Exploration of Medicine

Open Exploration

Open Access Review

Involvement of protein kinases associated signal transduction mechanisms in cardiac diseases

Jaykrishan Prasad[1], Anureet K. Shah[2], Naranjan S. Dhalla[1,3]*

[1]Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, MB R2H 2A6, Canada
[2]School of Kinesiology, Nutrition and Food Science, California State University, Los Angeles, CA 90032, USA
[3]Department of Physiology and Pathophysiology, Max Rady College of Medicine, University of Manitoba, Winnipeg, MB R3E 3P5, Canada

***Correspondence:** Naranjan S. Dhalla, Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, MB R2H 2A6, Canada. nsdhalla@sbrc.ca
Academic Editor: Akiko Mammoto, Medical College of Wisconsin, USA
Received: July 1, 2023 **Accepted:** September 18, 2023 **Published:** December 8, 2023

Cite this article: Prasad J, Shah AK, Dhalla NS. Involvement of protein kinases associated signal transduction mechanisms in cardiac diseases. Explor Med. 2023;4:923–41. https://doi.org/10.37349/emed.2023.00185

Abstract

Protein kinases, a family of enzymes responsible for regulating various cellular processes, have been implicated in the development and progression of various heart diseases, making them attractive therapeutic targets. This review focuses on the role of protein kinases induced phosphorylation and protein phosphatase-induced dephosphorylation in cardiovascular disorders, including heart failure, ischemic heart disease, arrhythmias, hypertension, and diabetic cardiomyopathy. This paper explores the potential of novel kinase-targeted therapies and emerging technologies for the prevention and treatment of these conditions. It also discusses the involvement of protein kinase A (PKA), protein kinase C (PKC), phosphoinositide 3-kinases (PI3Ks), mitogen-activated protein kinases (MAPKs), and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) in heart dysfunction and alterations in their function that contribute to their respective cardiac disorders. Furthermore, this article presents a comprehensive overview of protein kinases in cardiac disorders and the potential of innovative kinase-targeted therapies, advanced technologies, and multidisciplinary approaches for the effective prevention and treatment of cardiovascular diseases, ultimately aiming to improve patient outcomes and quality of life.

Keywords

Protein kinases, heart failure, myocardial infarction, atherosclerosis, arrhythmias, hypertension, diabetic cardiomyopathy

Introduction

Protein kinases are highly regulated enzymes that are capable of adding phosphate groups to their substrates for phosphorylation in an adenosine triphosphate (ATP)-dependent fashion [1]. The enzymes such as protein kinase A (PKA), Ca^{2+}/calmodulin-dependent protein kinase (CaMK), protein kinase C (PKC), phosphoinositide 3-kinase (PI3K), and mitogen-activated protein kinase (MAPK) are involved in

augmenting various cellular and metabolic activities in both healthy and ailing cardiac conditions [2, 3]. These kinases have been shown to play a role in the development of heart failure, cardiac hypertrophy, myocardial infarction, and diabetic cardiomyopathy [2, 3]. Inhibition of these kinases has been reported to improve cardiac function, making them viable targets for drug development; however, the effects of these pathways depend on the duration and strength of the stimulus, as well as the type of kinase isoform [4, 5]. One such example is PKC-β inhibition by the drug ruboxistaurin, which not only was observed to reduce diastolic dysfunction and myocyte hypertrophy but was also shown to maintain contractility in diabetic cardiomyopathy [4]. Furthermore, it demonstrated the capacity to mitigate pathological fibrosis and alleviate impaired cardiac function subsequent to myocardial infarction [4]. It is therefore important to consider that cardiac protein kinases derived from different sources may not account for the specific kinases expressed in cardiomyocytes; however, some novel kinases have been identified which could serve as potential therapeutic targets for failing human hearts [3]. Another example in this regard is related to the activation of MAPK in response to diverse extracellular stimuli and the involvement in both cell growth and cell death as well as in both ischemia-reperfusion injury and cardioprotection due to ischemic preconditioning [5]. It was pointed out that the complexities involved in understanding the role of MAPK in both cardiac physiological and pathophysiological processes are due to the presence of several members of the MAPK family and their isoforms, which show different activation/inactivation characteristics, as well as differences in the signal transduction pathways in response to various extracellular stimuli [5]. In fact, the spectrum of various kinases expressed in cardiomyocytes has been categorized, and it has been suggested that understanding the input of several kinases into the cardiomyocyte signaling network is essential for fine-tuning therapeutic approaches for heart disease [3, 4].

Generally, protein kinases are composed of a catalytic subunit and a regulatory subunit, and exist in a dormant state unless activated by a regulatory stimulus [6]. In addition, up to 50 gene products lack important catalytic residues and are thus referred to as protein pseudokinases [6]. There are 518 members of the human protein kinase gene family and 106 pseudogenes (genes that do not code for proteins) while phosphorylating these proteins can enhance or decrease enzyme catalysis and change other internal regulation such as transcription and/or translation [7]. Furthermore, kinases and pseudokinases can interact allosterically with other proteins and add an important regulatory feature to the protein kinase family group [7]. These enzymes require a divalent cation such as Mg^{2+} for their reaction to occur, and the phosphorylation sites on a protein can be stimulatory or inhibitory [7]. As such, protein kinases are known to play a vital role in many cellular processes, such as metabolism, transcription, cell division, and movement, programmed cell death, and immune response, as well as nervous system function [7].

It is now well established that various protein kinases are intimately involved during the activation of a wide variety of signal transduction pathways by both extracellular stimuli and intracellular stresses for modifying the structure and function of the heart [3, 5, 8–15]. The extracellular mechanical signals include ventricular stretch and an increase in ventricular wall tension due to pressure or volume overload whereas the extracellular chemical signals include various hormones such as norepinephrine, angiotensin II (AngII), endothelin-1, insulin, and adrenomedullin as well as other growth factors. On the other hand, the intracellular stress signals for the activation of some protein kinases include hydrogen peroxide (H_2O_2), inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), peroxisome proliferator-activated receptor-α (PPAR-α) and G-protein coupled estrogen receptor beta (G-ERβ). It is pointed out that several protein kinases including PKA, PKC, CaMK, P13K, and MAPK have two or more isoforms with some overlapping characteristics but distinct biological functions [3, 5, 12–20]. General characteristics of some protein kinases and their involvement in some cardiovascular functions in health and disease are depicted in Table 1 [21–33]. Furthermore, these protein kinases have been shown to exert both beneficial and detrimental effects depending upon the intensity and duration of the stimulus as well as the isoform of the kinase involved in the process of signal transduction. Since most protein kinases are activated during the development of different types of cardiovascular diseases, the beneficial effects of their inhibition in some cardiovascular pathologies are shown in Table 2 [11, 34–41]. Although some activators and several inhibitors for each of these protein kinases have been identified, none of these agents are

specific in nature because of the presence of various isoforms of each enzyme in the myocardium [2–8]. It is also noteworthy that different protein phosphatases have been reported to be present in the heart and are involved in dephosphorylating the phosphorylated target sites as a consequence of each protein kinase [2–5]. In fact, the process of dephosphorylation by protein phosphatases is considered to regulate and maintain the balance of phosphorylation activity of protein kinases in health and disease [42–44]. Some protein phosphatases, extracellular, and intracellular activators as well as inhibitors for different protein kinases are shown in Table 3 [2, 3, 5, 7, 16, 45–47].

