L. M. Agius [2010] Med. Hypotheses Res. **6**: 43-50.

HYPOTHESIS

Uncoupled Endothelial/Cardiomyocyte Patterns of Dysfunctionality in Clinical Heart Failure

Lawrence M. Agius*

Department of Pathology, Mater Dei Hospital, Tal-Qroqq, University of Malta Medical School, Msida, Malta, Europe

Abstract. Essential coupling and uncoupling of ventricular cardiac contractility in terms of the realized interaction of right with left ventricular function would implicate cyclical action and reaction patterns of development of heart muscle physiology and pathophysiology. In terms beyond simple enumeration of interacting parameters, there evolves an individual cardiomyocyte inter-relationship with supplying endothelial cell bed comprising endocardial sensor mechanisms and a centralized pulmonary vascular endothelium. It is in view of realized consequence to such cyclical contractility of integral muscle mass of individual ventricles that the development and refashioning of heart physiology encompasses further evolutionary patterning based on remodelling of action and reaction phenomena. In final analysis, the restructuring of both functional and morphologic phenotypes of ventricular muscle mass implicates a progression of ischemic events based on parametric derivation of essential blood-heart barrier functionality or dysfunctionality.

Correspondence: Dr. A. M. Agius, Department of Pathology, Mater Dei Hospital, Tal-Qroqq, University of Malta Medical School, Msida Malta, Europe. Tel: 356-25456444. Fax: 356-25456449. E-Mail: lawrence.agius@um.edu.mt

Received on 10-4-2009; accepted on 04-02-2010.

1. Introduction

It is in terms of a complex interactivity of endothelial cells with individual cardiomyocytes that there evolves a schematic representation of dynamic forces conducive towards maintenance and sustained reproducibility of the cardiac rhythmic contractility. Either right or left ventricular compact muscle mass operatively induces an aggregate signalling phenomenon in further participation of onset and progression of cardiac muscle action. NADPH oxidase generates reactive oxygen radicals. Adenosine is important in inducing normal myocardial function (Ribe' *et al.*, 2008). One might view the rhythmicity of ventricular function as only one aspect of a continuous spectrum of action of activated or dysfunctional endothelium affecting the endocardium or coronary arterial system.

2. Global dysfunctionality

Particularly significant is an overall global dysfunctionality of the cardiac contractility in terms of onset and progression of endothelial pathology. There evolves a full participation of the injurious event as evidenced by ischemic injury to the left ventricle. Overexpression by endothelium of cysteinyl leukotrienes exacerbates myocardial ischemic/reperfusion injury by increasing endothelial permeability and increasing inflammatory gene expression (Jiang *et al.*, 2008). The relative protection of the right ventricle to ischemic injury appears largely a derived functionality of the enhanced sensor role of right ventricular endocardium.

Individual dysfunctionality of injured cells promotes an overall progression linked primarily to heart failure or myocardial infarction, with enhanced left ventricular remodelling, peri-infarct apoptosis and impaired function. Interactivity is prone to amplify injury to the individual cardiomyocyte in terms of progression of the represented ultrastructural lesions at the level of the endothelium.

3. Endothelial cells

Endothelial cells span a represented array of injuries affecting endocardium, the coronary endothelium and particularly the intramyocardial capillary network at the level of the individual cardiomyocyte. Dividing progenitor cells positively influence differentiation to inhibit pathological remodelling of cardiac myocardium (Di Meglio *et al.*, 2007).

Simple projection of the interactivities implicated in clinical ventricular dysfunction equates with a distancing of the cardiomyocyte cell mass from endocardium and vascular endothelium. There evolves a particularly sensitive interaction between constitutive and represented pathways borne out by the fully expressed interventions of ischemia and reperfusion injuries as distinct events in their own right. Ischemic preconditioning significantly reduces DNA fragmentation and apoptotic myocyte death after ischemia-reperfusion injury (Iliodromitis *et al.*, 2007).

