixed obstruction (resulting in pain and ECG abnormalities at high work loads) and superimposed transient worsening of the obstruction (resulting in pain at rest). MACALPIN *et al.* directly observed coronary spasms during coronary surgery in one patient. DHURANDHAR *et al.* (1972) and CHENG *et al.* (1972) have presented arteriographic evidence of spasms in a major coronary artery during angina in a total of 3 patients. The response to various therapeutic interventions, including bypass surgery, is variable and does not provide any definitive clues to the pathophysiology.

GUAZZI *et al.* (1971) reported great success with propranolol. The mechanism is obscure and their results have not been verified by other investigators (MACALPIN).

Documented cases of nonatheromatous ischemic heart disease following withdrawal from chronic industrial nitroglycerin exposure (LANGE *et al.*, 1972) have frequently been quoted to support the occurrence of spasm in major coronary arteries. Regional vasomotor effects in smaller vessels have not been demonstrated, nor have they been ruled out. Collateral correlation was absent in 17 of the 19 patients studied by MACALPIN.

Pain Characteristics

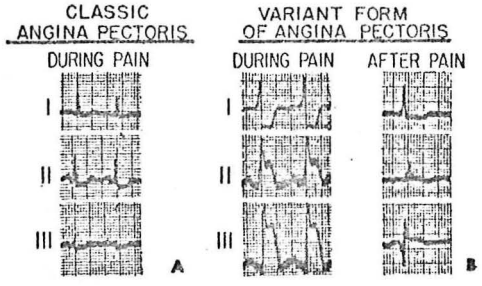
The chest pain in Prinzmetal's angina is typical of angina pectoris in location and quality. The pain is characteristically cyclical and often series of attacks recur at a particular time of the day, *e.g.*, at night or early morning.

Electrocardiographic Findings

The ECG at rest is usually normal between attacks of angina. Eighteen of the 20 patients studied by MACALPIN *et al.* (1973) had a normal resting ECG with the exception of transient T wave abnormalities following severe symptoms and occasionally persisting for months.

The typical ECG response during pain is illustrated in Figure 10, reproduced from the original publication by PRINZMETAL *et al.* (1959).

Figure 10



Comparison of electrocardiographic characteristics of classic angina pectoris and the variant form. A, Classic angina pectoris: ST segments show depression without reciprocal ST elevation. Electrocardiogram obtained after exercise. B, variant form of angina pectoris: During spontaneous pain, ST segments show elevation in leads II and III with reciprocal ST depression in lead I. Immediately after pain, the electrocardiogram returns to normal or to pre-pain pattern.

Marked S-T elevation is present in leads II and III with reciprocal S-T depression in lead I. ECG abnormalities normally precede the onset of pain and may also occur in the abscence of pain. T wave abnormalities present during pain-free intervals are frequently abolished during attacks.

Ventricular arrhythmias, including ventricular tachycardia, are present in about 40% of all patients, and are particularly common during severe attacks. High degree A-V blocks in patients with involvement of the right coronary artery is frequently associated with Adams-Stokes attacks. Two of 7 patients seen at Parkland Hospital (DONSKY *et al.*, to be published) had transient complete A-V block.

The S-T response to exercise is variable. S-T elevation of the same type as during a spontaneous attack is precipitated in some patients. In others, ischemic S-T depression occurs during exercise at high work load levels (MACALPIN *et al.*).

Hemodynamic Findings

GUAZZI *et al.* (1971) have described a regularly recurring hemodynamic sequence of events during spontaneous attacks. Beginning at the time of onset of ECG abnormalities they demonstrated a progressive decrease in arteial blood pressure, a decrease in cardiac output that averaged 25%, an increase in peripheral systemic resistance and an increase in right atrial pressure. Mean left ventricular rate of ejection fell. At the time the pain and the ECG abnormalities started to subside, arterial pressure and cardiac output started to rise and eventually exceeded the control values. Simultaneously, right atrial pressure decreased to normal values. The sequence is consistent with transient left ventricular failure. The overshoot or supernormal phase may be related to sympathetic stimulation.

Angina Pectoris With Normal Coronary Arteriogram

A syndrome of anginal pain associated with ECG abnormalities at rest and during exercise in women with normal coronary arteriograms was recently described by two independent groups (ELIOT AND MIZUKANI, 1966; LIKOFF *et al.*, 1967). Similar series have later been presented by several authors, *e.g.*, KEMP *et al.* (1967), DWYER *et al.* (1969), WAXLER *et al.* (1971), NEILL *et al.* (1972), BEMILLER *et al.* (1972), ARBUGAST AND BOURASSA (1973).