Table 1. Protein kinases and their general functions

Kinases	Function in the heart	Activation mechanism	Common heart problems	Alteration of protein kinase function
PKA	Regulates cation channels, intracellular Ca^{2+} handling, and contractility [21]	Activated by β-adrenergic receptor signaling and cAMP production [22]	Heart failure, arrhythmias	Prolonged activation due to sympathetic nervous system activity; can contribute to cardiac dysfunction [22]
PKC	Regulates cation channels, contractility, and gene expression [23]	Activated by various signaling molecules such as AngII [24]	Heart failure, arrhythmias, cardiomyopathy	Increased activation due to various signaling molecules such as AngII; can contribute to cardiac dysfunction [25]
PI3Ks	Regulates cardiac hypertrophy, angiogenesis, and glucose metabolism [26]	Signaling molecules including growth factors and cytokines [26]	Coronary artery disease, heart failure, cardiomyopathy	Increased activation due to various signaling molecules such as growth factors and cytokines; can contribute to cardiac dysfunction [27]
MAPKs	Regulates cardiac hypertrophy, inflammation, and apoptosis [28]	Activated by various signaling molecules including growth factors and cytokines [29]	Coronary artery disease, heart failure, cardiomyopathy	Increased activation due to various signaling molecules such as oxidative stress and inflammation; can contribute to cardiac dysfunction [30]
CaMKII	Regulates ion channels, intracellular Ca^{2+} handling, and gene expression [31]	Activated by increases in intracellular Ca^{2+} levels [32]	Heart failure, arrhythmias, myocardial infarction	Increased activation due to various signaling molecules such as β-adrenergic receptor signaling and changes in intracellular Ca^{2+} levels; can contribute to cardiac dysfunction and arrhythmias [33]

cAMP: cyclic adenosine monophosphate

Table 2. Pathologies of the heart and how protein kinases are involved

Ailment	Mechanism of heart dysregulation	Protein kinases affected	Drug effects on protein kinases	Heart problem alleviation
Heart failure	Impaired contractility, Ca^{2+} handling, and gene expression [34]	PKA, PKC, CaMKII [34]	Inhibition of protein kinases [35]	Improved contractility and relaxation, reduced heart rate and blood pressure [36, 37]
Ischemic heart disease	Reduced blood flow to the heart, oxidative stress, and inflammation [38]	PKC [39]	Vasodilation, reduced oxygen demand [40]	Improved blood flow and decreased ischemia-induced damage [41]
Atherosclerosis	Plaque buildup in arteries, inflammation, and oxidative stress [39]	PKC, MAPKs, NF-κB [11]	Lowering of cholesterol and lipid levels, anti-inflammatory effects [41]	Improved endothelial function [11]
Arrhythmias	Abnormal heart rhythms and altered ion channel function [40]	PKA, PKC, CaMKII [34]	Inhibition of protein kinases [35]	Improved ion channel function and rhythm control [40]
Diabetic cardiomyopathy	Altered glucose and lipid metabolism, and oxidative stress [41]	PKC, Akt, PKD [41]	Improved glucose and lipid metabolism, reduced oxidative stress [41]	Improved cardiac function [41]
Hypertension	High blood pressure and increased cardiac workload [38]	PKC, CaMKII [11]	Inhibition of protein kinases, reduced cardiac workload and blood pressure [11]	Reduced blood pressure, improved cardiac function [11]

NF-κB: nuclear factor kappa B; Akt: protein kinase B; PKD: protein kinase D

In this review, it is planned to discuss the role of various protein kinases and their associated phosphorylation activities in maintaining cardiovascular function in both health and disease. In particular, the regulatory role of some protein kinases such as PKA, CaMK, PKC, PI3K, and MAPK in modifying diverse

Table 3. Activators, inhibitors, and respective phosphatases for protein kinases

Kinases	Activators	Inhibitors	Phosphatases
PKA	Norepinephrine, epinephrine, isoproterenol, vasopressin, cAMP [2, 3, 16]	Compound H89, compound KT572-2A, protein kinase inhibitor peptide [2, 3, 16]	Protein phosphatase-2A [2, 3, 16]
PKC	Norepinephrine, AngII, 5-hydroxytryptamine, endothelin, DAG [2, 3, 7]	Breviscapine, chelerythrine, ruboxistaurin, compound Gö 6983 [2, 3, 45]	Protein phosphatase-1 (PHLPP) [7, 45]
PI3Ks	Catecholamines, PPARα, G-ERβ [3, 7]	Wortmannin [3, 7]	PIP3-PTEN [3, 7, 46]
MAPKs	TNF-α, IL-1 (for p38 MAPK), growth factors, PMA (for ERK1/2) [2, 3, 5]	Compound 5820580, compound 58202190, compound FR167653 (for p38 MAPK) [2, 3, 5]	MKP-1 [2, 3, 5]
CaMKII	Ca^{2+}-calmodulin [31, 32, 47]	Compound KN93 [31, 32, 47]	Calcineurin [31, 32, 47]

PHLPP: PH domain and leucine rich repeat protein phosphatase 1; DAG: diacylglycerol; PIP3: phosphatidylinositol 3,4,5-trisphosphate; PTEN: phosphatase and tensin homolog; PMA: phorbol 12-myristate 13-acetate; ERK1/2: extracellular signal-regulated protein kinase 1 and 2; MKP-1: MAPK phosphatase-1

subcellular functions in the heart will be emphasized. Some general characteristics of these protein kinases will also be described to identify them as targets for drug development for the improvement of heart function in cardiovascular disorders. Furthermore, the involvement of different protein kinases in some diseases such as heart failure, atherosclerosis, myocardial infarction, ischemia-reperfusion injury, arrhythmias, hypertension, and diabetic cardiomyopathy will be indicated to describe their functional significance. In addition, this paper will highlight recent advancements in gene therapy, stem cell-based disease modeling, tissue engineering, and regenerative medicine approaches for the treatment of heart disease, involving protein kinases as targets. There is also an emphasis on the importance of early detection and prevention strategies, including the application of artificial intelligence, machine learning, wearable devices, and precision medicine for personalized therapeutic interventions. Thus, this article is intended to provide an updated state of knowledge concerning the role of some protein kinases in the pathogenesis and therapeutics of cardiovascular disease.

Protein kinases and signal transduction pathways

PKA is a member of the human protein kinase gene family [8] which was the first protein kinase discovered as a part of the cascade/signaling pathway for catalyzing the phosphorylation of phosphorylase kinase [9]. Phosphorylation and dephosphorylation processes are one of the major ways by which proteins are regulated and serve an important role in the signal transduction pathways of PKA [10]. The activity of these proteins is regulated by the interconversion of two forms of a molecule, one of which is phosphorylated and the other is dephosphorylated [47]. The interconversion of these two forms is controlled by a protein kinase that is activated by a ligand namely cAMP [48]. This process is reversible, allowing for the rapid and efficient transduction of signals [49]. The signal transduction pathway of PKA in the heart involves the activation of β-adrenergic receptors by catecholamines (such as epinephrine and norepinephrine) [22]. This triggers the dissociation of G proteins, which then activates adenylyl cyclase to produce cAMP [50]. Increased cAMP levels activate PKA, which in turn phosphorylates downstream targets including L-type Ca^{2+} channels, ryanodine receptors (RyRs), and phospholamban [21]. This results in an increase in Ca^{2+} influx into the cell, release of Ca^{2+} from the sarcoplasmic reticulum, and enhanced uptake of Ca^{2+} into the sarcoplasmic reticulum. The elevated cytoplasmic Ca^{2+} levels also activate the thin filament via troponin C, which then leads to contraction of the heart muscle [51]. Other protein kinases namely protein kinase G and Akt have been suggested to be involved in signal transduction for cardioprotection by nitric oxide [52, 53]. Accordingly, cyclic guanosine monophosphate (cGMP) formed upon stimulation of guanylate cyclase by nitric oxide, activates protein kinase G for activating big conductance potassium channels in mitochondria. Such an effect of nitric oxide on mitochondria is associated with reduced production of reactive oxygen species and activation of cardioprotective Akt as well as ERK1/2. Such a mechanism is consistent with the view that different protein kinases exert their actions by affecting different targets in the heart.

PKC is a family of phosphotransferases that are involved in a wide range of physiological processes including differentiation, proliferation, membrane transport, and gene expression [23]. This group of

kinases is activated by DAG produced in response to agonist-induced hydrolysis of inositol phospholipids [54]. It is capable of translocating to the plasma membrane or cytoplasmic organelles, or even the nucleus, upon cellular activation [55]. The signal transduction pathway of PKC in the heart involves the activation of G protein-coupled receptors (GPCRs) by various stimuli, such as hormones or neurotransmitters [24]. This leads to the activation of phospholipase C, which cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) into DAG and inositol 1,4,5-trisphosphate (IP3) [56]. DAG, together with Ca^{2+}, activates PKC, which phosphorylates downstream targets such as L-type Ca^{2+} channels, phospholamban, and RyRs similar to PKA [57]. This results in an increase in Ca^{2+} influx into the cell, release of Ca^{2+} from the sarcoplasmic reticulum, and enhanced uptake of Ca^{2+} into its lumen. The elevated cytoplasmic Ca^{2+} also activates thin filaments via troponin C, leading to heart muscle contraction [25].

