BASIC SCIENCE REVIEW

MYOCYTE CONTRACTILE DYSFUNCTION WITH HYPERTROPHY AND FAILURE: RELEVANCE TO CARDIAC SURGERY

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Despite significant improvements in the intraoperative management of patients undergoing cardiac surgery, postoperative left ventricular (LV) pump dysfunction occurs and often requires inotropic and/or vasodilator therapy. This LV pump dysfunction can contribute to a complex postoperative course.^{1,2} It is likely that the number of cardiac surgical procedures, such as coronary artery bypass grafting (CABG), will increase in the future due to several factors. First, the relative number of patients surviving an initial myocardial infarction and the relative proportion of elderly patients have both increased and therefore may ultimately require CABG.³ The purpose of this review is to place these conditions in the context of cardiac surgery with particular emphasis on the ischemia/reperfusion injury that may occur during the intraoperative period. Although a number of systemic and neurohormonal factors clearly influence LV pump function and hemodynamics in the postoperative setting, this review will focus on basic systems within the cardiac myocyte that are altered in hypertrophy and/or failure, which may in turn influence contractility in the perioperative setting. This review will be a structure-function presentation in which the myocyte will be dissected into key structural components that are directly related to contractile performance.

Sarcolemmal systems

The sarcolemma contains channels and energy-dependent pumps that play a fundamental role in both the gen-

eration of the action potential and excitation-contraction coupling. The most common electrophysiologic abnormality is a prolongation of the action potential. A representative action potential from a normal and failing human myocyte is shown in Fig 1. Membrane repolarization is initiated by the K⁺ efflux of the delayed rectifier current, which is later joined by an additional outward K⁺ current to return the sarcolemma to the resting membrane potential.⁴ The prolongation of the action potential with hypertrophy and/or failure is likely due to alterations in key sarcolemmal channels and currents that contribute to the action potential repolarization. Specifically, the delayed rectifier current, which is directly responsible for repolarization, is reduced in myocardial hypertrophy^{5,6} and has been associated with a prolongation of the action potential.^{7,8} With the use of gene transfection techniques, enhanced production of K⁺ channels that contribute to the delayed rectifier current has been shown to correct action potential prolongation.⁹ This observation supports the ionic basis for changes in action potential morphology, including defects in K⁺ currents that are operable during action potential repolarization. The prolongation of the action potential in hypertrophy and/or failure may result in early depolarization, which may create a re-entry circuit, thereby promoting arrhythmias.^{10,11} The Na⁺/K⁺ adenosine triphosphatase (ATPase), which contributes to the maintenance of the resting action potential, is altered in severe hypertrophy and/or failure¹²⁻¹⁴ and may contribute to a more positive and unstable resting potential. These molecular defects that contribute to changes in the action potential with hypertrophy and/or failure may have particular relevance to the development of ventricular arrhythmias after cardiac operations.¹⁵

Excitation-contraction coupling

Normal myocyte contraction depends on a highly organized sequence of molecular and mechanical events between the sarcolemma, the sarcoplasmic reticulum (SR), and the contractile apparatus. After sarcolemmal

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Fig 1. The action potential (*left panels*) and transient outward K^+ current (*right panels*) of normal (*top*) and failing (*bottom*) human ventricular myocytes. A common abnormality associated with myocyte hypertrophy and/or failure is a prolongation of the action potential. The transient outward K^+ current density (I_{to}) was reduced in failing human myocytes. A reduction in key K^+ currents involved in sarcolemmal repolarization likely contributes to action potential prolongation in hypertrophy and/or failure. V , Voltage; pA/pF , picoamps/picofarads. (From Tomaselli GF, Beuckelmann DJ, Calkins HG, Berger RD, Kessler PD, Lawrence JH, et al. Sudden cardiac death in heart failure: the role of abnormal repolarization. *Circulation* 1994;90:2534-9. Reprinted with permission of Lippincott Williams & Wilkins.)