Age and Sex: Clinical Data

A majority of the patients in the published series have been women, usually in their forties, but the syndrome also occurs in men. BEMILLER *et al.* (1973) assembled a group of 21 men.

Abnormal serum lipids and glucose tolerance are rare (BEMILLER *et al.*, 1972).

Considerable attention has been given to the psychosomatic aspects of the syndrome. Neurotic or hypochondriacal behavior was reported in 40% of the patients in the large series published by WAXLER *et al.*, (1971). Other investigators have been unable to demonstrate any consistent behavioral pattern (LIKOFF *et al.*, 1967; NEILL *et al.*, 1972).

Myocardial Oxygen Supply

The coronary angiogram is by definition normal in this group of patients with angina. A variety of mechanisms other than coronary atherosclerosis have been considered as the cause of myocardial ischemia. A normal coronary angiogram does not rule out small vessel disease of the myocardium. However, small vessel disease is usually associated with other clinical conditions, *e.g.*, musculoskeletal or neuromuscular heritable disease (Friedreich's ataxia, progressive muscular dystrophy) or large vessel coronary atherosclerosis, postoperative cardiac surgery, systemic activities, amyloidosis, or diabetes (JAMES, 1967 and 1970).

Clinical findings in patients with small vessel disease of the myocardium usually include cardiomegaly, arrhythmias, and marked T wave abnormalities, features that rarely are present in patients with angina without coronary artery disease.

Five deaths have been reported among patients with this syndrome (ELIOT AND BRATT, 1969; DWYER *et al.*, 1969; and BEMILLER *et al.*, 1972). In no case has small vessel disease or coronary atherosclerosis been present but subendocardial infarction was evident in the patients described by ELIOT AND DRATT (1969). Thus, there is no evidence for any anatomical vascular abnormality causing a reduction of coronary blood flow, but anatomical evidence for severe myocardial ischemia may nonetheless occasionally be present.

Alternate mechanisms affecting myocardial oxygen supply have been advocated. A defective oxygen extraction has been postulated by ELIOT *et al.* (1967, 1969), associated with cigarette smoking and due to a puzzling rightward shift of the oxyhemoglobin dissociation curve. Other investigators have failed to confirm

the presence of any hemoglobin abnormality (NEILL *et al.*, 1972). Arterio - venous oxygen differences across the myocardium are within the normal range which argues against the presence of any significant generalized abnormality with respect to oxygen delivery and extraction (NEILL *et al.*, 1972).

Pain Characteristics

LIKOFF *et al.* (1967) described the pain as having all the modalities of angina pectoris, including relief with nitroglycerin, in 9 of 15 patients, and DWYER *et al.* (1969) found typical angina characteristics in 9 of 10 patients.

Other investigators, *e.g.*, NEILL *et al.* (1971), have stressed the atypical features of the chest pain. They determined that only 9% of 86 patients in their series had classical angina pectoris.

The quality of pain was frequently described as sharp, pinching or tingling, and the location was precordial rather than retrosternal in more than half the patients. Relief by nitroglycerin, considered to be a relatively specific sign of significant coronary artery disease (HORWITZ *et al.*, 1972), was obtained in 47%. The duration of pain was frequently longer than in classical angina pectoris. The chest pain had been of sufficient severity to warrant hospitalization in 62%, and 4 patients were completely incapacitated by pain.

Precipitating Events

Pain is precipitated by exertion in a majority of the patients. All patients in the series published by LIKOFF *et al.* (1967) had exercise-induced pain, but 40% had pain also at rest. The incidence of effort-induced pain was at least 50% also in other series (KEMP *et al.*, 1967; DWYER *et al.*, 1969; NEILL *et al.*, 1972).

Attempts to precipitate pain under laboratory conditions have yielded variable results. Atrial pacing produced pain in 3/10 patients studied by DWYER *et al.* (1969) and in 10/10 reported by ARBOGAST AND BOURASSA (1973).

Electrocardiographic Findings

The resting ECG is normal in most patients in this group. Eighty-nine patients out of a total of 148 reported by LIKOFF *et al.* (1967), DWYER *et al.* (1969), WAXLER *et al.* (1971), NEILL *et al.* (1972), and BEMILLER *et al.* (1973), or 60%, had a normal ECG at rest. ST&T wave changes accounted for most of the abnormalities. Evidence for remote myocardial infarction was not found. Signifi-

cant segmental S-T depression of the ischemic type during or after exercise was present in 81 of 186 patients or in 60% in the combined series quoted above. NEILL *et al.* (1972) also used hypoxia to provoke ischemia. They reported positive exercise tests in 8/11 patients and an ischemic ECG response to hypoxia in 10/11.

