The protective effects of exercise and phosphoinositide 3-kinase (p110α) in the failing heart

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ABSTRACT

Despite the development of a wide range of therapies, heart failure remains a leading cause of death in Western society. New therapies are needed to help combat this debilitating condition. Exercise is becoming an increasingly important feature of rehabilitation programmes for patients with heart failure. Before the 1980s, patients with heart failure were advised not to exercise as it was thought that exercise would increase the risk of a cardiac event (such as myocardial infarction). However, in recent years both aerobic and resistance training have been shown to be safe and beneficial for patients with heart failure, improving exercise tolerance and quality of life, and preventing muscular deconditioning. The molecular mechanisms responsible for exercise-induced cardioprotection are yet to be elucidated, however studies in transgenic mice have identified PI3K(p110α) (phosphoinositide 3-kinase p110α) as a likely mediator. PI3K(p110α) is a lipid kinase which is activated in the heart during chronic exercise training, and is important for maintaining heart structure and function in various pathological settings. In the present review the protective effects of PI3K(p110α) in the failing heart and its potential as a therapeutic strategy for the treatment of heart failure is discussed.

INTRODUCTION

HF (heart failure) is a debilitating condition in which the ability of the heart to meet systemic demands for oxygenated blood is compromised. Mortality rates due to HF have declined over the past few decades [1] due to better awareness and treatment of risk factors (such as hypertension [2,3]), and the development of pharmacological agents [4–6] and implantable devices [7]. However, HF still carries a high risk of mortality: more than one in three patients die within a year of diagnosis [8–10]. Given that the incidence of HF is predicted to rise over the next two decades (owing to an aging population and increased survival rates following MI (myocardial infarction) [11,12]), it is imperative to investigate new therapies for the prevention and treatment of HF.

The benefits of regular physical activity in the prevention of CVD (cardiovascular disease) are well

Key words: cardiac hypertrophy, exercise, heart failure, phosphoinositide 3-kinase (PI3K), protection.

Abbreviations: ACEI, ACE (angiotensin-converting enzyme) inhibitor; AngII, angiotensin II; ANP, atrial natriuretic peptide; ARB, AT1 (AngII type 1) receptor blocker; BNP, brain natriuretic peptide; CVD, cardiovascular disease; DCM, dilated cardiomyopathy; EF, ejection fraction; ET-1, endothelin-1; GLUT-4, glucose transporter-4; GPCR, G-protein-coupled receptor; HF, heart failure; IGF-1, insulin-like growth factor-1; LV, left ventricular; MAPK, mitogen-activated protein kinase; MHC, myosin heavy chain; MI, myocardial infarction; NEFA, non-esterified fatty acid; NFAT, nuclear factor of activated T-cells; PI3K, phosphoinositide 3-kinase; caPI3K, constitutively active mutant of PI3K(p110α); dnPI3K, dominant-negative mutant of PI3K(p110α); PIP3, phosphatidylinositol 3,4,5-trisphosphate; SERCA2a, sarcoplasmic/endoplasmic reticulum Ca2+-ATPase; peak VO2, peak oxygen consumption.

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established [13–16]; however, it was only in the 1990s that exercise training began to be implemented, in conjunction with other therapies, in the rehabilitation of patients with HF (see [17]). Exercise training has been shown to lower blood pressure in people with hypertension [18,19], and improves peak VO2 (peak oxygen consumption) and quality of life in patients with HF (see [20]). Although some of the beneficial effects of exercise can be explained by changes to the vasculature and skeletal muscle [21,22], evidence from animal models indicates that exercise training also exerts beneficial effects on the heart, by attenuating LV (left ventricular) remodelling processes such as pathological hypertrophy and fibrosis [23], increasing the oxidative capacity of the myocardium [24], and promoting cardiomyocyte survival [25]. Some of the cardioprotection induced by exercise may be due to activation of an enzyme known as PI3K(p110α) (phosphoinositide 3-kinase p110α). PI3K(p110α) is a lipid kinase that is activated in the heart during chronic exercise training [26], and is important for maintaining heart structure and function in pathological settings such as pressure overload and DCM (dilated cardiomyopathy) [23]. The present review discusses the effects of exercise training in patients with HF and outlines the role of PI3K(p110α) in mediating exercise-induced cardioprotection. The potential of PI3K(p110α) as a therapeutic strategy in the treatment of HF is also discussed. We begin with an overview of the pathophysiology of HF.