depolarization, the L-type Ca^{2+} channel becomes activated, resulting in a Ca^{2+} current across the sarcolemma, which activates the calcium release channels of the SR, as shown in Fig 2. After calcium release channel activation, a bolus release of Ca^{2+} from the SR engages the myofilament apparatus, resulting in sarcomere shortening. The return to resting sarcomere length is an energy-dependent process that has been termed active relaxation.⁴ Active relaxation primarily consists of the re-uptake of intracellular Ca^{2+} by SR Ca^{2+} ATPase (SERCA-2), thus reducing the concentration of intracellular Ca^{2+} . For the purposes of this review, specific alterations in excitation-contraction coupling that occur in hypertrophy and/or failure will be divided into two events: contraction and active relaxation.

Contraction. Since Ca^{2+} influx through the L-type Ca^{2+} channel is the initial trigger for excitation-contraction coupling, a defect in function and/or density will alter myocyte contractility.^{16,17} Accordingly, the function of the L-type Ca^{2+} channel has been the focus of several investigations.¹⁷⁻²⁰ The majority of these studies have reported a reduction in L-type Ca^{2+} current and/or channel density in hypertrophied and/or failing myocytes. For example, Mukherjee and associates¹⁶ reported a decrease in L-type Ca^{2+} current that was associated with intrinsic defects in contractile function

with the development of pacing-induced heart failure. The peak levels of Ca^{2+} released into the cytosolic compartment have been demonstrated to be decreased in severe hypertrophy and/or failure.²¹ The Ca^{2+} discharged from the SR binds to troponin C, resulting in conformation changes of the contractile apparatus. These changes allow for myofilament cross-bridge formation and, thus, myocyte shortening. A decrease in SR Ca^{2+} release would inhibit the ability of the myofilament apparatus to undergo the conformational changes necessary for cross-bridge formation. Second, the absolute reduction of Ca^{2+} will result in a diminished number of cross-bridges formed during a contractile cycle, leading to diminished contractile force generation. Several mechanisms may be responsible for the reduced release of Ca^{2+} . First, there appears to be a reduction in the trigger Ca^{2+} current marked by L-type Ca^{2+} channel dysfunction. Second, SR calcium release channels appear to be reduced^{22,23} or dysfunctional^{24,25} in severe hypertrophy and/or failure. A summary of the alterations in Ca^{2+} dynamics that occur in myocyte hypertrophy and/or failure appears in Fig 2.

The fundamental contractile unit of the myocyte is the sarcomere. The sarcomere is composed of actin and myosin filaments, tropomyosin, and the troponin complex: troponin C, troponin I, and troponin T. Although a

Fig 2. A schematic of key alterations that can contribute to abnormal excitation-contraction coupling in the hypertrophied and/or failing myocyte. In the normal myocyte (*left*), sarcolemmal depolarization results in a trigger Ca^{2+} (I_{Ca}) current through the L-type channel, which activates a bolus release of Ca^{2+} from the SR calcium release channels (CRC). The increased cytosolic Ca^{2+} causes conformational changes in the myofilament apparatus, which results in cross-bridge formation and sarcomere shortening. Active relaxation consists of Ca^{2+} re-uptake into the SR by SR Ca^{2+} ATPase (SERCA-2). The rate of SR Ca^{2+} uptake is influenced by the SERCA-2 regulatory protein phospholamban (PLB). Cytosolic Ca^{2+} concentrations can be further reduced through the slower actions of the sarcolemma $\text{Na}^+/\text{Ca}^{2+}$ exchanger and a sarcolemmal Ca^{2+} ATPase (not shown). Alterations in the expression and/or function of key components of the excitation-contraction coupling process may affect Ca^{2+} handling and homeostasis with severe hypertrophy and/or failure (*right*). There is a reduction in the L-type Ca^{2+} current and/or expression, which can result in a blunted trigger Ca^{2+} current and thereby reduce the release of Ca^{2+} through the CRC. A reduction in SERCA-2 expression and function have been reported in severe hypertrophy and/or failure, which would result in two consequences. First, a reduction in SERCA-2 would result in a reduced capacity for SR Ca^{2+} re-uptake. Second, stoichiometric alterations between SERCA-2 and PLB would result in reduced SERCA-2 sensitivity to Ca^{2+} . The slowed removal of Ca^{2+} from the intracellular compartment would result in an increase in diastolic Ca^{2+} . Furthermore, the $\text{Na}^+/\text{Ca}^{2+}$ exchanger is up-regulated, presumably as a compensatory mechanism (albeit slower) to remove cytosolic Ca^{2+} levels.

