“Variant” Angina Pectoris

Classical angina pectoris is characterized by recurrent attacks of retrosternal pain brought on by effort and emotion and relieved by rest and the administration of nitroglycerin. It is well known that this classical syndrome has many variations and modifications. In 1959, and again in 1960, Prinzmetal and his colleagues described what they called a “variant form of angina pectoris.” According to these authors, this syndrome exhibits important features which differentiate it from classical angina.1, 2

The characteristics of the variant form of angina were listed as follows:

1. The anginal pain occurs at rest or during normal activity and is not provoked by exercise or emotion.
2. The pain is often more severe and of longer duration than the usual anginal pain.
3. In some patients, the pain is cyclic in character and often recurs at the same time of day or night.
4. Severe attacks of pain are accompanied by elevation of RS-T segments with reciprocal changes, as seen in the acute injury pattern of myocardial infarction. The RS-T elevation is transient and returns to its pre-attack pattern after subsidence of pain. There is also an increase in the amplitude of R waves during a severe anginal attack.
5. Patients have narrowing of a single major coronary artery.
6. The area of myocardium giving rise to RS-T elevation corresponds to the distribution of one large coronary artery and subsequent infarction occurs in the same area of the heart that gave rise to the elevated RS-T segment.
7. Presumably, increased vascular tonus in a vessel with atherosclerotic narrowing may transiently lead to critically diminished blood supply to an area of myocardium.

Because of its rather dramatic manifestations, variant angina has been deemed a new and unique clinical entity with distinct anatomic, prognostic, and therapeutic implications. Careful perusal of both the older literature and the rapidly expanding newer literature on this subject suggests that “Prinzmetal’s angina” is neither new nor unique. Nor does it define a sufficiently homogeneous group of patients to be of practical clinical utility.

Cases similar to those described by Prinzmetal and his colleagues were reported as early as 1931.4-9 These authors recognized that transient RS-T changes occurring during anginal pain may be similar to those seen in acute myocardial infarction. However, they also recognized that such changes may be associated with an otherwise diverse clinical picture.

Typical effort angina has been not infrequently reported to occur in association with RS-T elevation.3, 5, 9-10 In some cases the pain may occur on effort and at rest.12, 13, 17 Occasionally, pain associated with RS-T elevation has been precipitated by emotion.15, 18 It is true that some authors have observed the electrocardiographic changes and pain with the patient at rest and not with exertion.10-22 This is not unexpected, since ischemic electrocardiographic changes occur with exercise in only about eighty percent of patients with angina pectoris due to coronary artery disease.23 In some cases of variant angina, various electrocardiographic changes after exertion were observed without elevation of the RS-T segments.15, 22 In one case, RS-T elevation, and at other times RS-T depression, have been observed in the same patient,12 suggesting ischemia at different locations of the myocardium.

Pain associated with RS-T elevation need not be more severe nor of longer duration than other anginal pain. The intensity spectrum of pain in both the classical and the variant types of angina (as well as in acute myocardial infarction) may extend from no pain at all to slight pain to very severe pain. Although Prinzmetal’s patients all described severe pain, occasional patients may describe only a mild burning sensation.3 In some patients, RS-T elevation may appear without any pain or with only sweating.3, 12, 18, 24, 25

The cyclic appearance of anginal pain in variant angina may be missing. In addition, cyclic rest pain is sometimes seen in cases exhibiting only depression of RS-T segments. Cyclic pain in typical angina pectoris, often occurring at the same time each night, may be due to incipient congestive heart failure, excessive autonomic activity, or hypertensive crisis.

Excessive autonomic activity, characterized by significant increases in heart rate and blood pressure, may occur during those periods of sleep associated with rapid eye movements26 and that stage of sleep characterized as “D” sleep.27 Periods of rapid eye movements have been reported to occur regularly just prior to episodes of nocturnal angina in some patients.
with coronary artery disease.28 Attacks related to the mass reflex, such as that elicited by bladder distention in paraplegics,28-31 may be associated with excessive autonomic activity — especially, a tremendous rise in blood pressure.