**HEART FAILURE**

Chronic HF is characterized by diminished cardiac output and/or pooling of blood in the venous system [27]. Progressive loss of cardiac function causes pulmonary congestion and peripheral oedema, which can lead to the decomposition of organs such as the lungs and kidney. Patients with HF suffer from a range of symptoms, including lack of energy, breathlessness, dry mouth, drowsiness, numbness or tingling in the hands and feet, insomnia, cough, anorexia, anxiety and depression [28]. These symptoms contribute to the reduced quality-of-life experienced by patients with moderate-to-severe HF.

HF is associated with structural and metabolic remodelling. LV remodelling is a maladaptive process which alters the structure of the myocardium via cardiomyocyte hypertrophy, increased interstitial fibrosis and cardiomyocyte apoptosis (Figure 1). LV remodelling occurs in a number of pathological settings, such as MI, hypertension, valvular heart disease and cardiomyopathies [29], and contributes to the progressive deterioration of LV function associated with chronic HF (see [30]). HF is also associated with alterations in myocardial energetics (such as shifts in substrate utilization, depletion of high-energy phosphate stores and decreased oxidative phos-
following stimulation by hormones such as AngII (angiotensin II), ET-1 (endothelin-1) and catecholamines (see [46] for a detailed review). Activation of GPCRs results in a number of downstream signalling events, such as activation of MAPKs (mitogen-activated protein kinases) (e.g. ERK1/2 (extracellular-signal-regulated kinase 1/2), JNK (c-Jun N-terminal kinase) and p38 MAPK; see [47]) and dephosphorylation of NFAT (nuclear factor of activated T-cells) transcription factors by calcineurin [48]. Current pharmacological approaches for HF target hypertrophic signalling pathways by blocking the interaction between pathological hypertrophic agonists and their receptors, or by preventing the formation of AngII (see the section ‘Current treatments for HF’ below).

**Interstitial fibrosis**

Interstitial fibrosis refers to the accumulation of collagen between cardiomyocytes. Collagen is an important structural component of the extracellular matrix, forming a fibrous network around the muscle cells of the heart (see [49]). However, increased levels of interstitial collagen (due to increases in collagen synthesis and/or decreases in collagen degradation) are detrimental for heart function, distorting tissue structure and causing mechanical stiffness [42,50]. Increased interstitial fibrosis has been observed in numerous pathological settings such as hypertension [51] and cardiomyopathies [52], and is present in the failing heart. *In vitro* studies have demonstrated that AngII stimulates collagen synthesis in cardiac fibroblasts [53], indicating that the hypertrophic agonist AngII is also involved in the regulation of fibrosis (Figure 2).

**Cardiomyocyte apoptosis**

The role of cardiomyocyte apoptosis in the progression of HF is controversial. Numerous studies have reported increased levels of apoptosis in cardiac tissue following MI and in the failing heart (see [54,55]); however some researchers have questioned the methods used to detect apoptosis, and whether the low levels of apoptosis reported actually contribute to the progressive loss of cardiac function in HF [56]. In 2003, Hayakawa et al. [57] showed that treating transgenic mice with a caspase inhibitor reduced cardiomyocyte death and ameliorated contractile dysfunction associated with peripartum cardiomyopathy. Furthermore, low levels of cardiomyocyte apoptosis were sufficient to cause LV dilation and contractile dysfunction (i.e. DCM) in transgenic mice expressing a cardiac-specific constitutively active form of caspase 8 [58]. These studies support the hypothesis that the slow chronic loss of cardiomyocytes via apoptosis contributes to the pathogenesis of HF (Figure 1).

