Ann. Rev. Pharmacol. Toxicol. 1982. 22:115–43

PHARMACOLOGICAL SALVAGE OF MYOCARDIUM

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INTRODUCTION

Because of the need to reduce the massive toll of myocardial infarction, delineation of the pathophysiology of the process and characterization of new therapeutic approaches have been explored vigorously. Clearly, atherosclerosis of the coronary arteries is the major underlying cause and has been a primary focus of research. In addition possible precipitating factors such as isolated or associated coronary vasospasm and altered platelet or endothelial cell function have been evaluated. This selective review concerns approaches designed to limit the extent of myocardial infarction after the process has been initiated based on the hypothesis that ischemic cell death is a dynamic process amenable to modification by appropriately timed therapeutic interventions. The evolution of infarction in response to an initiating critical reduction of perfusion appears to be potentially modifiable for 6–9 hours, especially in epicardial regions of jeopardized tissue (1–4). Interventions designed to salvage jeopardized tissue may diminish the ultimate extent of irreversibly injured myocardium if they succeed in favorably influencing the local balance between myocardial oxygen supply and demand.

As methods of quantifying the mass of myocardium undergoing infarction (infarct size) were developed, assessment of potentially therapeutic interventions became a focus of laboratory and clinical research (5). Supportive measures in coronary care units began to embrace not only efforts to ensure cardiac electrical stability and maintenance of the peripheral circulation but also protection of ischemic myocardium with the view that such protection might favorably affect prognosis. Both pharmacologic and

0362-1642/82/0415-0115$02.00

mechanical interventions are now being employed widely for this purpose. This review will consider pharmacologic modalities employed in the setting of myocardial ischemia to limit ultimate infarct size. Because of space limitations, only selected references have been cited.

Infarct Size and Prognosis

Among the 550,000 patients victimized by acute myocardial infarction each year in the United States alone, approximately 15% (or 75,000) die annually from the consequences of intractable left ventricular failure (6, 7). Infarct size appears to be one determinant, since victims of cardiogenic shock exhibit infarction involving greater than 40% of left ventricular mass (8). Those with persistent, severe dysrhythmias exhibit extensive loss of viable myocardium (9–11). Cumulative mortality 1 month after the onset of infarction is several-fold greater among patients with large compared to small infarcts (12, 13). Elevations of pulmonary artery diastolic pressure and reduction of cardiac index directly reflect cumulative creatine kinase (CK) release from the heart, an index of the overall extent of infarction (14), as well as angiographic (14) and radioventriculographic (15) estimates of infarct size.

Survivors of acute ischemic insults with extensive infarction often exhibit marked, cardiac functional impairment (clinical class III or IV) in contrast to those with modest infarcts (generally class I or II) (12). As might be expected, infarct size has its greatest impact on mortality during the first 6 months after onset of infarction, but its influence is evident in overall survival rates throughout a follow-up interval of as long as 4 years (16). Obviously, other factors such as the progression of underlying coronary disease become progressively more important as determinants of late mortality (17–21), with triple-vessel disease having a particularly poor prognosis (17, 21).

Determinants of Infarct Size

Coronary arteries supplying myocardium undergoing acute infarction generally exhibit severe atherosclerotic changes, but complete obstruction is not always apparent. Thrombi or coronary arterial spasm have been suggested as proximate precipitating insults, but there has been no unequivocal demonstration of either as a general, immediate cause of infarction. In fact, the syndrome of acute myocardial infarction in the presence of angiographically normal coronary arteries is well recognized. Although specific precipitants of acute myocardial infarction remain difficult to elucidate, the mass of ultimately infarcted tissue is determined not only by the anatomical distribution of occlusive coronary artery disease but also by the magnitude of collateral blood flow and the metabolic status of myocardium at risk. It

has been hypothesized that a zone of potentially salvageable cells surrounds regions of irreversible injury and that the fate of such cells may be influenced by the balance between energy supply and demand (1–4). However, such cells may remain viable for only 6–9 hours after coronary occlusion unless flow is modified or oxygen demand diminished promptly and substantially.

Although coronary collateral vessels have been recognized for decades, factors required for development of nutritionally adequate collateral formation remain poorly understood. It appears that *de novo* formation of collaterals capable of providing flow sufficient to substantively protect jeopardized myocardium occurs only over relatively prolonged intervals, of the order of several weeks (22).

In addition to delineation of the pathogenesis of acute myocardial infarction and factors underlying angiogenesis, investigations have been performed utilizing manipulation of metabolic requirements of the myocardium, based on the assumption that infarct size is related to the deficit between myocardial oxygen requirements and oxygen supply. The definitive nature of the relationship has not been elucidated, since issues such as threshold, linearity, and modifying influences of accumulated metabolites have not yet been resolved fully. Nevertheless, many agents that affect myocardial oxygen consumption modify ultimate infarct size.

The major determinants of myocardial oxygen consumption are contractility, heart rate, and wall tension (23). Wall tension is, of course, a function of both ventricular volume and developed intraventricular pressure. Minor determinants of oxygen consumption include electrical activation of the heart, maintenance of the active state, shortening of myofibrils per se (the Fenn effect), and the basal metabolic rate of the heart. Any intervention capable of affecting these determinants may influence the balance between myocardial oxygen supply and demand and may therefore influence infarct size. Accordingly, protection of jeopardized, ischemic myocardium has been attempted by judicious manipulation of several of these factors, with efforts employed to avoid compromising ventricular function in the process.

