MEDICAL GRAND ROUNDS

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CORONARY ARTERY SPASM

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The patient was diagnosed as having Prinzmetal's variant angina pectoris and was enrolled in the ongoing verapamil study.

These three cases illustrate the spectrum of coronary artery spasm that we have seen here at Parkland over the past 18 months. The first patient, W.S., is a young man with arteriographically normal coronary arteries who experienced chest pain only at rest--not with physical exertion or emotional excitement--and in whom severe right coronary artery spasm was provocable with ergonovine. The second patient, W.P., also had angiographically normal coronary arteries in the baseline state, and with ergonovine provocation he developed severe spasm of the proximal right coronary artery. In contrast to W.S., however, W.P. complained of chest pain induced by physical exertion and relieved by rest. Finally, the third patient, B.S., had fixed arteriosclerotic coronary artery disease with concomitant ST segment elevation. Similar to W.P., she complained of chest pain with exertion.

Today I would like to review with you the spectrum of coronary artery spasm in ischemic heart disease. Over the past several years coronary artery spasm, superimposed on either fixed arteriosclerotic coronary artery disease or radiographically normal coronary arteries, has been shown clearly to be the cause of Prinzmetal's variant angina pectoris. More recently, coronary artery spasm has been incriminated as an important contributing factor to both typical angina pectoris and acute myocardial infarction. Thus, coronary artery spasm may play a far more important role in the pathogenesis of ischemic heart disease than was previously thought possible (1).

In the early descriptions of typical angina pectoris, both Latham (2) and Osler (3) suggested that it was probably due to spasm of a large coronary artery. Subsequently, however, pathologic and pathophysiologic studies suggested that fixed coronary artery stenoses due to arteriosclerosis were responsible for myocardial ischemia and infarction, and experimental studies, most often performed in anesthetized, open-chest animals, showed that the metabolic requirements of the myocardium, not neural mechanisms of coronary vascular control, were the principal determinants of coronary blood flow. Thus, by the late 1950s, neurally-induced coronary artery constriction was not believed capable of causing drastic reductions in coronary blood flow, and, therefore, coronary artery spasm was no longer considered to be a cause of the various manifestations of ischemic heart disease.

In 1959, Prinzmetal, et al (4) revived interest in coronary artery spasm when they described a group of patients with so-called "variant" angina pectoris and postulated that this clinical syndrome is due to coronary artery spasm superimposed on fixed proximal atheromatous stenoses.

Subsequently, experimental studies in conscious animals demonstrated that coronary blood flow is, to be sure, regulated by the metabolic requirements of the myocardium, but, in addition, can be greatly influenced by neural mechanisms. At the same time, the development, perfection, and wide application of coronary arteriography have provided important evidence concerning the existence of coronary artery spasm in man. In this review I would like

(a) to place neural influence on the coronary arteries in its proper perspective among the various mechanisms responsible for the control of coronary blood flow;

(b) to examine the disease entity known as Prinzmetal's "variant" angina pectoris and to clarify the contribution of coronary artery spasm to this syndrome;

(c) to discuss in some detail the uses, limitations and risks of provocative tests for eliciting coronary artery spasm in man;

(d) to evaluate critically the available evidence that coronary artery spasm is a cause of typical angina pectoris and acute myocardial infarction; and

(e) to assess the efficacy of a new group of pharmacologic agents, known collectively as calcium antagonists, in the treatment of variant angina, typical angina, and acute myocardial infarction.

Regulation of Coronary Blood Flow

Like flow in any vascular bed, coronary blood flow is related directly to the perfusion pressure gradient (the difference between the pressure in the proximal large coronary arteries and that in the right atrium) and inversely to the resistance of the coronary vascular bed. The latter, in turn, is influenced by several factors (5,6). First, blood flow to the left ventricular myocardium varies strikingly during different phases of the cardiac cycle. With the onset of isovolumic contraction, the coronary arteries that supply the left ventricle are compressed by the actively contracting myocardium. As a result, blood flow through the arteries supplying the left ventricle falls abruptly (7). As systole progresses, this extravascular compression of the coronary arteries persists. However, the perfusion pressure in the coronary arteries rises quickly, so that coronary blood flow in late systole is slightly higher than during isovolumic contraction. With isovolumic relaxation, the "throttling action" of the left ventricular myocardium diminishes quickly, and coronary blood flow rises markedly (8). Then, throughout the remainder of diastole, coronary blood flow declines gradually as coronary artery perfusion pressure slowly falls. This marked variation in flow during the different phases of the cardiac cycle is less prominent in the portion of the right coronary artery that

supplies the right ventricle, since the right ventricular myocardium exerts little extravascular compression. Quantitatively, blood flow in the coronary arteries to the left ventricular myocardium during systole ranges from 7-45% of coronary flow during diastole (8). Under resting conditions, extravascular compression of the coronary arteries accounts for about 25% of the total resistance to coronary blood flow (9). During tachycardia, this contribution increases to about 55%, since at faster heart rates the fraction of the cardiac cycle occupied by systole is increased (10). The restriction to coronary blood flow created by systolic contraction is not uniform across the left ventricular wall; rather, it is highest in the endocardium and lowest in the epicardium. Several experimental studies have demonstrated that tension within the left ventricular myocardium increases progressively across the left ventricular wall, from the subepicardium to the subendocardium (11-13). This gradient in compression is responsible, at least in part, for the greater vulnerability of the endocardium than of the epicardium to ischemic damage.

Different segments of the coronary arterial bed react differently to various metabolic stimuli and pharmacologic agents (14). The larger, so-called "conductance" vessels are found on the epicardial surface, whereas the smaller precapillary vessels (so-called "resistance" vessels) lie within the myocardium. Under normal conditions the large vessels contribute very little to overall coronary vascular resistance, and fluctuations in resistance primarily reflect changes in the lumen of the small vessels (5). With neurogenic stimulation, however, the large conductance vessels may constrict markedly, causing an increase in coronary vascular resistance.

Second, many early studies, most of them performed either on isolated preparations or in anesthetized, open-chest animals, demonstrated that coronary blood flow is regulated primarily by the metabolic requirements of the myocardium. The observed close relation between coronary blood flow and myocardial oxygen consumption suggests that a product (or combination of products) of myocardial metabolism exerts local control of coronary vascular tone. Thus, when coronary blood flow is reduced or when myocardial metabolism is elevated, the local concentration of the metabolite (or metabolites) rises, acting to relax smooth muscle in the pre-capillary arterioles (resistance vessels), and thus reducing coronary vascular resistance and increasing coronary blood flow. Several substances and their combination have been suggested as mediators linking myocardial metabolic activity and coronary vascular tone, including oxygen (reduced partial pressure of oxygen)(15-19), carbon dioxide (increased partial pressure of carbon dioxide), hydrogen ion, potassium ion (20), lactic acid, increased osmolarity (21), prostaglandins (22-24), adenine nucleotides, and adenosine (5,25-27). There-

fore, the reduction of coronary vascular resistance caused by an accumulation of myocardial metabolites results from dilatation of the small, pre-capillary resistance vessels. Although the large conductance vessels dilate during an infusion of adenosine, they do not appear to respond to alterations in myocardial metabolism (28).