myosin isoform switch was previously considered to occur only in animal models of failure,²⁶⁻²⁹ a recent study has identified that it occurs in the failing human myocyte. Specifically, Lowes and associates³⁰ have reported a reduction in the expression of the cardiac specific α -myosin heavy chain coupled with a reciprocal increase in the expression of the β -myosin heavy chain in severe hypertrophy and failure.³⁰ The β isoform of the myosin heavy chain causes a slower velocity of shortening when compared with the α -myosin heavy chain.³¹ Therefore, these changes in myosin heavy chain expression with severe hypertrophy and/or failure may directly contribute to alterations in LV ejection performance. Although there appears to be no change in cardiac troponin I in the setting of hypertrophy and/or failure, its

presence in the serum has been used as a marker for acute myocardial ischemia.³² Interestingly, it appears that CABG coupled with cardiopulmonary bypass can be associated with the release of cardiac troponin I.³³ The transient loss of troponin I in cardiac myocytes after CABG may further exacerbate contractile dysfunction in the setting of hypertrophy and/or failure.

While studies regarding the contractile apparatus in the setting of severe hypertrophy and/or failure are currently ongoing, in general terms the myofilament apparatus appears to be structurally intact. In contrast, the intracellular environment that surrounds the contractile elements is substantially abnormal in the setting of hypertrophy and/or failure and is likely to be a major contributory cause of LV contractile dysfunction.

Fig 3. Intracellular free Ca^{2+} levels of normal myocytes before and after simulated hyperkalemic cardioplegic arrest and rewarming. Intracellular Ca^{2+} levels increased from baseline as cardioplegic arrest was induced, and the increase persisted through the early reperfusion period. The increased intracellular Ca^{2+} induced by the depolarizing cardioplegic arrest may have particular relevance in the setting of hypertrophy and/or failure. (From Dorman BH, Hebbar L, Clair MJ, Hinton RB, Roy RC, Spinale FG. Potassium channel opener-augmented cardioplegia: protection of myocyte contractility with chronic left ventricular dysfunction. *Circulation* 1997;96[9 Suppl]:II253-9. Reprinted with permission of Lippincott Williams & Wilkins.)

Active relaxation. The resequestration of Ca^{2+} into the SR occurs primarily through the actions of SERCA-2 and the influence of the regulatory protein phospholamban. The regulatory influence of phospholamban on SERCA-2 is dependent on the phosphorylation state. When phosphorylated, phospholamban enhances SERCA-2 Ca^{2+} affinity and uptake, whereas dephosphorylated phospholamban diminishes SERCA-2 Ca^{2+} function. Defects in the resequestration of Ca^{2+} into the SR have been clearly identified in severe hypertrophy and/or failure, which is manifested by increased intracellular diastolic Ca^{2+} .³⁴⁻³⁷ At the myocardial level, defects in Ca^{2+} homeostasis will result in a slowed LV myocardial relaxation. Furthermore, defects in SR Ca^{2+} re-uptake would result in increased diastolic Ca^{2+} concentrations, which, in turn, cause decreased sensitivity of the contractile apparatus to intracellular Ca^{2+} concentrations. Alterations in Ca^{2+} resequestration that occur in severe hypertrophy and/or failure are likely due to several factors. The majority of studies have reported decreased protein expression and/or function of SERCA-2 in severe hypertrophy and/or failure.³⁸⁻⁴² For example, Hasenfuss and associates⁴¹ reported a 36% reduction in SERCA-2 protein levels in the failing human myocardium. In a recent study by Dillman,⁴³

