Considerable evidence indicates that impairment of cardiac function is an important feature of the "shock syndrome" and that it contributes significantly to the development of terminal cardiovascular collapse and death (1-4). However, some studies of experimental shock are not entirely in accord with this conclusion (5). In any case, it is clear that shock is a multisystem disease involving alterations in many physiological and biochemical processes, including those of the heart, and numerous vicious cycles, any one or a combination of which can lead to eventual irreversibility to treatment.

An overall summary of some of the most prominent vicious cycles in the shock syndrome is illustrated in Figure 1. The main cycle can be entered at any one of several points, e.g., blood loss, heart failure, burns, or other forms of trauma. Whatever the initiating factor, the subsequent course is similar in many respects with compensatory mecha-

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**FIGURE 1**

*Some of the vicious cycles of shock. Abbreviations: Bld. Coag. = blood coagulability, BP = systemic blood pressure, BV = effective blood volume, Cap. = capillary, CBF = coronary blood flow, CO = cardiac output, HR = heart rate, MDF = myocardial depressant factor, Met. = metabolic, Const. = constriction, and Pulm. = pulmonary. < = Decrease and > = increase.*
Mechanisms acting to maintain the immediate function of the heart and the brain at the long-term expense of many tissues. From the point of view of the heart, myocardial hypoxia develops when the decrease in coronary perfusion pressure is so great that it cannot be balanced by the concomitant decrease in coronary vascular resistance. The other reflex and hormonal compensatory mechanisms that are mediated largely by the sympathetic nervous system and the adrenal glands have well-known damaging effects on the heart. Therefore, with the relentless nature of the demands imposed on the heart, progressively more severe and eventually critical impairment of cardiac function will occur as the shock period is prolonged.

This review focuses specifically on the various types of anatomic injury to the heart and some of the possible mechanisms for the cardiac failure that eventually results. Most of the references are to studies of experimental hemorrhagic hypotension in animals, but the findings from these investigations are applicable to the situation in humans and, in general, to other types of shock, i.e., endotoxin, traumatic, etc.

Subendocardial Hemorrhage and Necrosis.—Frequent reports have appeared de-

![Image of a heart](image-url)
scribing the occurrence of myocyte necrosis and hemorrhage in the subendocardial region of the myocardium in animals subjected to hemorrhagic shock (6-8). These studies have predominantly been in dogs, but other animals (8, 9) including man are similarly affected. The lesions occur in the presence of normal coronary arteries, although it is reasonable to expect exaggeration of the effect in patients with coronary atherosclerosis. Figure 2 shows striking superficial subendocardial hemorrhage in the left ventricular outflow tract of a 37-year-old woman who expired following massive hemorrhage. Microscopic examination revealed myocyte necrosis. Since this type of hemorrhage frequently involves the region of the conducting fibers of the left bundle, as it does in this case, it is not surprising that hemorrhagic shock is often complicated by arrhythmias.

Necrotic and hemorrhagic changes of this kind, however, are not unique to the shock state but are found in many other situations. For example, hemorrhagic necrosis of the endocardium has been seen following surgery involving heart-lung bypass in dogs (10), pigs (10), calves (11), and humans (12). It has been suggested that this condition results from inadequate perfusion of the myocardium or from the occurrence of ventricular fibrillation (12). Ghidoni et al. (13) produced changes of this type in calves subjected to ventricular fibrillation during cardiopulmonary bypass surgery. Similar lesions have also been shown to occur after excessive endogenous secretion (14) or exogenous administration (15) of catecholamines and after stellate ganglion sympathetic stimulation (16). Some investigators (17) have reported myocardial lesions after intracranial injury; these lesions have been attributed to “activation of sympathetic centers.” In all of these situations there are elements of both hypoxia and increased catecholamine effect.

We have demonstrated that treatment of animals in shock by methods that decrease the hypoxia or the catecholamine effect reduces or eliminates the development of subendocardial hemorrhagic lesions. These methods include surgically induced heart block, which prevents the tachycardia response in shock (18), administration of beta-sympathetic blocking agents (19), cardiac denervation and adrenalectomy (20, 21), or hyperbaric oxygen treatment (22).