**Metabolic remodelling**

In addition to structural remodelling, the failing heart undergoes several changes in myocardial energetics (see [31,32] for detailed reviews). For example, in the normal adult heart NEFAs (non-esterified fatty acids; ‘free fatty acids’) are the preferred substrate for the generation of...
ATP. During the early stages of HF NEFA oxidation decreases, while glucose metabolism appears to increase [31]. This switch in substrate utilization is an adaptive response to increase the efficiency of ATP production (as more ATP is produced per atom of oxygen used; see [59]). However, in advanced HF there is a shift from glucose metabolism to fatty acid metabolism as the heart becomes resistant to insulin [31]. Impaired glucose uptake may contribute to cardiac dysfunction via its effects on excitation–contraction coupling (see [60]), while the return to NEFA oxidation leads to increased oxygen consumption and decreased cardiac efficiency [59].

**EXERCISE TRAINING IN PATIENTS WITH HF**

Numerous studies have demonstrated that regular exercise training improves exercise tolerance and quality-of-life in patients with stable chronic heart failure (e.g. [73–80]; see [20] for a critical review). Exercise intolerance is a hallmark of chronic HF, and contributes to the reduced quality-of-life experienced by patients with moderate-to-severe HF [28]. The physiological and biochemical mechanisms responsible for exercise intolerance are still being elucidated. Traditionally, reduced exercise tolerance in HF patients was attributed to LV dysfunction; however, there appears to be little correlation between peak VO\textsubscript{2} (an index of exercise tolerance) and EF (ejection fraction; an index of LV function) in patients with HF [81,82]. Exercise intolerance appears to derive mainly from changes to the vasculature and skeletal muscle, such as a shift in the proportion of slow-twitch type I to fast-twitch type II muscle fibres [83,84], a reduction in oxidative enzyme activity (see [85]), a decrease in the number of capillaries surrounding each muscle fibre [83,86] and loss of skeletal myocytes via apoptosis [87]. Exercise training improves exercise tolerance by reversing these alterations, i.e. by improving peripheral blood flow and skeletal muscle oxidative metabolism (see [22]).

There is evidence that exercise training also exerts positive effects on the heart. In 2003, Giannuzzi et al. [88] showed that regular aerobic exercise training attenuated LV remodelling and improved EF in patients with stable chronic HF [88]. Animal studies have shown that exercise training prior to cardiac insult reduces infarct size and improves LV function following MI [89,90], and prevents apoptosis in mouse hearts subjected to ischaemia/reperfusion injury [91]. Exercise training prolonged survival in mice with DCM [23] and in hypertensive HF rats [92], and improved LV function in transgenic mice that develop heart failure due to a lack of α\textsubscript{2A}- and α\textsubscript{2C}-adrenoceptors [93]. Furthermore, mild exercise training reversed the pathological cardiac phenotype associated with a mouse model of hypertrophic cardiomyopathy [94]. As mentioned previously, dephosphorylation of NFAT transcription factors by calcineurin contributes to pathological hypertrophic responses. Exercise training reduced NFAT activity in the hearts of mice with hypertrophic cardiomyopathy [94], indicating that exercise training can exert direct beneficial effects on the heart. A large component of the protection induced by exercise is due to adaptations within the heart [25,95], i.e. independent of exogenous influences from the blood or other adaptations within the body [95]. Recent studies in rodents suggest that exercise-induced cardioprotection may be due to activation of an enzyme known as PI3K(p110α) [23,90]. The following section outlines the roles of PI3K(p110α) signalling in the heart, and possible mechanisms by which PI3K(p110α) protects the failing heart.
PI3Ks