cardiac myocytes were transfected with DNA for SERCA-2, which resulted in increased synthesis and protein levels. The enhanced protein expression of SERCA-2 in this study increased Ca^{2+} re-uptake.⁴³ This in vitro study emphasizes the importance of the loss of expression and function of SERCA-2 on Ca^{2+} homeostasis. Although it appears that SERCA-2 is reduced in severe hypertrophy and/or failure, the changes in the regulatory protein phospholamban appear to be more complex. In animal models of hypertrophy and failure, a reduction in the expression of phospholamban has been documented.⁴⁴ In human studies, a reduction in messenger RNA (mRNA) phospholamban levels has been reported,^{39,45,46} but absolute protein levels appear to be unchanged in severe hypertrophy and/or failure.^{39,46,47} This may represent an imbalance in the transcription and/or translation rates of phospholamban in severe hypertrophy and/or failure. Nevertheless, if SERCA-2 levels decrease without a comparable change in phospholamban expression, alterations in the stoichiometry between these proteins can result. Using transfection techniques, Hajjar and colleagues⁴⁸ over-expressed the phospholamban protein in cardiac myocytes. The increased ratio of phospholamban to SERCA-2 resulted in slowed Ca^{2+} re-uptake into the

SR and increased resting Ca^{2+} concentrations. These studies demonstrate the importance of the phospholamban/SERCA-2 stoichiometric relationship in maintaining SR Ca^{2+} re-uptake and intracellular Ca^{2+} concentrations, a relationship that may be altered in the setting of severe hypertrophy and/or failure.

The slower $\text{Na}^+/\text{Ca}^{2+}$ exchanger also participates in the extrusion of cytosolic Ca^{2+} during active relaxation. There appears to be up-regulation of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger gene expression and activity in hypertrophy and/or failure.⁴⁹⁻⁵² The up-regulation of this protein may initially serve as a compensatory mechanism resulting from the reduction of SERCA-2 function. This may eventually result in an overall reduction in the amount of cytosolic Ca^{2+} available for SR uptake and subsequent release for excitation-contraction coupling.

SR re-uptake of cytosolic Ca^{2+} is an energy-dependent process.⁴ Therefore increased intracellular Ca^{2+} levels will require increased hydrolysis of ATP for resequestration and maintenance of a normal resting cytosolic Ca^{2+} concentration. In hypertrophied myocardium, reduced basal levels of high-energy phosphates such as ATP have been reported.⁵³ This reduction in intrinsic levels of high-energy phosphates will also impede energy-dependent resequestration of Ca^{2+} and thereby cause increased cytosolic Ca^{2+} levels in hypertrophy and/or failure.⁵⁴ Hypothermic, hyperkalemic cardioplegic arrest is associated with an increase in intracellular Ca^{2+} .⁵⁵⁻⁵⁷ For example, in an in vitro model of cardioplegic arrest and rewarming, increased intracellular Ca^{2+} levels have been recorded, which persisted in the early reperfusion period (Fig 3).⁵⁵ Furthermore, additional studies with cardioplegic arrest and rewarming have reported a prolongation of the isovolumic pressure decline,^{58,59} indicative of abnormalities in myocyte active relaxation. Thus conventional cardioplegic arrest may alter Ca^{2+} homeostatic mechanisms, which can persist in the early reperfusion period. These alterations in Ca^{2+} homeostasis may exacerbate pre-existing abnormalities in severe hypertrophy and/or failure which, in turn, would contribute to LV dysfunction in the early postoperative period.

Myocyte receptor systems

A number of sarcolemmal receptor systems are affected with the development of hypertrophy and/or failure.⁶⁰⁻⁶² This review will focus on the prototypical β -adrenergic receptor (β -AR) system as it is the receptor system most often pharmacologically manipulated in the early postoperative setting. Under ideal circumstances, intracellular phosphorylation targets after β -AR stimulation are the L-type Ca^{2+} channel, phospholamban, and troponin I of the contractile apparatus.