Third, early investigations performed in anesthetized, open-chest animals (29-32) demonstrated that stimulation of cardiac adrenergic nerves exerts only a slight effect on the coronary vascular bed (31, 33). However, more recent experiments in conscious animals have shown that such adrenergic stimulation can profoundly influence coronary blood flow. Activity of both alpha and beta receptors has been demonstrated in the coronary vascular bed of the intact unanesthetized dog after the systemic administration of various catecholamines (34). The infusion of norepinephrine induces a brief decline followed by a sustained increase in coronary vascular resistance, accompanied by a reduction in coronary sinus oxygen tension (35). The early vasodilatation, which is presumably secondary to augmented myocardial metabolism, can be largely eliminated by beta-adrenergic blockade. The later increase in coronary vascular resistance induced by norepinephrine can be prevented by alpha-adrenergic blockade and is undoubtedly produced by a direct effect on alpha receptors in the coronary vascular bed. This sustained coronary vasoconstriction caused by norepinephrine in unanesthetized animals is not present in the presence of anesthesia (35).

Numerous recent studies have demonstrated the capacity for the development of neurally-mediated coronary vasoconstriction. For example, the production of severe baroreceptor hypotension increases heart rate and blood pressure and, at the same time, reduces coronary vascular resistance (36). However, when this reflex tachycardia and augmentation of myocardial contractility are abolished with propranolol, coronary vascular resistance increases. This increase in coronary vascular resistance can be prevented by surgical interruption of the cardiac efferent adrenergic nerves (37). In the presence of intact efferent nerves and functioning beta receptors, the coronary vasodilatation induced reflexly by baroreceptor hypotension is due to augmented cardiac metabolic activity. When this beta-receptor-mediated activity is blocked with propranolol, alpha-mediated coronary vasoconstriction is unmasked (38).

Other studies have demonstrated that coronary artery vasoconstriction mediated by alpha-adrenergic activity is evident even in the presence of powerful vasodilatory influences. First, during reactive hyperemia, at a time when coronary vasodilatation occurs as a result of powerful metabolic stimulation, excision of the left stellate ganglion and the administration of phentolamine cause a substantial reduction in coronary vascular resistance (39). Second, it has been shown in the closed-chest, anesthetized dog that alpha-adrenergically mediated coronary artery vasoconstriction competes with metabolically mediated vasodilatation. As a result of this activation of coronary vasoconstrictor mechanisms, the increase in coronary blood flow caused by metabolic vasodilatation

can be restricted, thereby increasing oxygen extraction and decreasing coronary venous oxygen content (40). Third, in the conscious dog during exercise, alpha-adrenergic blockade with phentolamine causes a greater increase in coronary blood flow and a more profound decrease in coronary vascular resistance than that occurring in the absence of such blockade, further supporting the concept that adrenergic coronary vasoconstriction occurs even during physical activity (41). Fourth, electrical stimulation of the carotid sinus nerves in the conscious dog causes a fall in coronary resistance, which is unaffected by both atropine and propranolol. However, after alpha-receptor blockade with phentolamine or sympathetic blockade with guanethidine, coronary vasodilatation does not occur with carotid sinus nerve stimulation (42), thus demonstrating that the coronary vasodilatation consequent to electrical stimulation of the carotid sinus nerves results from a reduction in resting sympathetic tone. Finally, spontaneous increases in coronary blood flow independent of changes in heart rate and arterial pressure have been observed in sleeping baboons, again supporting the contention that a baseline level of alpha constrictor tone that is susceptible to reflex withdrawal is present (43).

In short, numerous animal studies have clearly demonstrated that coronary blood flow can be influenced markedly by stimulation or blockade of the alpha adrenergic receptors that richly supply the large (conductance) coronary arteries. In addition, stimulation of the parasympathetic nervous system may indirectly stimulate the sympathetic nerves, leading to vasoconstriction of the large coronary arteries. For this reason, parasympathomimetic agents, such as methacholine, have been reported to cause vasoconstriction; in contrast, the parasympatholytic drug, atropine, has been shown to induce vasodilatation (44).

Coronary blood flow, therefore, is regulated by several factors. Flow to the left ventricular myocardium varies markedly in different phases of the cardiac cycle, owing to the "throttling action" of the left ventricular myocardium. Early experimental studies using largely in vitro techniques or anesthetized animals demonstrated that coronary blood flow is, in large part, regulated by the metabolic requirements of the myocardium and that neural influences are relatively unimportant in the overall control of myocardial blood flow. In contrast, more recent investigations employing conscious animals have shown that coronary blood flow can be affected markedly by adrenergic stimulation or blockade. The profound differences between anesthetized and conscious animals are probably due to the differing experimental preparations. General anesthetic agents are known, first, to diminish reflex control of the circulation (45); second, to depress substantially the myocardial contractile state (46); and, third, to have a direct dilating effect on the coronary resistance vessels (35, 47). Therefore, by their very design, experimental studies performed in anesthetized animals minimize the contribution of the autonomic nervous system to the regulation of coronary blood flow. In the normal conscious animal and in man, neurogenic influences on the coronary circulation are potentially of great importance.

Prinzmetal's "Variant" Angina Pectoris

A. Clinical Characteristics As already noted, in 1959 Prinzmetal, et al (4) described a group of patients with what they called "variant" angina pectoris. The clinical features of this syndrome are distinctly different from those of typical angina pectoris in several respects. First, the patients described by Prinzmetal, et al typically had chest pain at rest rather than with physical exertion or emotional stimulation. Second, the episodes of chest pain tended to recur at roughly the same time every day, often in the early morning hours, awakening the patient from sleep. Third, patients with variant angina were found to have ST segment elevation (rather than depression) on the electrocardiograms recorded during chest pain. Fourth, the episodes of chest pain were sometimes accompanied by various degrees of atrioventricular block as well as ventricular ectopic activity, and occasionally, patients were found to have transient episodes of ventricular tachycardia or ventricular fibrillation. Finally, the chest discomfort of variant angina pectoris was relieved quickly by nitroglycerin, after which the ST segment elevation resolved. Prinzmetal, et al hypothesized that these patients had severe proximal stenoses of one (or more) large coronary artery, on top of which spasm periodically occurred. Coronary arteriography was not performed on this original group of patients.

Over the past 20 years many observers have both confirmed the existence of variant angina, as described by Prinzmetal, et al, and elucidated more completely the underlying pathophysiology. As coronary arteriography became more widely used in the 1960s, additional patients with the same clinical presentation--chest pain occurring at rest and associated with electrocardiographic ST segment elevation--in whom coronary spasm occurred in association with pre-existing atheromatous coronary artery stenoses were described (48,49). More recently the occurrence of coronary artery spasm without underlying atheromatous coronary artery disease has been demonstrated in some patients with variant angina (49-55). In fact, Selzer and his associates have suggested that patients with coronary artery spasm fall into one of two distinct groups, based on the presence or absence of underlying fixed atheromatous stenoses (56). On the one hand, those in whom it is superimposed on fixed lesions frequently note chest pain with exertion early in their clinical course, but only later do they have chest discomfort at rest. These patients commonly have a history of myocardial infarction. The electrocardiograms recorded during chest pain usually demonstrate ST segment elevation in the anterolateral leads. On the other hand, the individuals in whom coronary artery spasm occurs without underlying arteriosclerosis do not have angina during physical exertion, and the history is usually negative for myocardial infarction. These patients generally are young and female; their electrocardiograms obtained during chest pain most often show ST segment elevation in the inferior leads; in addition, they often demonstrate disturbances of atrioventricular conduction and bradyarrhythmias.