Categories of Agents

Theoretically, the most direct means of improving the balance between oxygen supply and demand entails augmentation of myocardial perfusion by surgical revascularization (24), percutaneous transluminal coronary angioplasty (25), or coronary recanalization with thrombolytic agents (26). Antispasmodic and antiplatelet drugs have been championed by some because of their potential to facilitate perfusion. Indirect approaches to improving myocardial oxygen and/or energy supply encompass admin-

istration of oxygen (27), the use of oxygenated fluorocarbon microaggregates (28), administration of solutions of glucose-insulin-potassium (29), use of beta-adrenergic agonists and other drugs with positive-inotropic effects to improve perfusion pressure and coronary blood flow, and administration of hyaluronidase (30). The efficacy of such approaches will obviously depend in part on the presence of residual flow to the ischemic area sufficient to deliver the agent in adequate quantities. This assumption has not yet been thoroughly substantiated in man. Other interventions are designed to improve the balance between oxygen supply and demand by decreasing demand, such as administration of beta-adrenergic blockers, vasodilators, or induction of hypothermia. Alteration of the process of injury itself through employment of agents such as calcium antagonists or anti-inflammatory drugs is an additional approach to salvaging ischemic myocardium.

Animal Preparations Studied

The choice of a particular experimental animal preparation is often predicated on convenience, cost, and logistical considerations on the one hand, and fidelity in mimicking the human disease process on the other. Most studies of interventions designed to modify myocardial ischemic injury have been performed with dogs, but some have used primates, pigs, rats, or cats. Although dogs offer some advantages related to expense, heart size, and the wealth of available information characterizing myocardial performance and metabolism in this species, results in studies with dogs may not simulate those anticipated in patients because of the richness of precapillary, intercoronary arteriolar anastomoses that provide substantial blood flow to even central regions of the ischemic zone (22). In contrast, human myocardium has a paucity of such arteriolar communications. Pig hearts appear to resemble human hearts in this respect more than canine hearts do. However, their electrophysiological instability introduces additional difficulties.

MODIFICATION OF METABOLIC DEMAND

Beta-Adrenergic Blocking Agents

Early experimental (31) and clinical (32) studies suggested beneficial effects of beta-adrenergic blocking agents on the evolution of myocardial necrosis after the onset of myocardial ischemia. Conversely, effects of beta-adrenergic agonists which increase heart rate and contractility exacerbate injury (33). Furthermore, metabolic, "oxygen wasting" effects of catecholamine stimulation of the heart mediated by lipolysis have been implicated as being independently injurious.

The benefit derived from reduction of heart rate appears to depend principally on a consequent increase in endocardial blood flow in ischemic zones.

Although decreased regional perfusion is evident in normal myocardium after administration of propranolol, the ratio of endocardial to epicardial blood flow increases in ischemic zones (34, 35) when heart rate is decreased. Dimethylpropranolol, an analog without beta-adrenergic blocking actions, but one capable of reducing heart rate by a direct, non-beta-adrenergic blocking effect, increases the flow ratio comparably and augments endocardial flow in absolute terms as well (36). Atrial pacing sufficient to maintain heart rate at pretreatment levels (36) or preclusion of a beta-adrenergic blocker induced decrease in heart rate (37) abolishes the otherwise increased endocardial blood flow. Thus, beta-adrenergic blocking agents may increase oxygen supply to ischemic myocardium, an effect mediated by decreased heart rate, the consequently prolonged diastolic interval, and correspondingly enhanced coronary flow or decreased coronary vascular resistance due to reduced intramural tissue pressure. The significance of unopposed alpha-adrenergic vasoconstriction of coronary arteries in the presence of a beta-adrenergic blocker remains difficult to evaluate in man since coronary blood flow during myocardial ischemia may already be maximally auto-regulated secondary to vasodilator metabolites.

Oxygen supply may be affected by propranolol in other ways as well. Propranolol shifts the oxygen-hemoglobin dissociation curve to the right in vitro and in vivo. Thus, in patients with chronic, stable angina, the oxygen tension at which hemoglobin is half-saturated increases from 28.9 ± 0.9 to 31.7 ± 0.7 torr after treatment with propranolol (38), representing a potential 38.5% increase in oxygen delivery. Propranolol reverses enhanced platelet aggregation in patients with angina (39) and decreases arterial-venous platelet count differences in patients with coronary artery disease (40). Although these observations are provocative, further work is needed to clarify the clinical implications of effects of beta-adrenergic blocking agents on hematologic factors.

Several observations suggest that propranolol (and inferentially other beta-adrenergic blocking agents as well) improves the myocardial oxygen supply/demand ratio by reducing demand. Thus, some protection of jeopardized myocardium can be demonstrated independent of reduction of heart rate and/or effects of such agents on myocardial perfusion. In experimental animals subjected to myocardial ischemia, propranolol reduces heart rate and blunts the rise of P_{CO_2} in ischemic myocardium, suggesting decreased metabolic demands, altered washout of CO_2, or both. Since comparable reduction of P_{CO_2} elevations occur with propranolol despite atrial pacing (41), the protective effect of beta-adrenergic blockade appears to be at least partly independent of negative chronotropic effects. This conclusion is supported by results of other studies in which maintenance of heart rate by pacing did not abolish the beneficial effects of propranolol on ST segment

elevation, CK release (42), or reduction in left ventricular wall motion abnormalities (43). In addition, propranolol decreases oxygen consumption (35), possibly by maintaining the ability of subcellular systems to sequester calcium that otherwise declines as a result of ischemia (44).