One particular level of complexity of the injury to the cardiomyocytes revolves around concepts of preserved viability of the target cells. Myocardial infarcts heal by scar formation rather than by cardiomyocyte regeneration (Robey and Murry, 2008). Spasm of coronary arterial medial muscle constitutes a central operative field of activity that is integrally reflected in the development of both sensor dysfunctionality of the endocardial endothelium and the ongoing progression of the chronic heart failure and ischemia to cardiomyocytes. Adult cardiomyocytes appear capable of proliferation in response to myocardial injury as seen after left ventricular cryoinjury in mice (van Amerongen *et al.*, 2008).

Integral organ dysfunctionality represents a constitutional disarray of injuries that overlaps in terms particularly of potentially compensatory mechanisms in response to the injury to cardiomyocytes.

4. Cardiac organ systems

It is in terms of the further redefinition of the injury as shown by the increased apoptotic rate or necrosis of individual cardiomyocytes that there develop novel expressions of cardiac organ dysfunctionality. An imbalance of the compensatory mechanisms allows for the emergence of a form of injury dependent largely on defined parameters of dynamic interactivity between endothelium and cardiac muscle mass. Endothelial progenitor cell transplantation induces higher capillary density, greater proliferation rate of cardiomyocytes, a lower myocyte apoptosis and reduced infarct size (Cho *et al.*, 2007)

The direct control of the injury as reactivity of endothelium towards finalized or end-stage pathology reflects an evolving form of progressiveness of the failing heart. Dysfunction of myocardial contractility may improve subsequent to progenitor cell transplantation in the left ventricle (Pelachio *et al.*, 2007). One might further re-define the basic dynamics of the injury at the level of the individual cardiomyocyte in terms of how injury can and does further transform remodelling attempts as compensated functionality of the ventricles.

Dysfunctionality of right and left ventricles is only an expressed end-point in reconstituted representation of the injury to the endothelium in the first instance.

One might view the manifestations of injury as clinical states of dysfunctionality in terms of decompensated recoverability of the individual cardiomyocyte. There evolves an injury that is further redefined as progressive transformation of morphologic phenotype and as gene expression profiles. Insulin suppresses free fatty acid, a lower vascular endothelial growth factor and matrix metalloproteinase with potential benefit to myocardium (Chaudhuri *et al.*, 2007).

Endothelial cells, vascular smooth myofibers and cardiomyocytes express functional pattern-recognition receptors that sense pathogen-associated molecular patterns as in atherosclerosis and sepsis (Mitchell *et al.*, 2007)

5. Nitric oxide action

Nitric oxide synthase appears one constitutive parameter in determining the viability mechanisms in cardiomyocyte functionality or dysfunctionality. Insulin simultaneously activates both Akt and c-Jun NH2-terminal kinase; the latter further increases the phosphorylation of Akt, which minimizes myocardial ischemia/reperfusion injury (Liu *et al.*, 2007).

The endocardial endothelial cells are a source of significant amounts of produced nitric oxide in terms especially of the targeting of cardiomyocytes by injurious agents at a capillary level.

The small contribution of inducible nitric oxide is particularly significant as represented failure of compensatory events controlling cardiac muscle growth, rhythmicity and overall global dysfunctionality.

The multiple interactivities of the various cell-signaling pathways in determining the form of an injury to the individual cardiomyocyte represent a variant re-expression of possible compensatory events as projected by progression of clinical heart failure. A transplanted heart undergoes fibrous atrophy together with apparent compensatory hypertrophy of the cardiomyocytes (Nozynski *et al.*, 2007). The invariably progressive nature of the failing heart constitutes a modelled pathway of injury both at the level of the individual cardiomyocyte and endothelial cell.

Cyclic mechanical strain induced by rhythmic contractions of myocardial fibers appears to promote cardiomyogenesis of embryonic stem cells and upregulation of cardiac gene expression (Gwak *et al.*, 2008).

The distinctive characterization of the endothelial cells constituting a spectrum of organ components of the heart spans aspects of hemodynamic stress and oxidative injury as further complied by reactivity of the

dysfunctional or activated endothelial cell in endocardium, coronary vasculature and intramyocardial capillary network.

6. Specific targeting

Specificities of targeting modalities in remodelling of heart muscle mass arise from distinctive dysfunctionalities of the blood-heart barrier. Represented injury of aggregates of cardiomyocytes further involves a transformation of repertoires of patterned reactivity of the endothelium. The concept of the pulmonary vascular endothelium as a central cellular mechanism specifically targeting the individual cardiomyocyte allows for redefinition of the various modes of possible activation of endothelial cells. Bone marrow-derived progenitor cells contribute to endothelial homeostasis, repair and angiogenesis. Cardiac pressure overload upregulates endothelial and myocardial progenitor cells (Muller *et al.*, 2008).