The signal transduction pathway of CaMK in the heart involves the binding of Ca^{2+} to calmodulin (protein that binds Ca^{2+}) and activates CaMK [47]. The activated CaMK also phosphorylates various targets which include L-type Ca^{2+} channels, phospholamban, and sarco/endoplasmic reticulum Ca^{2+}-adenosine triphosphatase (SERCA) [31]. This results in an increase in Ca^{2+} influx into the cell, as well as release from the sarcoplasmic reticulum, and enhanced uptake of Ca^{2+} into this membrane tubule network [32]. High cytoplasmic Ca^{2+} levels cause troponin C to activate the thin filament, leading to contraction of the heart. It is important to mention that CaMK also has non-contractile functions in cardiac muscle, such as regulating gene expression and cell growth [46].

PI3K is another signaling molecule that is known to have a dual role in heart disease, with both maladaptive and adaptive roles [58]. The signal transduction pathway of PI3K in the heart starts with the binding of growth factors or insulin to their respective receptors, leading to the activation of receptor tyrosine kinases (RTKs) as well as recruitment and activation of PI3K [59]. PI3K then converts PIP2 to PIP3, which then recruits and activates downstream signaling molecules, including Akt and phosphoinositide-dependent kinase 1 (PDK1) [60]. Akt phosphorylates and regulates a variety of targets involved in cardiac growth, metabolism, and survival transcription factors such as mechanistic target of rapamycin (mTOR), glycogen synthase kinase 3 beta (GSK3β), and forkhead box class O (FOXO) [26]. The downstream targets of Akt and its associated signaling pathways help to regulate various cellular processes, such as protein synthesis, glucose uptake, and apoptosis, to maintain normal cardiac function [26].

MAPKs are enzymes that play a pivotal role in regulating cardiac contractility by affecting the expression and activity of the *SERCA2* gene [61]. The signaling pathway for MAPK begins with various external signals like cytokines, growth factors, and/or even stress [29]. These signals bind to specific receptors on the cell membrane, which triggers a chain reaction of kinases [29]. This begins with the activation of small G proteins, such as rat sarcoma (Ras), which then activates rapidly accelerated fibrosarcoma (Raf) [62]. Raf, in turn, activates MAPK kinase (MEK), which phosphorylates and activates MAPK's ERK1/2 [63]. Once activated, ERK1/2 can move into the nucleus, where these interact with transcription factors [such as Ets transcription factor Elk-1 (Elk-1) and cellular oncogene c-Fos (c-Fos)] leading to changes in gene expression and resulting in various cellular responses, such as cell proliferation, differentiation, and survival [63]. It is also important to mention that the MAPK signal pathway also consists of two other branches: the p38 and c-Jun N-terminal kinase (JNK) pathway [28]. Activation of p38 reduces SERCA2 gene expression and protein levels, as well as the activity of the SERCA2 gene promoter leading to cell differentiation and survival [26]. The JNK pathway on the other hand is responsible for the regulation of cell death and inflammation [28].

Protein kinases in heart failure

Heart failure is a complex cardiovascular disease that is invariably associated with a diminished capacity of the heart to pump blood efficiently to meet the body's metabolic needs [64]. This can be caused by various underlying disorders, including coronary artery disease, hypertension, diabetes, valvular heart disease, and myocardial infarction [64]. As heart failure develops, it induces a variety of symptoms, including dyspnea, fatigue, swelling, and a decreased capacity to exercise, all of which have a negative effect on the patient's quality of life [64]. Furthermore, this disease is linked to cardiac remodeling, metabolic abnormalities, and

Ca^{2+}-handling defects dysregulation in heart function [45]. It is pointed out that β_1-adrenergic signaling pathway is often impaired in heart failure and there occur alterations in PKA activity and downstream effects [65]. Such a defect leads to a decreased ability of cardiomyocytes to handle Ca^{2+}, which contributes to the progression of heart failure [66]. Particularly, the levels of cAMP and PKA activity are depressed, leading to hypophosphorylation of the contractile proteins and alterations in Ca^{2+} handling by the sarcoplasmic reticulum, which impair cardiac function [66]. It is also noteworthy that several PKC isoforms participate in different aspects of cardiac remodeling and these diverse processes also contribute to the development of heart failure [66]. In this regard, it is pointed out that activation of PKC has been demonstrated to cause cardiomyocyte hypertrophy and fibrosis, which leads to cardiac dysfunction and contribute to arrhythmias and sudden death in patients with heart failure [66].

The PI3K/Akt signaling pathway has also been shown to be crucial for cardiac growth, metabolism, and survival, and its dysregulation has been linked to the pathogenesis of heart failure [46]. Disruption of PI3K/Akt signaling has been demonstrated to result in a decreased capacity for glucose uptake, impaired mitochondrial function, and an increased propensity for cell death in cardiomyocytes [46]. On the other hand, MAPKs including ERK1/2, JNK, and p38, are involved in various cardiac processes including remodeling, apoptosis, and inflammation [67]. The dysregulation of JNK and p38 signaling has been linked to heart failure, however, ERK1/2 has been shown to have protective cardiac effects [67]. In fact, reactive oxygen species have been shown to be involved in the oxidation of myofilaments, and p38 MAPK is considered to be involved in the progression of heart failure [68]. Since CaMKII is crucial to the regulation of excitation-contraction coupling and gene expression in the heart, a decrease in CaMKII signaling has also been linked to the development of heart failure [69]. Thus, the occurrence of cardiac dysfunction in heart failure seems to involve changes in various protein kinases and associated signal transduction defects [70].

Protein kinases in ischemic heart disease

Ischemia is a medical condition that occurs due to reduced blood supply to organs, which can lead to tissue damage and cell death as a consequence of hypoxia and substrate lack [5, 71, 72]. When it occurs in the heart it is referred to as ischemic heart disease, which is a cardiovascular defect induced by the narrowing/blockage of the heart's own coronary arteries. The reduced blood flow and oxygen supply to the heart can cause angina, heart attack, and myocardial infarction [73]. Reperfusion of the ischemic heart on the other hand, refers to the restoration of blood flow to an ischemic area after a period of reduced blood supply; however, this restoration of blood flow, if instituted after some delay, can cause additional harm to the tissue due to the generation of reactive oxygen species and inflammation, leading to ischemic reperfusion injury (I/R injury) [74, 75]. Short episodes of ischemia followed by reperfusion (ischemic preconditioning) have been found to be protective for the heart and improve cardiac function by reducing proteolysis and cytokine levels [75, 76]. It is pointed out that alterations in various isoforms of PKC have been shown to be associated with different effects in ischemic heart disease. PKCδ was observed to promote I/R injury after ischemia, but PKCε was seen as protective [27]. PKCδ downregulates SERCA2 and activates JNK as well as p38 MAPK due to I/R injury. Activation of JNK and p38 was shown to affect the phosphorylation of PKC's downstream products, as well as increase the susceptibility to reactive oxygen species-induced apoptosis [77]. During ischemic preconditioning PKA was seen as protective by reducing the activity of calpain, a protease which hydrolyzes structural proteins [78]. The protective effects of PKA include decreases in sarcolemma sensitivity, cytoskeleton protein breakdown, and apoptosis during ischemic preconditioning. However, opposite effects were observed when beta-blockers were administered, while beta-agonists enhanced PKA cardioprotection [73, 78].

It should be mentioned that the role of PKC in cardioprotection due to ischemic preconditioning is controversial as it is species-dependent. This view is supported by the fact that, unlike rats and rabbits, the cardioprotective effect of ischemic preconditioning in pigs was not attenuated by staurosporine, an inhibitor of PKC or genistein, an inhibitor of tyrosine kinase [79, 80]. However, combined inhibition of PKC and tyrosine kinase by staurosporine and genistein was observed to attenuate the cardioprotective effect of ischemic preconditioning in pigs [80]. These observations indicate that a complex signaling cascade

involving both PKC and tyrosine kinase may be involved in preventing cardioprotection by ischemic preconditioning. It is also noteworthy that connexin 43, which is co-localized with PKCα and p38 MAPKα and is phosphorylated by these kinases, has been reported to play a role in cardioprotection by ischemic preconditioning [81, 82]. Such a role of connexin in ischemic preconditioning was not found to involve intracellular communication through gap junctions but instead was a consequence of increased co-localization of protein kinases with connexin 43 during ischemic preconditioning [81, 82].