PI3Ks catalyse the phosphorylation of phosphoinositides at the 3′ position of the inositol ring, and have been implicated in a wide range of biological functions including cell growth, differentiation, survival and migration, glucose homeostasis and immunity (see [96] for a detailed review). There are three classes of PI3K (classes I–III). Class I is further divided into two subclasses, IA and IB. PI3K(p110α) is a class IA PI3K. Class IA PI3Ks consist of a catalytic subunit (p110α, β or δ) and a regulatory subunit (p85, p55 or p50). The regulatory subunit recruits the catalytic subunit to the plasma membrane by binding to phosphotyrosine residues in the intracellular domain of receptor tyrosine kinases, such as the IGF-1 receptor (Figure 3). This brings the catalytic subunit into proximity with lipid substrates in the plasma membrane and results in the generation of second messengers such as PIP3 (phosphatidylinositol 3,4,5-trisphosphate) (Figure 3). Class IB PI3K(p110γ), is recruited to the plasma membrane by binding to the βγ subunits of dissociated Gq proteins following stimulation of GPCRs. Activation of PI3K(p110γ) is detrimental for heart function [97], reducing cardiac contractility [98] and promoting internalization of β-adrenergic receptors [99]. In the present review we have focused on the actions of PI3K(p110α).

EXERCISE-INDUCED HEART GROWTH IS MEDIATED BY PI3K(p110α)

As noted above, PI3K(p110α) lies downstream of receptor tyrosine kinases such as the IGF-1 receptor. Stimulation of IGF-1 receptors by IGF-1, a peptide hormone released during exercise [100], induces physiological cardiac hypertrophy via activation of PI3K(p110α) [43–45] (Figures 2 and 3). Consistent with these findings, cardiac formation of IGF-1, but not of AngII or ET-1, was elevated in athletes compared with healthy men [100], indicating that physiological hypertrophy is mediated by different hormones to pathological hypertrophy. As mentioned previously, physiological hypertrophy maintains or enhances heart function in the absence of fibrosis or cell death, unlike pathological hypertrophy which is detrimental for heart function [33].

Studies in transgenic mice expressing a constitutively active or dominant-negative mutant of PI3K(p110α) (caPI3K and dnPI3K respectively) have helped to identify the role of PI3K(p110α) signalling in the heart. In these mice, the modified PI3K genes are under the control of the α-MHC promoter, which drives transgenes exclusively in cardiomyocytes [43]. Under basal conditions, caPI3K mice display a 6.5-fold increase in cardiac PI3K(p110α) activity which is associated with a 20% increase in heart size. dnPI3K mice have a 77% reduction in cardiac PI3K(p110α) activity, which corresponds to a 20% decrease in heart size [43]. Importantly, PI3K transgenic mice show no signs of pathology under basal conditions [43,44]. The first strong evidence that PI3K(p110α) mediates the effects of exercise came from a study which showed that decreasing cardiac PI3K(p110α) activity (i.e. in dnPI3K mice) attenuated exercise-induced hypertrophy [44]. The role of PI3K(p110α) as a critical mediator of physiological hypertrophy was confirmed in 2005, when Luo et al. [101] demonstrated that mice lacking the p85 subunit of PI3K(p110α) had a reduced heart size under basal conditions and exhibited a blunted hypertrophic response to chronic exercise training.
Proposed roles of PI3K(p110α) (Figures 2 and 4).

**PROTECTIVE EFFECTS OF PI3K(p110α) IN THE FAILING HEART**

Chronic swim training prolonged survival in a mouse model of DCM [23]. The increased lifespan of the exercised DCM mice was attributed to activation of cardiac PI3K(p110α), as increasing PI3K(p110α) activity in the hearts of DCM mice (by crossing DCM mice with caPI3K transgenics) had the same effect as swim training (∼20% increase in lifespan). In contrast, reducing cardiac PI3K(p110α) activity (by crossing DCM mice with dnPI3K mice) dramatically accelerated the progression of HF, confirming that PI3K(p110α) is important for maintaining heart structure and function in a setting of DCM.

