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Myocardial Ischemia is Potentiated by Intramural Perforating Vascular Constriction During Ventricular Contraction

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Abstract: Constriction of intramural perforating vessels would induce dynamic episodes of significant myocardial ischemia in patients with atherosclerotic epicardial coronary arteries. Ventricular hypertrophy, both as a primary cardiomyopathy of unknown etiology and also as a secondary consequence or reaction to sustained arterial hypertension or aortic stenosis, would promote ischemia of the myocardium due to compromised blood flow in ventricular perforating intramural vessels. Cyclical episodes of ischemia would progress on contraction of the hypertrophied left ventricle. Dynamic contractility and viability of the myocardium appear primarily influenced by an inherently highly variable transmural blood flow, with induced ischemic episodes during systole. Cyclical myocardial ischemia would progress largely as a parametric function of systolic and diastolic contractility and rhythmicity, which determine, in turn, dynamics of blood flow delivery through perforating vessels in the left ventricular wall.

Key words: Intramural, perforating, potentiated, myocardial ischemia, vascular contraction

INTRODUCTION

Oxygen non-availability and dysfunctional contractility of the dilated or hypertrophied myocardium: Transitions between different isoforms of the myosin heavy chain would occur not only during normal development of the human heart, but also as generic pathologic states of heart failure, hypertension and cardiomyopathies[1]. These considerations are evaluated in the context of systolic fiber dysfunction acting as an important determinant of myocardial contractility during reperfusion[2]. Also, angiographic assessment of collateral blood flow does not necessarily correlate with myocardial perfusion and function; this would implicate an angiogenic response in cases of ischemia[3].

What would appear common to an essential state of heart failure and of hypertrophic cardiomyopathy? In fact, a progressive loss of perfusion-contraction matching might characterize sustained moderate ischemia to the myocardium[4].

In left ventricular hypertrophy there is increased susceptibility for subendocardial ischemia due particularly to increased extravascular factors compressing the intramural coronary vasculature, as seen especially during exercise[5]. In contrast to normal hearts, hypertrophied left ventricle depends more on the opening of K+ ATP channels to increase coronary flow during exercise. This is because of the extravascular compression of intramural vessels[6].

Heart failure, subsequent to decompensation of the hypertrophied left ventricle, supervenes in patients suffering from longstanding severe arterial hypertension or from aortic valve stenosis and would approximate to the pathophysiology of hypertrophic cardiomyopathy. This applies particularly with regard to postsystolic thickening resulting from myocardial ischemia and reperfusion[7]. Decreased vascular density and vascular hypertensive changes would contribute with increased extravascular compression to an increase in vascular resistance to limit coronary blood flow[5]. In patients with aortic valve stenosis, hemodynamic parameters change in relation to phasic coronary blood flow velocity profile[8].

Th myocardial hypertrophy in hypertrophic cardiomyopathy might induce an essential uncoupling between myocardial hypertrophy and enhanced effectiveness of systolic ventricular contractility generally associated with ventricular hypertrophy. Assessment of distribution of blood supply via the first septal perforating artery would be indicated in hypertrophic cardiomyopathy patients due to the considerable variability in vascular size and distribution[9].

Such uncoupling between degree of hypertrophy and effective contractility of ventricular muscle might operate as attributes of the ventricular mass and geometry of the affected heart. For example, the borderzone myocardium around a region of expanding infarction would constitute a unique region of perfused hypercontractile myocardium distinct from the hibernating or stunned state[10]. Also,

with regard to disturbed intracoronary hemodynamics related to myocardial bridging, there is not only systolic vessel compression but also a persistent diastolic diameter reduction, retrograde flow and a reduced flow reserve[11].

The actual process of a significant hypertrophy of the ventricular muscle would considerably alter the ventricular muscle mass and geometry. In hypertrophic cardiomyopathy, a correlation has been established between the degree of anterior motion of anterior mitral valve leaflet and prognosis. Functional mitral regurgitation is of poor prognostic import in ischemic cardiomyopathy[12].