Thus alteration in the expression, function, and/or activation of the β -AR system will influence key components of the excitation-contraction coupling process, thereby affecting myocyte contractile function. In hypertrophy and/or failure, a decrease in β -AR density has been reported. For example, Bristow and associates⁶³ reported a 62% reduction of the β_1 receptor subtype in failing human myocardium. This may be in response to a persistent elevation of circulating catecholamines that can occur in the latter stages of hypertrophy and/or failure.^{64,65} In addition, there appears to be a reduction in the ability of existing β_1 receptors to respond to circulating catecholamine levels.⁶⁶⁻⁶⁸ This has been defined as receptor desensitization.⁶⁹⁻⁷¹ This desensitization of available β_1 receptors appears to be multifactorial, which includes alterations both at the level of the receptor and at intracellular transduction pathways. Seconds to minutes after β -AR exposure to receptor agonist, phosphorylation of the β -AR by receptor-associated kinases may occur, resulting in receptor uncoupling.^{66,69,72} A further downstream mechanism for alterations in β -AR signaling is likely to be due to alterations in the guanine nucleotide-dependent coupling protein (G protein). Although studies do not report a change in the density of the stimulatory G protein in severe hypertrophy and/or failure,⁷³⁻⁷⁵ studies have shown an increase in the density of the inhibitory G protein⁷⁶⁻⁷⁸ that would result in a reduction of adenylate cyclase activity. In addition, an apparent desensitization of adenylate cyclase has been reported, which would further diminish β -AR-mediated contractility.⁷⁹ Thus, although a number of defects exist in the β -AR with severe hypertrophy and/or failure, the end result will be diminished cyclic adenosine monophosphate production which, in turn, will influence contractile performance in the setting of hypertrophy and/or failure.

Increased sympathetic activity and the resultant increase in plasma catecholamines commonly occurs in the cardiac surgical setting and may contribute to β -AR desensitization.⁸⁰⁻⁸² Using atrial myocardial specimens, Booth and colleagues⁸³ reported diminished adenylate cyclase activity after cardiopulmonary bypass with β -AR stimulation. In an isolated myocyte system of hyperkalemic cardioplegic arrest, reduced contractile response to the β -AR system has been demonstrated after reperfusion and rewarming.^{55,84} A representative contraction profile of isolated myocytes under normothermic conditions and after simulated cardioplegic arrest is shown in Fig 4. Although exposure to the β -receptor agonist isoproterenol resulted in an overall increase in myocyte contractility, this response was blunted after cardioplegic arrest and rewarming. This is indicative of

Fig 4. A representative contractile profile of a control myocyte under normothermic conditions (*left panel*) and after cardioplegic arrest (*right panel*). Myocytes were stimulated at 1 Hz by means of methods described previously.^{16,55,84} In normothermic control myocytes, a robust increase in contractile performance was observed after β -receptor stimulation. After hypothermic, cardioplegic arrest, steady-state myocyte contractility was reduced in comparison with normothermic control conditions. Furthermore, β -adrenergic stimulation after cardioplegia resulted in a blunted contractile response. These results indicate alterations in the β -adrenergic signaling pathway after hypothermic cardioplegic arrest. Thus the reduction in the β -adrenergic response that may exist in hypertrophied and/or failing myocardium may be heightened and/or exacerbated in the cardiac surgical setting.

a reduction in β -AR response to receptor stimuli. Thus the diminished β -AR response that may exist in patients with pre-existing hypertrophy and/or failure may be further reduced in the setting early after cardiac surgery.

Myocyte cytoskeleton

The extramyofibrillar cytoskeleton of the myocyte provides a structural framework for myofibrillar assembly and contributes to sarcomere alignment and the transduction of sarcomere shortening into overall myocyte shortening. The cytoskeletal network ranges from the largest components, microtubules (25 nm), to endosarcomeric proteins at a size of 2 nm. It has been demonstrated that increased β -tubulin occurs in the hypertrophied myocyte isolated from patients and animal models of severe pressure overload in the adult.⁸⁵ This increase in microtubule density has been reported with severe hypertrophy to be a compensatory response for heightened stress placed on the myocardium. Furthermore, the increased density of the microtubule network within the myocyte may actually impair contractile performance in hypertrophy and/or failure.^{86,87} These studies have provided evidence that increased microtubule network density could cause a viscous resistive load impeding sarcomere shortening. Indeed,