In addition to effects on oxygen supply and demand, effects of beta-adrenergic stimulation and blockade on lipid metabolism in the heart have been strongly implicated as factors influencing ischemic injury. Lipolysis in adipose tissue liberates circulating free fatty acids available for uptake and metabolism by the heart. It is well appreciated that catecholamines stimulate, and beta-adrenergic blocking agents inhibit, this process. Direct effects on myocardial oxygen demand or infarct size mediated by extracardiac lipolysis have not been documented, but infusion of intralipid, which elevates circulating triglycerides and free fatty acid concentrations, increases myocardial oxygen consumption by 25% (45). Catecholamines and circulating free fatty acids may act synergistically to increase infarct size (46). Thus, benefit of beta-adrenergic blockade may be conferred not only from direct effects on the heart but also by the decreased catecholamine concentrations observed after its implementation (47), effects presumably mediated via presynaptic receptors.

Intracardiac lipolysis by myocardial triacylglycerol lipase is presumably modulated by beta-adrenergic mechanisms. However, this process has not been characterized thoroughly.

After coronary artery occlusion in dogs, infarct size estimated from epicardial ST segment changes is reduced by beta-pyridyl-carbinol treatment, an antilipolytic agent (48). Similarly, in patients with acute myocardial infarction given propranolol, the respiratory quotient increases from 0.81 to 0.93, indicative of diminished dependence of metabolism on fatty acid oxidation, and glucose extraction is enhanced from 0.4 to 3.0% (49). The diminished fatty acid metabolism suggested may be responsible for the decreased overall metabolic rate. However, no definitive data are yet available establishing directly effects of beta-adrenergic blockade on intracardiac lipolysis based on concomitant myocardial lipid analyses, direct determination of myocardial oxygen consumption, and observed infarct size.

The mechanisms by which exogenous fatty acids may augment myocardial oxygen demand remain poorly understood. A futile recycling of free fatty acids and triglycerides through alpha-glycerophosphate with attendant degradation of ATP and/or lower P/O (high energy Pi produced/oxygen consumed) ratios with fatty acid compared to carbohydrate metabolism have been suggested (46) but little definitive information is available. Additional work is necessary to delineate the extent to which the so-called oxygen wasting effects of catecholamines contribute to injury sustained by ischemic myocardium and to clarify their dependence on lipid metabolism.

Beta-adrenergic blockers have been shown to decrease infarct size in vivo in dogs. Administration of such agents before (31, 50, 51) and up to 3–6 hours after coronary occlusion (52–54) decreases infarct size judging from ECG changes (60–62, 64), CK release into the circulation (50), myocardial CK depletion (54), gross morphology (50), histologic criteria (50, 54), and analysis of nitroblue tetrazolium staining of myocardium (51). Analogous results have not been reported widely with other species, such as the pig, in which the coronary circulation and coronary collaterals more closely resemble those in humans. Apparently, effects on perfusion or reperfusion of the involved area are necessary conditions for benefit (56). In most studies with canine preparations in which hemodynamic data are reported, use of propranolol in the setting of acute myocardial ischemia induces moderate decreases in heart rate, stroke volume and cardiac output of approximately 10–20%, variable changes in pulmonary artery wedge pressure, and slight increases in systemic vascular resistance.

Reports of effects of beta-adrenergic blockers in patients with acute myocardial ischemia include those of Snow (32), who found a decrease from 29 to 13% in early mortality among patients with infarction when propranolol (10–20 mg) was administered every 8 hours for 2 weeks. Although these results have not been confirmed consistently, variation in dosage or delay before initiating therapy may account for some discrepancies. In an early important but uncontrolled study, practolol reduced the extent of ST segment elevation in nine patients with acute myocardial infarction (57), and subsequently such beneficial changes were found to be dependent upon angiographically demonstrable persistence of flow within the ischemic area (58). In randomized samples of patients with acute myocardial infarction, patients treated for 24 hours within 4 hours of the onset of chest pain exhibited a 27% decrease in CK release after propranolol-treatment compared to control regimens (59). In another series among patients aged 65 or less, mortality at 1 year was decreased from 20.4 to 9.3% after prolonged treatment with alprenolol (60), though infarct size was not determined. In another study, the extent of completed myocardial infarction was decreased in patients with threatened infarction treated with propranolol (61), but the control group had an uncommonly high incidence of infarction (62). These results suggest that beta-adrenergic blockade may modify the evolution of myocardial injury induced by ischemia, in addition to conferring electrical stability upon the heart after completion of infarction (63).

Beta-adrenergic blockade may favorably alter myocardial oxygen consumption by increasing supply and decreasing demand, thereby contributing to the preservation of high-energy phosphorylated compounds in ischemic myocardium (56). Although these agents appear to be useful clinically, results of controlled, prospective randomized clinical trials em-

ploying endpoints in addition to mortality, such as infarct size, are needed for definitive assessment of their value in protecting jeopardized, ischemic myocardium.

Temperature

Myocardial oxygen consumption is influenced markedly by temperature. Hypothermia has become the primary mode of myocardial preservation during cardiac surgery, since even a modest decline of temperature to 30°C can halve myocardial oxygen requirements (64). Nevertheless, hypothermia for preservation of ischemic tissue in patients with evolving myocardial infarction has not been employed widely, in part because of attendant logistic difficulties and potential impairment of patient comfort. On the other hand, evaluation of pharmacologic agents that act centrally to modify core temperature or thermo-mechanical techniques to achieve the same result may be warranted.

Vasodilators

Patients with myocardial infarction may benefit from peripheral arterial or venous vasodilators if overall myocardial oxygen balance is improved as a result of net effects of reduction of impedance to ventricular ejection, maintenance of sufficient diastolic pressure for coronary perfusion, and diminution of ventricular volume to lower wall stress without compromising cardiac output or precipitating deleterious tachycardia. Some vasodilators may exert direct effects on coronary vascular resistance thereby increasing perfusion to ischemic regions, though potential benefit of this type is likely to be limited when atherosclerotic vessels (65) or coronary steal is responsible for ischemia. Among the many agents in this general class that are available, each should be considered independently with respect to its site of action within the vascular bed.