Hemodynamic and Metabolic Features

Data on hemodynamic and metabolic responses to stress are conflicting. Groups of investigators using similar techniques have arrived at opposite conclusions, and there is often a dissociation between the hemodynamic, metabolic, and electrocardiographic findings within study groups.

ARBOGAST AND BOURASSA (1973) have recently reported a normal or even supranormal cardiac response to pacing stress manifested by an increase in cardiac output despite a fall in left ventricular filling pressure. The normal hemodynamic response was associated with a high rate of abnormal ECG responses (10/11 ischemic changes) and abnormal myocardial lactate extraction (5/11 patients).

A similar groups of patients studied by DWYER *et al.* (1969) demonstrated a drastically different hemodynamic response to stress. None of their patients had an abnormal ($\geq$ 12 mm Hg) left ventricular filling pressure at rest and an abnormal increase during exercise. BEMILLER *et al.* (1972) also reported high filling pressures at rest and during exercise. By contrast, less than 10% of the patients described by BEMILLER *et al.* (1973) had abnormal left ventricular end-diastolic pressures at rest.

The over-all findings with respect to abnormal lactate production during stress are equally variable, ranging from significant abnormality to 1/11 patients (NEILL *et al.*, 1972) to 10/14 (BEMILLER *et al.*, 1973).

Prognosis

A benign prognosis with respect both to survival and symptoms is a striking feature of the syndrome of angina pectoris with normal coronary arteries. The chest pain tends to decrease in intensity and frequency or disappear spontaneously in about 50% of patients followed for a year or more (NEILL *et al.*, 1972; BEMILLER *et al.*, 1973; WAXLER *et al.*, 1971). Myocardial infarction and sudden death appears to be drastically rare. Only one sudden death (with normal cardiac findings at autopsy) occurred in these three series, representing about 300 patient years of exposure. There were no instances of acute myocardial infarction.

Etiology and Pathophysiology

The etiology and pathophysiology of the syndrome of angina pectoris with normal coronary arteries remain obscure. It has not even been conclusively documented that the patients in this group have myocardial ischemia. A large number of pathophysiological hypotheses have been advanced. Two of the most appealing, abnormal oxygen extraction and small vessel disease, can no longer be supported. As in Prinzmetal's angina, abnormal vasoregulation on the arteriolar level cannot be ruled out, but there is no positive evidence for this mechanism.

Most recent discussions favor the view that the syndrome is related to neurocirculatory (or vasoregulatory) asthenia and somehow due to an inappropirate sympathetic drive. There is, as yet, only indirect evidence to support this explanation. The syndrome of atypical angina, a neurotic personality, hyperkinetic circulation, and ECG abnormalities suggesting ischemia but frequently precipitated by standing as well as by exercise, has been considered typical for neurocirculatory asthenia (HOLMGREN *et al.*, 1959; FRIESINGER *et al.*, 1965). Previous reports indicate that circulatory and electrocardiographic abnormalities may be abolished by physical training (HOLMGREN *et al.*, 1959) or β-adrenergic blockade (FRIESINGER *et al.*, 1965; FURBERG, 1967). However, the result of long-term treatment with β-blocking agents in a recent series of patients who have had coronary angiography is highly variable. Only about 50% experience significant improvement (WAXLER *et al.*, 1971) Systematic acute experiments with automic blockade have not been performed.

III. ELECTROPHYSIOLOGICAL CORRELATIONS

The review of the clinical features of transient myocardial ischemia demonstrates a wide pathophysiological spectrum. The electrocardiographic responses to ischemia are equally varied. In general, classical angina is associated with segmental S-T depression. A disproportionately severe constriction of a single major vessel (as in many patients with Prinzemtal's angina and in patients with classical angina recovering from an acute myocardial infarction) often produces S-T elevation. .

Patients with ST-T abnormalities at rest frequently fail to demonstrate an increased degree of abnormality during stress-induced angina. Occasional patients with significant coronary artery disease have a normal ECG at rest as well as during maximal exercise. Furthermore, a group of patients with atypical angina, normal coronary arteries and equivocal evidence for myocardial ischemia, frequently show ECG abnormalities indistinguishable from those associated with true ischemia.