B. Coronary Arteriography Although many patients with Prinzmetal's variant angina have been shown to have severe coronary artery spasm at the time of coronary arteriography, there has been some disagreement about whether the spasm is truly spontaneous or catheter-induced. Catheter-induced coronary artery spasm, presumably resulting from mechanical stimulation of the coronary ostia, has several typical features. First, it is principally an arteriographic finding localized to the initial segment of the involved coronary artery, most commonly the right coronary artery (57,58), either at or within a few millimeters of the catheter tip. Second, despite the reduction in the transluminal diameter of the involved artery, there is usually no marked reduction of coronary blood flow. Third, the patient often has no chest discomfort or electrocardiographic changes suggestive of myocardial ischemia during the occurrence of spasm; and fourth, the coronary artery spasm consistently and quickly resolves when the catheter tip is removed from the coronary ostium (58).

Catheter-induced coronary artery spasm has been reported to occur in 0.25-1.0% of patients undergoing coronary arteriography (50,59). The uncommon occurrence of spasm during this procedure may be attributable to several factors. For one thing, it is routine in most cardiac catheterization laboratories to administer sedatives before the catheterization, which may exert an inhibitory influence on coronary artery spasm. Also, in some laboratories sublingual nitroglycerin is administered routinely just before coronary arteriography, thus lessening the chance of noteworthy spasm. Moreover, most radiographic contrast agents used today for coronary arteriography act as direct vasodilators (59). Therefore, in most catheterization laboratories, precautions are taken before the procedure to minimize the occurrence of catheter-induced coronary artery spasm. In fact, when both sedatives and nitroglycerin are avoided during coronary arteriography, the incidence of catheter-induced spasm rises to approximately 3% (59).

The clinical implications of catheter-induced coronary artery spasm are unclear. Several reports have suggested that patients with catheter-induced spasm are more likely to have spontaneous spasm (57,59,60), but there is no solid evidence to confirm or to refute this suggestion. Further studies with careful attention to both catheter-induced and spontaneous coronary artery spasm are required to clarify this point.

C. Provocative Testing for Coronary Artery Spasm Ergonovine maleate, an ergot alkaloid and alpha-adrenergic agonist with a direct vasoconstrictive effect on vascular smooth muscle, has been used to induce coronary artery spasm in patients with Prinzmetal's variant angina pectoris under carefully controlled conditions, either in the Coronary Care

Unit (61) or, more commonly, at the time of coronary arteriography (62,63). When administered intravenously in repetitive doses of 0.025 to 0.05 milligrams, this agent is relatively sensitive and specific for provoking coronary artery spasm in patients with variant angina (64). However, rarely a patient with Prinzmetal's angina pectoris diagnosed on clinical grounds does not respond to ergonovine (65). In a total dose exceeding 0.40 milligrams, ergonovine maleate may induce coronary artery spasm, with resultant myocardial ischemia, not only in patients with variant angina but also in those with typical angina pectoris (66).

In low doses and in carefully controlled clinical situations, ergonovine is a relatively safe drug. However, it has occasionally been reported to cause severe hypertension, grand-mal seizures, intracerebral hemorrhage, and even death (67). In patients with variant angina the induction of coronary artery spasm with ergonovine may lead to atrioventricular block or ventricular ectopic activity (63). In addition, prolonged coronary artery spasm due to ergonovine may cause myocardial infarction. Because of the hazard of the development of one of these serious complications, it is recommended that ergonovine be administered in gradually increasing doses, beginning with a very low dose, and only in a location where appropriate resuscitative equipment, drugs, and personnel are readily available. Ergonovine-induced coronary artery spasm is quickly relieved by nitroglycerin.

Methacholine, a parasympathomimetic agent, also has been administered either intramuscularly or subcutaneously to induce coronary artery spasm (44,68). Like ergonovine, this pharamcologic agent is capable of producing marked coronary artery spasm both in patients with severe underlying arteriosclerotic coronary artery narrowing and in those without fixed stenoses. Other provocative maneuvers have been utilized occasionally to induce coronary artery spasm. The cold pressor test (immersion of the patient's hand in ice water for 1-4 minutes) produces fairly potent alpha adrenergic stimulation. Aortic blood pressure rises 20-30 mm Hg, and heart rate usually increases slightly. In most patients clinically diagnosed as having variant angina, coronary artery spasm is produced by this maneuver (69,70). Vigorous hyperventilation in combination with the intravenous infusion of Tris-buffer (pH 10) also induces coronary artery spasm in most patients with a clinical diagnosis of Prinzmetal's variant angina (71). As with ergonovine-induced spasm, coronary artery spasm caused by any of these maneuvers is promptly relieved by nitroglycerin.

Although several agents or maneuvers are available for the provocation of coronary artery spasm, no study has been performed to compare them to one another. It is the subjective impression of most investigators across the country that ergonovine administration is the strongest available provocation, but this impression is based on no data.

In the Cardiac Catheterization Laboratory at Parkland Memorial Hospital, we have administered ergonovine to 35 patients over the past 18 months, and we have observed 3 positive responses. All recipients of ergonovine develop mild-moderate diffuse narrowing of the coronary arteries, so that the coronary arteriograms performed after ergonovine routinely demonstrate coronary arterial vasoconstriction when compared to the arteriograms performed prior to ergonovine (72). Only those patients with discrete and focal narrowing are said to have a positive response.

When ergonovine administration is deemed appropriate, several precautionary measures should be instituted. First, some patients develop high-degree atrioventricular block at the same time that they develop chest pain and electrocardiographic ST segment elevation. Therefore, it is wise to insert a temporary pacemaker in the right ventricle prior to ergonovine administration. Alternatively, if the pacing catheter is not actually positioned in the right ventricle, it should at least be in the right atrium or vena cavae, from which it can be advanced quickly to the right ventricle if necessary. Second, nitroglycerin should be readily available for the prompt treatment of an induced episode of coronary artery spasm. Ideally, this should be in the intravenous form. If, for some reason, intravenous nitroglycerin is not available, sublingual nitroglycerin should be immediately accessible. In all probability, intravenous sodium nitroprusside also is effective in the therapy of an induced episode of coronary artery spasm.

Third, the ergonovine should be administered in small doses, each separated by at least 3 minutes. Before the administration of each dose, a 6 lead electrocardiogram should be examined carefully for subtle ST-T wave changes, and coronary arteriography should be performed, <u>even in the absence of chest discomfort and ECG changes.</u> During an episode of variant angina, events transpire in the following order:

(a) The patient develops coronary artery spasm demonstrable arteriographically as a focal stenosis or even a total occlusion of the involved coronary artery.

(b) After several minutes, ST segment elevation occurs in the appropriate electrocardiographic leads, manifesting <u>transmural</u> myocardial ischemia.

(c) After several more minutes, chest pain occurs.

(d) In response to the pain, the patient's heart rate and systemic arterial pressure increase.

