The mechanism of myocardial infarction and unexpected sudden cardiac death remains incompletely defined. The frequent absence of complete coronary arterial obstruction in both these conditions has challenged the concept of arterial obstruction followed by infarction or sudden death or both. Several independent observations are herein developed into a working hypothesis for the pathogenesis of myocardial infarction and sudden death. This is based upon the unique anatomic, pathologic and physiologic features of the heart during infarction and unexpected sudden death.

The two major morphologic types of infarction are transmural (40 percent) and subendocardial (60 percent). The former almost always occurs in the presence of arterial obstruction (90 percent); the latter usually occurs in the presence of diseased, though patent, coronary arteries. Fresh transmural infarcts may be associated with new or old occlusions. Such occlusions are usually divided equally between fibrin thrombosis and hemorrhage into an atheromatous plaque. Furthermore, old occlusions are frequently noted (44 percent) in the hearts of individuals who have died of noncardiac causes in the absence of any pathologic evidence for myocardial necrosis. Fresh transmural infarcts by definition involve the subendocardium thereby making oxygen demand the greatest. The capillary bed is at near capacity utilization at rest and is entirely unperfused during systole. Thus there is evidence for the inordinate predisposition of the subendocardium to undergo necrosis as well as the likelihood of its involvement in unexpected sudden cardiac death. It should be recalled that all transmural infarcts by definition involve the suben-
NORMAL MYOCARDIAL CIRCULATION


docardium but that subendocardial infarcts by definition exclude the other layers of the heart.

HYPOTHESIS

In the process of myocardial infarction, the subendocardium is almost always involved and commonly the earliest events for necrosis can be found in this layer. It is thus reasonable to consider the possibility that the initial site for myocardial infarction and sudden death is the subendocardium and to attempt to relate the morphologic forms of these conditions to initial subendocardial coagulation necrosis. The inaccessibility of the subendocardium in both experimental animals and man has limited investigation of the early effects of ischemia on this layer. Let us assume that the mechanism for initial subendocardial necrosis parallels observations following protracted periods of ischemia on skeletal muscle of animals. It is recognized that conditions unfavorable to myocardial oxygenation affect the subendocardium by initially producing ischemia which, with time, can lead to necrosis.

Of interest is the observation in animals that following release of a limb tourniquet, the skeletal muscles are incapable of sustaining reflow. Many observations (Fig 2) may explain this inability to re-establish flow in the posts ischemic state: arteriolar spasm, impaction of micro-emboli arising from within the tourniquet zone or the aggregation of red blood cells, anoxic ischemic swelling of trapped white blood cells, increased adhesiveness or stickiness of the endothelial surface for one or more of the formed blood elements, direct injury to endothelial cells with fragmentation, formation of gaps, loss of fluid and stasis, loss of fluid into perivascular cells, such as the muscle fibers, compression by perivascular cells, which swell and come to impinge directly upon the vessel, swelling of the endothelium, constriction by collagen fibers or bundles which are caused to stretch as the tissue is expanded by edema, the formation of histamine type leaks secondary to injury to the mast cells with ensuing stasis, formation of platelet thrombi during the first few instants of reflow.

OBSTRUCTIVE FACTORS AT THE MICROCIRCULATORY LEVEL

FIGURE 2. Obstructive factors at the microcirculatory level. 1, Swelling of perivascular tissue; 2, swelling of endothelial cells; 3, endothelial blebs; 4, compressive left ventricular pressure (Reprinted by permission, S. Karger, Basel).
SUBENDOCARDIAL ISCHEMIA

![Diagram of Subendocardial Ischemia](image.png)

Figure 3. Subendocardial ischemia. Stippled area represents subendocardial ischemia resulting in obliteration of the microcirculation and producing an end-arterial system. For A, B, and Arrows see Figure 1 (Reprinted by permission, S. Karger, Basel).

and, intravascular clotting (not believed to be a significant mechanism). It may be assumed that obstruction similar to that described for skeletal muscle may thus occur in ischemic cardiac muscle with a resulting inability to reinstitute blood flow.