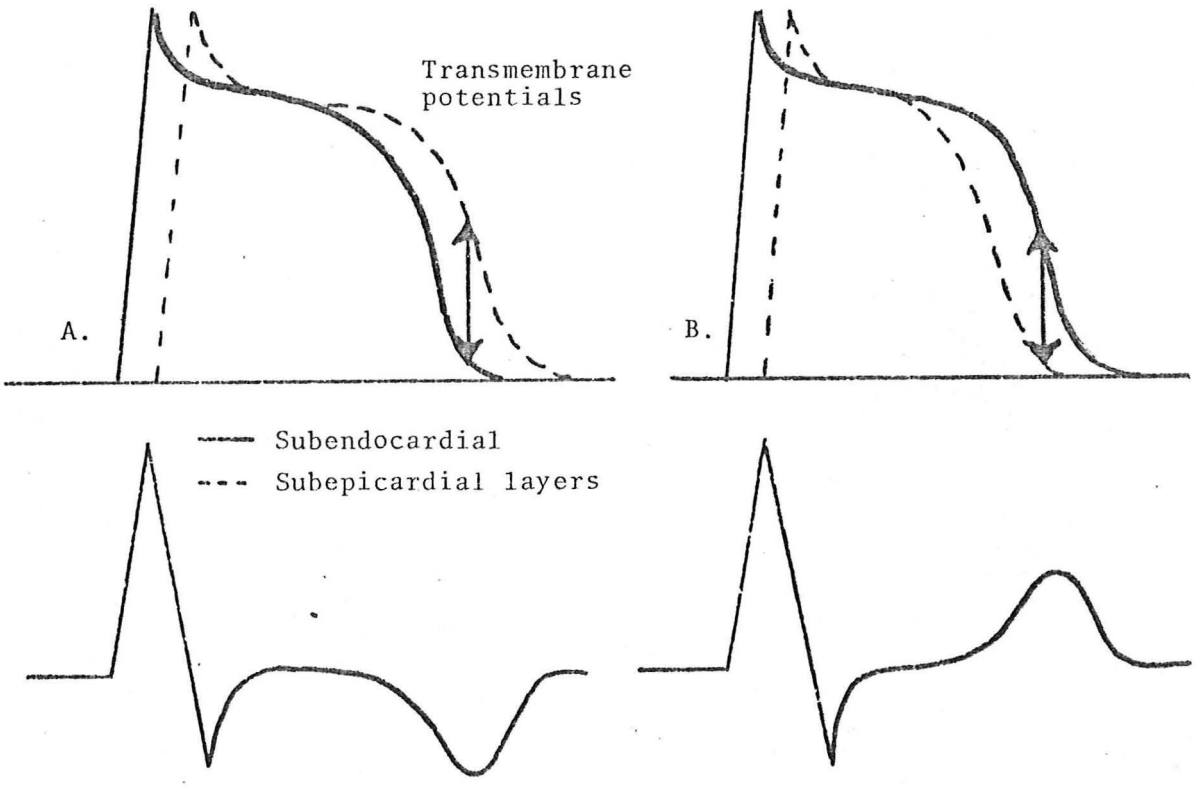
Recent electrophysiological and electrocardiographic studies

have produced important information delineating the inherent limitations of the electrocardiogram as a diagnostic tool in myocardial ischemia.

Generation of the Normal ST-T Segment

The surface electrocardiogram reflects potential differences corresponding to differences between groups of myocardial cells with respect to the state of excitation. This concept is illustrated by a simple two compartment heart model based on the typical ventricular membrane potential*. Depolarization starts in the septal and apical endocardial layers and progresses toward the epicardium and the base. If the duration and configuration of the membrane potential were identical in all layers, then these differences would generate an electrocardiogram with QRS and T waves of opposite polarity (Figure 11).

Fig. 11. Two-compartment heart model.



* An excellent review of the ionic basis of the cardiac action potential and the relation between the electrical and mechanical activity of the heart has recently been published by FOZZARD AND GIBBONS (1973).

However, it has been demonstrated conclusively by measurements of the functional refractory period that the duration of the myocardial action potential is nonuniform (BURGESS *et al.*, 1972). The duration is shorter in the epicardial than in the endocardial layers and shorter at the base of the heart than at the apex. The duration of the action potential is inversely related to the activation sequence. This arrangement minimizes dispersion of recovery time and may serve as a protective mechanism since disparity in refractory periods predisposes to ventricular arrhythmias (HAN *et al.*, 1964). Transmural differences with respect to the duration of the membrane potential are somewhat greater than differences with respect to activation. This explains why the normal T wave is upright - the potential gradient between epicardial and endocardial layers has the same direction during recovery as during activation (Figure 11B).