PI3K(p110α) appears to protect the heart in settings of disease by attenuating LV remodelling processes such as pathological hypertrophy and fibrosis. Aortic banding is a surgical technique used to induce pathological hypertrophy in mice [102]. Aortic banding caused a 40% increase in heart size in non-transgenic mice, but only a 17% increase in caPI3K mice and an 80% increase in dnPI3K mice [23]. dnPI3K mice exhibited severe lung congestion and LV dysfunction after 1 week of pressure overload, while caPI3K mice maintained good cardiac function [23]. The exaggerated hypertrophic response in mice with reduced cardiac PI3K(p110α) activity and the suppressed hypertrophic response in mice with elevated cardiac PI3K(p110α) activity suggests that activation of PI3K(p110α) maintains cardiac function in settings of disease by attenuating pathological heart growth (Figures 2 and 4).

Histological analysis revealed that mice with reduced cardiac PI3K(p110α) activity had higher levels of interstitial fibrosis [23]. Microarray analysis confirmed that the expression of fibrotic genes such as procollagen, fibronectin and fibrillin was elevated in banded dnPI3K mice and reduced in banded caPI3K mice (compared with banded non-transgenic mice) [23], suggesting that PI3K(p110α) is a negative regulator of fibrosis (Figure 4).

Banded dnPI3K mice also had higher levels of foetal gene expression compared with non-transgenic mice [23]. Re-expression of foetal genes such as ANP (atrial natriuretic peptide) and BNP (brain natriuretic peptide), β-MHC and α-skeletal actin is a key characteristic of pathological, but not physiological, cardiac hypertrophy [44,103,104]. It is thought that up-regulation of foetal genes is part of the response of the heart to stress [105–107], thus higher levels of foetal gene expression are indicative of greater cardiac stress. Swim training reduced the expression of ANP, BNP and α-skeletal actin in mice with DCM [23], and aerobic exercise training reduced BNP expression [as well as expression of the pathological hypertrophic agonist noradrenaline (norepinephrine)] in patients with HF [108], indicating that exercise training reduces cardiac stress associated with disease. Whether this protection is due to increased cardiac PI3K(p110α) activity is yet to be determined, as banded caPI3K mice had lower levels of ANP compared with dnPI3K mice, but similar levels of BNP expression and higher levels of α-skeletal actin [23].

Down-regulation of SERCA2a is another feature of pathological hypertrophy that contributes to LV dysfunction (see [109]). Constitutive activation of PI3K(p110α) attenuated the drop in SERCA2a expression in mice subjected to aortic banding [23]. Exercise-induced improvements in cardiac function in mouse and dog models of HF were associated with normalization of calcium-handling proteins such as SERCA2a [93,110]. Furthermore, increasing SERCA2a protein levels improved cardiac function in rats subjected to pressure overload [111] and in pigs with HF [112], suggesting that the restoration of SERCA2a expression in caPI3K mice subjected to aortic banding contributes to the maintenance of heart function in these mice.

PI3K(p110α) may also protect the failing heart via inhibition of apoptotic pathways. *In vitro* studies have shown that PI3K promotes cell survival via activation of its downstream effector, Akt (also known as protein kinase B) [113–115] (Figure 3). Recently, Zhang et al. [90] showed that chronic exercise training reduced infarct size and inhibited cardiomyocyte apoptosis in rats subjected to myocardial ischaemia/reperfusion injury, and that treatment with a PI3K inhibitor prior to reperfusion reversed the effects of exercise training. This study provides evidence for the anti-apoptotic effects of PI3K in settings of cardiac stress.

Finally, activation of PI3K(p110α) might protect the heart via effects on myocardial energetics. As noted previously, early stages of HF are associated with a shift from NEFA oxidation to glucose metabolism. This is an adaptive response which helps the stressed heart produce ATP more efficiently [59]. Inhibition of glucose uptake and metabolism in settings of cardiac stress (i.e. insulin resistance) is detrimental for heart function, and is likely to contribute to HF [59]. Chronic swim training
improved insulin-stimulated glucose uptake in rat heart and this was associated with increased translocation of GLUT-4 (glucose transporter-4) to the plasma membrane [116]. GLUT-4 lies downstream of PI3K/Akt [117] and exercise-induced improvements in insulin sensitivity were blocked with the PI3K inhibitor LY294002 [116], implicating PI3K in exercise-induced sensitization of the myocardium to insulin (Figure 3).