A ratio of endothelial-cardiomyocyte interaction promotes the progressiveness of an injury that is primarily sensed at the endocardial level.

The surprisingly high endocardial-cardiomyocyte cell ratio at the level of the right ventricle distinguishes dynamics of progression of potential injury also in the left ventricle. One might further recognize injury beyond the simple representation of onset dynamics of ischemia or of heart failure. Matrix metalloproteinase 2 may play roles at intracellular and extracellular sites in cardiac ischemia/reperfusion injury. Caveolins are lipid raft proteins involved in cell signalling (Cho *et al.*, 2007).

Barrier dynamics in hemodynamic flow of the injured state constitute an array of possible transformations of either/or viability status. An activated endothelial state is particularly suggestive of vulnerability in onset progression to a wide spectrum of injuries ranging in terms of a potentiality of functional and morphological change at the cellular level. Neuropeptide Y is involved in compensatory or detrimental remodelling of myocardial muscle subsequent to hemodynamic overload or infarction and angiogenesis (McDermott and Bell, 2007).

7. Communicability

Adhesion molecules and gap-junctional communications allow for further reconstructive pathways in compensation and potential recoverability of the individual cardiomyocyte beyond the simple characterization of the ventricular muscle mass.

There evolves an injury that schematically allows for representation not only at the cellular level but particularly at the interactive stage of the organ components of the failing heart.

During cardiac development, the epicardium gives rise to endothelial and vascular smooth myofibers and also possibly cardiomyocytes (Limana *et al.*, 2007).

Cardiac function, and also cardiac dysfunctionality in heart failure, constitute derived parameters of the intrinsic rhythmicity of cardiac contraction. Fibroblast growth factor-2 regulates contractile function of the myocardium during infarct repair (Virag *et al.*, 2007). It is beyond characterization of an injury that recurs with each cardiac contraction that there would be determined progression of the clinical heart failure. Conditioning of the injury allows for a further specified injury that is superimposed on basic dysfunctionality of the endothelium lining the endocardium and the vasculature supplying the ventricular muscle mass. Circulating endothelial progenitor cells can differentiate to express a cardiomyocyte phenotype, induced by notch signalling (Koyanagi *et al.*, 2007). The compact nature of cardiomyocyte mass helps reconstitute events as further shown by the interactivity between different compensated forms of injury.

Severity of injury specifically allows modulation of the initial transformation in clinical cardiac dysfunctional states. Endothelial mitochondria may sense levels of oxygen in the

blood and relay to cardiac myocytes to modulate also vasodilatory response mediated by endothelial nitric oxide (Davidson and Duchen, 2007).

Only in terms of how an injury develops are there evolving pathways of compromised recovery as seen particularly after a myocardial ischemic event. The heart is composed of diverse cell lineages arising apparently from a progenitor cell with vascular cardiomyocyte potential (Kattman *et al.*, 2007).

8. Dynamics of overlap

Simple dynamics of overlap of a series of injuries at the level of the individual cardiomyocyte relate particularly to transition states spanning the activated endothelial cell, on the one hand, and the dysfunctional endothelium, on the other. Macrophage colony stimulating factor induces vascular endothelial growth factor production and viability of cardiomyocytes (Okazaki *et al.*, 2007).

Contractility of the injured cardiomyocyte muscle mass of the left ventricle determines modes of progression as transformed dynamics of interchange between endothelium and various injurious events ranging from oxidative stress to ischemia and reperfusion.

There develops an individualized form of injury to cardiomyocytes that is invariably reflected in the progression of an injury primarily and constitutively patterned on the rhythmic contractility of the individual ventricles. Cardiac regeneration may result from vascular differentiation of stem cells or even from stem cell-mediated reverse remodelling (Guan and Hasenfuss, 2007).

The central sensor functionality of the pulmonary vascular endothelium allows for the development of redefined pathways as signalling and targeting events in constitutive injury to the ventricular muscle mass.

