6 Update in Intensive Care and Emergency Medicine

Acute Heart Failure

Edited by

C. Perret and J. L. Vincent

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Contents

Abnormal Ventricular Function

S. M. Ayres

Introduction

Segmental ventricular dysfunction associated with acute myocardial infarction (AMI) is the most common form of acute ventricular failure. Pump failure is the most common cause of death in patients with acute myocardial infarction who do not succumb to fatal arrhythmias. Detailed pathologic studies reveal that 37–70% of the left ventricular surface is infarcted in patients hospitalized in coronary care units with shock as the presumed cause of death [1]. The volume of infarcted tissue, rather than its location, determine ventricular function and the ability of the heart to pump adequate amounts of blood to the peripheral circulation. Most patients dying with coronary shock have extremely severe coronary artery disease with extensive involvement of the left coronary artery. In one study, 68% of patients dying with cardiogenic shock had three vessel disease compared to 35% dying with severe heart failure; 80% of both groups had more than 75% occlusion of the left anterior descending coronary artery [2]. Patients dying from AMI without shock, in one study, exhibited well-demarcated infarct zones that comprised less than 30% of the left ventricle while those dying with shock had a ragged edge and contained many damaged cells, suggesting continuation of the ischemic process. These patients and those dying with shock in the absence of AMI had scattered islands of necrosis in both ventricles [3]. These studies allow a general understanding of the pathogenesis of coronary atherosclerosis and its consequences: angina, unstable angina, acute myocardial infarction, chronic congestive heart failure and shock. Most infarctions involve the full thickness of the myocardial wall and are termed "transmural infarcts." Since blood flow is most dynamic in the subendocardial layers, some infarcts are limited to the subendocardium and part of the intramural myocardium and are termed "subendocardial infarcts." While myocardial infarction appears to be initiated by coronary thrombosis in most situations, the size and location of the ultimate infarct is related to the severity of coronary atherosclerosis, the amount of myocardium perfused by the affected vascular bed, the presence of vascular spasm, the character of the collateral circulation and the oxygen requirements of the myocardium.

Compartmentalization of Ventricular Function in AMI

At least three zones of myocardial tissue can be assumed to exist following acute myocardial infarction: a central dead zone, a surrounding zone of ischemic but

potentially viable tissue and a zone of non-ischemic "normal" tissue. The ability of the heart to efficiently pump blood is dependent upon the oxygen balance of the ischemic but not yet necrotic zone. Any event which increases oxygen demand by increasing heart rate, contractility or wall tension, or which diminishes oxygen supply by decreasing coronary blood flow, will decrease oxygen availability in the ischemic zone. Jeopardized but potentially viable tissue will become necrotic. Extension of the infarction will initiate a vicious circle leading to further decrease of cardiac function and, possibly, to circulatory collapse.

Regional myocardial function is closely related to coronary blood flow. Acute constriction of coronary flow leads to substantial declines in subendocardial perfusion and regional ventricular function. Ventricular function returns to normal if perfusion is restored prior to the development of myocardial necrosis. Pressure-flow relationships are much more complicated in clinical coronary disease where multiple areas of constriction and variable degree of collateral vessel formation produce widespread consequences when overall flow is temporarily reduced. Canty and Klocke [4] attempted to simulate the human atheromatous condition by ligating collaterals in conscious animals with chronic coronary stenosis. They showed that moderate reductions in regional systolic function occur with less reduction in flow than would be necessary to produce similar declines in function with acute reductions in coronary flow. They also showed periods of dissociation between perfusion and function suggesting post-ischemic dysfunction (stunned myocardium).

Herman et al. [5] demonstrated the importance of segmental dysfunction to overall global ventricular performance. They demonstrated that regional abnormalities of contractility or asynergy were commonplace in patients with ischemic heart disease. Four distinct patterns of dysfunction were identified: akinesis, or total lack of motion of a wall segment; dyskinesis, or paradoxical systolic expansion of a segment; asyneresis, or diminished wall motion; and asynchrony, or disturbed temporal sequence of contraction. Patients with asynergy had substantially lower stroke indices than those with normal contractile patterns; ventricular end-diastolic pressures were somewhat higher in those with asynergy compared to those having a normal pattern of contraction. These authors also noted that abnormalities in regional lactate metabolism frequently occurred without asynergy, suggesting that the metabolic abnormality might precede the contractile one. Their study emphasized the importance of ventricular dimensions as a prognostic index of therapeutic response; isoproterenol improved ventricular function in 13 of 16 patients with end-diastolic volumes of more than 110 ml/M^2 but seemed to have a neutral or deleterious effect with smaller ventricles.