One can only speculate upon the additional effect of compressive forces generated by lateral subendocardial and midcardiac tissue contraction combined with substantial lateral ventricular pressure. Such forces would be expected to further compress the early ischemic subendocardial tissue acting to further obliterate its collaterals. Thus, an end-arterial system is created and blood flow is compromised into and out of the ischemic subendocardial region (Fig 3). Consequently the cross-sectional area perfused by the subendocardial capillaries would be greatly reduced or eliminated in the involved region. The decrease in perfused cross-sectional area would be reflected by an increased arterial resistance with potentially impeded coronary flow.

At this point, whether or not the subendocardial infarction expands to become a transmural myocardial infarction would depend in part upon the major arterial supply to the subendocardium; and,
the continuation of inordinate myocardial work during the period of ischemia. The former is determined by the degree of arterial obstruction which preexists (Fig 4) at the time subendocardial necrosis takes place or which develops later. The latter is determined by preexisting conditions such as hypertension, or individual conditions such as denial of pain or lack of symptoms of myocardial ischemia with continuation of effort in the presence of subendocardial necrosis. Initial subendocardial necrosis combined with preexistent arterial disease would predispose the individual to transmural myocardial infarction in the areas subserved by the obstructed major arterial supply. In a condition where increased subendocardial resistance produces stasis in a patent arterial supply, hemorrhage into an atheromatous plaque or thrombus may develop secondarily, again setting the stage for transmural myocardial infarction. Where patent major coronary arterial systems exist, where the work of the heart is not sustained at a high level, and where major coronary arterial stasis does not develop, patency of the collateral circulation between adjacent subendocardial layers and the patent major coronary arterial system should be maintained. This would tend to prevent extension of the subendocardial necrosis into the midcardiac layers and to halt the progress of a transmural infarction. At this stage a subendocardial infarction will exist and persist independent of its transmural counterpart.

Undoubtedly, preexistent major coronary arterial disease will predispose to subendocardial necrosis proximal to the area subserved. If blockage has already occurred at a major avenue for arterial perfusion, it will compromise the blood supply when the subendocardium undergoes necrosis. It remains only for the adjacent subendocardium to outrun its collateral interconnections and its blood oxygen supply. With this sequence of events, transmural infarction may be an almost unavoidable consequence (Fig 5). The progression of a subendocardial infarction to a transmural one could be based upon associated factors which tend to increase myocardial work during the presence of the acute necrotic subendocardial phase. Such an increase in myocardial work increases resistance and generates a potential extension of the necrosis through the wall, secondary perhaps, to occlusion of the major arteries.

The above concepts can now be applied to the mechanism of sudden unexpected cardiac death. Investigators are of the relatively uniform impression that this form of death is the result of a myocardial electrical disturbance. Could this form of death be the result of the proposed initial subendocardial necrosis? The conduction system is known to have a lower tissue oxygen requirement than does the adjacent myocardial fiber. Accordingly, the Purkinje system would be less sensitive to...
hypothesis although electrolyte changes could occur secondary to hypoxia. It is logical to assume that the Purkinje system is the innocent bystander to the initial phase of subendocardial necrosis. During this phase there is a known electrolyte imbalance which occurs as a result of membrane deterioration. This creates an electrical dipole system which can interact with the adjacent Purkinje network. Such an irritable focus may set the stage for an autonomous ventricular impulse. The adjacent ischemic areas create an area of poor conduction permitting retrograde reentry phenomena. Thus it is possible that in the early, almost undetectable phase of subendocardial necrosis that an isolated area of reentry could develop in the ventricle bringing about ventricular tachycardia, fibrillation and death. Alternately profound bradycardias have also been known to be associated with the early phase of acute myocardial infarction. Perhaps on the basis of vasovagal stimulation these events can lead to a deterioration in forward flow in an already impaired coronary circulation setting the stage for the same type of irritability described above.

