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Baseline Parametric Potentiation Of Myocardial Ischemia Beyond Coronary Microcirculatory Patency

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Abstract: A basic series of mechanistic steps might actually operate not only in the generation of Ischemia to the myocardium, but particularly in the development of a progressive form of myocardial Ischemia that is determined to a significant degree by a previously established baseline level of sustained myocardial Ischemia. In this sense, perhaps, dynamic contractility of the left ventricle, in terms of the alternating periods of dilatation accomodation of end-diastolic ventricular volume, would in a final analysis constitute a simple superimposition of a number of hemodynamic parametric alterations towards a progressive deterioration in blood supply. This Ischemia would be induced by previous episodes of reduced blood supply and also compensated for by hemodynamic blood flow and pressure adaptations as constituted by myocardial-vascular coupling mechanisms. In various ways, impaired coronary blood flow would institute further hemodynamic systems of vascular-wall origin that would progressively alternate with repeated myocardial ischemic events of both cyclical and acyclical nature. Indeed, vascular patency might operatively reflect myocardial contractility with regard to a whole series of vasodilatatory events and of stenosing lesions that regulate the influence even of attributes of ischemic myocardial effects during systole. It would perhaps be in defining terms of previously maintained levels of persistent myocardial Ischemia that baseline shifts of injury to ventricular muscle would both predetermine and also provide mechanistic potentiation for further ischemic events both as systolic and as end-diastolic phenomena. It is aspects of a myofiber propensity for a potentiating role towards establishment of baseline parameters of determined blood perfusion level at the microcirculatory level that one might realize systems of progressive deterioration of myocardial blood supply beyond just simple considerations of patency of the coronary vasculature.

Key words: Myocardial Ischemia, parametric potentiation, microcirculatory patency

INTRODUCTION

Increased susceptibility to cardiomyofiber ischemic necrosis beyond the immediate ischemic events themselves: An essential distinction exists between permanent ischemic damage and potentially transient ischemic damage. On such a distinction would depend any potential therapeutic benefit obtainable by proper management of a patient with myocardial Ischemia. Also, significant pathogenetic implications appear involved in the recognition of coronary lesion instability as detectable clinically as unstable angina pectori [1]

It would appear true that a significant element of any ischemic cerebral or myocardial lesion is, at least initially, potentially reversible. Such a potentiality for reversibility of an ischemic focus has been termed the cerebral penumbra but an identical concept is conceivably applicable also to cases of myocardial Ischemia[2].

What factors might determine progression of transient to permanent Ischemia? Is transient Ischemia inherently prone to become permanent, and would such a phenomenon depend largely on a fixed time frame?

Does a zone of transient Ischemia tend to evolve to a zone of permanent Ischemia simply because there is in the first place a given degree of Ischemia? For example, specific attributes of an initially inflicted ischemic injury may perhaps help account for an elevated troponin 1 level that predicts an adverse clinical event in the face of normal creatine kinase and myoglobin levels in serum[3] . This appears true also with respect to infarct size estimation by troponins[4].

Such considerations appear of central significance in myocardial ischemic cases, where the myocardium is inherently subjected to periodic episodes of Ischemia during the essential period of ventricular systole.

The greater work of systole is probably a major factor contributing to the exquisite susceptibility of the left versus right ventricle, in the development and progression of Ischemia.

It is significant that the whole phenomenon of ventricular Ischemia is not simply one wholly translatable in terms of occlusion of the supplying coronary arteries.

In this sense, for example, successful outcome following primary percutaneous transluminal coronary angioplasty is variable and not necessarily strictly correlated with vessel patency[5].

In addition, exercise-induced Ischemia that develops subsequent to successful percutaneous coronary angioplasty may be associated with endothelial dysfunction of these vessels[6].

The susceptibility of ischemic heart disease arises directly from the intrinsic physiologic hemodynamics of blood supply to the left ventricle, as a direct consequence of regularly or irregularly rhythmic episodes of significant Ischemia to much or all of the left ventricular muscle during forceful systolic contraction . Indeed, percutaneous transluminal coronary angioplasty often necessitates not only subsequent repeated performance, but generally also delays the performance of coronary surgical revascularization[7].

Due to ventricular contractility there arises a particular susceptibility to the development of frequent transient episodes of Ischemia and also to the subsequent frequent development of permanent Ischemia of the left ventricle. Such susceptibility patterns of recurrent ischemic injury appear to depend especially on the coronary flow reserve status as determined by post-reperfusion remodeling of injured ventricular myocardium[8].