By virtue of the presence of different types and isoforms in the hearts, MAPKs are known to participate in both physiological and pathological processes [2, 3, 5]. MAPK is activated during ischemic heart diseases such as angina, myocardial infarction, and I/R injury [83] and thus MAPK signaling plays a critical role in cell survival and proliferation as well as cell death and apoptosis [84]. In fact, p38 MAPK has been demonstrated to serve as a mediator of ischemic preconditioning [85]. However, during myocardial infarction and angina, activation of MAPK signaling leads to increased cardiac damage and dysfunction, while specific activation of the p38 MAPK pathway has been implicated in the development of myocardial hypertrophy and fibrosis, which result in heart failure [86]. Recently, p38 MAPK has been shown to suppress neutrophil-heart-adipose tissue crosstalk and act as a switch in cardiac adaptation to cardiac dysfunction during the development of heart failure [87]. While PI3K signaling is also an important cardio-protective survival pathway, the expression of PI3K and Akt1/2 is down-regulated in ischemic heart disease [88]. In fact, during myocardial infarction, opposite effects are observed as activation of PI3K signaling has been shown to protect against myocardial injury and promote cardiac cell survival [89]. CaMK dysregulation was also seen in I/R injury and ischemic heart disease by altering Ca^{2+} handling, but the CaMKII-δ9 isoform was seen as having a protective effect by inhibiting inflammation of the heart [90]. It is thus evident the pathogenic or protective actions of various protein kinases in ischemic heart disease are dependent upon the activation of their specific isoforms.

Protein kinases in atherosclerosis

Atherosclerosis is a common condition of the cardiovascular system that is characterized by the buildup of plaque such as cholesterol, fats, macrophages, and other substances/minerals in arterial walls, and results in reduced blood flow to vital organs including the heart, brain, and kidneys [91]. Over time, the plaques become calcified, which will lead to a greater degree of arterial constriction and other atherosclerotic lesions, involving cytokines and oxidized lipoproteins, that lead to endothelial damage [91, 92]. Atherosclerosis is caused by multiple risk factors, including high blood pressure, smoking, high cholesterol, diabetes, a sedentary lifestyle, and obesity. As a result, decreasing the risk factors through lifestyle changes and medications can help prevent or slow the progression of atherosclerosis [92]. It is pointed out that PKA has been demonstrated to be one of the main regulators of macrophage inflammatory responses, and is believed to contribute to the development of atherosclerosis [93]. In particular, PKA modulates the Toll-like receptor 4 (TLR4) inflammatory responses, which are involved in the progression of atherosclerosis [93]. It has been proposed that PKA activity is linked to a protein that is involved in cholesterol transport and metabolism called ATP-binding cassette subfamily A member 1 (ABCA1) [94]. ABCA1 promotes the efflux of cholesterol from cells to form high-density lipoprotein (HDL) particles, also known as “good cholesterol” [95]. The regulation of ABCA1-mediated cholesterol efflux is carried out by sphingosine kinase upon activation by sphingosine-1-phosphate [96]. In the state of atherosclerosis, PKA activity is suppressed and lower levels of phosphorylated signaling molecules like cAMP-response element binding protein (CREB) and IL-10 were discovered, while higher levels of TNF-α had increased [94]. Different PKC isoforms have been reported to be involved in steps leading to atherosclerosis, and depending on the systems and tissue cells examined, PKC isoforms can be either pro- or anti-inflammatory [95]. PKCα and PKCζ regulate macrophage cholesterol efflux, while PKCδ is the main isoform that regulates smooth muscle cell apoptosis and plays an essential role in regulating smooth muscle functions during atherosclerosis [95]. To add, both PKCβ and PKCδ are involved in receptor-mediated uptake of oxidized LDLs (low-density lipoproteins) by macrophages, leading to foam cell formation [95].

Current research also indicates both PKCβ and PKCδ should be therapeutic targets for mitigating atherosclerosis [97]. It should also be noted that MAPK activation is involved in oxidized LDL-induced macrophage proliferation, granulocyte-macrophage colony-stimulating factor (GM-CSF) production, and apoptotic signals [98]. MAPKs such as JNK, p38, and MKP-1 are known to be involved in the formation of foam cells as well as in the growth of atherosclerotic lesions [99]. More importantly, p38 is recognized as an active, inflammation-driven process in both atherosclerosis and aortic valve sclerosis [100] and it was concluded that p38 MAPK signaling in different cell types is associated with these two cardiovascular diseases [100]. It is also pointed out that PI3K plays an important role in the regulation of leukocyte recruitment, monocyte migration, reactive oxygen species production, and endothelial cell apoptosis [101]. More specifically, the isoform PI3Kγ primarily controls leukocyte infiltration in the myocardium and arteries, which is a key factor in atherosclerosis [102]. Inhibition of PI3K, on the other hand, can weaken endocytic clearance mechanisms leading to increased plaque necrosis, inflammatory response, and more vascular vulnerabilities [102]. Several studies have also demonstrated that calmodulin and CaMKs contribute to the development of atherosclerosis, and suppressing calmodulin or CaMKs with inhibitors or genetic manipulation has been shown to alleviate atherosclerotic severity [103]. In particular, CaMKIIδ binds to CREB and myocyte enhancer factor 2 (MEF2), inducing their phosphorylation and inducing transcription of the target genes [103]. These elevated levels of transcription factors promote cell proliferation in atherosclerosis and should be important targets when it comes to drug and gene therapy as well [103].

Involvement of protein kinases in arrhythmias

An arrhythmia is an irregular heartbeat pattern, which can be caused by heart disease, electrolyte imbalances, and side effects from medication [104]. Ventricular arrhythmias are the most serious and include ventricular premature complexes (VPCs) and sustained ventricular tachycardia [104]. Sudden cardiac death can be caused by ventricular arrhythmias, particularly fatal ones like ventricular tachycardia and fibrillation [105]. These types of arrhythmias are usually triggered by cardiac injury due to chronic ischemia, acute myocardial infarction, and various stressful conditions that cause elevated levels of circulating catecholamines and AngII [105]. The common way to classify arrhythmias is based on the rate of conduction and is usually divided into bradyarrhythmia [a heart rate less than 60 beats per minute (bpm)] and tachyarrhythmia (heart rate that is higher than 100 bpm) [106]. In arrhythmias, different studies have shown that the activity and expression of PKA and PKC isoforms can be altered, leading to changes in cardiac ion channel function and excitation-contraction coupling [107, 108]. PKA activity was increased in ventricular arrhythmias induced by ischemia/reperfusion injury. Increased PKA activity leads to abnormal Ca^{2+} handling and contractile dysfunction in the heart muscle, which contributes to the development of ventricular arrhythmias [107]. In another study, it was shown that PKC expression was upregulated in a rat model of atrial fibrillation [108]. Upregulation of PKC led to changes in the expression and function of ion channels involved in regulating atrial repolarization, which contributed to the development and maintenance of the arrhythmia [108].

In addition to PKA and PKC, other protein kinases such as MAPK, PI3K, and CaMK have also been identified to be involved in the development of arrhythmias [109]. Activation of PI3K has been linked to arrhythmia in diabetic hearts, as well as in conditions of heart failure [110]. The PI3K pathway is involved in the regulation of cardiac growth, and its disruption has been linked to the development of fibrous scarring which can interfere with normal electrical function and reduced contractility, both of which can lead to arrhythmia [111]. Furthermore, there is evidence to suggest that the PI3K and MAPK pathways interact to influence the development of arrhythmias [112]. This interaction is involved in the regulation of NF-κB nuclear translocation, reactive oxygen species generation, and MAPKs [113–115]. It has also been shown that CaMK activity is upregulated in patients with atrial fibrillation and that inhibition of CaMK can prevent the development of atrial fibrillation in animal models [33]. In spite of the extensive work which has been carried out to establish the involvement of different protein kinases in various types of

arrhythmias, the exact mechanisms of their participation in the induction of arrhythmias are not fully understood.