NITRATES In normal dogs, nitroglycerin directly dilates the coronary vessels (66, 67) and produces impressive increases in the ratio of endocardial to epicardial blood flow to zones rendered ischemic (34, 35, 68), irrespective of the presence or absence of collateral vessels (69) or maintenance of heart rate and blood pressure at pretreatment levels (37). However, absolute increases in endocardial flow are not seen invariably. Coronary steal does not occur (70). Beneficial effects of nitrates on ischemic myocardium include an increase in the threshold for ventricular fibrillation and a decrease in its incidence (71, 72), particularly when a hypotensive effect is prevented by concomitant administration of phenylephrine (72). Infarct size in dogs is diminished when methoxamine is used concomitantly with nitroglycerin to preclude hypotension or reflex tachycardia (73–75). Nitroglycerin alone

may be of benefit in some circumstances particularly when congestive heart failure is a consequence of myocardial ischemia (76, 77).

Results differ in pigs. In this species nitroglycerin reduces regional blood flow in jeopardized myocardium and increases ST segment elevation. Phenylephrine returns blood pressure and heart rate to control levels, but the combination produces no increase in regional blood flow or reduction of ST segment elevation compared to controls (78).

In patients with acute myocardial infarction, infarct size is reduced by nitroglycerin (79, 80) and coronary blood flow increases. However, the absolute magnitude of increases in subendocardial blood flow from 0.09 to 0.13 ml/min/g is very small and the effects on infarct size have been somewhat inconsistent (81).

In general, in patients with acute myocardial infarction nitroglycerin has been administered intravenously, with or without an alpha-adrenergic agonist. Almost universally, it decreases pulmonary artery occlusive pressure, left ventricular end-diastolic pressure, and systemic arterial blood pressure (82–84) as a function of pre-treatment hemodynamics and of dosage. In excessive doses or after administration to patients with low ventricular filling pressure, deleterious hypotension and tachycardia may predominate. In contrast, judicious use avoiding these reflex changes by titration of dosage, maintenance of adequate systemic arterial resistance with methoxamine, or maintenance of adequate left ventricular filling pressure by administration of fluids appear to be beneficial.

The effects of nitroglycerin on coronary vascular resistance and regional myocardial blood flow even in the absence of striking systemic hemodynamic alterations (37) bears on its mechanism of action. Although a sulfhydryl-containing receptor site for nitroglycerin has been described (85), definitive understanding of the interaction of nitrates with vascular smooth muscle is not yet available. Prostaglandin E has been implicated in mediating nitroglycerin-induced coronary artery vasodilation since its local concentration rises after administration of nitroglycerin and since indomethacin blocks the increase of this moiety and blunts the apparently associated decrease in coronary vascular resistance (67). However, it is possible that the phenomenon is a secondary one. Others have suggested preservation of oxidative phosphorylation by nitroglycerin (86), but the results are not conclusive. Organic nitrates appear to inhibit platelet aggregation (87) and may therefore facilitate myocardial oxygenation in ischemic zones by maintaining patency of vessels. However, since intracoronary administration of nitroglycerin achieving equipotent local concentrations is not as effective in relieving pacing-induced angina (65) compared to systemic administration, coronary vascular actions may not be primary.

In concert, available information suggests that except in patients with

demonstrable coronary vasospasm as the factor responsible for ischemia, the primary benefit conferred by nitroglycerin to ischemic myocardium is that attributable to peripheral vascular arteriolar dilatation and venodilation with consequent reduction of left ventricular preload and afterload and hence reduction of myocardial oxygen requirements. Data indicate that nitrates exert beneficial effects on ischemic myocardium in dogs, especially when excessive tachycardia and hypotension are avoided. However, further work is necessary to determine unequivocally whether these benefits apply to patients with dissimilar coronary anatomy and to delineate fundamental mechanisms of action of nitrates responsible for potentially favorable effects.

NITROPRUSSIDE Intravenous administration of nitroprusside diminishes arteriolar resistance and therefore reduces impedance to ventricular ejection, increases cardiac output, decreases pulmonary artery occlusive pressure, and myocardial oxygen requirements (75, 88, 89). Cardiac output may be augmented in patients with cardiogenic shock whether or not counterpulsation is used to support arterial diastolic pressure (90). Although nitroprusside is similar to nitrates in some respects, crucial differences exist. Thus, nitroprusside relaxes isolated normal coronary arterial strips in vitro (67) and reduces ST segment elevation in vivo in canine myocardium rendered ischemic (84), but it may exert adverse effects in patients with coronary artery disease by decreasing regional myocardial blood flow to ischemic zones, regardless of the presence of collateral vessels (69). Apparently, nitroprusside vasodilates resistance vessels, resulting in redistribution of blood flow away from zones of ischemia, thereby producing coronary steal, in contrast to nitroglycerin (69, 91). Despite increasing cardiac output and reducing pulmonary artery occlusive pressure, nitroprusside may elicit arterial hypoxemia (88, 92), due to induced ventilation/perfusion mismatches. Net effects of nitroprusside on infarct size have not yet been defined unequivocally. However, it has become clear that use of nitroprusside in the setting of acute myocardial infarction in the absence of hypertension must be undertaken cautiously.