maneuvers that alter microtubule stability at the level of the isolated myocyte influence contractility. For example, when microtubules are depolymerized in pressure-overload hypertrophy, contractility returns to normal.⁸⁵ Of interest, hypothermic exposure caused microtubule reorganization in hypertrophied and normal myocytes, which affects contractile function.⁸⁶ When pressure-overloaded myocytes were exposed to profound hypothermic conditions, microtubule depolymerization occurred. With subsequent warming, the contractile function of the hypertrophied myocytes was normalized, indicative of an improvement in contractile function (Fig 5). Thus hypothermia and cardioplegic arrest in hypertrophied myocardium may influence microtubule stability and thereby contractile performance with reperfusion and rewarming. However, these issues remain speculative and warrant further study.

Congestive heart failure

Congestive heart failure (CHF) is a constellation of signs and symptoms including peripheral and pulmonary edema, fatigue on minimal exertion, and shortness of breath. CHF is an insidious disease process that progresses over time and, therefore, should be considered a chronic disease state. After an initial myocardial

Fig 5. The effects of hypothermia on the extent (*top*) and velocity (*bottom*) of sarcomere shortening in normal left ventricular (LV) and hypertrophied right ventricular (RV) feline cardiac myocytes. After hypothermic exposure ($<10^{\circ}\text{C}$) and rewarming, the extent and velocity of sarcomere shortening in hypertrophied myocytes was normalized. These changes are associated with alterations in cytoskeletal tubulin polymerization. PA, Pulmonary artery. (Reprinted with permission from Tsutsui H, Ishihara K, Cooper G IV. Cytoskeletal role in the contractile dysfunction of hypertrophied myocardium. *Science* 1993;260:682-7, copyright 1993 American Association for the Advancement of Science.)

insult, mechanisms are invoked that attempt to compensate for the intrinsic decline in LV myocardial contractility. Early compensatory symptoms may be minimal or nonexistent in these initial stages of the CHF process. However, sustained activation of these compensatory mechanisms can actually contribute to and/or accelerate the progression of CHF. One of the more notable compensatory response mechanisms in the CHF process is the activation of neurohormonal axes.⁸⁸⁻⁹⁰ These include the sympathetic adrenergic system, the renin-angiotensin-aldosterone system, and the endothelin system.

Activation of the sympathetic adrenergic system is a hallmark feature of disease progression in CHF.⁹¹⁻⁹³ In the initial stages of CHF, increased catecholamine pro-

duction has been postulated to serve as a compensatory mechanism for the intrinsic reduction in LV myocardial contractile performance. Plasma catecholamines rise in a temporal manner in CHF, and significantly elevated levels have been shown to be a prognostic index of disease severity and progression.^{94,95} For example, a relationship exists between plasma catecholamines and survival.^{96,97} Prolonged exposure to elevated plasma catecholamines and, in turn, chronic activation of the β -AR system can result in a number of deleterious consequences. As discussed earlier in this review, sustained β -AR activation can result in β -AR desensitization and subsequent down-regulation of the β_1 receptor.⁶⁶⁻⁷¹ The effects of sympathetic adrenergic activation may contribute to LV myocardial remodeling and hypertrophy and, therefore, structurally contribute to CHF. In addition, excessive local production and/or release of norepinephrine concentrations can be deleterious to cardiac myocyte viability. Isolated cardiac myocyte studies have shown concentration-dependent effects of norepinephrine on cell death possibly through apoptosis.^{98,99} Finally, the activation of the sympathetic adrenergic system enhances the production and release of other potent vasoactive peptides, particularly angiotensin II and endothelin-1.^{96,100}