Protein kinases in hypertension

Hypertension is a condition in which the blood pressure in vascular walls is increased. It is associated with numerous cellular signaling pathways, including the renin-angiotensin-aldosterone system (RAAS) and AngII type 1 receptor (AT-1) signaling [116, 117]. The RAAS involves the production of a peptide called AngII which binds to two major GPCRs: AT-1 and the AngII type 2 receptor (AT-2) [117]. AngII is responsible for various intracellular signaling pathways which, when dysregulated, can lead to hypertension [117]. This serious condition is known to result in kidney disease, heart disease, and stroke if left untreated [116]. Treatment of hypertension can be modulated with lifestyle changes such as exercise, diet, stress reduction, and medications to control blood pressure if lifestyle changes are not effective [118]. Several studies have demonstrated that both PKA and PKC play an important role in the development of hypertension [119]. PKC activation directly phosphorylates myofilament proteins that control cardiac function, and plays a key role in the hypertensive heart/failure process [119]. Furthermore, it has been observed that enzyme hyperactivation of different intracellular targets due to the phosphorylation by PKA and PKC leads to abnormally high cAMP levels, resulting in hypertensive cardiac hypertrophy [119] and alterations in contractile peak tension [120]. Furthermore, MAPK, PI3K, and CaMK levels have been shown to be increased during hypertension [121–123]. An increase in PI3K activity was shown to increase Rho activity [121]. It is pointed out that, Rho is a small guanosine triphosphatase (GTPase, with many isoforms) that plays a crucial role in the regulation of vascular smooth muscle tone and blood pressure. Activation of Rho leads to vasoconstriction and contributes to the development of hypertension [124]. Additionally, upregulated CaMK activity in hypertension has been implicated in the development of endothelial dysfunction, hypertension-induced cardiac hypertrophy, and vasoconstriction [123]. Inhibition of CaMK has been shown to improve endothelial function and reduce blood pressure in animal models with hypertension [123]. Lastly, MAPK has also been linked to the function of vascular smooth muscle tone, endothelial dysfunction, and cardiac hypertrophy by promoting oxidative stress and inflammation [122]. Inhibition of MAPK activity however reduced high blood pressure and improved endothelial function in hypertensive animal models. Therefore, targeting the MAPK pathway may represent a promising strategy for the development of antihypertensive therapies and the improvement of cardiac function in hypertension [125].

Protein kinases in diabetic cardiomyopathy

Chronic diabetes is normally associated with diabetic cardiomyopathy, which is characterized by a decline in cardiac function and an increased risk of heart failure [126]. Although the causes of diabetic cardiomyopathy are not fully understood, it is thought to involve structural, functional, and metabolic changes in the heart [126]. High blood sugar levels cause damage to the heart muscle over time and lead to impaired cardiac function [127]. Furthermore, it has been shown that hyperglycemia is not only a central factor in the pathogenesis of cardiac dysfunction in chronic diabetes but it also can trigger a series of maladaptive events such as cardiomyocyte apoptosis, collagen deposition, and cardiac fibrosis [127]. Additionally, diabetes-induced hyperglycemia and hyperinsulinemia can result in capillary damage and myocardial hypertrophy with mitochondrial dysfunction [126]. Insulin resistance, inflammation, and oxidation products of catecholamine such as aminochrome and oxyradicals have also contributed to the development of diabetic cardiomyopathy [126, 127]. Some of the cellular defects in diabetic cardiomyopathy include low myosin adenosine triphosphatase (ATPase) activity, dysregulation of Ca^{2+} homeostasis, reduced rate of cardiac contraction/relaxation, and altered flow of ionic current within the heart muscle [128]. In addition, hyperglycemia and subsequent increases in oxidative stress led to alterations in PKA and PKC signaling pathways, contributing to the pathogenesis of diabetic cardiomyopathy [127]. In particular, PKA activity has been reported to be reduced in the hearts of diabetic animals [129]; the decrease in PKA activity contributes to impaired β-adrenergic signaling, which is crucial

for regulating cardiac contractility and function, ultimately leading to diminished cardiac performance [130]. On the other hand, PKC activation is generally enhanced in diabetic cardiomyopathy [131]. Specifically, the activation of the PKCβ isoform has been implicated in the development of myocardial dysfunction [132]. Increased activation of PKCβ in diabetic cardiomyopathy leads to alterations in the phosphorylation status of several downstream targets, such as troponin I, which results in impaired myocardial contractility [132]. Moreover, elevated PKC activity has been linked to increased fibrosis, apoptosis, and inflammation in the diabetic myocardium, further exacerbating the progression of diabetic cardiomyopathy [133].

It is noteworthy that CaMKII has been reported to be hyperactivated in the diabetic myocardium [134]. This hyperactivation leads to increased phosphorylation of its downstream targets, such as RyR2, which in turn results in impaired Ca^{2+} handling and reduced myocardial contractility [134]. Additionally, CaMKII hyperactivation has been associated with increased oxidative stress, mitochondrial dysfunction, and apoptosis further exacerbating the progression of diabetic cardiomyopathy [135]. PI3K signaling, on the other hand, particularly the PI3K/Akt pathway, which is essential for regulating cardiac cell survival, growth, and metabolism [135], is often dysregulated, leading to impaired insulin signaling and reduced glucose uptake in cardiomyocytes in diabetic cardiomyopathy [136]. Moreover, the decreased activation of Akt has been linked to increased apoptosis and cardiac dysfunction in chronic diabetes [137]. Lastly, the activation of JNK and p38 MAPK is generally enhanced, leading to increased inflammation, fibrosis, and apoptosis in the diabetic myocardium [138]. Conversely, the activation of ERK, which is known to promote cell survival, is often impaired in diabetic cardiomyopathy, further contributing to myocardial dysfunction [139]. These observations provide compelling evidence for the involvement of different changes in various protein kinases in the development of cardiac dysfunction in chronic diabetes.

Protein kinases and investigational methods

As we continue to discover and understand new protein kinases and their roles in heart dysfunction, the future of research should focus on developing targeted therapies to modulate their activities. Small molecule inhibitors, gene therapy, and RNA-based therapeutics such as antisense oligonucleotides and RNA interference have shown promise in preclinical models for treating heart diseases [140–142]. Additionally, the use of pluripotent stem cells for disease modeling and drug discovery has become a very valuable tool for understanding cardiac disorders and testing new therapeutic strategies [143, 144]. By combining these advanced techniques and focusing on newly discovered protein kinases, it is possible to develop innovative treatments to alleviate cardiac disorders and improve patient outcomes. Furthermore, building on the advancements in targeted therapies and the use of stem cells, it would be prudent to explore the potential of combining these approaches with tissue engineering and regenerative medicine to alleviate heart disease. Tissue engineering techniques, such as 3D bioprinting and scaffold-based approaches, have shown great promise in creating functional cardiac tissue for transplantation and repairing damaged heart tissue [145]. In particular, 3D bioprinting with patient-derived stem cells can help to overcome immune rejection and other challenges associated with traditional heart transplantation surgeries [146].

In addition to the development of novel therapies, early detection and prevention of heart disorders will play a crucial role in reducing the burden of cardiovascular disease [147]. The development of brand-new disruptive technologies such as artificial intelligence, machine learning, and wearable devices can help to identify individuals at high risk and monitor patients in real-time for early intervention and disease prevention [148]. For example, artificial intelligence algorithms can analyze electrocardiograms and other medical data to predict the onset of cardiac events and guide personalized therapeutic strategies [149]. Furthermore, the advancement of precision medicine, which focuses on tailoring treatments based on a person's genes, environment, and lifestyle choices, can help optimize patient care and improve outcomes [150, 151]. Thus, by combining knowledge of both the existing and new protein kinases with high throughput genomics, transcriptomics (study of transcription genomes), and proteomics data (proteomes and their functions), it has been suggested to develop personalized, specific therapies to prevent and treat

heart diseases more effectively [150]. Since none of the existing inhibitors is specific for any protein kinase, there is a real need for developing agents which are kinase isoform-specific. Furthermore, extensive research needs to be carried out to establish the exact function of each protein kinase isoform. It is suggested that a combination therapy with inhibitors of different protein kinases be investigated for optimal beneficial effects in cardiovascular diseases. It is emphasized that the future of researching protein kinases and heart diseases involves combining different approaches like molecular biology, tissue engineering, regenerative medicine, artificial intelligence, and precision medicine. By using these advanced technologies together, it is likely to improve our knowledge of how protein kinases impact cardiac disorders, create new treatments, and enhance early detection and prevention methods. These breakthroughs are really promising and will have the potential to help millions of patients around the world by easing their cardiovascular problems and improving their quality of life.