A whole series of phenomena may contribute to the establishment of ischemic heart disease as the commonest cause of death in Western countries, thus even assuming epidemic proportions. Ischemic necrosis of the left ventricle represents the full effects of a compromised blood supply delivered to the myocardium that evolves in apparent cascade-like fashion. This is in response to a vast range of factors that render the left ventricle particularly susceptible to the damaging effects of Ischemia. In this regard, akinesia of the myocardium as distinguished for example by contrast echocardiography using intravenous octafluoropropane and real time perfusion imaging may constitute parallel systems of progression of reversible versus irreversible states of potential myocardial recoverability[9].

Is it possible, for example, that a mild degree of Ischemia of the left ventricle is particularly prone to become considerably more severe with subsequent systolic contraction of that left ventricle? Is it true that successive waves of systolic contraction of the left ventricle are particularly conducive to the development of essential cascade series of events arising from, and subsequently propagated as, an established state of significant myocardial Ischemia?

On the other hand, in persistent stunning, a tendency for a shift in the flow/function relationship of the myocardium appears to evolve due to a change in substrate utilization thus a 30% reduction in coronary blood flow does not induce a fall in myocardial function[10].

Such concepts indicate the probable step by step gradient phenomenon of evolving Ischemia that is suggested especially by crescendo angina attacks. Is it perhaps true to maintain that a progressive shift in ischemic baseline constitutes a major susceptibility factor related to the intrinsic ventricular contractile function of the heart? Indeed, such a phenomenon of increased baseline susceptibility to Ischemia helps account for sudden cardiac death developing post-infarction with characteristically limited predictability, except in terms of ejection fraction and digital Holter ECG[11].

The ventricular muscle tends to undergo a progressive lowering of the protective threshold against ischemic damage under a number of pathophysiologic conditions. In such circumstances, the myocardium may lose the effectiveness of a whole host of mechanisms that normally protect it against progressive Ischemia.

The left ventricle, once it has experienced episodes of significant Ischemia, may be particularly prone to eventually develop permanent ischemic damage, and such a phenomenon is at least partly independent of any stenosis of the supplying coronary arteries. Such a lowering in baseline susceptibility to ischemic myocardial injury contrasts with the apparent cardioprotective effects as exerted apparently by repeated episodes of physiologic stress[12] .

It is perhaps invalid to simply translate the susceptibility of the myocardium to ischemic damage in terms of simply a slowly stenosing atherosclerotic plaque, even if this progresses as a complicated lesion. For example, multiple mechanistic pathways appear to converge in preconditioning the myocardium to effects of Ischemia in patients suffering from diabetes mellitus[13] . Diabetes mellitus is a major determinant affecting the one-year mortality rate after myocardial infarction[14].

Once the myocardium experiences an episode of significant Ischemia, it may anatomically become susceptible to successive waves of ischemic injury arising largely as a function of several pathophysiologic processes.

Many of these may originate as attributes of the myocardium rather than as purely a phenomenon of progressive occlusion of the supplying coronary artery or arteries. In fact, there is evidence of ventriculo-arterial uncoupling and of altered left ventricular mechanical efficiency during acute myocardial Ischemia, with consequent late decreased arterial compliance[15].

The systolic rhythmic contractions of the left ventricle appear central to an essential susceptibility of the myocardium to increasing ischemic damage in terms partly independent of parameters of essential progression of such ischemic episodes arising from vascular luminal compromise.

What appears to develop is a pathophysiologic increase in susceptibility of the left ventricular myocardium to the damaging effects of Ischemia, in terms also of actual precipitation of necrosis or of progressive Ischemia of myofibers.

In this regard, it may be significant also that a raised white cell count in peripheral blood constitutes an active destabilization process affecting coronary artery plaques, related to the acute ischemic event itself[16].

What perhaps particularly distinguishes the left ventricular myocardium is the progressive increase in susceptibility to ischemic necrosis of its constituent myofibers irrespective of any absolute decrease in blood supply or of duration of the Ischemia.

Ischemic heart disease may represent an acquired phenomenon of increased susceptibility to necrosis of cardiomyocytes, once specific cascade series of events develop. This may be largely distinct from any given parameters of the strictly Ischemic phenomenon itself. In this sense, for example, inhibition of angiotensin II action, as mediated by an increase in bradykinin, appears to ameliorate effects of reduced coronary blood flow during atrial pacing[17].

Impaired full relaxation of infarcted left ventricular muscle with loss of contractility in predisposing to cardiogenic shock: A transformation regulating the control of stroke volume appears central to the responsive adaptability of circulatory dynamics to a wide variety of stress and exercise conditions.

In particular, there appears to operate an integrative phenomenon coordinating factors determining end-diastolic volume of the left ventricle. End-diastolic volume, in fact, appears to be one major determinant of the stroke volume, and heart rate would actually operate to essentially modify to a certain extent such end-diastolic volume. Hence, in at true sense, heart rate operates at two essentially distinct levels of operative intervention one that determines the end-diastolic volume of the left ventricle and the other that determines the effective cardiac output as a product of both this stroke volume and the heart rate per minute.