When we administer ergonovine, we attempt to induce angiographically-demonstrable coronary artery spasm and possibly ECG changes, but we prefer to titrate the ergonovine such that chest pain, if it occurs at

all, is mild. For this reason, coronary arteriography should be performed after each ergonovine injection, even if the patient reports no chest pain. Our typical protocol for ergonovine administration is, as follows:

(1) Baseline (pre-ergonovine)
    (a) Record arterial pressure
    (b) Record 6 lead ECG
    (c) Coronary arteriography
(2) Ergonovine 0.025-0.05 mg IV
    3 minute wait
    (a) Note arterial pressure
    (b) Record 6 lead ECG
    (c) Coronary arteriography
(3) Ergonovine 0.025-0.05 mg IV
    3 minute wait
    Repeat BP measurement, ECG, and coronary arteriography
(4) Ergonovine 0.05 mg IV
    3 minute wait
    Repeat BP measurement, ECG, and coronary arteriography

Ergonovine is administered in doses of 0.05-0.10 mg every 3-4 minutes until (a) the patient develops angiographic evidence of coronary artery spasm, (b) the patient develops ECG changes of ischemia, (c) the patient develops chest discomfort, or (d) a total dose of 0.40 mg is administered. If ECG changes or chest pain occur, coronary arteriography is performed as rapidly as possible, then nitroglycerin is given. If a total of 0.40 mg of ergonovine does not induce chest pain, coronary arteriography is repeated once again.

Several centers have administered ergonovine not only to patients with arteriographically normal coronary arteries but also to those with multivessel arteriosclerotic coronary artery disease. Specifically, Curry, et al (63) administered ergonovine to 30 patients with fixed coronary artery disease and had no substantial problems, even though some of these individuals had severe proximal coronary artery stenoses in the baseline state. More recently, Maseri, et al (73) also have injected ergonovine into patients with severe underlying coronary artery disease, apparently without problem. Anecdotally, however, numerous cardiologists from around the country have encountered problems when ergonovine is given to a patient with severe underlying coronary artery disease, including acute myocardial infarction and sudden death.

D. Other Techniques for Demonstrating Coronary Artery Spasm Although many patients with Prinzmetal's variant angina have been shown to have severe coronary artery spasm at the time of coronary arteriography, there has been disagreement about whether the spasm is truly spontaneous or catheter-induced. Newer diagnostic techniques have shown clearly that regional myocardial blood flow declines drastically during an episode of

variant angina, then returns to normal after the episode is resolved. Myocardial scintigraphy with both thallium-201(73-75) and ^{131}I-labeled macroaggregated human serum albumin (76) has demonstrated that transmural deficits of tracer uptake are present during episodes of chest pain with ST segment elevation; in contrast, scintigrams obtained in the absence of chest pain and electrocardiographic changes may be completely normal. In addition, coronary blood flow, as measured by the thermodilution technique, has been shown to fall considerably during an episode of spontaneous variant angina, then to return to normal and even to overshoot to hyperemic levels after disappearance of chest discomfort (77). These studies offer convincing evidence that coronary artery spasm in patients with Prinzmetal's variant angina is spontaneous rather than catheter-induced, since no coronary arteriographic catheters were in place at a time when coronary blood flow to a portion of the left ventricular myocardium was reduced dramatically.

E. Diagnosis of Coronary Artery Spasm Although the definitive diagnosis of coronary artery spasm is made by coronary arteriography, continuous electrocardiographic monitoring has added substantially both to our understanding of spasm and to a better appreciation of its frequency. As mentioned previously, the electrocardiographic changes of transmural ischemia (ST segment elevation) occur before the onset of chest pain. Detailed studies utilizing continuous electrocardiographic monitoring clearly have demonstrated that many episodes of ST segment elevation appear and resolve without the patient's ever developing chest discomfort. Specifically, of Maseri's 6009 spontaneous episodes of reversible electrocardiographic ST segment alterations, pain occurred in only 32%, whereas the other 68% were painless. When present, pain occurred from 30 seconds to several minutes after the onset of the electrocardiographic changes (73). Thus, continuous electrocardiographic monitoring has revealed a great deal about the appearance and disappearance of coronary artery spasm and has demonstrated convincingly that spasm occurs much more frequently than was appreciated previously.

In addition to expanding our knowledge of coronary artery spasm, continuous electrocardiographic monitoring has helped substantially to design the catheterization procedure so as to demonstrate spasm convincingly and yet safely. In most of our patients, electrocardiographic monitoring is performed for several days prior to coronary arteriography. Most of these patients have multiple episodes of ST segment elevation during the monitoring period, some painless and others associated with chest pain. The ST segment elevation that occurs helps to localize the anatomic site of ischemia and, therefore, may provide a clue of which coronary artery is likely involved. Knowing this, frequent arteriograms of the specific coronary artery can be obtained easily and quickly after each injection of ergonovine. For instance, by continuous electrocardiographic monitoring the patient demonstrates ST segment elevation in an inferior lead. With baseline coronary arteriography,

the patient is found to have widely patent coronary arteries and a dominant right coronary artery (that is, the right coronary artery supplies the inferior portion of the left ventricle). In such a patient, it is likely that coronary artery spasm, if provocable with ergonovine, will occur in the right coronary artery. Therefore, the right coronary artery is arteriogrammed after each ergonovine injection. In contrast, if continuous electrocardiographic monitoring does not localize the spasm to one coronary artery, one has no choice but to arteriogram both coronary arteries after each ergonovine injection.

F. Unusual Clinical Presentations of Variant Angina Pectoris The original description of variant angina pectoris by Prinzmetal, et al (4) was that of a group of patients who developed chest pain with ST segment elevation at rest. Some of these patients had no symptoms or electrocardiographic changes during physical exertion, whereas others developed chest discomfort and ST segment depression with exercise. With the development of coronary arteriography, it became clear that many patients with variant angina pectoris have fixed coronary artery disease in one or more major coronary arteries. If this disease is sufficiently severe, these patients may develop typical angina pectoris with physical exertion or emotional excitement, since myocardial oxygen supply cannot meet the greatly increased demand placed on the myocardium. Such typical angina pectoris is manifested electrocardiographically by ST segment depression, since the ischemia is usually confined to the subendocardium. In contrast, if coronary artery spasm is superimposed on such fixed disease, transmural myocardial ischemia results, leading to chest pain and ST segment elevation. In most patients with variant angina pectoris and underlying coronary artery disease, then, typical angina with ST segment depression may occur with exercise, and variant angina with ST segment elevation occurs at rest. Recently, a group of patients have been described who developed chest pain and ST segment elevation during exercise (78,79). When coronary arteriography was performed during supine bicycling, these patients had demonstrable coronary artery spasm. Therefore, in an occasional patient, physical exertion actually can trigger coronary artery spasm, thus producing ST segment elevation.

In the vast majority of patients with variant angina pectoris, coronary artery spasm is confined to one coronary artery, most commonly the right coronary artery. Dunn et al (80) have described recently a 60-year old male truck driver who had provocable spasm in two coronary arteries. By thallium scintigraphy, transient perfusion deficits were demonstrated both inferolaterally and anteroseptally, thus implying that spasm occurred in both the right and the left anterior descending coronary arteries.