Both light and electron microscopy reveal that the necrotic lesions are similar to those produced by occlusion of a coronary artery followed by reflow (23) or by agents such as norepinephrine and isoproterenol in the presence of blood flow (14, 15).

No adequate thesis has yet been advanced to explain the subendocardial hemorrhage. In our experience subendocardial hemorrhage is less likely to be seen and is certainly less prominent in animals killed following shock without reinfusion of shed blood. Since the degree of subendocardial hemorrhage is often not in proportion to the amount of myocyte necrosis, it seems likely that an undefined component of vascular injury is present.

Zonal Lesions.—Another type of myocardial lesion described previously (24-27) has been termed a “zonal lesion” (Fig 3). This type of lesion consists of a zone of apparent hypercontraction at the end of a myocyte, adjacent to an intercalated disc, with local scalloping of the sarcolemma, marked shortening of the sarcomeres adjacent to the intercalated disc, fragmentation of the Z bands, bizarre bending and distortion of the myofilaments, and displacement of the mitochondria away from the intercalated disc. The mitochondrial displacement permits recognition of the fully developed zonal lesion by light microscopy. In histochemical preparations demonstrating mitochondrial enzymes such as succinic dehydrogenase, a zonal lesion appears as a clear zone with a thick dark margin adjacent to an intercalated disc.

Zonal lesions have similarities with the alterations in myocardial fine structure seen in certain dystrophies (28) and in the development of experimental hypertrophy (29) and with the lesions produced by excess catecholamine stimulation (14-16). These similarities include sarcomere shortening and Z-band alterations. There are, however, distinct differences which set apart zonal lesions as a form of myocyte injury unique to a state of hypovolemia. These differences include early, prominent fragmentation of Z bands, predilection for the intercalated disc region, lack of increased electron density as seen in contraction bands, and lack of abnor-
Zonal lesions can be prevented by some of the same manipulations that prevent hemorrhage and necrosis, including heart block (18), administration of anti-beta-adrenergic agents (19), and cardiac denervation plus adrenalectomy (20, 21). However, they are potentially reversible (26) and can be etiologic alterations in the ultrastructure of mitochondria in spite of their displacement (30). This maintenance of normal orthodox mitochondrial ultrastructure is additional evidence that zonal lesions, in contrast to catecholamine-induced myofibrillary necrosis (14–16), are reversible and do not represent lethal myocyte injury. Zonal lesions occur in the same general subendocardial regions of the heart as do the necrotic lesions, but each may occur independently of the other.

Zonal lesions are almost always found following hemorrhagic shock in certain experimental animals: 15 of 15 dogs (19), 4 of 5 cats, 4 of 5 pigs, but only 1 of 6 rabbits (8). They are also found in man (31), but the incidence has not been determined. Zonal lesions have been demonstrated as early as 15 minutes after the onset of oligemic hypotension, and they increase proportionally differentiated from the hemorrhagic and necrotic lesions on the basis of their response to hyperbaric oxygen treatment. When oxygen at 3 atm is supplied to dogs in shock, myocardial oxygen consumption is significantly augmented (32), defects in myocardial carbohydrate metabolism are reversed (33), and subendocardial hemorrhage and necrosis are essentially prevented (22). However, the severity of the zonal lesions is undiminished. Increased oxygen consumption, metabolic effects, and prevention of subendocardial hemorrhage and necrosis indicate that the availability of oxygen to the subendocardial region of the left ventricle in hemorrhagic shock is increased by hyperbaric oxygen treatment. Coupled with this fact, the widespread distribution and the undiminished severity of zonal lesions suggest that zonal lesions probably are not the result of tissue hypoxia (22).

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progressively in number as the shock period is prolonged. Although they are potentially reversible (26), these lesions, which distort the contractile elements of the myocyte, may reasonably be considered to contribute to the functional deficit that leads to myocardial failure in late shock.