Conclusions

From the foregoing discussion, it is evident that different protein kinases, including PKA, PKC, MAPK, PI3K, and CaMK, play a pivotal role in the pathophysiology of various cardiovascular diseases such as heart failure, myocardial infarction, atherosclerosis, arrhythmias, hypertension, and diabetic cardiomyopathy. These kinases are involved in multiple signaling pathways that modulate cellular processes including inflammation, oxidative stress, endothelial function, vascular smooth muscle tone, and cardiac contractility. As the understanding of the molecular mechanisms underlying these diseases continues to grow, it has become increasingly clear that targeting these protein kinases and their associated signaling pathways may provide novel therapeutic strategies for the treatment and prevention of cardiovascular disorders. Furthermore, the future of cardiovascular research will likely involve a multidisciplinary approach, combining the development of targeted therapies, stem cell technology, tissue engineering, regenerative medicine, artificial intelligence, and precision medicine, the goal is to advance knowledge of protein kinases and their roles in cardiac disorders. By employing these advanced technologies, it should be possible to create new treatments, improve early detection and prevention methods, and develop personalized therapeutic strategies to better address the unique needs of individual patients. Moreover, leveraging artificial intelligence and machine learning algorithms in conjunction with genomics, transcriptomics, and proteomics data will facilitate the identification of novel protein kinase targets and the development of innovative therapies tailored to specific patient populations. Furthermore, the study of protein kinases and their involvement in cardiovascular diseases offers a promising avenue for the development of novel, targeted therapies that have the potential to significantly improve patient outcomes. By harnessing the power of advanced technologies and multidisciplinary approaches, it is likely to make substantial progress in understanding the molecular mechanisms driving heart problems and translate these findings into effective clinical interventions. As the complex roles of protein kinases in cardiovascular disorders continue to be elucidated, the prospect of reducing the global burden of heart disease becomes increasingly attainable, ultimately improving the quality of life for millions of patients worldwide.

Abbreviations

ABCA1: adenosine triphosphate-binding cassette subfamily A member 1

Akt: protein kinase B

AngII: angiotensin II

ATP: adenosine triphosphate

CaMK: Ca^{2+}/calmodulin-dependent protein kinase

cAMP: cyclic adenosine monophosphate

DAG: diacylglycerol

ERK: extracellular signal-regulated protein kinase

I/R injury: ischemic reperfusion injury

IL: interleukin

JNK: c-Jun N-terminal kinase

MAPK: mitogen-activated protein kinase

PI3K: phosphoinositide 3-kinase

PKA: protein kinase A

PKC: protein kinase C

RyR: ryanodine receptor

SERCA: sarco/endoplasmic reticulum Ca^{2+}-adenosine triphosphatase

TNF: tumor necrosis factor

Declarations

Acknowledgments

The infrastructure support for this project was provided by the St. Boniface Hospital Research Foundation, Winnipeg, Canada. Thanks are also due to Ms. Khushman Kaur for preparing this manuscript.

Author contributions

JP: Investigation, Writing—original & draft. AKS: Formal analysis, Data curation, Writing—review & editing. NSD: Conceptualization, Writing—review & editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

References

1. Ruehr ML, Russell MA, Bond M. A-kinase anchoring protein targeting of protein kinase A in the heart. J Mol Cell Cardiol. 2004;37:653–65.
2. Dhalla NS, Müller AL. Protein kinases as drug development targets for heart disease therapy. Pharmaceuticals (Basel). 2010;3:2111–45.

3. Nusier M, Elimban V, Prasad J, Shah AK, Dhalla NS. Regulatory role of protein kinases in signal transduction pathways in heart and disease. Scr Med. 2023;54:181–95.
4. Chen J, Li Y, Du C, Wei T, Shan T, Wang L. Protein kinases in cardiovascular diseases. Chin Med J (Engl). 2022;135:557–70.
5. Michel MC, Li Y, Heusch G. Mitogen-activated protein kinases in the heart. Naunyn Schmiedebergs Arch Pharmacol. 2001;363:245–66.
6. Fuller SJ, Osborne SA, Leonard SJ, Hardyman MA, Vaniotis G, Allen BG, et al. Cardiac protein kinases: the cardiomyocyte kinome and differential kinase expression in human failing hearts. Cardiovasc Res. 2015;108:87–98.
7. Roskoski R Jr. A historical overview of protein kinases and their targeted small molecule inhibitors. Pharmacol Res. 2015;100:1–23.
8. Schwartz PA, Murray BW. Protein kinase biochemistry and drug discovery. Bioorg Chem. 2011;39: 192–210.
9. Graves JD, Krebs EG. Protein phosphorylation and signal transduction. Pharmacol Ther. 1999;82: 111–21.
10. Cohen P. The Croonian Lecture 1998. Identification of a protein kinase cascade of major importance in insulin signal transduction. Philos Trans R Soc Lond B Biol Sci. 1999;354:485–95.
11. Touyz RM, Schiffrin EL. Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells. Pharmacol Rev. 2000; 52:639–72.
12. Taylor SS, Buechler JA, Yonemoto W. cAMP-dependent protein kinase: framework for a diverse family of regulatory enzymes. Annu Rev Biochem. 1990;59:971–1005.
13. Hook SS, Mean AR. Ca^{2+}/CaM-dependent kinases: from activation to function. Annu Rev Pharmacol Toxicol. 2001;41:471–505.
14. Krishna M, Narang H. The complexity of mitogen-activated protein kinases (MAPKs) made simple. Cell Mol Life Sci. 2008;65:3525–44.
15. Sugden PH, Bogoyevitch MA. Intracellular signalling through protein kinases in the heart. Cardiovasc Res. 1995;30:478–92.
16. Barefield D, Sadayappan S. Phosphorylation and function of cardiac myosin binding protein-C in health and disease. J Mol Cell Cardiol. 2010;48:866–75.
17. Kikkawa U, Nishizuka Y. The role of protein kinase C in transmembrane signalling. Annu Rev Cell Biol. 1986;2:149–78.
18. Hudmon A, Schulman H. Neuronal Ca^{2+}/calmodulin-dependent protein kinase II: the role of structure and autoregulation in cellular function. Annu Rev Biochem. 2002;71:473–510.
19. Walker EH, Perisic O, Ried C, Stephens L, Williams RL. Structural insights into phosphoinositide 3-kinase catalysis and signalling. Nature. 1999;402:313–20.
20. Bogoyevitch MA, Sugden PH. The role of protein kinases in adaptational growth of the heart. Int J Biochem Cell Biol. 1996;28:1–12.
21. Fearnley CJ, Roderick HL, Bootman MD. Calcium signaling in cardiac myocytes. Cold Spring Harb Perspect Biol. 2011;3:a004242.
22. Edwards AS, Scott JD. A-kinase anchoring proteins: protein kinase A and beyond. Curr Opin Cell Biol. 2000;12:217–21.
23. Keenan C, Kelleher D. Protein kinase C and the cytoskeleton. Cell Signal. 1998;10:225–32.
24. Schechtman D, Mochly-Rosen D. Adaptor proteins in protein kinase C-mediated signal transduction. Oncogene. 2001;20:6339–47.
25. Stern MD. Theory of excitation-contraction coupling in cardiac muscle. Biophys J. 1992;63:497–517.
26. Romero-Becerra R, Santamans AM, Folgueira C, Sabio G. p38 MAPK pathway in the heart: new insights in health and disease. Int J Mol Sci. 2020;21:7412.