That the end-diastolic volume itself effectively determines also to an important extent the stroke volume would further indicate the centrality of the end-diastolic volume of the left ventricle as the parameter that by far predominates in this regard hemodynamically, particularly under conditions of stress or of hyperthermia, dehydration, or exercise. Such events might to an important extent relate to coronary atherosclerosis as a chronic inflammatory series of reactions implicating possibly also innate immunity and toll-like receptors[18].

In broad terms, the degree of filling capacity of the left ventricle and the actual degree of filling of this left ventricle, would, to a highly significant extent, centralize the effects of the major forms of influence that might modify or radically transform cardiac output under a vast range of pathologic conditions that in fact it is the end-diastolic filling volume in the left ventricle that would transform, for example, an adequate circulatory dynamic balance to an abnormal one. Perhaps contractility of left ventricular muscle, on the one hand, and end-diastolic ventricular filling volume, on the other, would constitute a centrally operative axis that allows potential recoverability of the heart and consequently the integrity of the circulatory system when these are subjected to disease or to stress. Also, it is significant that reperfusion time by means of percutaneous coronary intervention is important for survival of patients with cardiogenic shock[19]. Attempts at reverse remodeling, particularly of the unloaded failing heart, would perhaps help optimize improvements of contractile dysfunction as mediated by myocardial responsiveness to beta-adrenergic stimulation and mechanical assistance[20]

Myocardial infarction as a disease almost exclusively of the left ventricle would be considered in cases of cardiogenic shock to represent not simply a loss of a large contractile mass of left ventricular muscle but also to profoundly influence the relationships of such contractility with end-diastolic filling volume of the ventricle. Also, regional ejection time as measured by pulsed Doppler tissue imaging and measurements of regional peak systolic velocity would reliably reflect viability of involved myocardium[21]. Probably many patients suffering from massive myocardial infarction involving some or more than 40% of the left ventricular muscle mass would suffer from impaired filling of the left ventricle during diastole due to disturbances of the contractility and also relaxation accommodation of the left ventricle. It is perhaps particularly in terms of an impaired accommodating capacity due to impaired relaxation of the infarcted left ventricular muscle that a loss of full contractility seriously predisposes to cardiogenic shock.

Such considerations should be interpreted within a context of a raised C-reactive protein and of an essential role apparently of inflammatory factors operatively influencing outcome of coronary artery disease in the development of cardiogenic shock[22].

Stereotyped evolution of ventricular dynamics in progression or resolution of myocardial Ischemia: There appears to commonly develop an adaptability of the myocardium to angina-associated episodes of Ischemia. The actual physiologic adaptability of the myocardium to periodic episodes of Ischemia (and this might constitute significantly evolving Ischemia) during systolic ventricular contraction would be suggestive of a myocardial ability to sustain progressively increasing periods of Ischemia. In this regard, differences in outcome between patients with and without residual intracoronary thrombus following primary angioplasty for acute myocardial infarction appear to depend on baseline clinical differences rather than on the thrombus per se[23].

It is conceivable that significant Ischemia during ventricular contraction occurs as specific periods of ventricular systole or even as specific variations from normal of ventricular systolic contraction.

Certain determinants either qualitatively or quantitatively characterize the ventricular systolic contraction that is, in certain patients, particularly prone to induce anginal myocardial Ischemia. Indeed, cardiac resynchronization therapy (biventricular pacing) appears to improve left ventricular function and also exert better control of angina in symptomatic patients[24].

Myocardial angina and myocardial ischemic changes, as seen morphologically, essentially affect the left ventricle. Part of the heart that constitutes not only the main cardiac muscle mass, but also undergoes the most ventricular contraction, is subjected to significant Ischemia in terms of such associated myocardial contraction.

High rates of ventricular tachycardia may constitute one set of circumstances predisposing in this way to systole-associated Ischemia of the myocardium. Indeed, changes in structural and functional attributes of the left ventricle following myocardial infarction and remodeling would constitute an important substrate for subsequent development of serious ventricular arrhythmias[25].

Quantitative aspects of ventricular contractions do not appear to fully account for the development of anginal attacks at a particular moment in time even in the presence of evolving atherosclerotic lesions.

The very dynamics of anginal pain appear to be a direct function of certain attributes of contraction/systole-associated myocardial Ischemia. Even when one considers anginal pain associated with physical exertion or stress, it appears that the intrinsic dynamics of the evolving left ventricular Ischemia during such attacks may actually be stereotyped. In fact, understanding such an intrinsically stereotyped evolution in successive development of episodes of anginal pain may largely have to take into account aberrant attributes of the left ventricular contraction/systole cycle that alternates with ventricular dilatation, so as to devise strategies for early and effective abortion of episodic myocardial Ischemia.

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