Cardiotoxins.—A third element that can contribute to decreased myocardial functional capacity in shock involves the various toxic products of peripheral ischemia. It has been demonstrated that metabolic acidosis, such as that which occurs in severe shock, can complement myocardial hypoxia in decreasing myocardial contractility (34). This effect can be camouflaged by excess adrenergic activity in shock, but, when the latter is blocked, the negative effects of the acidosis become apparent (35). Several more specifically defined cardiotoxic shock factors have been proposed (36). The best characterized of these factors is the myocardial depressant factor described by Lefer and his associates (37, 38) and others (39–41), but with conflicting findings by some workers (42–44). The myocardial depressant factor is thought to be a small peptide that is produced by lysosomal hydrolases in the ischemic pancreas. It supposedly has a negative inotropic effect on the heart. It is unlikely that the myocardial depressant factor is a causative agent for the anatomic lesions in the heart, since zonal lesions occur too early in the course of shock and the hemorrhagic and necrotic lesions

![Figure 4
Factors contributing to heart failure in shock. BF = blood flow, CA = catecholamines, Hem. = hemorrhage, Inotr. = inotropic, Necr. = necrosis, Sat. = saturation, Sub-endo = subendocardial, and VV = ventricular volume; see Figure 1 for other abbreviations.](http://circres.ahajournals.org/)

*Circulation Research, Vol. 35, December 1974*
occur in situations that do not give rise to pancreatic ischemia (16). However, it is quite reasonable to expect an additive effect of myocardial depressant factor plus anatomic injury to the myocyte, with the progressive increase in both damaging elements leading to eventual myocardial failure.

Figure 4 summarizes the interacting factors that can contribute to heart failure in the shock syndrome. The subendocardial hemorrhagic and necrotic lesions have been shown to be due to hypoxia. Although the decreased coronary blood flow may not be sufficiently low to produce an overall myocardial oxygen deficit, the subendocardial region is in a vulnerable position in terms of oxygen supply, because the intramural coronary arteries penetrate perpendicularly from the epicardium through the ventricular wall, so that systolic compression tends to reduce the flow to the inner layers of the ventricles more than it reduces the flow to the outer layers. Actual measurement of regional blood flow using radiolabeled microspheres has shown that, although during normal flow in dogs there is equal distribution of blood to the inner and outer layers (45), in other situations the ratio is unequal. For example, tachycardia results in a disproportionate decrease in flow to the inner layers (46). A similar reduction occurs with ischemia (45), and it is likely that in hemorrhagic shock the low diastolic pressure is inadequate to perfuse the subendocardial layers of the left ventricle. In addition, the decreased oxygen saturation resulting from injury to the lung in shock can contribute to the myocardial necrotic effect. Zonal lesions are probably reversible lesions produced in a strongly, rapidly beating heart with low intraventricular volume. They are not primarily related to hypoxia; in fact, they appear to be unique to hypovolemia. Decreased splanchnic blood flow, in turn, results in the production of cardiotoxic substances, including myocardial depressant factor. The additive effects of the necrotic and zonal lesions and the cardiotoxins eventually lead to cardiac failure.

In conclusion, lesions of two morphologically and etiologically different types develop in the hearts of animals, including man, that have been subjected to hemorrhagic shock. It is our thesis that, as the lesions become progressively more severe and extensive, they contribute significantly to the disruption of the contractile machinery of the myocardium and to the eventual cardiac failure that follows.

References

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27. HlOTT DW: Ultrastructural changes in heart muscle after hemorrhagic shock and isoproterenol infusions. Arch Int Pharmacodyn Ther 180:206-216, 1969


45. PITTE B, BECKER L: Regional myocardial blood flow during acute ischemia. In Atherosclerosis and Coronary Heart Disease, edited by W Likoff, BL Segal, and W Insull. New York, Grune Stratton, 1972, p 150

The Heart in Shock
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doi: 10.1161/01.RES.35.6.805

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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