OTHER VASODILATORS Improved ventricular performance and protection of jeopardized ischemic myocardium in patients with acute myocardial infarction have resulted from administration of phentolamine (67, 78, 93, 94), particularly when hypertension or severe left ventricular failure is present. Phentolamine decreases ventricular ectopic activity and ventricular tachycardia induced by reperfusion in dogs (75). However, phentolamine may augment ST segment elevation in dogs subjected to coronary occlusion (76). No detailed results are yet available defining regional myocardial

blood flow in response to phentolamine administered during myocardial ischemia. Thus, its value during uncomplicated, acute myocardial infarction in man remains somewhat speculative.

Trimethaphan is a ganglionic blocking agent that reduces enzymatically estimated infarct size in patients with myocardial infarction associated with hypertension (95). However, its use in the absence of hypertension has not been evaluated.

Other agents with vasodilator properties such as dipyridamole (96) and chlorpromazine (97) appear to be of benefit in some circumstances accompanying acute myocardial ischemia. However, clinical experience and definitive results of clinical investigation with these agents in this setting are not yet available.

Analgesia

Pharmacologically induced analgesia is a cornerstone of treatment for patients with acute myocardial infarction, for physiological as well as humanistic reasons. However, systematic evaluation and comparison of diverse agents is not generally available, particularly with respect to effects on infarct size. Since many agents exert vasoactive as well as analgesic effects, such comparisons are pertinent.

Morphine sulfate, administered intravenously, remains the most commonly used agent. It is usually given in an initial bolus of 5 to 10 mg intravenously, followed by 1 to 2 mg doses every 3 to 5 min until adequate analgesia is achieved. With care, hypotension and respiratory depression can generally be avoided. Nevertheless, other adverse effects may be encountered. Morphine can elicit coronary vasoconstriction in dogs (98), increase ST segment elevation in cats after experimental coronary occlusion (99), increase the tension-time index in many of the patients undergoing coronary revascularization (100), or reduce cardiac index in patients with acute myocardial infarction (101). These side effects can be avoided by preventing peripheral venous pooling with appropriate positioning of the patient, administration of atropine to blunt vagotonia and, rarely, use of an antihistamine to antagonize effects of morphine-induced histamine release. On the other hand, morphine appears to dilate human coronary arteries (102) and increases the threshold for repetitive ventricular premature contractions (103). On balance, the benefit gained from analgesia with morphine appears to outweigh potentially deleterious effects.

An alternative to morphine and its congeners recently employed in patients with acute myocardial infarction is nitrous oxide, administered by inhalation (104). This agent often eliminates pain without inducing significant hemodynamic alterations or increasing infarct size (105). It is likely to become more commonly used, particularly when relative contraindica-

tions to conventional analgesics are present. Thrombocytopenia is not a frequent or severe problem when prolonged use and/or concentrations exceeding 50% in the inspired gas are avoided.

INCREASED ENERGY SUPPLY

Oxygen

In coronary care units oxygen is utilized routinely for treatment of myocardial infarction because of the common occurrence of arterial hypoxemia. Although oxygen is often beneficial, indications for its use in individual patients should be assessed in each case.

Among patients with coronary artery disease, angina occurs at higher heart rates and greater overall left ventricular work loads when ischemia is induced by atrial pacing accompanied by 100% oxygen administration compared to inhalation of room air (106). Even low concentrations of carbon monoxide increase myocardial ischemia (107) and lower the anginal threshold (108). With mild coronary artery disease, 100% oxygen administration improves myocardial lactate extraction (109, 110), but patients with severe triple vessel coronary disease may exhibit increased lactate production, possibly because of adverse effects of oxygen on peripheral vascular resistance.

Reduced inspired air oxygen tensions of 10% increase ST segment elevation and myocardial CK depletion in dogs subjected to myocardial ischemia (111). Polarographically-determined, intramyocardial oxygen tension is inversely related to the magnitude of regional, epicardial ST segment elevation (112), probably reflecting, in part, additionally decreased oxygenation of the ischemic zone due to vasodilation of vessels supplying normal zones and shunting of blood away from the maximally jeopardized area (113). On the other hand, moderate increases in oxygen tension in the inspired air from a normal of 20 to 40% decrease epicardial ST segment elevation and reduce myocardial CK depletion 24 hours later in dogs subjected to coronary occlusion (28). Hemodynamic effects of high partial pressures of oxygen include increased total peripheral resistance, increased mean arterial blood pressure, and decreased cardiac output (109, 110, 114, 115). Since all these may be deleterious in the face of ischemia, augmented oxygen tension may paradoxically increase ischemic injury (116).

Administration of supplemental oxygen to patients with acute myocardial infarction and arterial oxygen saturation of less than 90% results in increased cardiac output, augmented oxygen transport to the tissues, variable changes in peripheral resistance and cardiac function, and decreased work of breathing without augmentation of peripheral vascular resistance. In contrast, in patients with initial arterial oxygen saturation exceeding

90%, cardiac output declines and delivery of oxygen to the tissues decreases, in part because of an increase in peripheral resistance (117). Hyperbaric oxygen has been evaluated in experimental animals with myocardial ischemia and patients with coronary artery disease (118, 119). In general its administration is neither practical nor of established long-term benefit. In addition, it may induce coronary artery vasoconstriction (120).

These data suggest that use of supplemental oxygen is indicated for treatment of patients with acute myocardial ischemia provided that arterial oxygen saturation is determined and found to be less than 90%.

Fluorocarbons

Fluorocarbon (perfluorochemical) emulsions can dissolve up to 60% oxygen by volume and provide an alternative to blood replacement for selected patients (121). Such emulsions have been employed for perfusion of isolated kidneys prior to transplantation and for perfusion of isolated, canine stomachs to maintain normal mechanical and myoelectrical activity (122). Isolated rat cardiac muscle remains functional for 60 min when immersed in fluorocarbon perfusate (123). Recently, such perfusates have been shown to reduce infarct size in dogs (28) and further evaluations seem warranted to assess their value in protecting ischemic myocardium.