G. Prognosis The prognosis of patients with Prinzmetal's angina has been considered grave because of frequent progression to myocardial infarction and death. Data concerning the incidence of myocardial infarction and death in patients with this syndrome vary. Prinzmetal, et al (4) reported 32 patients: three (9%) died, 12(38%) evolved a myocardial

infarction, and angina resolved spontaneously in 3 of 23 (13%). In this preliminary report, total figures on the duration of follow-up were not specified, but the incidence of death and infarction was clearly high. In 1971, Silverman and Flamm (48) reviewed the prognosis of patients with Prinzmetal's angina. Of 15 patients, 9(60%) had either myocardial infarction or death during an average follow-up period of less than two years. MacAlpin, et al (53) reported an 8-9% incidence of death and a 13-14% incidence of myocardial infarction during the first three months after diagnosis in a group of patients with variant angina. Although most survivors of infarction became pain-free, some continued to have angina with effort, and a few continued to have variant angina. Selzer, et al (56) have noted a striking difference in prognosis based on the presence or absence of obstructive coronary artery disease. In 9 patients with minimal or no coronary artery disease, none experienced a myocardial infarction or sudden death during follow-up; in contrast, of 20 patients with underlying arteriosclerotic coronary disease, 13 developed a clinical picture of unstable angina pectoris and required coronary artery bypass grafting. Of the remaining 7, 4 had myocardial infarctions, and 3 of these 4 died. Thus, the prognosis of patients with Prinzmetal's variant angina seems related to the extent and severity of underlying coronary artery disease. Those without underlying disease have a relatively good prognosis, although they occasionally have myocardial infarction and/or sudden death (81). Those individuals with arteriosclerotic disease have a guarded prognosis.

One should not forget that the prognosis of patients with variant angina may be altered substantially by the recently-developed calcium-antagonistic drugs, such as nifedipine and verapamil. These will be discussed in detail in a later section.

Coronary Artery Spasm as a Cause of Typical Angina Pectoris and Myocardial Infarction

For over half a century typical angina pectoris has been considered to result from an imbalance between a fixed, restricted myocardial oxygen supply and temporarily enhanced metabolic demand. Similarly, acute myocardial infarction has been thought to occur when this imbalance is severe and prolonged. In recent years, however, evidence in support of coronary artery spasm as a possible contributing factor to typical angina pectoris, acute myocardial infarction, and sudden death, both in patients with arteriographically normal coronary arteries and in those with underlying arteriosclerotic coronary artery disease, has accumulated.

Over the past ten years a group of patients with typical angina pectoris or myocardial infarction who are shown to have widely patent coronary arteries at the time of coronary arteriography has been identified (82, 83). In the former group the presence of myocardial ischemia has been

demonstrated by the myocardial production of lactate (82), whereas in the latter, infarction has been documented by the evolution of typical electrocardiographic and serum enzyme changes (84). The cause of the ischemic process in these patients has been a point of much conjecture and argument. Although many believe coronary artery spasm to play a crucial part in the production of myocardial ischemia or infarction (or both) in these patients, its causal role has never been proved unequivocally (85). However, a number of observations lend considerable credibility to the role of coronary artery spasm in producing the various manifestations of ischemic heart disease. For one thing, in munitions workers chronically exposed to nitroglycerin, angina pectoris, myocardial infarction, and sudden death have been shown to develop when they are suddenly withdrawn from their working environment (86). Coronary artery vasoconstriction presumably occurs in response to the potent vasodilatation induced by exposure to nitroglycerin. Then, as nitroglycerin is withdrawn, this vasoconstrictive influence remains powerful, resulting in marked reductions in coronary blood flow. At the time of coronary arteriography, these patients have been shown to have widely patent coronary arteries, and one was found to have spasm of coronary and peripheral arteries. Secondly, several patients with Prinzmetal's variant angina have had well-documented myocardial infarctions in the region of the heart supplied by the coronary artery shown to be susceptible to spasm (87-90). In certain cases, therefore, it appears that myocardial infarction can result from coronary artery spasm even in the absence of arteriosclerotic coronary artery disease (91).

In patients with underlying arteriosclerotic coronary disease, changes in coronary artery tone may contribute to the occurrence of angina pectoris and even of myocardial infarction. In response to a cold stimulus, coronary vascular resistance increases more in patients with obstructive coronary artery disease than in those with radiographically normal coronary arteries (92). This coronary vasoconstriction appears to be mediated by stimulation of alpha-adrenergic receptors, since it can be blocked by phentolamine. This abnormal rise of vascular resistance may contribute to myocardial ischemia in some patients with coronary disease. Finally, coronary arteriography performed within 12 hours of acute myocardial infarction demonstrated that coronary artery spasm was present in 40% of patients studied (6 out of 15) (93), but it is not clear whether the spasm was responsible for or contributed to the infarction or was simply a secondary phenomenon.

Convincing evidence that coronary artery spasm may be a very common cause of angina pectoris with ST segment elevation or depression comes from a series of carefully performed hemodynamic, scintigraphic, and coronary arteriographic studies in patients with angina pectoris and

acute myocardial infarction by Maseri, et al (73). Continuous electrocardiographic and hemodynamic monitoring in patients with angina pectoris at rest revealed, first, that chest discomfort always followed the concomitant electrocardiographic signs of myocardial ischemia and, second, that episodes of chest discomfort at rest accompanied by ST segment and T wave abnormalities were seldom preceded by an increase in the hemodynamic determinants of myocardial oxygen demand (i.e., elevations of heart rate and systemic arterial pressure). Scintigraphic studies with thallium-201 revealed variable degrees of transient reduction in myocardial perfusion at the time that ST segment changes (elevation or depression) occurred. Coronary arteriographic studies in 37 patients with angina pectoris demonstrated severe coronary artery spasm in vessels with variable amounts of atherosclerotic narrowing. Therefore, coronary artery spasm may occur in the presence of widely variable degrees of underlying arteriosclerotic coronary artery disease and, if sustained, may lead to acute myocardial infarction and sudden death. Thus, there may be a broad spectrum of manifestations of coronary artery spasm, including typical angina pectoris with ST segment depression, variant angina pectoris with ST segment elevation, and acute myocardial infarction, either subendocardial or transmural.

Therapy of Variant Angina Pectoris; Recent Advances in Therapy of Typical and Unstable Angina Pectoris

A. Medical Therapy The medical therapy of Prinzmetal's variant angina pectoris is similar in some respects to that of typical angina, but at the same time, there are very important differences. First, both types of angina respond promptly to sublingual or intravenous nitroglycerin. Coronary arteriographic studies have demonstrated that the coronary artery spasm occurring during episodes of variant angina is quickly dissipated by nitroglycerin. Second, in the patient with typical angina pectoris, beta-adrenergic blockade is usually highly beneficial, whereas in some patients with Prinzmetal's variant angina, beta-receptor blockade may actually be detrimental (94), since such blockade allows alpha-receptor-mediated coronary artery vasoconstriction to occur unopposed. At the same time, beta-adrenergic stimulation promotes coronary artery vasodilatation in patients with variant angina and, therefore, is apparently beneficial. Third, alpha-adrenergic blockade with phenoxybenzamine or phentolamine is sometimes beneficial in the patient with variant angina.

Fourth, several new agents for the medical treatment of ischemic heart disease recently have been introduced in the United States for investigational purposes. They exert their effects by directly antagonizing the effect of calcium ions on both myocardial contractility and coronary arterial tone and, as such, are collectively termed calcium "antagonists" or "blockers." Some of these have been utilized extensively in Japan and

in Europe over the past 10-15 years. Since these agents have created considerable enthusiasm in the United States over the past 2-3 years, it is anticipated that at least some of them will become generally available in the near future.