Also, it is in view of the vast array of endothelial cell component pathways that there develops a sensitive responsiveness to injury on the part of the individual cardiomyocyte.

Systemic participation of the injury is linked particularly to the neural mechanisms and to cell-to-cell communicability at the level of gap-junctions between endothelial cells or cardiomyocytes. Such a homeostatic model for the myocardium implicates various cell populations including in particular cardiac fibroblasts during development (Banerjee *et al.*, 2007).

Membrane interdigitations of the individual endothelial cells allow for a sensor functionality that further progresses as dysfunctionality of the activated endothelium.

9. Modelled injury

There evolves a modelled form of injury that spans new dynamic states of interchange between individual cardiomyocytes and as further characterized by hemodynamic stress and oxidative states of reperfusion.

One allows for the development of an injury that redefines limits of capability in terms of how an individualized target self-determines autocrine and paracrine functionality between endothelium and cardiomyocyte muscle mass of either the right or left ventricle.

The distinctiveness of the right ventricle as contrasted with the left ventricle underlines the uniqueness of the contractile state of either ventricle both in terms of delay in onset of the contraction and also as a spreading phenomenon of cardiac contraction.

Only insofar as there evolve whole schematic pathways of possible injury does the ventricular muscle mass incorporate possible extension of the modulated injury to the endothelium.

A primary consideration of the vascular bed endothelium accounts for evolving states of ischemia of the left ventricular muscle mass that implicate dominant forms of infarction progressing subsequently as possible heart failure.

10. Reactive identity

Identity of the reactive nature of the dysfunctional endothelial cell is suggestive of forms of transformation and of the basic expression of genes that allow for progression of the injured state of the targeted cardiomyocytes. Interactivity is a mode of transferred transformation that highlights injury beyond simple dynamics of prior defined pathways of cell signalling. Ontogenic hierarchies in development of the heart muscle and related endothelium are simple superimpositions of the characterized potential responsiveness to injury at the individual cell level, whether represented by the endothelial cell or the cardiomyocyte.

Ratios of interchange between endothelium and myofibers indicate a realized representation of injury beyond dynamics of simple transformation steps. Only a subset of endothelial genes is induced in cultured cardiomyocytes (Walikson *et al.*, 2007).

The dysfunctional endothelium constitutes an ill-defined group of pathologic phenotype representations that allows for progression of the injury affecting vessels, endocardium and ventricular muscle mass.

The Purkinje cells present immediately subendocardially would constitute a valid model in inter-communicability between vascular and endocardial endothelium with cardiomyocytes.

11. Cardiomyocytes

The myofibers should be viewed integrally as a ventricular muscle mass component determining responsiveness to a potentially wide variety of injuries ranging in terms particularly of the degree of oxygenation at the individual cellular level. Noncellular differentiation effects also mediate beneficial effects of transplanted stem cells (Cho *et al.*, 2007).

The evolutionary course of right ventricular sensor mechanisms within the context of a centrality for pulmonary vascular endothelium promotes further realization of a complex coupling of rhythmic contractility with subsequent diastolic filling of both ventricles. Endothelial pairing and coupled cardiomyocyte interaction permit further progression of injury beyond simple enumeration of the contraction phases of either ventricle in established cardiac action.

INTEGRAL CARDIAC FUNCTIONALITY

Integral cardiac functionality subsequently develops as a strictly derived parameter in the cooperative evolution of contraction of either ventricle in further evolution of diastolic relaxation and receptive filling of the right ventricle.

Repetitive action and reaction promote further contractility as cyclical evolution in maintaining viability of the individual cardiomyocyte. Cardiac ischemic cell death appears a regulated event (Iwase *et al.*, 2007). One can recognize a developmental reactivity as coupled endothelial-cardiomyocyte action beyond the simple realization of the contraction cycle affecting the integral cardiac muscle mass. Extracellular matrix proteins such as laminins and endothelial cells affect cardiomyocyte action but the underlying mechanisms are largely not known (Knoll *et al.*, 2007).

12. Complex profile of action and reaction

Difficulty in the delineation of a complex profile of action and reaction is manifested as onset dynamics of contraction of the integral ventricular muscle mass. The relativity of such action and reaction is primarily a function of the inter-relationship between the right and left ventricles as largely interdependent actions of the heart muscle mass.