Agents Employed to Improve Cardiac Output and Facilitate Myocardial Oxygenation or Energy Supply

BETA-ADRENERGIC AGONISTS For treatment of severe left ventricular failure, use of agents with positive inotropic effects may be indicated. Although beta-adrenergic agonists such as isoproterenol improve ventricular performance, they markedly augment myocardial oxygen consumption, lactate production (124), and infarct size in animals (5, 33). Norepinephrine may increase myocardial oxygen consumption even more because it induces profound peripheral vasoconstriction with consequent elevation of left ventricular afterload. It may precipitate malignant ventricular dysrhythmia directly, or secondary to compromised myocardial energetics.

Dopamine is often particularly useful for patients with decreased cardiac output, increased left ventricular filling pressure, but persistent hypotension. Although it exhibits beneficial vasodilatory effects on renal and splanchnic vessels (125, 126) mediated via dopaminergic receptors, at higher doses it elicits peripheral vasoconstriction and coronary artery vasoconstriction mediated via $alpha_1$-adrenergic receptors (127). Resultant reductions in myocardial perfusion may partly explain the increased myocardial oxygen consumption sometimes observed (127), and may account for the increased ST segment elevation seen in patients with acute myocardial infarction without left ventricular failure (128).

Dobutamine is a catecholamine congener with beta-1-adrenergic, cardioselective and positive inotropic effects with little or no peripheral or coronary vasoconstrictor action (127, 129, 130). In patients with acute myocardial infarction, dobutamine improves left ventricular performance without augmenting enzymatically estimated infarct size (131, 132). Accordingly, it appears to be the beta-adrenergic agonist of choice for treatment of left ventricular failure associated with acute myocardial infarction.

GLUCOSE-INSULIN-POTASSIUM Because glycogen depletion occurs promptly in myocardium rendered ischemic and anaerobic glycolysis becomes the primary pathway for energy production, intravenous administration of glucose-insulin-potassium has been proposed to facilitate availability of substrate and to prevent hypokalemia. Hypoglycemia has been shown to increase infarct size in experimental animals (133), and administration of glucose-insulin-potassium protects ischemic myocardium under selected conditions (134), decreases infarct size (29), and stablilizes cardiac rhythm (46), even under conditions of marked hypoxia (46, 135–137).

In patients, treatment with glucose-insulin-potassium lowers the concentration of plasma free fatty acids and modestly increases heart rate, mean systolic blood pressure, and cardiac index. The frequency and severity of ventricular ectopic activity decreases (29, 138). Although early results of a nonrandomized study reported benefit (139), other prospective, controlled studies (138, 139) do not report definitive effects on infarct size and demonstrate only equivocal effects on mortality. Thus, therapy with glucose-insulin-potassium for patients with acute myocardial infarction remains experimental.

OTHER AGENTS WITH POSITIVE INOTROPIC EFFECTS Digitalis glycosides are the most commonly used, non-beta-adrenergic agents with positive inotropic effects for patients with acute myocardial infarction. In normal hearts, contractility and myocardial oxygen consumption increase in response to digitalis. Thus, it is not surprising that infarct size increases (sic) in both experimental animals (141) and patients (142) with hemodynamically uncomplicated infarction. When congestive heart failure and cardiomegaly supervene, however, infarct size decreases in response to digitalis, presumably because indirect beneficial effects on myocardial oxygen consumption due to reduction of ventricular wall stress override direct effects augmenting oxygen consumption associated with increased contractility. Combined treatment with propranolol may decrease left ventricular wall tension and reduce ST segment elevation by negating otherwise adverse effects of digitalis on myocardial energetics in the absence of congestive heart failure (143). Whether complete negation of the positive inotropic

effect induced by cardiac glycosides occurs under these conditions as well is a moot point. The coronary vasoconstrictor effect of digoxin mediated by alpha-adrenergic receptors and blocked by phentolamine must also be considered as a potential disadvantage (144). In concert, available information suggests that digitalis should not be employed routinely for treatment of hemodynamically uncomplicated myocardial infarction in the absence of congestive heart failure or clinically responsive supraventricular tachycardia.

Other agents with positive inotropic effects such as glucagon or amnirone have not yet been thoroughly evaluated with respect to modification of infarct size. However, there is little reason to suspect that their augmentation of cardiac contractility would be devoid of the adverse effects observed with digitalis in the absence of mitigating factors such as increased left ventricular dimension and wall tension that may be influenced favorably.

HYALURONIDASE Because enhanced diffusion of substrate into ischemic zones of the heart may facilitate anerobic metabolism, thereby augmenting production of ATP, hyaluronidase has been employed to protect jeopardized, ischemic myocardium. Improved washout of deleterious metabolites or augmentation of regional perfusion by diminution of interstitial edema have been additional goals.

Hyaluronidase is present in many tissues and in many organisms. It is an enzyme that catalyzes the degradation of a complex acidic mucopolysaccharide, hyaluronic acid, a major constituent of connective tissue ground substance, to form primarily tetrasaccharides, disaccharides, or both (145, 146). In 1958, de Oliveira demonstrated that ST segment elevation became less marked within 5 hours after intravenous administration of hyaluronidase to patients with acute myocardial infarction and within 5–10 min in dogs subjected to coronary artery occlusion (147). Myocardial water content was noted to be 76.79 $\pm$ 0.24% in control dogs, 80.50 $\pm$ 0.24% in placebo-treated dogs, and 77.88 $\pm$ 0.24% in hyaluronidase-treated dogs after coronary artery occlusion (148). The hypothesis was therefore advanced that hyaluronidase decreased edema formation in ischemic myocardium, thereby facilitating transport of substrate, removal of metabolites, or both. Others subsequently confirmed these initial findings (149).