The decrease in duration of the action potential across the ventricular wall is not quite linear. The middle layers of the myocardium tend to recover earlier than anticipated from the over-all relation between time of activation and time of recovery (BURGESS *et al.*, 1972). This nonlinearity does not affect the concept presented in the two compartment heart model but has other important effects. The main effect is to generate cancelling electrical fields. Voltage fields arising at the boundary of the subendocardial and middle layers are directed opposite to those arising at the boundary between the middle and the subepicardial layers. Computer analysis suggests that the net effect is cancellation of 92 to 99% of the electrical forces during repolarization as viewed from the body surface (BURGESS *et al.*, 1969). The degree of cancellation is high also during QRS but not nearly as high as during ST-T. Estimates vary between 70 and 90%. The fact that it is possible to detect only about 5% of the electrical activity during repolarization explains the general lability of the ST-T segment.

Primary ST-T Wave Abnormalities General Considerations

Primary ST-T wave abnormalities are defined as changes that are due to altered repolarization characteristics as opposed to *secondary ST-T abnormalities* due solely to an altered sequence of ventricular depolarization, *e.g.*, the ST-T changes associated with an uncomplicated bundle branch block. The following mechanisms are involved in the production of primary ST-T wave abnormalities (SURAWICZ, 1972):

1. *Uniform changes* in the slope and duration of the ventricular transmembrane potential

2. *Nonhomogenous repolarization* due to

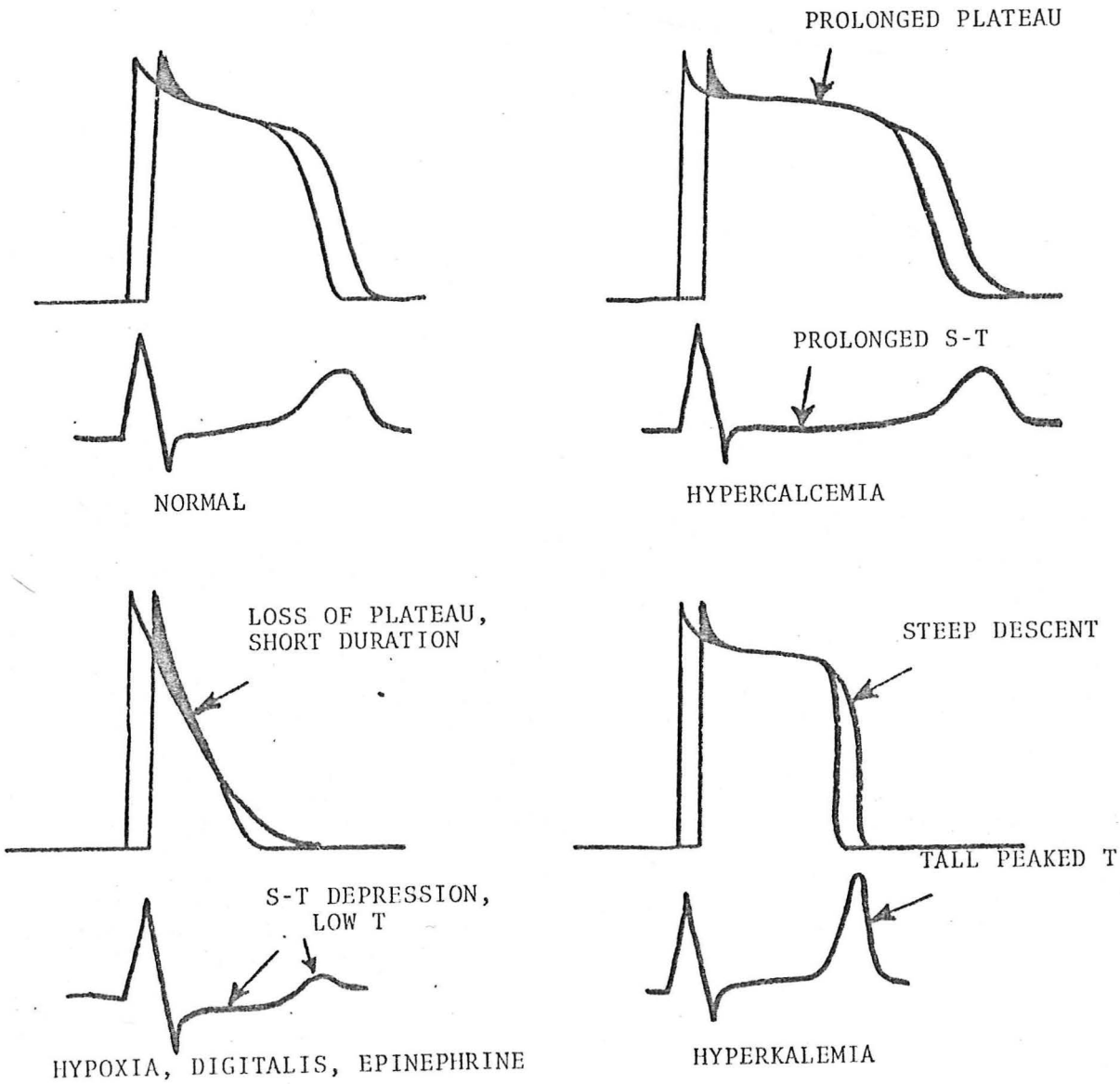
   a. Local changes in the slope and duration of the ventricular transmembrane potential

   b. Local changes in resting membrane potential

The effect on the ECG of uniform changes in the membrane potential caused by electrolyte abnormalities and drugs is illustrated in Figure 12.