Function of the Normal Ventricle

Myocardial cells contain many strands called myofibrils that, under the light microscope, are seen to be crossbanded. Each myofibril is composed of a series of repeating elements, the sarcomere, each delineated from its neighbour by dark lines, the Z lines. Another line, the M line, is observed in the center of each sarcomere, while a dark central zone is termed the A band. Lighter areas adja-

cent to the Z lines are termed I zones. Generously sprinkled between the myofibrils are cylindrically shaped structures, the mitochondria, which are the sites for oxidative phosphorylation. The tremendous oxygen requirements of the myocardium may be suspected from the observation that over one-fourth of the total myocardial mass is occupied by these mitochondria. The transverse tubular system (T tubules) and the sarcoplasmic reticulum constitute an intracellular storage and transportation system. The T system is composed of sarcolemmal invaginations which arise near the Z lines and branch throughout the cell. The sarcoplasmic reticulum, in contrast, is not continuous with the extracellular space but expands into thin-walled cisternae as it approaches the T system. A relatively small proportion of the myocardial cell is allocated to the nucleus and the cytoplasm; important glycolytic enzymes are contained in the latter and constitute an important alternate source for energy generation that may maintain membrane integrity during periods of stress.

The effector proteins, actin and myosin, and two regulatory proteins, troponin and tropomyosin, form the molecular basis of muscle contraction. Each myosin molecule bears two heads that extend laterally and form cross bridges with the thinner filaments of actin during systole. These cross bridges propel the actin fibers towards the center of the sarcomere so that they shorten and develop tension in the same manner that many hands on a rope develop tension and ultimately take-up on the rope in a tug-of-war. Depolarization of the sarcolemma releases calcium from the sarcoplasmic reticulum and initiates contration by binding to troponin. Calcium binding to troponin produces conformational changes in tropomyosis that make it shift out of the way so that actin-myosin bridges can form. Metaphorically, tropomyosin acts like a parent sitting between a teen-age boy and girl. The parent exerts an inhibitory effect on romance. A phone call may be envisioned as calcium release, removing the parent from an inhibitory position and permitting a short-lived period of embrace.

The myosin heads have an additional function; they contain an enzyme ATPase, that is activated by contact with actin and hydrolyzes ATP, releasing energy for muscle contraction. Only ionized magnesium and ATP are needed to produce contraction in the absence of tropinin and tropomyosin; when they are present, bridging does not occur unless ionized calcium is available. There are important relationships between myosin ATPase and velocity of muscle shortening and it may function as an important regulator of myocardial contractility. ATP seems to serve as a relaxing agent or "plasticizer" as well as an energy source. When bound to the myosin heads, cross-bridging is inhibited and the muscle is relaxed; when the bound ATP is hydrolyzed to ADP and inorganic phosphate, energy is released and muscle contraction occurs. The dead heart, for example, is in a state of rigor because ATP has been consumed and its inhibitory effect removed. Since unbridled ATPase activity would lead to a state of continued contraction, its dependence upon ionized calcium assumes great importance. Calcium not only relieves tropomyosin inhibition but also activates ATPase so that ATP hydrolysis and actin-myosin bridging can occur simultaneously.

The overall force of the contraction is a function of the number of binding sites between actin and myosin. Sonnenblick et al. [6] proposed that the Frank-Starling law of the heart is related to stretching of the sarcomere. The authors

showed that the maximum muscular force is generated when the sarcomere is 2.2μ in length, the length that theoretically provides the greatest area for actin and myosin interaction. If the sarcomere is shorter, there is less opportunity for actin and myosin interaction. If the fiber is stretched beyond the optimal length, the filaments are partially engaged, decreasing the force of contraction.

The amount of blood ejected by each systolic contraction is directly related to the extent of myocardial fiber shortening and reduction in circumferential size. Studies on isolated muscle fibers have shown that the extent of shortening is related to the initial stretch of the muscle (the preload), the load the muscle is asked to move as it shortens (the afterload) and the rate of generation of cross-linkages between actin and myosin (the state of contractility).

Applying these determinants to the intact ventricle requires the measurement of volume. Pressure-volume curves were first described by Frank [7] but was somewhat eclipsed by the studies of Patterson et al. [8] who emphasized the relationships between end-diastolic pressure and stroke output. Much of this shift was methodologic because the latter group did not measure ventricular volumes. In a sense, the Starling emphasis was on the amount of blood ejected from the ventricle while the Frank emphasis was on the amount remaining in the heart at the end of systole. Although many investigators made important contributions to the study of ventricular control, Braunwald et al. [9] developed an approach particularly useful for bedside evaluation. They demonstrated, both in isolated muscle and in intact animal and human hearts, that stroke output was determined by preload (ventricular end-diastolic fiber length), afterload (systemic vascular resistance and the internal resistance of the ventricle to contraction), and myocardial contractility. Sibbald et al. [10] took the analysis one step further by pioneering the use of radionuclide ventriculography to measure ventricular preload and diastolic compliance in critically ill patients.