13. Evolutionary implications

Full evolutionary implications of cardiac action allied to viability issues of individualized

ventricular contractility develop largely as realized manifestations of ischemic injury in conjunction with such parameters as essential coupling of the endothelial cell with the individual cardiomyocyte. The blood-heart barrier attests to the subsequent emergence of such coupling as dynamic interchange of the endocardial sensing and the pulmonary vascular receptivity of blood from the right ventricle.

Integral representation of cardiac muscle contractility is representative of a delay in action of the injurious agent in terms encompassing simulated or real effective consequence to ventricular ischemia.

Centrality of the pulmonary vascular endothelium is a derived phenomenon in the subsequent coordination of action of the blood-heart barrier insofar as the ischemic episodes affecting left ventricular muscle are rhythmically inter-related.

Relaxation and contraction of the individual cardiomyocyte further contribute to the remodelling of the ventricular muscle mass that is continually developed and refashioned in terms of the endothelial cell-bed perfusing the cardiac muscle.

14. Concluding remarks

Ischemic episodes affecting the myocardial muscle mass arise in strict parametric relationship to the evolving remodelling of action and reaction patterns of rhythmic contractility cycles. The evolution of the basic interactions of individual cardiomyocytes with endothelial cells comprises an integral dependence of a sensor endocardial functionality on coronary endothelial cells and intramyocardial capillary networks. It is highly significant that basic premises governing the interaction of blood supply with cardiomyocyte contractility cycling further evolve in terms of how central pulmonary endothelium controls tissue reactive patterns and endothelial-cardiomyocyte coupling.

In terms beyond delineation of right and left ventricular dysfunction or of ischemic episodes affecting cardiac contractility, there would develop a simplified, schematic representation of the injurious events as onset and progression dynamics of modelling and remodelling of blood-heart barrier function or dysfunction.

References

Banerjee I, Fuscler JW, Price RL, Borg TK and Baudino TA [2007] Determination of cell types and numbers during cardiac development in the neonatal and adult rat and mouse. Am J Physiol Heart Circ Physiol 293: H1883-1891.

Chaudhuri A, Janicke D, Wilson M, Ghanim H, Wilding GE, Aljada A, *et al.* [2007] Effect of modified glucose-insulin-potassium on free fatty acids, matrix metalloproteinase, and myoglobin in St-elevation myocardial infarction. Am J Cardiol 100: 1614-1618.

Cho HJ, Lee N, Lee JY, Choi YJ, Ii M, Wecker A, *et al.* [2007] Role of host tissues for sustained humoral effects after endothelial progenitor cell transplantation into the ischemic heart. J Exp Med 204: 3257-3269.

Cho WJ, Chow AK, Schulz R and Daniel EE [2007] Matrix metalloproteinase-2, caveolins, focal adhesion kinase and c-Kit in cells of the mouse myocardium. J Cell Mol Med 11: 1069-1086.

Davidson SM and Duchen MR [2007] Endothelial mitochondria: contributing to vascular function and disease. Circ Res 100: 1128-1141.

Di Meglio F, Nwizynska D, Castaldo C, Arcucci A, De Santo L, de Feo M, *et al.* [2007] *In vitro* progenitors and precursors of cardiac cell lineages from human normal and post-ischemic hearts. Eur J Histochem 51: 275-282.

Guan K and Hasenfuss G [2007] Do stem cells in the heart truly differentiate into cardiomyocytes. J Mol Cell Cardiol 43: 377-387.

Gwak SJ, bhang SH, Kim IK, Kim SS, Cho SW, *et al.* [2008] The effect of cyclic strain on embryonic stem cell-derived cardiomyocytes. Biomaterials 29: 844-856.

Iliodromitis EK, Lazou A and Kremastinos DT [2007] Ischemic preconditioning: Protection against myocardial necrosis and apoptosis. Vasc Health Risk Manag 3: 629-637.

Iwase H, Robin E, Guzy RD, Mungai PT, vanden Hoek TL, Chandel NS, *et al.* [2007] Nitric oxide during ischemic attenuates oxidant stress and cell death during ischemia and reperfusion in cardiomyocytes. Free Radic Biol Med 43: 590-599.