Figure 12

Uniform Changes in the Shape and Duration of the Transmembrane Potential and Their Effect on the Surfact ECG



T wave abnormalities associated with cerebrovascular accidents represent an example of nonhomogenous repolarization. The sympathetic innervation of the heart is lateralized. The left stellate ganglion supplies the posterior aspect and the right stellate ganglion the anterior aspect of the heart. The typical T wave pattern clinically associated with CVA has been reproduced by direct unilateral stellate ganglion stimulation both in experimental animals and in man. Sympathetic stimulation *shortens* the duration of the transmembrane potential. The resulting paradoxical QT *prolongation* is most likely an effect of the marked cancellation of the ECG manifestations of recovery and due to unmasking of previously cancelled electrical activity (ABILDSKOV, 1972). The similarity of the T wave changes in CVA and in acute subendocardial infarction is well known.

Ischemic ST-T Wave Abnormalities

Ischemic ST-T abnormalities in the absence of myocardial infarction are produced by nonhomogenous repolarization.

The effect of hypoxia and anoxia on the action potential of cardiac muscle is similar to the effect on nerve and skeletal muscle potentials. TRAUTWEIN and collaborators (1954, 1956) have studied the effect of hypoxia on the transmembrane potential of papillary muscle. Two stages were regularly observed:

1. Loss of the plateau and a moderate decrease (<20%) in duration of the action potential

2. Decrease in resting or diastolic potential from about 90 to 70-80 mV and a decreased amplitude of positive overshoot and of the velocity of depolarization

The changes in (1) and (2) are reversible. Restoration of a normal oxygen tension causes a postanoxic overshoot with increase of resting potential and duration of the action potential exceeding baseline values by some 20%.

Chronic adaptation to hypoxia (simulated high altitude) is associated with an increase in the duration of the ventricular membrane potential measured at normal oxygen tensions (SALDENA *et al.*, 1972) and a somewhat blunted response to superimposed acute hypoxia.

The reduction in duration of the membrane potential in acute ischemia and the prolongation in chronic ischemia are paralleled by corresponding changes in the duration of the functional refractory period following experimental myocardial infarction (MANDEL *et al.*, 1968). Furthermore, these changes are also compatible with the typical evolution of the T wave abnormalities in acute infarction with a tall upright T during the hyperacute phase and a deeply inverted T with QT prolongation at a later stage.

The mechanisms involved in the production of the typical pattern of acute injury as recorded from a central epicardial electrode (S-T elevation and increased T wave amplitude) have been controversial, but SAMSON AND SCHER (1960) have presented data from intact dog hearts that are in agreement with the transmembrane potential changes described by TRAUTWIN *et al.*