Since increased sympathetic adrenergic activity was viewed as an appropriate compensatory mechanism, early attempts were made to augment these effects through direct activation of the β -AR by oral agonists or phosphodiesterase inhibitors, which increased the levels of circulating adenosine monophosphate.^{101,102} The rationale was to increase intrinsic myocardial contractility and thereby improve overall LV ejection performance. Short-term treatment with β -AR agonists or phosphodiesterase inhibitors resulted in an improvement in LV function and symptoms.¹⁰³ However, these effects lessened as treatment continued, and long-term clinical trials demonstrated increased mortality after several months of therapy.^{104,105} These observations led to the hypothesis that overstimulation of the β -AR system may be deleterious and that β -AR blockade may be beneficial. This concept emerged slowly since it appeared counterintuitive to inhibit a mechanism that positively influenced myocardial contractility.¹⁰⁶ In fact, the acute response after initiation of a β -AR antagonist was the predicted negative inotropic effect and transient worsening of CHF symptoms.¹⁰⁷ However, studies have demonstrated that long-term treatment with β -AR antagonists resulted in improved LV ventricular function, as well as reduced mortality.¹⁰⁸ Most recently, the nonselective β -AR antagonist carvedilol has been approved for the treatment of mild to moderate CHF.¹⁰⁹⁻¹¹¹ In addition to directly demonstrating

that prolonged sympathetic activation contributes to the CHF process, the institution of β -AR antagonists in the pharmacologic armamentarium of patients with CHF may present a new challenge in intraoperative management after cardiac surgery.

Activation of the renin-angiotensin-aldosterone system is also a hallmark of severe chronic CHF.¹¹² Renin cleaves the angiotensin proform, angiotensinogen, to angiotensin I. Angiotensin II is then formed through the cleavage of angiotensin I by angiotensin-converting enzyme, or ACE. Angiotensin II acts both as a direct vasoconstrictor of vascular smooth muscle cells and in conjunction with the sympathetic adrenergic system to increase vascular tone.¹¹³⁻¹¹⁵ Angiotensin II can cause increased circulating volume through fluid and sodium retention.^{113,116,117} Finally, angiotensin II appears to have trophic and mitogenic effects at the cellular level.^{118,119}

In patients with CHF who have systolic dysfunction, the administration of ACE inhibitors reduces afterload and LV wall stress.¹²⁰⁻¹²³ These beneficial loading effects of ACE inhibition result in increased LV ejection performance. ACE inhibitors also promote sodium excretion through the reduction in aldosterone and vasopressin production. In addition, ACE inhibitors may influence myocardial remodeling by blocking the mitogenic effects of angiotensin II on cardiac myocytes and fibroblasts.¹²⁴⁻¹²⁷ Several clinical CHF trials have demonstrated that ACE inhibition reduced overall mortality, primarily through a reduction in the progression of the CHF disease process.¹²⁸⁻¹³¹ Thus ACE inhibition provides beneficial effects on LV function and myocardial remodeling and has become the standard of treatment for patients with CHF.

In patients with CHF, aldosterone levels may increase by over 20-fold compared with normal levels.¹³² A recent clinical study examined the effects of the aldosterone receptor antagonist, spironolactone, in the setting of CHF.¹³³ The results from this study demonstrated an additive beneficial effect when spironolactone was used in conjunction with standard ACE inhibitor therapy.¹³³ Thus new pharmacologic strategies are becoming available that can selectively modulate specific neurohormonal receptor systems and may have particular relevance in patients presenting with severe hypertrophy and/or CHF for cardiac surgery.

The endothelins are a family of bioactive peptides consisting of three isoforms: endothelin-1, endothelin-2, and endothelin-3, with endothelin-1 being the most potent and biologically active.¹³⁴ Specifically, through the activation of the endothelin A receptor subtype, endothelin-1 can cause significant and prolonged constriction of vascular smooth muscle.¹³⁵ Thus endothelin-1 is involved in the regulation of systemic and

pulmonary vascular resistance properties. The vasoconstrictive properties of endothelin-1 are exemplified by clinical studies that have demonstrated that endothelin-1 receptor blockade significantly reduces systemic vascular resistance in hypertension.¹³⁶ Moreover, the profound effects of endothelin-1 with respect to pulmonary vascular resistance were demonstrated by the involvement of this bioactive peptide in the setting of primary pulmonary hypertension.¹³⁷ In the setting of CHF, endothelin-1 production is increased and, as such, has been implicated to directly contribute to the progression and/or exacerbation of the disease process.¹³⁸ In fact, a nonselective endothelin receptor antagonist, bosentan, has been successfully used in patients with CHF, resulting in a reduction in systemic and pulmonary vascular resistance.^{139,140}