In the healthy mouse heart, acute insulin-induced PI3K activation increases glucose utilization and reduces fatty acid oxidation [118]. In contrast, chronic activation of PI3K(p110α) (i.e. in the hearts of capPI3K mice) enhances the fatty acid oxidative capacity of the heart (although this was accompanied by increases in glucose oxidation and glycolysis) [119]. Further investigation into the role of PI3K(p110α) in myocardial energetics is needed, as increasing glucose metabolism and enhancing myocardial sensitivity to insulin have been identified as potential targets for the metabolic modification of insulin resistance in HF [32].

In summary, PI3K(p110α) activation is important for maintaining heart structure and function in settings of CVD. PI3K(p110α) protects the heart by attenuating LV remodelling processes such as pathological hypertrophy, fibrosis and apoptosis (Figure 4). Further investigation into the protective effects of PI3K(p110α) signalling in the failing heart may lead to the development of new therapies for the treatment of HF.

**THERAPEUTIC POTENTIAL OF PI3K(p110α)**

Despite the range of drugs available for the treatment of HF, complications frequently arise. HF patients commonly present with comorbidities such as hypertension, chronic renal disease, diabetes, osteoarthritis (in the elderly) and anaemia, which increases the potential for drug intolerance and incompatibility [120]. Long-term use of diuretics can lead to drug resistance and reduced renal perfusion [121], while the use of β-blockers, ACEIs and ARBs can lead to hypotension, worsening renal function and hyperkalaemia [61]. There is a clear need for new therapeutic strategies for the treatment of HF.

Activation of PI3K(p110α), via exercise training or pharmacological approaches, offers a novel therapeutic strategy for preventing LV remodelling in patients at risk of developing HF. While ACEIs and ARBs slow LV remodelling by targeting pathological hypertrophy signalling pathways, activation of PI3K(p110α) attenuates LV remodelling by activating physiological hypertrophy signalling pathways as well as inhibiting pathological signalling pathways (Figures 2 and 4). Pharmacological agents designed to activate PI3K(p110α) would need to be cardiac-specific, as PI3K is ubiquitously expressed and plays an important role in cell growth and differentiation in numerous cell types. Hyperactivation of PI3K [due to mutations in the PI3K regulator, PTEN (phosphatase and tensin homologue deleted on chromosome 10)] has been shown to contribute to tumorigenesis [122] and the gene encoding PI3K(p110α) is mutated in various forms of cancer [123–125]. Cardiac-specific activation of PI3K(p110α) might be achieved using a gene-therapy approach. Gregorevic et al. [126] have developed a technique for delivering genes to the myocardium using AAV (adeno-associated viral) vectors.

Pharmacological agents targeting PI3K would also need to be isoform-specific. Although activation of class IA PI3Ks (i.e. p110α and p110β) is beneficial in settings of disease, activation of the class IB PI3K(p110γ) is detrimental for heart function [97]. PI3K(p110γ) is a negative regulator of cardiac contractility [98,127] and may contribute to the progression of HF by promoting internalization of β-adrenergic receptors [99].

**SUMMARY**

Chronic HF remains a leading cause of death in Western society. Chronic exercise training has direct beneficial effects on the heart. PI3K(p110α) is a signalling protein that is activated in the heart during chronic exercise training, and protects the heart in settings of disease by attenuating LV remodelling processes such as hypertrophy, fibrosis and apoptosis. Activation of PI3K(p110α) may prove to be a novel therapeutic strategy for the treatment of chronic HF.

**FUNDING**

Work in the author’s laboratory is supported by the National Health and Medical Research Council of Australia [grant numbers 367600, 317835] and the National Heart Foundation of Australia [grant number CR 04M1716]. L.P. and K.L.O. are supported by Australian Postgraduate Awards and Baker Foundation Postgraduate Awards.

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Received 2 June 2008/31 July 2008; accepted 11 August 2008
Published on the Internet 2 February 2009, doi:10.1042/CS20080183