Several reports relate to reduction of infarct size in dogs given hyaluronidase after coronary artery occlusion. The number of myocardial sites exhibiting ST segment elevation before treatment that subsequently displayed histologic signs of necrosis has been noted to decrease from 97 to 55% (30), glycogen granules have been significantly preserved (150), and hyaluronidase was effective even when its administration was delayed for 6 hours (but not for 9 hours) after coronary occlusion (151). Regional blood flow in

ischemic zones remained constant, beginning 15 min after occlusion in contrast to the progressive decrease noted during the subsequent 6 hours in controls (152). These observed differences in blood flow may account for some of the salutary effects on myocardial preservation. Reduction of infarct size has been inferred from decreased Q-wave development, preservation of R-wave amplitude and myocardial morphology 21 days after coronary occlusion in dogs (153). Thus, hyaluronidase appears to decrease necrosis when given as late as 6 hours after coronary occlusion, at least in canine preparations.

However, results in pigs differ (154). In this species, hyaluronidase administered intravenously in a single dose 1 hour after occlusion of the left anterior descending coronary artery had no significant effect on ST segment elevation, hemodynamics, or angiographically determined wall motion. Comparison to results in experiments with dogs is difficult since myocardial necrosis was not assessed directly, hyaluronidase was given only once, and the studies were terminated after 6 hours. Nevertheless, the disparate results may reflect species differences.

Only one randomized, controlled study of patients treated with hyaluronidase has been reported (155). Among 91 patients with anterior infarction randomized to control or hyaluronidase treatment continued for 48 hours, electrocardiographic criteria indicated a reduction in ischemic injury with a decrease from 59.3 $\pm$ 4.9% to 46.4 $\pm$ 4.9% of new Q-waves in leads with initial ST segment elevation compared to values in controls. However, more direct criteria of salvage such as plasma MB-CK values, radioventriculographic evidence of preserved regional ventricular function, or improved overall survival are not yet available. Accordingly, the ultimate place of hyaluronidase in the armamanterium of agents useful for limitation of infarct size in man must await results of controlled, prospective studies now in progress.

Several considerations regarding potential mechanism(s) of action of hyaluronidase are pertinent. Histochemical studies with Alcian green indicate a qualitative decrease in hyaluronic acid in ischemic dog myocardium 4 hours after intravenous administration of hyaluronidase (30). Recently, supporting biochemical analyses have demonstrated dissolution of ground substance (156). However, commercially available hyaluronidase is heterogeneous and the efficacy of purified hyaluronidase or its individual isoenzymes compared to that of other substances present has not yet been established. Influences of hyaluronidase on perfusion via the collateral coronary artery circulation and the dependence of apparent efficacy of the agent on such phenomenon have not been clarified. Since heparin appears to be a potent inhibitor of hyaluronidase (156) and since it has often been used

concurrently in patients treated with hyaluronidase, interpretation of results of clinical studies may require further consideration and clarification.

Coronary Thrombolysis

With increased recognition of the potential importance of platelet aggregates and thrombi to coronary occlusion underlying infarction, recanalization of occluded vessels has been attempted by intracoronary infusion of thrombolytic agents such as streptokinase (26, 157–160). Typically 1000 to 2000 units/min are infused for 1 hour in patients presenting within the first several hours after the onset of ischemia manifested by chest pain and electrocardiographic changes typical of acute myocardial infarction in whom complete coronary occlusion can be documented. Patency has been restored in approximately 75% of cases, with concomitant relief of pain. Advantages of the intracoronary route of administration appear to include diminished likelihood of systemic bleeding and delivery of the agent to plasminogen within the interstices of the clot before the streptokinase has become bound to circulating plasminogen. Although this modality of treatment offers promise, the incidence of possible complications such as exacerbation of myocardial hemorrhage or reperfusion injury must be defined and the interval during which objectively measured myocardial injury can be modified favorably must be delineated to avoid indiscriminate or injudicious use of thrombolysis.

Modification of the Process of Cellular Injury Per Se

CALCIUM ANTAGONISTS The rationale underlying use of calcium antagonists to protect ischemic myocardium is based information from several types of biological systems in which membranes rendered permeable to calcium potentiate cell death by permitting ingress of extracellular calcium driven by the concentration gradient with consequent mitochondrial damage, possible activation of lipolytic enzymes, and enhancement of calcium dependent ATPase activity with depletion of high energy phosphate stores. Since ingress of calcium can be prevented by calcium antagonists, their use has been hypothecated to protect ischemic myocardium against calcium-mediated injury. Three agents have been extensively studied in this regard: nifedipine, verapamil, and dilitiazem. All three apparently block influx of calcium into cells but by disparate mechanisms of action (161). In addition, they may differentially alter intracellular calcium access to vulnerable loci.

Nifedipine appears to reduce the transmembrane flux of calcium by diminishing the slow inward current without altering the kinetic parameters of the current (161) and hence retards entry of calcium into ischemic myocytes, increases coronary blood flow, prevents ischemic contracture,

and preserves myocardial CK content (162–164). Administration of nifedipine to conscious dogs 30 min after left anterior descending coronary artery occlusion increases blood flow to ischemic zones for as long as 23.5 hours and reduces infarct size by 1.5 to 3-fold (163). Analogous findings have been obtained in other species (162). However, beneficial effects in vivo may be attributable to diminished cardiac work due to a significant fall in arterial resistance and blood pressure. Thus, infarct size reduction may not depend exclusively on altered calcium concentrations in myocardium but may reflect vasodilatory properties of the drug, at least in part. On the other hand, protective effects manifested by enhanced physiological function and maintained biochemical and ultrastructural integrity have been elicited with nifedipine in ischemic isolated perfused hearts and globally ischemic canine hearts in which flow was controlled and hence indirect effects could be excluded (162, 165).