Jiang W, Hall SR, Moos MP, Cao RY, Ishii S, Oganyankin KO, *et al.* [2008] Endothelial cysteinyl leukotriene-2 receptor expression mediates myocardial ischemia-reperfusion. Am M Pathol 172: 592-602.

Kattman SJ, Adler ED and Keller GM [2007] Specification of multipotential cardiovascular progenitor cells during embryonic stem cell differentiation and embryonic

development. Trends Cardiovasc Med 17: 240-246.

Knoll R, Postel R, Wang J, Kratzner R, Hennecke G, Vacaru AM, *et al.* [2007] Laminin-alpha 4 and integrin-linked kinase mutations cause human cardiomyopathy via simultaneous defects in cardiomyocytes and endothelial cells. Circulation 116: 515-525.

Koyanagi M, Bushoven P, Iwasaki M, Urbich C, Zeiher AM and Dimmeler S [2007] Notch signaling contributes to the expression of cardiac markers in human circulating progenitor cells. Circ Res 101: 1139-1145.

Limana F, Zacheo A, Mocini D, Mangoni A, Borsellino G, Diamantini A, *et al.* [2007] Identification of myocardial and vascular precursor cells in human and mouse epicardium. Circ Res 101: 1255-1265.

Liu HT, Zhang HF, Si R, Zhang QJ, Zhang KR, Guo WY *et al.* [2007] Insulin protects isolated hearts from ischemia/reperfusion injury: cross-talk between PI3-K/Akt and JNKs. Sheng Li Xue Bao 59: 651-659.

McDermott BJ and Bell D [2007] NPY and cardiac diseases. Curr Top Med Chem 7: 1692-1703.

Mitchell JA, Ryffel B, Quesniaux VF, Cartwright N and Paul-Clark M [2007] Role of pattern-recognition receptors in cardiovascular health and disease" Biochem Soc Trans 35(Pt 6): 1449-1452.

Muller P, Kazakow A, Semenov A, Bohm M and Laufs U [2008] Pressure-induced cardiac overload induces upregulation of endothelial and myocardial progenitor cells. Cardiovasc Res 77: 151-159.

Nozynski J, Zakliczynski M, Zembala-NozynskiE, Konecka-Mrowka D, Przybylski R, Nikiel B, *et al.* [2007] Remodeling of human transplanted myocardium in ten-year follow-up: a clinical pathology study. Transplant Proc 39: 2833-2840.

Okazaki T, Ebihara S, Asada M, Yamanda S, Saijo Y, Shiraishi Y, *et al.* [2007] Macrophage colony-stimulating factor improves cardiac function after ischemic injury by inducing vascular endothelial growth factor production and survival of cardiomyocytes. Am J Pathol 171: 1093-1103.

Pelacho B, Nakamura Y, Zhang J, Ross J, Heremans Y, Nelson-Holte M, *et al.* [2007] Multipotent adult progenitor cell transplantation increases vascularity and improves left ventricular function after myocardial infarction. J Tissue Eng Regen Med 1: 51-59.

Ribe' D, Sawbridge D, Thakur S, Hussey M, Ledent C, Kitchen I, Hourani S and Li JM [2008] Adenosine A 2A2 receptor signalling regulation of cardiac NADPH oxidase activity. Free Radic boil Med 44: 1433-1442.

Robey TE and Murry CE [2008] Absence of regeneration in the MRL/Mp J mouse heart following infarction or cryoinjury. Cardiovasc Pathol 17: 6-13.

van Amerougen MJ, Harmsen MC, Petersen AH, Popa ER and van Luyn MJ [2008] Cryoinjury: a model of myocardial regeneration. Cardiovasc Pathol 17: 23-31.

Virag JA, Rolle ML, Reece J, Hardouin S, Feigel EO and Murry CE [2007] Fibroblast growth factor-2 regulates myocardial infarct repair: effects on cell proliferation, scar contraction, and ventricular function. Am J Pathol 171: 1431-1440.

Welikson RE, Kaestner S, Evans AM and Hauschka SD [2007] Embryonic cardiomyoccyte expression of endothelial genes. Dev Dyn 236: 2512-2522.