Endothelin-1 receptor stimulation activates a number of intracellular signaling pathways that continue to be an area of active investigation.¹⁴¹⁻¹⁴⁴ The downstream events of endothelin-1 stimulation with respect to the myocyte are likely to involve activation the Na^+/H^+ exchanger as well as several Ca^{2+} regulatory processes.¹⁴⁵⁻¹⁴⁷ The end result of endothelin-1 receptor stimulation in normal myocytes is an increase in contractile performance. However, in the context of LV failure, endothelin-1 receptor activation results in a reduction in contractility.^{148,149} The negative inotropic effects of endothelin-1 with pre-existing LV failure is likely the result of the exacerbation of intrinsic defects in Ca^{2+} homeostasis. Thus, in patients with CHF admitted for cardiac surgery, the systemic and myocardial effects of endothelin-1 may have particular importance.

Future directions

An important consideration in preventing further alterations in ionic currents and Ca^{2+} homeostatic mechanisms in the hypertrophied and/or failing myocardium would be to alter extracellular stimuli that could influence these intracellular processes. For example, the institution of cardiopulmonary bypass results in the activation of several neurohormonal systems, including the sympathetic adrenergic system, as well as the synthesis of bioactive peptides that persist in the postoperative period.¹⁵⁰⁻¹⁵² Heightened sympathetic adrenergic activity and the resulting release of catecholamines with respect to the effects on the β -AR system have been discussed earlier in this review. With respect to bioactive peptides, plasma levels of endothelin-1 have been shown to be increased during cardiopulmonary bypass, and these elevations persist into the postoperative period.¹⁵² Thus, in patients with pre-existing hypertrophy and/or CHF, increased endothelin-1 levels in the setting of cardiopulmonary bypass may directly contribute to LV

myocardial dysfunction by direct negative inotropic effects. More recently, endothelin-1 receptor antagonists have been developed and successfully used in patients with LV pump dysfunction.^{153,154} Thus new pharmacologic strategies are becoming available which can selectively modulate specific receptor systems that may have particular relevance in patients presenting for cardiac surgery with severe hypertrophy and/or CHF.

Summary

As the number of patients with pre-existing myocardial hypertrophy and/or CHF increases, the elucidation of mechanisms that potentially contribute to LV dysfunction after cardiac surgery is warranted. The results from recently performed studies, some of which have been reviewed here, suggest that underlying contributory factors for the exacerbation of LV dysfunction in patients with pre-existing hypertrophy and/or failure in the postoperative cardiac setting are changes in ionic currents and Ca^{2+} homeostasis. Therefore strategies that are focused on these ionic defects in LV hypertrophy and/or failure may have therapeutic benefit in the cardiac surgical setting. For example, the induction of myocardial electrical quiescence and cardioplegic arrest has been successfully achieved through the use of potassium channel openers that maintain the negative resting membrane potential of the myocyte.⁵⁵ In isolated myocyte systems, the use of potassium channel openers has been demonstrated to prevent intracellular Ca^{2+} accumulation during the cardioplegic arrest period, which translated into reduced cytosolic Ca^{2+} levels with reperfusion and rewarming.⁵⁵ Furthermore, the use of potassium channel openers in the intact LV has been demonstrated to maintain indices of LV ejection performance with reperfusion and rewarming in the setting of cardiopulmonary bypass.¹⁵⁵ Thus strategies that facilitate cardioplegic arrest without detrimental effects on ionic currents and intracellular Ca^{2+} dynamics may have important implications with pre-existing LV hypertrophy and/or failure.

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