Verapamil, which reduces calcium entry into the cell by modifying the kinetic parameters of the slow inward current, reduces ST segment elevation in dogs subjected to left anterior descending coronary artery occlusion (166, 167). However, it does not retard CK tissue depletion or change myocardial blood flow (167). A lack of benefit of verapamil on ischemic myocardium has been observed also based on concordance between observed and projected infarct size after verapamil comparable to that seen under control conditions in dogs (168). However, verapamil (and dilitiazem) inhibit the increase in resting tension otherwise seen with hypoxia in perfused rabbit hearts (169) and pretreatment with verapamil, as well as with nifedipine and dilitiazem, preserves oxidative phosphorylation, high-energy phosphate stores, and prevents calcium accumulation in ischemic myocardium (170, 171). Thus, reduction of calcium transmembrane influx by these drugs may be beneficial under some conditions even in the absence of afterload reduction, particularly when the active agent is administered prophylactically, or very early after the onset of ischemia.

Possibly analogous phenomena may account for the observation that lidocaine reduces infarct size in dogs without causing myocardial depression (172), when dosage is fivefold higher than that used clinically. In view of the known mechanisms of action of lidocaine, these results suggest that modulation of ionic fluxes besides those of calcium may influence infarct size or that other actions of lidocaine on the cell membrane may be protective.

Anti-Inflammatory Agents

CORTICOSTEROIDS The hypothesis that release and activation of lysosomal hydrolases may potentiate myocardial injury (173) has led to investigation of the potentially protective effects of anti-inflammatory agents on

ischemic myocardium. In laboratory animals corticosteroids administered early after coronary artery occlusion increase coronary blood flow (175, 176) and reduce infarct size estimated electrocardiographically (174, 176) and histologically (177, 178), despite the absence of significant hemodynamic changes (174, 175, 177, 179, 180).

Results in patients have often been equivocal (179, 181) or deleterious (182, 183). This disparity appears to reflect important influences of the timing of administration, duration, and dosage. Whereas studies in animals indicate an acute decrease in infarct size, follow-up studies in man demonstrate delay in reparative processes and wound healing with prolonged cellular mummification, and increased incidences of scar thinning, ventricular aneurysm formation, and ventricular rupture (182, 183). Thus, in view of practical difficulties in initiating treatment sufficiently early after the onset of ischemia to maximize benefit and the late adverse effect of prolonged high dose corticosteroid treatment, we believe that the use of these agents should be avoided during the evolution of acute myocardial infarction.

NON-STEROIDAL AGENTS In response to ischemic cell death inflammatory processes are initiated that result in removal of cellular debris. Concomitantly, necrosis may be potentiated. A number of agents that inhibit components of the inflammatory process have been considered as potential modulators of infarct size.

Indomethacin, a potent inhibitor of cyclo-oxygenase, decreases regional blood flow in ischemic myocardium in dogs, increases ST segment elevation (184), and increases infarct size (185). Thus, the hypothesis that endogenous synthesis of vasodilator prostaglandins such as PGI_2 are protective by eliciting coronary vasodilation (186) and that inhibition of their synthesis by indomethacin may result in adverse effects is supported by these observations. A decrease in infarct size has been observed in cats given infusions of vasodilator prostaglandins (187). However, ibuprofen, an anti-inflammatory agent with much less prostaglandin synthesis-inhibiting potency than indomethacin, decreases infarct size in dogs subjected to coronary occlusion (188, 189) without producing deleterious thinning of ventricular scars (190). Since this agent exerts no significant systemic or coronary hemodynamic effects, results with it implicate favorable influences on ischemic myocardium at the cellular level by modification of prostaglandin metabolism.

Aprotinin inhibits kallikrein and retards the inflammatory response. It decreases infarct size in dogs and increases endocardial to epicardial blood flow-ratio (191). Cobra venom factor is an agent that interacts with C'_3 proactivator and mediates inactivation of C'_3. When administered to dogs

with coronary occlusion, it decreases the inflammatory response and reduces infarct size (192, 193). Trasylol, a protease inhibitor, apparently produces similar results (193). However, none of these agents has yet been evaluated fully or reported to be beneficial in patients with acute myocardial infarction.

SUMMARY

During the past decade, efforts to limit the extent of myocardium exhibiting infarction once ischemia has been initiated have focused on manipulation of myocardial oxygen supply and demand as well as the process of injury itself. Interventions of promise range from the conventional, moderate increase in inspired oxygen content, to administration of hyaluronidase or intracoronary thrombolysis to augment oxygen supply; use of beta-adrenergic blocking drugs and nitroglycerin to diminish demand; and administration of calcium antagonists and prostaglandin synthesis inhibitors to limit the injury process. The ultimate effects on infarct size and long-term mortality have yet to be established unequivocally for any of these approaches in the clinical setting of acute myocardial infarction, but significant preservation of ischemic myocardium with hypothermia and with administration of nifedipine during coronary-artery bypass surgery have been documented. Several prospective, large-scale, blinded, and random sample selection clinical trials are currently in progress. Their results should definitively elucidate the clinical utility of specific interventions under defined conditions and should help to further improve the management of patients with ischemic heart disease.

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