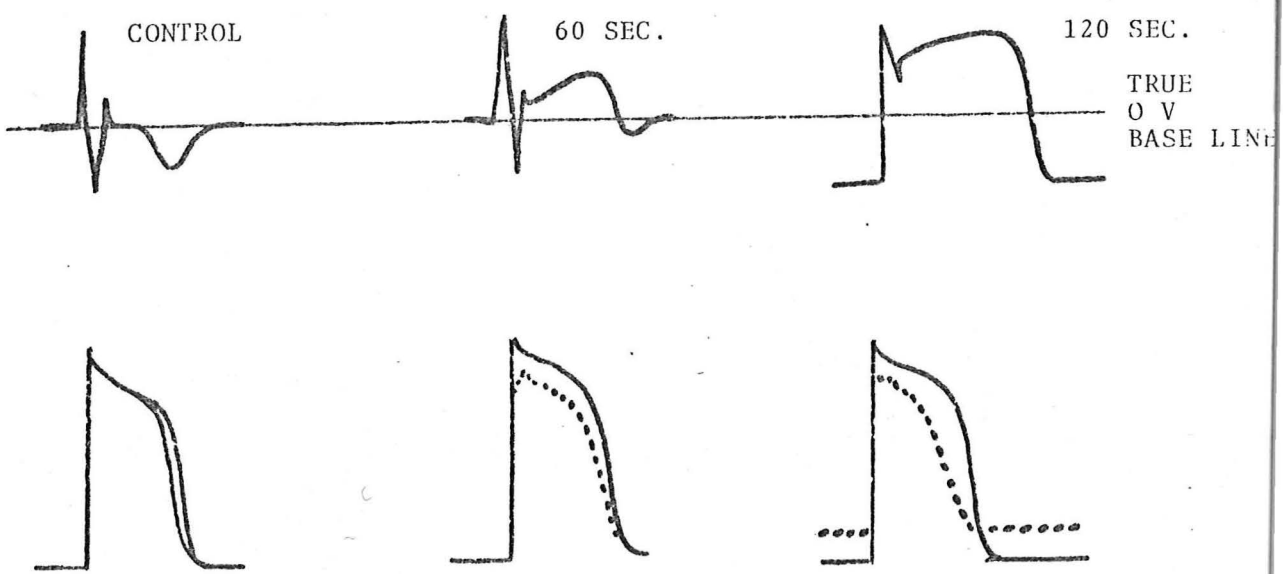
A crucial feature of their study was the use of direct-coupled amplifiers. Standard ECG equipment uses A.C.-coupled amplifiers that will filter out any voltage change occurring at a rate slower than about 0.05 to 0.1 cycles per second.

Salient findings are presented in diagrammatic form in Figure 13. A progressive increase in ST T became apparent shortly after ligation of the anterior descending branch of the left coronary artery (at approximately 40 seconds). Some 60 to 80 seconds later, the T-Q segment was depressed. Simultaneous recordings of transmembrane potentials demonstrated a decrease in duration of the potential during the initial phase. During the second phase, a decrease in resting membrane potential also became evident. There was no evidence for any depolarization abnormality.