1. Mechanism and Sites of Action of Calcium-Antagonistic Agents Both myocardial contractility and the tone of coronary arterial smooth muscle depend quantitatively on the presence of calcium ions. Both are enhanced by an increase in the extracellular calcium concentration and, in turn, are depressed by a reduction of extracellular calcium. Therefore, any intervention, whether physiologic or pharmacologic, which reduces the extracellular concentration of calcium will, as a result, cause a diminution of both myocardial contractility and coronary arterial tone. Physiologically, such an effect is induced by an increase in the extracellular hydrogen ion concentration. Pharmacologically, the calcium antagonists exert this effect. Specifically, these drugs inhibit the movement of calcium ions from their storage sites, which are located superficially on the cell membranes of excitable tissues. The splitting of ATP by the calcium-dependent myofibrillar ATPase is restricted. As a result, high-energy phosphate consumption, mechanical tension, and oxygen requirements of cardiac muscle are decreased. Similarly, by the same calcium-antagonistic action, contractile tone of vascular smooth muscle is diminished substantially, so that coronary and systemic arterial dilatation occurs. Thus, these pharmacologic agents (a) diminish myocardial oxygen consumption by directly reducing contractility, (b) decrease systemic vascular resistance by relaxing arterial smooth muscle, and (c) increase coronary blood flow by dilating the large coronary arteries (95).

2. Specific Pharmacologic Agents

a. PERHEXILINE MALEATE Perhexiline maleate [2-(2, 2 dicyclohexyl) ethyl piperidine] first became available in France in 1973 (96). In the anesthetized dog, it causes vasodilatation of the coronary, systemic, and pulmonary vascular beds, as well as a reduction of left ventricular work and myocardial oxygen consumption (97). Even in the presence of a moderate reduction of coronary arterial perfusion pressure, perhexiline maleate augments coronary blood flow (98). This reduction of coronary vascular resistance is caused by a direct effect of the drug on vascular smooth muscle.

Independent of its direct vasodilatory effect on the coronary arteries, perhexiline maleate causes a reduction of heart rate. Such bradycardia is believed due to a direct effect of the drug on the intrinsic pacemaker tissue of the heart, since both depolarization and repolarization are prolonged (99). In patients with coronary artery disease, perhexiline has been shown to diminish exercise-induced tachycardia (100, 101). In addition to its direct negative chronotropic effect, perhexiline maleate exerts a modest negative inotropic influence. However, forward

cardiac output is not depressed, since any reduction of left ventricular contractility is balanced by a concomitant diminution of systemic vascular resistance.

Perhexiline maleate has been shown to induce bronchodilatation in anesthetized animals and in patients with asthma. In this group of individuals, forced expiratory volume, lung volume, forced vital capacity, and maximum expiratory flow rate all are increased (102).

Perhexiline maleate is administered orally to patients with angina pectoris in a total daily dose of 200-800 milligrams; it is usually given in two equal doses. Following its oral ingestion, it is rapidly absorbed from the gastrointestinal tract, afterwhich it is metabolized in the liver by hydroxylation of the cyclohexyl radicals to mono- and dihydroxylated derivatives. There is substantial variability among individuals in the rate at which such hydroxylation occurs (96).

Over the past several years a handful of studies have attempted to evaluate perhexiline maleate in the treatment of typical angina pectoris. In patients with severe, incapacitating angina pectoris, perhexiline maleate in combination with beta-adrenergic blockade has been shown to induce total or at least substantial amelioration of symptoms in 53 of 67 patients (103). In double-blinded, crossover comparisons with placebo, this pharmacologic agent has been shown to reduce significantly the overall number of anginal episodes as well as the utilization of nitroglycerin tablets for the relief of anginal pain (104-106). When compared to both placebo and propranolol (administered in doses of 30-240 milligrams per day), perhexiline maleate (as much as 400 milligrams per day administered in two equal doses) was more effective than placebo and beta-adrenergic blockade in the relief of typical angina pectoris (107). Thus, perhexiline maleate appears to be efficacious in the medical therapy of typical angina pectoris.

Other studies have examined the utility of perhexiline maleate in the therapy of variant angina pectoris. In patients both with and without underlying fixed coronary artery disease, this agent appears beneficial in this subset of patients (108-110). The required daily dose for the complete suppression of variant angina is 200-800 milligrams; when it is tapered to below 100 milligrams, symptoms usually appear (110). Although perhexiline maleate is efficacious in patients with variant angina pectoris, it is inferior to nifedipine in its ability to control both spontaneous episodes as well as those induced with intravenous ergonovine (111).

Although perhexiline maleate appears to be an effective anti-anginal agent, its widespread clinical use has been hampered substantially by its numerous side effects. First, many patients placed on perhexiline eventually develop peripheral neuropathy. The rapidity with which the

neuropathy becomes manifest is dependent on the dosage and the overall duration of therapy. On an average daily dose of 200-400 milligrams, neurologic symptoms first appear about 12 months after the initiation of therapy (112). The patient usually complains of paresthesias and pain in the lower limbs. If therapy is continued, an increasingly severe sensory and motor neuropathy occurs, eventually involving all four extremities and the face. Ataxia, dizziness, and vomiting also may occur (113). An occasional patient develops sphincter disturbances and even papilledema. On objective testing, nerve conduction velocities are diminished, and the cerebrospinal fluid contains an elevated protein concentration (114). Pathologically, the neuropathy induced by perhexiline maleate is characterized by a severe loss of myelinated fibers. Osmiophilic bodies appear in the cytoplasm of the Schwann and endothelial cells (115). In all patients reported thus far, discontinuation of the drug has resulted in a disappearance of the neuropathy.

Second, perhexiline maleate causes a consistent and sometimes dramatic weight loss in patients maintained on the drug for a prolonged period of time. Third, hepatic dysfunction of varying severity occurs in those individuals placed on perhexiline. The serum glutamic oxaloacetic transaminase (SGOT) concentration is increased in 25-50% of patients to whom this drug is administered. More sensitive indicators of hepatic dysfunction, such as bromsulfophthalein elimination, are abnormal in up to 75% (116). In the great majority of patients, these mild abnormalities regress when the dosage is reduced. An occasional patient, however, goes on to develop cirrhosis (117).

In summary, perhexiline maleate appears somewhat efficacious in the therapy of both typical and variant angina pectoris. Because of its bronchodilatory effects, it may be especially suited for those patients with both symptomatic ischemic heart disease and pulmonary disease. Its clinical effectiveness is limited by its relatively common side effects, particularly the peripheral neuropathy.

b. DILTIAZEM Like perhexiline maleate, diltiazem has been shown to reduce coronary vascular resistance and to increase coronary blood flow (118). In concentrations sufficient to augment coronary flow, this drug induces a fall in both atrial and ventricular contractility (119,120) as well as a reduction in heart rate (121). In the anesthetized dog with coronary artery occlusion, diltiazem exerts a substantial beneficial effect on the severity of myocardial ischemic injury; specifically, it reduces the inhibition of anaerobic glycolysis, lowers tissue levels of lactic acid and free fatty acids, and improves contractility of the ischemic myocardium (119). In short-term experiments, mitochondrial function within the ischemic muscle is unaffected.