The actual process of progressive ventricular hypertrophy might contribute substantially to the morbidity and mortality due to impedance of coronary arterial inflow by cardiac contraction. Phasic flow effects arising from compression of intramural vessels is associated with reduced vascular short-axial diameter as compared to end-diastolic values and to increased longitudinal dimension[13].

Within such a context, variability in the predominant isoform of myosin heavy chain in cardiomyocytes might constitute both a cause and an effect of such ventricular hypertrophy as seen both in heart failure and in hypertrophic cardiomyopathy.

The higher efficiency of alpha-myosin heavy chain with its two or three times increased actin-activated ATPase activity and actin filament sliding velocity (as contrasted with myosin composed of beta-myosin heavy chain) would be counterbalanced by the two time cross-bridge force of beta-myosin over alpha-myosin. There would consequently be more economy for energy consumption by beta-myosin.

These two essential isoforms of myosin, fast and slow, the fast alpha-myosin being more active whereas the beta-myosin being more forceful, might constitute the two main alternate forms of functional myofiber specialization.

This sharp distinction between fast and slow myofibers, as active and forceful rapid contractility versus slow but sustained contractility, would correlate with specific attributes of the heart. Muscle mass and geometry would be significant in this regard, in cases of left ventricular dilatation after myocardial infarction[14].

Phenomena such as compensatory ventricular hypertrophy, ventricular dilatation and decompensation of ventricular mass, might represent the endresult of optional switching between fast active alpha-myosin and slow sustained beta-myosin contractility, influenced by such factors as circulating thyroid hormone levels.

Interstitial remodeling, as mediated by fibroblast activation and increased expression of tenascin and of smooth muscle myosin heavy chain, would tend to predict functional recovery after re-vascularization[15]. This is especially significant in a possible context of remodeling of small intramyocardial coronary arteries with a decrease in their lumen distal to marked stenosis of an epicardial coronary artery. Indeed, increased wall thickness and decreased lumen would tend to characterize microvascular remodeling in dysfunctional regions of ischemic myocardium[16].

Even in terms of an essential need for significant oxygen supply, the main mechanism of isoform switching between α and β myosin heavy chains would implicate variable oxygen availability to cardiomyocytes in patients with heart failure or hypertrophic cardiomyopathy. Myocardial viability would be influenced by a coexistently scarred and hibernating myocardium that secondarily induces dysfunctional contractility[17]. Such a phenomenon would perhaps operate in the terms of interdependence of endothelial activation and dysfunction with myocardial signaling that influences in particular contractility and rhythmicity[18].

Altered energy metabolism would trigger contractile dysfunctional tissue degeneration and death of cardiomyocytes[19]. In cardiac hibernation or stunning associated with depressed cardiac function and a reduced or normal coronary blood flow, altered cAMP homeostasis would tend to compensate, whereas Heat shock protein 72 would tend to protect against, the dysfunctional contractility[20].

In addition, abnormalities in the coronary microcirculation would operate to induce an increased susceptibility for subendocardial ischemia of the left ventricle and abnormal coronary pressure-flow relationships[21].

AFTER CORONARY BYPASS, SEVERE ATHEROSCLEROSIS AND DECREASED MYOCARDIAL COMPLIANCE INCREASE CORONARY VASCULAR RESISTANCE

Coronary re-vascularization, within three days of transmural infarction of the left ventricle, would increase mortality risk[22]. In this regard, peak systolic velocity and early diastolic velocity would be dependent on regional expression of cytokine genes, known in turn to negatively exert inotropic and lusitropic effect[23].

The actual volume of blood circulating in the coronary vessels during ventricular diastole would affect vascular resistance to blood flow. This would operate in combination with coronary tone in influencing regional blood flow as related to cardiac contractility stresses or strains and in limiting maximal coronary flow[24].

This is revealed by real time power modulation myocardial contrast echocardiography[25] and also by cardiac magnetic resonance imaging[26]. Particularly significant appears the existence of increased intramyocardial compliance on arterial hemodynamics during the ventricular diastolic phase. On the other hand, in chronic coronary artery stenosis, resting myocardial dysfunction would coexist with normal resting transmural blood flow[27].