27. Steinberg SF. Cardiac actions of protein kinase C isoforms. Physiology (Bethesda). 2012;27:130–9.
28. Adebayo SO, Olunuga TO, Durodola A, Ogah OS. Heart failure: definition, classification, and pathophysiology – a mini-review. Nigerian J Cardiol. 2017;14:9–14.
29. Wang Y, Huang S, Sah VP, Ross J Jr, Brown JH, Han J, et al. Cardiac muscle cell hypertrophy and apoptosis induced by distinct members of the p38 mitogen-activated protein kinase family. J Biol Chem. 1998;273:2161–8.
30. Severino P, D'Amato A, Pucci M, Infusino F, Adamo F, Birtolo LI, et al. Ischemic heart disease pathophysiology paradigms overview: from plaque activation to microvascular dysfunction. Int J Mol Sci. 2020;21:8118.
31. Saito T, Fukuzawa J, Osaki J, Sakuragi H, Yao N, Haneda T, et al. Roles of calcineurin and calcium/calmodulin-dependent protein kinase II in pressure overload-induced cardiac hypertrophy. J Mol Cell Cardiol. 2003;35:1153–60.
32. Beckendorf J, van den Hoogenhof MMG, Backs J. Physiological and unappreciated roles of CaMKII in the heart. Basic Res Cardiol. 2018;113:29.
33. Wang W, Shen W, Zhang S, Luo G, Wang K, Xu Y, et al. The role of CaMKII overexpression and oxidation in atrial fibrillation—a simulation study. Front Physiol. 2020;11:607809.
34. Bers DM. Cardiac excitation–contraction coupling. Nature. 2002;415:198–205.
35. Heineke J, Molkentin JD. Regulation of cardiac hypertrophy by intracellular signalling pathways. Nat Rev Mol Cell Biol. 2006;7:589–600.
36. Braunwald E. Heart failure. JACC Heart Fail. 2013;1:1–20.
37. Bristow MR. Pathophysiologic and pharmacologic rationales for clinical management of chronic heart failure with beta-blocking agents. Am J Cardiol. 1993;71:C12–22.
38. Dhalla NS, Temsah RM, Netticadan T. Role of oxidative stress in cardiovascular diseases. J Hypertens. 2000;18:655–73.
39. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473:317–25.
40. Nattel S. New ideas about atrial fibrillation 50 years on. Nature. 2002;415:219–26.
41. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. Circ Res. 2018;122:624–38.
42. Cheng HC, Qi RZ, Paudel H, Zhu HJ. Regulation and function of protein kinases and phosphatases. Enzyme Res. 2011;2011:794089.
43. Morrison DK, Murakami MS, Cleghon V. Protein kinases and phosphatases in the *Drosophila* genome. J Cell Biol. 2000;150:F57–62.
44. Qin S, Kitty I, Hao Y, Zhao F, Kim W. Maintaining genome integrity: protein kinases and phosphatases orchestrate the balancing act of DNA double-strand breaks repair in cancer. Int J Mol Sci. 2023;24:10212.
45. Saad NS, Elnakish MT, Brundage EA, Biesiadecki BJ, Kilic A, Ahmed AAE, et al. Assessment of PKA and PKC inhibitors on force and kinetics of non-failing and failing human myocardium. Life Sci. 2018;215:119–27.
46. McLean BA, Zhabyeyev P, Pituskin E, Paterson I, Haykowsky MJ, Oudit GY. PI3K inhibitors as novel cancer therapies: implications for cardiovascular medicine. J Card Fail. 2013;19:268–82.
47. Krebs EG. Role of the cyclic AMP—dependent protein kinase in signal transduction. JAMA. 1989;262:1815–8.
48. Zhang CC. Bacterial signalling involving eukaryotic-type protein kinases. Mol Microbiol. 1996;20:9–15.
49. Baillie GS, Scott JD, Houslay MD. Compartmentalisation of phosphodiesterases and protein kinase A: opposites attract. FEBS Lett. 2005;579:3264–70.

50. Kaestner L. Calcium signalling in cardiac myocytes. In: Calcium signalling. Berlin: Springer; 2013. pp. 24–5.
51. Carter CA. Protein kinase C as a drug target: implications for drug or diet prevention and treatment of cancer. Curr Drug Targets. 2000;1:163–83.
52. Heusch G, Boengler K, Schulz R. Cardioprotection: nitric oxide, protein kinases, and mitochondria. Circulation. 2008;118:1915–9.
53. Heusch G. Cardioprotection is alive but remains enigmatic: the nitric oxide-protein kinases-mitochondria signaling axis. Circulation. 2017;136:2356–8.
54. Martelli AM, Evangelisti C, Nyakern M, Manzoli FA. Nuclear protein kinase C. Biochim Biophys Acta. 2006;1761:542–51.
55. Kang JH, Toita R, Kim CW, Katayama Y. Protein kinase C (PKC) isozyme-specific substrates and their design. Biotechnol Adv. 2012;30:1662–72.
56. Singh RM, Cummings E, Pantos C, Singh J. Protein kinase C and cardiac dysfunction: a review. Heart Fail Rev. 2017;22:843–59.
57. Min W, Bin ZW, Quan ZB, Hui ZJ, Sheng FG. The signal transduction pathway of PKC/NF-κB/c-fos may be involved in the influence of high glucose on the cardiomyocytes of neonatal rats. Cardiovasc Diabetol. 2009;8:8.
58. Yao H, Han X, Han X. The cardioprotection of the insulin-mediated PI3K/Akt/mTOR signaling pathway. Am J Cardiovasc Drugs. 2014;14:433–42.
59. Aoyagi T, Matsui T. Phosphoinositide-3 kinase signaling in cardiac hypertrophy and heart failure. Curr Pharm Des. 2011;17:1818–24.
60. Ghigo A, Laffargue M, Li M, Hirsch E. PI3K and calcium signaling in cardiovascular disease. Circ Res. 2017;121:282–92.
61. Wheeler-Jones CP. Cell signalling in the cardiovascular system: an overview. Heart. 2005;91: 1366–74.
62. Liu P, Zhong TP. MAPK/ERK signalling is required for zebrafish cardiac regeneration. Biotechnol Lett. 2017;39:1069–77.
63. Muslin AJ. MAPK signalling in cardiovascular health and disease: molecular mechanisms and therapeutic targets. Clin Sci (Lond). 2008;115:203–18.
64. Bhullar SK, Dhalla NS. Experimental models for investigating the pathogenesis of heart failure. In: Sobti RC, editor. Advances in animal experimentation and modeling. Academic Press; 2022. pp. 103–22.
65. Wang J, Liu X, Arneja AS, Dhalla NS. Alterations in protein kinase A and protein kinase C levels in heart failure due to genetic cardiomyopathy. Can J Cardiol. 1999;15:683–90.
66. Dent MR, Das S, Dhalla NS. Alterations in both death and survival signals for apoptosis in heart failure due to volume overload. J Mol Cell Cardiol. 2007;43:726–32.
67. Zhang W, Elimban V, Nijjar MS, Gupta SK, Dhalla NS. Role of mitogen-activated protein kinase in cardiac hypertrophy and heart failure. Exp Clin Cardiol. 2003;8:173–83.
68. Heusch P, Canton M, Aker S, van de Sand A, Konietzka I, Rassaf T, et al. The contribution of reactive oxygen species and p38 mitogen-activated protein kinase to myofilament oxidation and progression of heart failure in rabbits. Br J Pharmacol. 2010;160:1408–16.
69. Netticadan T, Temsah RM, Kawabata K, Dhalla NS. Sarcoplasmic reticulum Ca^{2+}/calmodulin-dependent protein kinase is altered in heart failure. Circ Res. 2000;86:596–605.
70. Adameova A, Hrdlicka J, Szobi A, Farkasova V, Kopaskova K, Murarikova M, et al. Evidence of necroptosis in hearts subjected to various forms of ischemic insults. Can J Physiol Pharmacol. 2017; 95:1163–9.
71. Ross RS. Ischemic heart disease: an overview. Am J Cardiol. 1975;36:496–505.