Diltiazem has yet to be evaluated in patients with either typical or variant angina pectoris. As a result, its clinical efficacy and side

effects are largely unknown. In vitro assessments with guinea pig atria have demonstrated that calcium antagonism is more complete with nifedipine and verapamil than with diltiazem (122), but more extensive comparisons have not been performed. Because of its inhibitory influence on calcium movement, diltiazem has been suggested as a possible antiarrhythmic agent in patients with ischemic heart disease (123).

c. PRENYLAMINE Prenylamine lactate [N(3,3-diphenylpropyl)-1-methyl-2-phenylethylamine] has been available for clinical use outside the United States for about ten years. Similar to the other calcium antagonists, it has been shown in the experimental animal to augment coronary blood flow and simultaneously to depress myocardial contractility (124). In patients with angina pectoris, small doses of prenylamine (40-90 milligrams per day) have been disappointing in their ability to diminish the frequency and severity of anginal episodes (125). However, when it is administered in larger doses (120-240 milligrams per day in four equal doses), prenylamine is superior to placebo and of equal efficacy to that of beta-adrenergic blockade (126-128). Its adverse effects include gastrointestinal intolerance, nervousness, and sedation. In addition, two patients have been reported in whom prenylamine caused substantial QT interval prolongation, with resultant serious ventricular arrhythmias (129).

d. NIFEDIPINE Nifedipine [4(2'-nitrophenyl)-2, 6-dimethyl-3, 5-dicarbomethoxy-1, 4-dihydropyridine] is an especially potent vasodilator of both systemic and coronary arteries. In preliminary studies, it appears to be of potential benefit in a number of clinical situations. First, nifedipine has been shown to be an effective antihypertensive agent in patients with both acute hypertensive crisis as well as long-standing severe, intractable hypertension (130,131). In this setting, orally-administered nifedipine exerts a hypotensive action within 30 minutes and causes a maximum lowering of systemic arterial pressure 30-60 minutes after ingestion. However, its antihypertensive effects have largely disappeared by three hours after administration.

Second, nifedipine causes a substantial reduction of coronary vascular resistance (132). Despite a concomitant fall in coronary arterial perfusion pressure, coronary blood flow increases. As with the other calcium antagonists, nifedipine reduces both myocardial contractility and oxygen consumption. Therefore, nifedipine is very efficacious in the patient with ischemic heart disease, since it both increases myocardial oxygen supply (through its augmentation of coronary blood flow) and decreases myocardial oxygen demand (through its diminution of myocardial contractility and oxygen consumption).

Nifedipine has been evaluated in a relatively small number of patients with variant angina pectoris. In general, it has proved to be

efficacious in the control of variant angina (133), although some patients with this clinical syndrome obtain either partial or only minimal relief with this drug (134). As with perhexiline, diltiazem, prenylamine, and verapamil, nifedipine may exert an additive beneficial effect with nitroglycerin in the patient with ischemic heart disease, since the nitrates exert their salutary effects by a mechanism different from that of the calcium antagonists (87).

In the experimental animal with acute coronary artery occlusion, nifedipine produces a sustained increase in collateral coronary blood flow to the ischemic myocardium. Simultaneously, myocardial oxygen consumption is diminished. As a result of these effects, the severity of myocardial ischemic injury is reduced substantially (135). Further studies in the anesthetized dog with coronary artery occlusion have demonstrated that nifedipine administered in large doses (13 micrograms per kilogram) causes a drastic reduction of aortic pressure, a rise of heart rate, and a worsening of myocardial ischemic injury. In contrast, nifedipine administered in smaller doses (1 microgram per kilogram) causes only a modest decline of aortic pressure, no change in heart rate, an improvement in regional myocardial perfusion, and a reduction in the severity of myocardial ischemia (136,137).

Since recent studies have shown that calcium may play an important role in the pathogenesis of myocardial injury following ischemic arrest and reperfusion, there is considerable interest in the ability of slow-channel calcium blocking agents, such as nifedipine, to diminish such injury. In the experimental animal, nifedipine in a cardioplegic dose results in a preservation of myocardial structure and function that is similar to that obtained with potassium cardioplegia. In a lower, non-cardioplegic concentration, nifedipine does not offer more myocardial protection than simple hypothermia (138).

Well-designed and controlled studies to compare the various slow-channel calcium blocking agents are limited. In the patient with variant angina pectoris, nifedipine (administered in a dose of 20 milligrams every six hours) reduced drastically the number of episodes of chest pain occurring per day. In addition, nifedipine prevented ergonovine's provocation of coronary artery spasm at the time of cardiac catheterization. In these same patients, perhexiline maleate was more effective than placebo but not as effective as nifedipine (111).

Nifedipine's undesirable side effects apparently are infrequent. An occasional patient on nifedipine complains of headache. In vitro studies have demonstrated that nifedipine inhibits the entry of calcium into the pancreatic beta cell, thus interfering in some way with the glucose-induced release of insulin (139). Despite this demonstration in the experimental setting, nifedipine-induced hyperglycemia has not been a difficult

clinical problem.

e. VERAPAMIL Verapamil is a papaverine derivative that has been available in Europe since 1962. As a result of its being available for almost two decades, it has been investigated extensively in both experimental animals and man. From these studies has evolved considerable evidence that verapamil is an effective agent for the treatment of supraventricular tachyarrhythmias as well as ischemic heart disease.

In the experimental animal, verapamil reduces the rate of spontaneous impulse initiation by the sinoatrial node (140). In addition, it slows conduction through the atrioventricular node. His bundle electrocardiographic studies have demonstrated that verapamil impedes atrioventricular conduction proximal to the His bundle but exerts no effect on intraatrial or intraventricular conduction (141,142). Maximal delay occurs in the atrioventricular node itself. Therefore, in patients without obvious conduction system disease, verapamil causes prolongation of the PR interval without altering the QRS duration and QT interval (143). With increasing doses, sinoatrial node function is markedly depressed, and an occasional patient develops type 1 second degree atrioventricular block or nodal rhythm (144).

Verapamil has gained popularity outside the United States in the conversion of re-entrant atrial tachyarrhythmias to normal sinus rhythm as well as the control of the ventricular rate in atrial flutter and fibrillation. In the majority of patients with paroxysmal atrial tachycardia, intravenous verapamil is successful in reverting the patient to sinus rhythm (143, 145). In the patient with atrial flutter or fibrillation, intravenous verapamil causes a marked slowing as well as a regularization of the ventricular response (146). Uncommonly, verapamil causes a reversion to sinus rhythm (147). Although intravenous verapamil has proved very effective in the acute therapy of these supraventricular tachyarrhythmias, its efficacy when administered orally over the long-term is not as well characterized. In the patient with atrial tachyarrhythmias as a manifestation of the sick sinus syndrome, verapamil probably should be avoided completely, since its effects on sinoatrial and atrioventricular nodal function are greatly exaggerated (148).

In the anesthetized dog verapamil causes a reduction of coronary vascular resistance and an increase of coronary blood flow (149). Simultaneously, it induces a substantial diminution of left ventricular contractility (150). Systemic vascular resistance also declines, so that mean systemic arterial pressure falls modestly. In man, verapamil causes a modest decline of systemic arterial pressure as well as a fall of left ventricular contractility (151). In those individuals with coronary artery disease, its intrinsic negative inotropic effect is small, and its potent vasodilatory properties more than compensate for any intrinsic reduction of left ventricular contractility (152). As a result, even

in the patient with coronary disease, verapamil does not depress forward cardiac output. In patients without demonstrable coronary artery disease, verapamil induces a substantial increase in coronary blood flow (153). In contrast, in those with underlying coronary disease, it induces a modest decrease in coronary vascular resistance and a concomitant reduction in coronary arterial perfusion pressure, so that coronary blood flow is not altered significantly (153,154).