It appears significant that mid-wall myocardial enhancement on gadolinium cardiovascular magnetic resonance would correspond to fibrosis due to coronary artery disease rather than constitute a feature of dilated cardiomyopathy[28].

Two major groups of factors would directly influence the coronary circulation during ventricular diastole. Prolonged diastolic time fraction would protect myocardial perfusion in cases of reduced coronary blood flow[29].

One group of such factors would decrease resistance to blood flow. Another group, partly determined by the actual amount of blood circulating within that coronary vascular tree during diastole, together with perhaps collateral blood flow[30], would increase resistance to blood flow. Indeed, a degree of capillary blood flow in the perfusion territory of an infarct-related artery, on reperfusion, after acute infarction, would correlate with the amount of viable myocardium[31].

Maximal dilatation of the coronary vasculature would tend to induce both an increase and decrease in resistance to coronary blood flow, particularly since the maximal coronary vascular dilatation considerably increases blood flow through the coronary vasculature.

A common pathway of effects for anterograde flow along intramural vessels in diastole and for retrograde flow in systole appears implicated with regard to myocardial viability or contractility[13].

It is significant that both transmural heterogeneity of myocardial deformation events in different regions of the left ventricle and also considerable imbalance between contractility and blood flow, would arise after an episode of myocardial ischemia[32]. In this sense perhaps, dilatation of atherosclerotic coronary vessels would be impaired consequent to an increased amount of blood flow perfusion.

The effects of increased resistance afforded by an increase in blood volume within the coronary vasculature might prove particularly acute.

This would apply in particular with regard to concomitant microvascular pathology as expressed, for example, by the blood pool magnetic resonance imaging contrast agent Clariscan[33].

As coronary atherosclerosis progresses, this would become associated with a progressive increase in resistance to blood flow through these vessels subsequent to failed pulsatile dilatation.

The effective volume of blood circulating through the coronary vessels would significantly increase resistance to coronary blood flow in cases where coronary atherosclerosis reduces or largely eliminates any myocardial compliance.

Myocardial compliance tends to progressively decrease in cases of interstitial fibrosis in hearts that have been subjected to innumerable episodes of significant ischemia. A situation would develop whereby progressive loss of pulsatile dilatation of the coronary vessels is accompanied by a parallel decrease in intramyocardial compliance to coronary blood flow.

Collateral re-distribution of transmural blood flow, as induced by coronary vasodilators, would potentially induce significant coronary steal with consequent reduced perfusion of the subendocardium[34]. Indeed, collateral function is related to regional myocardial function as affected by coronary vascular occlusion[35].

Redistribution of blood flow patterns might be significantly worsened by increasing blood volume within the coronary vascular tree, as would be expected after coronary bypass operations. In such a situation, an effective increase in coronary blood volume, together with concurrent increase in resistance, would counteract effects of any associated increase in blood flow. A considerable portion of the collateral flow would be lost after recanalization in cases of chronic total coronary occlusion[36]. Severe coronary atherosclerosis would drastically alter relationships between blood volume and blood flow resistance in patients undergoing a coronary bypass procedure.

This would account for a significantly increased mortality risk subsequent to emergency coronary artery bypass procedures in patients suffering from an acute myocardial infarct[37].

The atherosclerosis would compromise pulsatile dilatation and compliance of the coronary vessels. When combined with a significant decrease in intramyocardial compliance, as induced by several previous episodes of significant myocardial ischemia, even minor increases in coronary blood volume could tend to significantly increase blood flow resistance.

CONCOMITANTLY DECREASED BLOOD SUPPLY AND INCREASED OXYGEN NEED IN ACUTE MYOCARDIAL INFARCTS

The one primary attribute of myocardial ischemia is of course insufficient delivery of blood, a phenomenon intrinsically dominated by oxygen insufficiency. This often proves critical in an organ such as the heart that

requires not only abundant oxygen supply, but also a particular pattern of blood supply that hemodynamically combines synchronization with the regular rhythmicity of contraction of the ventricular muscle[38].