The Effects of Ischemia and Hypoxia and Contractile Function

Acute or chronic reductions in perfusion deprive the myocardium of both oxygen and metabolic substrate. Developed tension may be observed after 1 min of ischemia and appears to precede any significant fall in ATP. The cource of metabolic events during early ischemia has been studied by combining anoxia with pharmacologic inhibition of anerobic glycolysis. When the heart is perfused with oxygen-free fluids, the developed pressure quickly falls to about one third of normal but maintains this pressure development for at least 30 min. Anerobic glycolysis is increased by twenty-fold and the conversion of pyruvate to lactate leads to oxidization of NADH and the synthesis of some additional ATP. The increase in anerobic glycolysis is not maintained for long, however, perhaps because intracellular acidosis lactate accumulation inhibits key glycolytic enzymes. When glycolysis is experimentally blocked, the developed pressure falls rapidly.

The concentration of ATP is the algebraic sum of synthesis and utilization. Decreased myocardial contractility decreases the utilization of ATP as the ischemic segments generate substantially lower levels of tension than normal and

may appear to be in a state of "hibernation." ATP is synthesized from phosphocreatine (PCr) reserves and the PCr concentrations fall rapidly while the concentrations of inorganic phosphate rise. Shifts in inorganic phosphate and PCr may be responsible for the decreases in contractile function observed when ATP concentrations are still close to normal. ADP is soon degraded to AMP and inosine monophosphate.

We began studying the oxygen and lactate of coronary sinus blood in patients with acute coronary disease more than 15 years ago. This technique allows the study of ischemic and non-ischemic myocardial compartments in human subjects with acute myocardial infarction. The blood supply to ischemic and non-ischemic compartments determine the representation of each compartment in mixed coronary sinus blood. Hyperperfusion of normal tissue could dilute blood draining ischemic segments and prevent recognition of small regions of ischemia or infarction. Blood draining a large volume of ischemic tissue dominates mixed coronary sinus blood in coronary shock so that abnormalities which indicate myocardial hypoxia are readily identified. With small myocardial infarctions, blood draining non-infarcted and non-ischemic compartments dominate, and coronary sinus blood may be normal. The substantial difference in infarct size between patients with AMI who exhibit or do not exhibit shock is shown by differences in coronary sinus blood. Myocardial oxygen extraction averaged 77% in patients with shock and 67% in those without shock. Coronary sinus lactate measurements revealed lactate production in shock and lactate extraction in patients not in shock [11].

The decreased distensibility of vessels in the ischemic zone produces a different coronary pressure-flow curve compared to that in the non-ischemic zone. Flow is linearly related to pressure in shock patients in the pressure range where autoregulation normally is observed. Flow increased an average of 8 ml/100 g/min for each 10 mm Hg increase in pressures. Thus, blood flow in the ischemic zone is pressure dependent while flow in the non-ischemic zone is less dependent upon pressure. We confirmed this hypothesis by demonstrating that l-norepinephrine increased lactate extraction in coronary shock but decreased lactate extraction in patients without shock [12].

Identification of Ventricular Dysfunction and Failure in the Critically Ill

The terms "decreased myocardial contractility" of "contractile failure" must be used with some precision in order to develop adequate therapeutic approaches. Although a reduced stroke output is good clinical evidence for ventricular failure, it cannot distinguish contractile failure from hypovolemia, and it cannot separate right ventricular failure from left ventricular failure. Moreover, as emphasized above, a normal stroke output may reflect inadequate ventricular reserve if it occurs in a setting such as sepsis. Similarly, an elevated pulmonary capillary wedge pressure suggests ventricular failure, but it could represent fluid overload, mechanical obstruction or increased ventricular stiffness. A normal pulmonary capillary wedge pressure could be found in a poorly functional ven-

tricle if ventricular compliance were increased (a "flaccid" of floppy dilated ventricle).

Measurement of events occurring during ejection (ejection fraction, fractional shortening, velocity of circumferential shortening) are sensitive to changes in preload and afterload as well as contractility. They are, however, useful in assessing the basal state in conditions producing chronic ventricular dysfunction and can assess inotropic and other therapeutic interventions *if the other determinants of stroke output are held constant*. The importance of preload reserve as an immediate response to contractile failure makes the measurement of ventricular volumes a sensitive indicator of ventricular failure. Indeed Braunwald [13] has stated that "When ventricular end-diastolic volume is clearly elevated (greater than 108 ml/M^2) and total stroke volume and/or cardiac index and work are either reduced or within normal limits, while heart rate and afterload are normal, *cardiac contractility is depressed*" (emphasis added). Despite potential problems with the use of ejection fraction, fractional shortening or the velocity of circumferential fiber shortening, the measurements are simple and provide rapid differentiation between normal and abnormally functioning hearts. Recently, force-velocity relationships of the intact heart have been analyzed by determining the reduction in systolic shortening as afterload is increased. Suga and Sagawa [14] demonstrated in isolated hearts that the relationship between end-systolic pressure and volume is relatively insensitive to end-diastolic volume or ejection resistance. The end-systolic pressure-volume relationship is linear and can be used to measure changes in the contractile state.