Animal studies have demonstrated clearly that verapamil exerts a salutary influence on myocardial ischemic injury (155, 156). In fact, verapamil selectively depresses contraction of the ischemic myocardium without substantially affecting that of normal muscle (157). In man, oral verapamil has proved effective in the treatment of patients with typical angina pectoris (158). In several well-designed clinical studies it has proved superior to placebo in reducing the frequency of anginal episodes and the utilization of sublingual nitroglycerin (159). At the same time, other studies have shown that verapamil (120 milligrams three times per day) and propranolol (100 milligrams three times per day) are equally efficacious in diminishing the frequency and severity of angina pectoris (160,161). In addition, verapamil appears to be efficacious in the medical therapy of variant angina pectoris (162). Finally, verapamil was compared to placebo in a double-blinded study in patients with unstable angina pectoris and was found to cause a substantial reduction in the frequency and severity of pain episodes (163).

Verapamil has been utilized in a very limited way as an antihypertensive agent. The intravenous injection of 5-10 milligrams may be effective in the patient with hypertensive crisis, but no clinical trials have been performed to compare the efficacy of verapamil to that of other intravenously-administered hypotensive agents (i.e., diazoxide, sodium nitroprusside). Similarly, verapamil administered orally as long-term maintenance therapy has been shown to lower systemic arterial pressure when given to mildly hypertensive patients with ischemic heart disease (161), but, again, no clinical studies have attempted to compare it with other established antihypertensive agents.

For the acute therapy of supraventricular tachyarrhythmias, verapamil is administered intravenously over one minute in a total dose of 10 milligrams. This may be followed by a continuous intravenous infusion at a rate of 0.005 milligrams per kilogram per minute. In children, the dose required to convert paroxysmal supraventricular tachycardia to sinus rhythm is usually 3.5-5.0 milligrams. Oral maintenance therapy for either supraventricular arrhythmias or angina pectoris ranges from 240-480 milligrams per day, given in four equal doses. Following its intravenous administration, a peak hemodynamic and electrophysiologic

effect occurs within 3-5 minutes. Subsequently, the hemodynamic alterations induced by the drug are dissipated rapidly (within 10-20 minutes). In contrast, its electrophysiologic effects are longer-lived, and the prolongation of the A-H interval is still detectable 6 hours after drug administration. Thus, there appears to be preferential uptake and binding of verapamil by the atrioventricular nodal tissues. Following its oral administration, maximal plasma levels are achieved within two hours (164). Verapamil is metabolized largely by the liver, and 80% of a given dose is excreted in the bile within 10 hours of administration.

Verapamil is generally well tolerated, although the overall incidence of adverse effects is reported as 9%, with severe reactions requiring its discontinuation in about 1%. Orally-administered verapamil is accompanied by a low incidence of gastric intolerance and constipation. An occasional patient complains of vertigo, headache, and nervousness. Intravenously administered verapamil may induce systemic arterial hypotension (143). It has been reported to cause bradycardia or high degree atrioventricular block. Its depressant effect on the left ventricle is said to be accentuated greatly by concomitantly-administered beta-adrenergic blockade. As a result, it is recommended that verapamil not be administered to patients already receiving beta-blockers. Massive ingestion of verapamil can lead to severe sinus node depression, complete atrioventricular dissociation, and severe hypotension (165).

Because of its direct negative inotropic influence, verapamil is contraindicated in those individuals with advanced cardiac failure, atrioventricular block, sick sinus syndrome, and cardiogenic shock. However, if cardiac decompensation is related to a rapid supraventricular tachyarrhythmia, verapamil may induce a prompt improvement in hemodynamic parameters by causing a reversion to normal sinus rhythm.

B. Surgical Therapy Although coronary artery bypass surgery is generally successful in relieving the pain of typical angina pectoris, its overall benefit in patients with variant angina is dependent on the extent and severity of underlying arteriosclerotic coronary artery disease. When bypass surgery is performed on those individuals without fixed coronary disease, there is an unusually high incidence of spontaneous graft closure (166), since blood flow through the native coronary arteries is adequate most of the time. In addition, since episodes of diffuse coronary artery spasm continue after operation, spasm in the area of insertion of the anastomosis of the graft to the native coronary artery may reduce flow sufficiently to cause thrombosis. Since coronary artery spasm may be mediated through increased activity of the adrenergic nervous system, two patients with variant angina reportedly have benefited from a combination of partial cardiac sympathectomy and saphenous vein bypass grafting (167). Patients with coronary artery spasm superimposed on arteriosclerotic coronary artery disease fare better with coronary artery bypass than those in whom spasm occurs in unobstructed coronary arteries. Although some patients with variant angina clearly derive

benefit from the bypass operation (168-170), their response may be slightly inferior to that of patients with typical angina pectoris (171, 172).

Conclusions

In recent years coronary artery spasm has taken on new importance as the definite cause of Prinzmetal's variant angina and as a very likely contributor to typical angina pectoris and myocardial infarction in some patients. The development of coronary arteriography and of methods for the continuous measurement of myocardial blood flow have demonstrated clearly that variant angina is due to spasm of a large coronary artery. More recent studies have attempted to incriminate coronary artery spasm as an important contributing factor to typical angina pectoris and myocardial infarction. Although spasm has been shown to occur in association with these common manifestations of ischemic heart disease, its frequency as a principal causal factor in the clinical occurrence of angina pectoris and myocardial infarction is unknown.

However, in view of the possible role of coronary artery spasm in the genesis of typical angina pectoris and myocardial infarction, therapeutic agents designed to alleviate such spasm are worthy of trial in patients with ischemic heart disease. First, nitroglycerin is well known to exert a beneficial effect in patients with typical angina pectoris. In addition, however, in patients with recent myocardial infarction who are hemodynamically stable, nitroglycerin may be beneficial by abolishing whatever coronary spasm is present.

Second, the pharmacologic agents known collectively as calcium antagonists appear very promising in the therapy of several cardiovascular disease entities. First, these drugs reduce systemic vascular resistance by directly relaxing arterial smooth muscle. As a result, they are somewhat efficacious in the acute and long-term treatment of systemic arterial hypertension. Second, at least some of the calcium antagonists exert a direct effect on the cardiac conduction system, and they have proved very effective in the acute and possibly long-term therapy of supraventricular tachyarrhythmias, specifically paroxysmal supraventricular tachycardia, atrial fibrillation, and atrial flutter. Third, these agents both augment myocardial oxygen supply (by improving coronary blood flow) and reduce myocardial oxygen demand (by decreasing myocardial contractility). As a result, they are very effective in the treatment of both typical and variant angina pectoris. In this regard, they seem at least as powerful as beta-adrenergic blockade, but, in contrast to the beta-blockers, the calcium antagonists cause bronchodilatation. It is anticipated that these agents will be used extensively in the therapy of supraventricular tachyarrhythmias and angina pectoris following their approval for use in the United States.

Third, alpha-adrenergic blockade with drugs such as phenoxybenzamine, phentolamine, or prazosin, a new antihypertensive agent with alpha-

adrenergic receptor blocking properties, may also alleviate the occurrence of typical angina pectoris and myocardial infarction by preventing alpha-adrenergically mediated coronary artery vasoconstriction. The intriguing possibility must be considered that the denervation of the coronary arteries and the interruption of adrenergic vasoconstrictor fibers have a role in the relief of angina in patients who have undergone surgical revascularization, particularly those in whom relief of pain persists despite the occlusion of the graft.

The development of methods to measure coronary blood flow continuously in conscious human subjects (173) and of noninvasive techniques using radionuclides for determining the distribution of coronary perfusion should allow elucidation of the specific role of coronary spasm in the various manifestations of ischemic heart disease and the identification of the subgroup of patients in whom coronary spasm plays an important part in the genesis of ischemia. This development should lead to the selection of more rational therapy.

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