With the advent of subendocardial ischemia, the uniform configuration and geometric nature of the left ventricle are permanently altered. A new condition exists in place of that which was present prior to infarction—a new biophysical system in which new events must be considered. The infarction of the subendocardium can set the stage for the immediately adjacent midmyocardial layers to become a new “physiologic subendocardium,” that is, the midmyocardium has now become the functional layer most adjacent to the left ventricular cavity. Mechanical ventricular events are then altered and may affect compromised redistributed circulation in midcardiac and adjacent subendocardial layers. By this process many areas of collateral interruption may occur on a pressure basis generated from the initial area of subendocardial infarction. Minor infarcts and patchy fibrosis may ensue.

The extensive subendocardial replacement by fibrous connective tissue creates a restrictive endocardiothopathy, the nature and extent of which will prevent adequate relaxation and contraction of the adjacent subendocardial and midcardiac layers. Myofibrosis can ensue in part by disuse atrophy or by altered pressure and wall stress. The latter alters collateral circulation creating a myriad of small endarterial systems each capable of inducing small intramural myocardial infarctions. Thus it is possible in considering the initial subendocardial events to identify possible explanations for extensive patchy fibrosis of the midcardiac layers as well. Transmural infarction can bring about a deterioration of collateral flow as well as an alteration of mechanical and stress function of the left ventricle in a similar but different pattern than occurs in subendocardial infarction.

Complications of myocardial infarction are thus predictable when the anatomic form of myocardial infarction is known. Both transmural and subendocardial infarctions share in common the production of ventricular arrhythmias. This is not surprising since reentry phenomena would be permitted by necrotic muscle whether transmural or subendocardial. In addition, both forms of myocardial infarction share papillary muscle dysfunction and secondary mitral regurgitation. This is not surprising since in both forms the subendocardium is damaged and since the papillary muscle is an appendage of the subendocardium. In transmural infarction, muscular support beyond the subendocardium (midcardiac and subepicardial layers) may be deficient, thus enhancing the mechanical dysfunction of the ventricle and the adjacent papillary muscle. At this point, however, the resemblance ends. Subendocardial infarction may, in time, give rise to progressive intramyocardial fibrosis of the left ventricle. It may be speculated that the progressive fibrosis is on the basis of isolated restrictive subendocardial fibrosis impairing the contractility of the overlying midmyocardial and subepicardial layers. Decreased contractility brings about a form of disuse atrophy and replacement by connective tissue which has a lower oxygen demand. In time, then, subendocardial infarction may induce extensive intramyocardial fibrosis based, in part, upon the extent of the initial infarction. Cardiac failure is the inevitable result of progressive myocardial fibrosis, or may result from a generalized fibrosis of the subendocardium, wherein a restrictive endocardiopathy is created.

Complications of transmural myocardial infarction, with the exception of those shared in common with the subendocardial forms, represent more devastating clinical and pathophysiologic phenomena. Major complications of transmural infarction are: the early onset of cardiac rupture, shock, cardiac failure, aneurysm formation, and mural thrombosis. Development of these phenomena is well understood in the light of the transmural nature of the initial myocardial infarction.

As mentioned, the patient with transmural myocardial infarction is also more apt to be the victim of cardiogenic shock. These hearts are diffusely and severely diseased, and in addition, it will be recalled that transmural myocardial infarction is most often accompanied by severe obstructive coronary disease to a greater degree than is subendocardial infarc-
tion. Thus, under conditions of stress, such as the infarction itself, alternate avenues of perfusion must occur by available existing collaterals.

REFERENCES
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Definition of Existentialism

Against the notion that the essence or nature of man determined the character and fate of every man, the existentialist believes that each individual's existence is a unique and primary fact, and that his essence or essential character is the gradual and ever-changing product of his existence in the flux of time. A man's essence is formed by his total past, to which he adds in every moment of his life. Usually the existentialist rejects the naturalistic approach to the study of man through biology and history and prefers the "phenomenological" approach through the study of consciousness, and of objective reality as phenomena appearing to consciousness. Obviously existentialism is too multiform and mutable but we shall provisionally define it as the philosophy of the individual mind confronted by the changing contemporary world.