That the left ventricle, rather than the right ventricle, is essentially susceptible to myocardial infarction would attest to an important role played by a fully synchronized blood flow to a left ventricle that is significantly relaxed only during diastole. Indeed, myocardial contrast echocardiography indices of coronary blood flow velocity appear to reliably predict recoverability of myocardial function after re-vascularization[39].

Myocardial ischemia would appear to arise subsequent to insufficient blood supply mainly during diastole, since normally during systole not much blood is delivered to the myocardium.

The post-acute myocardial infarction with a patent infarct-related artery would implicate a reduced apoptosis of cardiomyocytes that allows effective left ventricular remodeling to proceed[40].

One might postulate the existence of a full series of mechanisms that enhance blood delivery to the left ventricle during diastole. This might be related simply to the relaxed state of the ventricular myocardium during diastole that allows full dilatation of the intramural vessels also. In addition, when myocardial oxygen consumption is increased, as during exercise, coronary vasodilation and increased oxygen delivery are critical in preventing myocardial ischemia[41].

It is significant to note that primary percutaneous transluminal coronary angioplasty, even when successfully performed, might be associated with absence of anterograde blood flow in the infarct-related artery, or with angiographic no-reflow[42].

Despite the virtual absence of any anatomic evidence of pathology directly affecting intramural perforating arteries in many cases of ischemic heart disease, effective scar replacement in patients who survive the acute myocardial infarction would significantly restrict blood flow through the vessels.

Significant hemodynamic disturbances might involve perforating intramural vessels particularly in association with a luminal occlusion of the proximal major coronary artery.

Abnormal myocardial blood flow distribution would at times precipitate angina pectoris in patients with normal coronary angiograms[42]. Apoptotic rate affecting cardiomyocytes would be associated with an unfavorable post-infarction left ventricular remodeling and with early symptomatic post-infarction heart failure[44].

Abnormal blood flow patterns are particularly significant when they co-exist with abnormal contractile function of the left ventricle. The left ventricle would be especially susceptible to ischemia largely in terms of its vigorous contractility. Graded and reciprocal alterations in alpha and ss-adrenergic receptor densities would contribute to myocardial dysfunction, as associated with bypass surgery for ischemic heart disease[45].

Progressive ischemia due to various causes, including proximal atherosclerosis, platelet aggregation and microthrombi, vasospasm and chemical mediators, would be implicated, together with disturbance in blood flow pattern, in many patients with ischemic heart disease. Such patterns of disturbed blood flow would entail opening up and closing down of regional vascular beds. Restoration of blood flow in a vascular bed in the left ventricular wall would develop as an extensive myocardial infarct in a setting of longstanding coronary atherosclerotic narrowing[46].

Acute precipitation of a severe episode of ischemia affecting a sizeable region of the left ventricular wall would compromise luminal delivery of blood and also hemodynamically disturb the blood flow pattern in the intramural perforating vessels. These are probably significant in terms of abnormal contractility of the left ventricle. During diastole, the impaired blood flow through such intramural perforating vessels would not be restored sufficiently to relieve any ischemia. The early hypo-enhanced regions of myocardium after a significant ischemic event, as assessed by contrast-enhanced magnetic resonance imaging, would significantly underestimate the extent of irreversibly injured myocardium with regard to just concomitant microvascular obstruction[47].

Previous episodes of ventricular systole might provoke a progressive ischemic state that goes beyond a certain threshold value of irreversible ischemic injury.

The acute episode of ischemia would lead to myocardial infarction not only due to progressive decrease in blood flow to that region but also to a progressively increased myocardial need for oxygen. This would be related to previous episodes of significant ischemia.

Progressive decrease in blood supply, together with an increased need for even more blood and oxygen to be delivered to a region of the myocardium, would promote an acute myocardial infarction in a patient with long-standing coronary atherosclerotic narrowing. Abnormal percentage thickening of the left ventricular wall at rest and during catecholamine stimulation, would be

associated with abnormal myocardial blood flow reserve in cases of chronic coronary stenosis[48].

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