It is astonishing how rarely authors describing the "variant form" of angina have reported the level of blood pressure during attacks of pain. Since the description of the hypertensive crisis by Pal29 and the publication of the monograph by Bernál29 little attention has been paid to this interesting phenomenon.28 Lewis explained it by a "vasomotor storm."34 These attacks characteristically occur at the same time of day or night. In some of the early reported cases of variant angina,3,7 anginal attacks were associated with paroxysmal hypertension. Wilson and Johnston6 reported a blood pressure of 200/120 during an attack of anginal pain, while it was only 160/100 when the pain was absent. However, other authors have observed no increase in blood pressure during attacks of pain in the variant form of angina.14,16,21,35

Whether RS-T elevation or RS-T depression occurs during an attack of angina pectoris depends on which area of myocardium is involved in the ischemic process. The subendocardial region of the left ventricle is the most susceptible to impairment of blood flow. This is true whether ischemia and concomitant anginal pain are spontaneous or induced. The hallmark of subendocardial ischemia is RS-T depression. RS-T elevation is suggestive of subepicardial ischemia.36 Ischemia of intramural layers need not cause any electrocardiographic changes.37 This simplistic explanation represents only an approximation of the complexities inherent in the repolarization sequence during myocardial ischemia. The process is incompletely understood, but probably involves all borders of an ischemic area, not just those parallel to the subendocardium and subepicardium. Thus, the direction of deviation of RS-T segments is dependent on the complex factors which may render one area ischemic in preference to another. It is unlikely that any net sum of such factors can be ascribed to a single cause. It is illogical that such should define a syndrome.

The increase in R wave voltage during attacks of variant angina, which Prinzmetal and his colleagues noted, has also been noted by others.11 But this is not always observed. The opposite, diminished amplitude or loss of R waves, may be seen.38

In accordance with Prinzmetal's observations, obstruction of at least one large coronary artery was found in ninety percent of the cases of variant angina reported by Silverman and Flamm.13 However, Cheng and his colleagues found such a lesion in only one of their five cases.39 The coexistence of variant angina with normal coronary arteries by arteriogram or autopsy has been noted by others,16,21,22,39-41 At times, significant disease may be found in more than one large coronary artery.13,21

More than a generation ago, Parkinson and Bedford,8 and later Wilson and Johnston,6 suggested the possibility that "contraction of the coronary arteries" may be causally involved in anginal attacks associated with electrocardiographic changes of the kind produced by occlusion of a large coronary artery. Prinzmetal and his colleagues suggested that a temporary increase in vascular tonus in a large coronary artery with a narrowed lumen may be the cause of variant angina.1,2 Reversible spasm of a large coronary artery during coronary arteriography is now a well known phenomenon. Such spasm has also been demonstrated by coronary arteriography during attacks of spontaneous angina associated with RS-T elevation.42-44 These observations tend to support the speculations of Prinzmetal and of earlier workers. What is not yet clear is whether or not coronary arterial spasm may also play a role in exercise induced angina, angina associated with RS-T depression, or even acute myocardial infarction or sudden death in patients with coronary artery disease.

From the foregoing discussion, it is evident that the syndrome of "variant angina" was recognized and reported by sundry authors many decades prior to publication of Prinzmetal's series. Prinzmetal and his colleagues were quite cognizant of this.1,2 The fact that individual cases and small series continue to be reported after more than two score years lends credence to the role of variant angina as a medical curiosity. The failure of more than forty years of medical ingenuity to reap a homogeneous group of patients from the cohort with variant angina suggests that no such homogeneous group exists.

Actually, this syndrome is so heterogeneous that the term "variant of the variant" has been used.30 This syndrome occurs: at rest or with exertion; with or without RS-T elevation; with severe pain, with mild pain, or with no pain at all; with a hypertensive crisis or with no change in blood pressure; in patients with multiple vessel coronary artery disease, with disease of two or three vessels, or with normal coronary arteries.

It is our opinion that such terms as variant angina, angina inversa, Prinzmetal's syndrome, and variant of the variant should be discarded. It is more useful to describe the heterogeneity of this syndrome by stating the facts as they are: anginal syndrome in the presence of RS-T elevation resembling that seen in myocardial infarction; with or without pain, with or without blood pressure rise, at rest but occasionally
also on exertion, with narrowing of one or more coronary arteries or with a normal coronary vascular tree. Only with such accurate description can we hope to glean homogeneous subgroups from the morass of case reports that have plagued us since the 1930’s.

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