Figure 13

Transmembrane and Epicardial Potentials

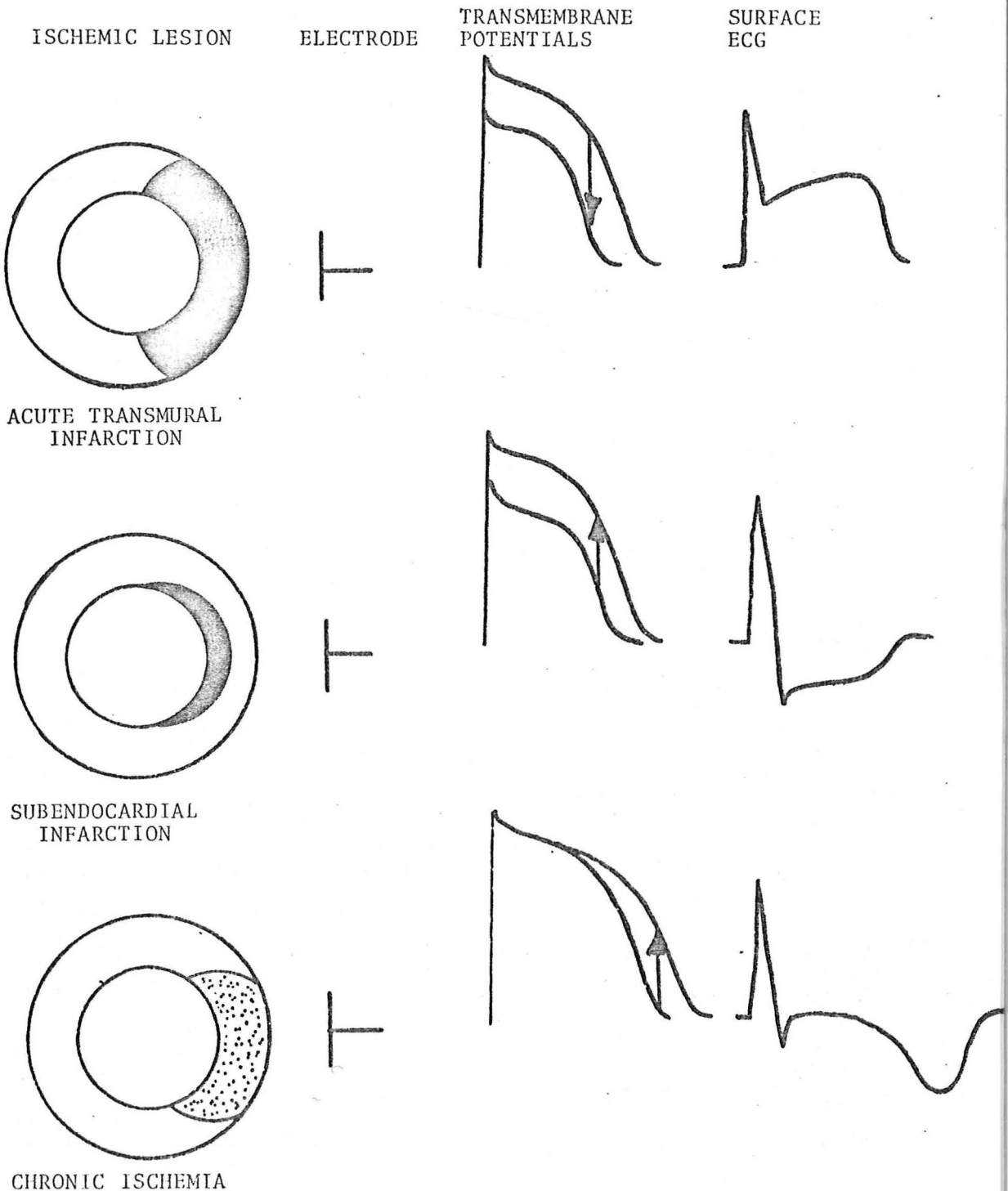
After Coronary Artery Ligation



SAMSON'S AND SCHER'S findings can easily be translated to the standard surface ECG utilizing the basic two compartment model as demonstrated in Figure 14.

Figure 14

Transmembrane and Surface Potentials in Various Ischemic Lesions



Arrows point at the representative transmembrane potentials of the area facing the electrode.

The failure of the standard ECG equipment to record D.C. voltages has the net effect of transposing the membrane potential from the injured area to the same baseline level as the potential from the intact area. The geometry of the boundaries across which the potential differences exist during repolarization are determined both by the extent and severity of the injury and by the normal sequence of recovery in the adjoining intact tissue.

The spatial relationship between electrodes, ischemic areas, and intact myocardium is altered during ischemia limited to the subendocardial layers. The positive electrode is facing the ischemic areas in transmural lesions and intact myocardium in subendocardial ischemia. The potential differences are reversed relative to the transmural lesion and S-T segment depression will be recorded.

The clinical impression that the correlate of S-T elevation is severe localized ischemia and that the correlate of S-T depression is perfectly compatible with the model. The subendocardial layers are more vulnerable than the subepicardial layers. General reduction of flow in a major coronary artery is likely to result initially in ischemia limited to the subendocardial layers. S-T depression will be recorded. Progressive reduction of flow will eventually cause alterations of the membrane potential characteristics also in the subepicardial layers. A boundary will then exist not only between subepicardial and subendocardial layers but more importantly, between the center and the periphery of the ischemia area. S-T elevation will be recorded at that time (KATO *et al.*, 1968). Infarcts which anatomically are limited to the subendocardial layers but involve more than 50% of the wall thickness behave electrically like transmural infarcts, *i.e.*, they are associated with S-T elevation rather than S-T depression (COOK *et al.*, 1958). This is consistent with an area of ischemia overlying the infarct creating boundary conditions similar to those present in the periphery of a transmural infarct.

Thus, S-T depression and S-T elevation are caused by identical changes at the cellular level. The presence or absence of one or the other is determined by the geometry of the boundary zones rather than by the severity of the ischemia as such.

Results of studies involving both surface potential mapping techniques (REID *et al.*, 1970) and computer modeling (ABILDSKOV *et al.*, 1972) indicate that the surface ECG is relatively insensitive to local changes during repolarization, *i.e.*, any electrode combination on the body surface - as opposed to an epicardial lead (KJEKSHUS *et al.*, 1972; KARLSON *et al.*, 1973) - will reflect the electrical activity of the entire heart.

This concept does not imply that there is no correlation between the anatomical position and the extent of ischemic lesions and waveform abnormalities in specific leads. Ischemic lesions

will be reflected preferentially in leads perpendicular to the boundary zone between intact and ischemic myocardium. On the other hand, cancellation effects caused by opposing potentials are due to a patchy distribution of ischemic lesions or due to the presence of ischemic lesions in the opposite wall may cause some ischemic heart disease to be electrically silent.

In summary, a review of current electrophysiological concepts demonstrates that it is possible to relate the varied clinical electrocardiographic manifestations of ischemia to well-defined events at the cellular level. Cancellation effects, due to the functional organization of the repolarization process, the anatomy of the heart and the anatomical distribution of ischemic lesions limit the diagnostic power of the ECG. The changes in membrane potentials caused by ischemia are not specific. Certain features can be reproduced by other agents. Sympathetic stimulation may produce electrocardiographic changes mimicking both acute and chronic ischemia.

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