Most studies of decreased contractile function have been performed in experimental models or patients with global ventricular dysfunction. Estimation of contractile function is considerably more difficult to evaluate the contractile state in patients with segmental ventricular dysfunction due to coronary artery disease. The ischemic or fibrotic segments show decreased rates of systolic shortening and may even bulge paradoxically with systole. Sympathetic neural activity increases the contractile state of the uninvolved myocardium so that global ejection rates and ventricular volumes remain within normal limits. Failure to increase ventricular ejection rates with exercise or identification of large non-contractile segments by radionuclide ventriculography or echocardiography is necessary to identify ventricular dysfunction in this situation.

Responses of the Ischemic Heart to Pharmacologic Intervention

Support of the failing ischemic heart has been a major therapeutic challenge. Catecholamine and digitalis glycosides generally have been thought to effect the determinants of myocardial oxygen demands – wall tension, heart rate and velocity of contraction – in an adverse manner. By definition an inotrope increases the velocity of contraction and catecholamine inotropes uniformly increase heart rate at some dose. The effect of an inotrope on wall tension is more complex since tension is related to intraventricular pressure and ventricular diameter by the LaPlace relationship. Digitalis and catecholamines that stimulate alpha-adrenergic receptors increase arteriolar resistance and thus intraventricular pres-

sure. Catecholamines with β-adrenergic properties may decrease ventricular dimensions and thus decrease myocardial wall tension. The effects of catecholamine inotropes also have different effects on myocardial blood flow. Those stimulating β-2-adrenergic receptors have direct vasodilating action on the coronary vascular bed. Even more significant, however, is the effect of decreasing diastolic pressures on decreasing transmural subendocardial coronary vascular resistance and thereby increasing blood flow. Isoproterenol with its strong β-2 dilating effect decreases aortic diastolic pressure and thereby decreases the diastolic pressure head available for coronary perfusion. Tachycardia is a two-edged sword. It increases myocardial oxygen consumption and at the same time decreases coronary perfusion by decreasing the time of diastole.

Decreasing ventricular size is of paramount importance for patients with failing hearts. A smaller heart consumes less oxygen, contracts more efficiently and protects the lungs by contracting at lower end-diastolic pressures. Fortunately, certain inotropes administered to individuals with dilated hearts improve myocardial oxygen dynamics and may reduce myocardial ischemic damage. Watanabe et al. [15] studied the effects of inotropes and vasopressors on infarct size measured by epicardial mapping. They raised arterial pressure by administering phenylephrine to dogs with normal hearts and with pharmacologically induced cardiac depression. Elevation of arterial pressure decreased infarct size in dogs with normal sized hearts. The same intervention increased left atrial pressure from 10 to 23 mm Hg in the depressed heart and increased infarct size. Oubain, in contrast, lowered mean atrial pressure from 25 mm Hg to 11 mm Hg in the failing heart and decreased infarct size. Isoproterenol increased infarct size at higher doses; doses of 0.05 μg/kg/min decreased left atrial pressure and infarct size.

The effects of isoproterenol, norepinephrine and nitroglycerine on the globally ischemic heart were studied by Vatner et al. [16]. The effects of isoproterenol in the ischemic heart were strikingly different from those in the normal heart. Coronary blood flow and the peak velocity of myocardial shortening increased markedly in the normal heart. The decrease in diastolic pressure led to a decrease in blood flow in the ischemic heart and the peak velocity of myocardial shortening fell by 60%. The decrease in regional systolic function indicates decreased myocardial oxygenation. Dobutamine, a β-1 agonist with less β-2 activity than isoproterenol, increased coronary blood flow by 23% and the velocity of shortening by 17%. Norepinephrine, in contrast, increased coronary blood flow by 74% because of a marked increase in perfusion pressure in the ischemic heart. In consequence, the velocity of segment shortening increased by 24%. The risk of vasodilator therapy in ischemic heart disease was demonstrated by the 59% decrease in coronary blood flow and 29% decrease in shortening velocity when nitroglycerine was administered. These studies provide an important insight into the interplay between agents that change perfusion pressure and those that increase myocardial contractility without significantly affecting perfusion pressure.

In another study in conscious dogs, Vatner and Baig [17] studied the responses of ischemic and non-ischemic myocardial segments by producing transient coronary occlusion. Occlusion did not affect the normal regions of the heart but