72. Heusch G. Myocardial ischemia: lack of coronary blood flow, myocardial oxygen supply-demand imbalance, or what? Am J Physiol Heart Circ Physiol. 2019;316:H1439–46.
73. Dhalla NS, Shah AK, Adameova A, Bartekova M. Role of oxidative stress in cardiac dysfunction and subcellular defects due to ischemia-reperfusion injury. Biomedicines. 2022;10:1473.
74. Tappia PS, Shah AK, Ramjiawan B, Dhalla NS. Modification of ischemia/reperfusion-induced alterations in subcellular organelles by ischemic preconditioning. Int J Mol Sci. 2022;23:3425.
75. Heusch G. Myocardial ischaemia–reperfusion injury and cardioprotection in perspective. Nat Rev Cardiol. 2020;17:773–89.
76. Marrocco V, Bogomolovas J, Ehler E, Dos Remedios CG, Yu J, Gao C, et al. PKC and PKN in heart disease. J Mol Cell Cardiol. 2019;128:212–26.
77. Sadat U. Signaling pathways of cardioprotective ischemic preconditioning. Int J Surg. 2009;7:490–8.
78. Nusier M, Alqudah M, Elimban V, Dhalla NS. Modification of ischemia/reperfusion induced infarct size by ischemic preconditioning in hypertrophied hearts. Can J Physiol Pharmacol. 2021;99:218–23.
79. Vahlhaus C, Schulz R, Post H, Onallah R, Heusch G. No prevention of ischemic preconditioning by the protein kinase C inhibitor staurosporine in swine. Circ Res. 1996;79:407–14.
80. Vahlhaus C, Schulz R, Post H, Rose J, Heusch G. Prevention of ischemic preconditioning only by combined inhibition of protein kinase C and protein tyrosine kinase in pigs. J Mol Cell Cardiol. 1998; 30:197–209.
81. Schulz R, Gres P, Skyschally A, Duschin A, Belosjorow S, Konietzka I, et al. Ischemic preconditioning preserves connexin 43 phosphorylation during sustained ischemia in pig hearts *in vivo*. FASEB J. 2003;17:1355–7.
82. Li X, Heinzel FR, Boengler K, Schulz R, Heusch G. Role of connexin 43 in ischemic preconditioning does not involve intercellular communication through gap junctions. J Mol Cell Cardiol. 2004;36: 161–3.
83. Bogoyevitch MA. Signalling via stress-activated mitogen-activated protein kinases in the cardiovascular system. Cardiovasc Res. 2000;45:826–42.
84. Martin ED, De Nicola GF, Marber MS. New therapeutic targets in cardiology: p38 alpha mitogen-activated protein kinase for ischemic heart disease. Circulation. 2012;126:357–68.
85. Schulz R, Belosjorow S, Gres P, Jansen J, Michel MC, Heusch G. p38 MAP kinase is a mediator of ischemic preconditioning in pigs. Cardiovasc Res. 2002;55:690–700.
86. Chang H, Li C, Wang Q, Lu L, Zhang Q, Zhang Y, et al. QSKL protects against myocardial apoptosis on heart failure via PI3K/Akt-p53 signaling pathway. Sci Rep. 2017;7:16986.
87. Bottermann K, Kalfhues L, Nederlof R, Hemmers A, Leitner LM, Oenarto V, et al. Cardiomyocyte p38 MAPKα suppresses a heart–adipose tissue–neutrophil crosstalk in heart failure development. Basic Res Cardiol. 2022;117:48.
88. Zhang Q, Wang L, Wang S, Cheng H, Xu L, Pei G, et al. Signaling pathways and targeted therapy for myocardial infarction. Signal Transduct Target Ther. 2022;7:78.
89. Yao Y, Li F, Zhang M, Jin L, Xie P, Liu D, et al. Targeting CaMKII-δ9 ameliorates cardiac ischemia/ reperfusion injury by inhibiting myocardial inflammation. Circ Res. 2022;130:887–903.
90. Singh RB, Mengi SA, Xu YJ, Arneja AS, Dhalla NS. Pathogenesis of atherosclerosis: a multifactorial process. Exp Clin Cardiol. 2002;7:40–53.
91. Riccioni G, De Santis A, Cerasa V, Menna V, Di Ilio C, Schiavone C, et al. Atherosclerotic plaque formation and risk factors. Int J Immunopathol Pharmacol. 2003;16:25–31.
92. Ma L, Dong F, Zaid M, Kumar A, Zha X. ABCA1 protein enhances Toll-like receptor 4 (TLR4)-stimulated interleukin-10 (IL-10) secretion through protein kinase A (PKA) activation. J Biol Chem. 2012;287:40502–12.

93. Ma L, Dong F, Denis M, Feng Y, Wang MD, Zha X. Ht31, a protein kinase A anchoring inhibitor, induces robust cholesterol efflux and reverses macrophage foam cell formation through ATP-binding cassette transporter A1. J Biol Chem. 2011;286:3370–8.
94. Zhu X, Lee JY, Timmins JM, Brown JM, Boudyguina E, Mulya A, et al. Increased cellular free cholesterol in macrophage-specific *Abca1* knock-out mice enhances pro-inflammatory response of macrophages. J Biol Chem. 2008;283:22930–41.
95. Fan HC, Fernández-Hernando C, Lai JH. Protein kinase C isoforms in atherosclerosis: pro- or anti-inflammatory? Biochem Pharmacol. 2014;88:139–49.
96. Vaidya M, Jentsch JA, Peters S, Keul P, Weske S, Gräler MH, et al. Regulation of ABCA1-mediated cholesterol efflux by sphingosine-1-phosphate signaling in macrophages. J Lipid Res. 2019;60: 506–15.
97. Miao LN, Pan D, Shi J, Du JP, Chen PF, Gao J, et al. Role and mechanism of PKC-δ for cardiovascular disease: current status and perspective. Front Cardiovasc Med. 2022;9:816369.
98. Senokuchi T, Matsumura T, Sakai M, Matsuo T, Yano M, Kiritoshi S, et al. Extracellular signal-regulated kinase and p38 mitogen-activated protein kinase mediate macrophage proliferation induced by oxidized low-density lipoprotein. Atherosclerosis. 2004;176:233–45.
99. Lawan A, Shi H, Gatzke F, Bennett AM. Diversity and specificity of the mitogen-activated protein kinase phosphatase-1 functions. Cell Mol Life Sci. 2013;70:223–37.
100. Reustle A, Torzewski M. Role of p38 MAPK in atherosclerosis and aortic valve sclerosis. Int J Mol Sci. 2018;19:3761.
101. Zhao Y, Qian Y, Sun Z, Shen X, Cai Y, Li L, et al. Role of PI3K in the progression and regression of atherosclerosis. Front Pharmacol. 2021;12:632378.
102. Ghigo A, Li M. Phosphoinositide 3-kinase: friend and foe in cardiovascular disease. Front Pharmacol. 2015;6:169.
103. Chen MF. The role of calmodulin and calmodulin-dependent protein kinases in the pathogenesis of atherosclerosis. Tzu Chi Med J. 2022;34:160–8.
104. Marazzato J, Blasi F, Golino M, Verdecchia P, Angeli F, De Ponti R. Hypertension and arrhythmias: a clinical overview of the pathophysiology-driven management of cardiac arrhythmias in hypertensive patients. J Cardiovasc Dev Dis. 2022;9:110.
105. Adameova A, Shah AK, Dhalla NS. Role of oxidative stress in the genesis of ventricular arrhythmias. Int J Mol Sci. 2020;21:4200.
106. Desai DS, Hajouli S. Arrhythmias. Treasure Island (FL): StatPearls Publishing; 2023.
107. Wehrens XH, Lehnart SE, Reiken S, Vest JA, Wronska A, Marks AR. Ryanodine receptor/calcium release channel PKA phosphorylation: a critical mediator of heart failure progression. Proc Natl Acad Sci U S A. 2006;103:511–8.
108. Aydin O, Becker R, Kraft P, Voss F, Koch M, Kelemen K, et al. Effects of protein kinase C activation on cardiac repolarization and arrhythmogenesis in Langendorff-perfused rabbit hearts. Europace. 2007;9:1094–8.
109. Smith LE, White MY. The role of post-translational modifications in acute and chronic cardiovascular disease. Proteomics Clin Appl. 2014;8:506–21.
110. Kang YJ. Cardiac hypertrophy: a risk factor for QT-prolongation and cardiac sudden death. Toxicol Pathol. 2006;34:58–66.
111. Dobrev D, Heijman J, Hiram R, Li N, Nattel S. Inflammatory signalling in atrial cardiomyocytes: a novel unifying principle in atrial fibrillation pathophysiology. Nat Rev Cardiol. 2023;20:145–67.
112. Zhang X, Yu Y, Lei H, Cai Y, Shen J, Zhu P, et al. The Nrf-2/HO-1 signaling axis: a ray of hope in cardiovascular diseases. Cardiol Res Pract. 2020;2020:5695723.
113. Xiao Z, Kong B, Yang H, Dai C, Fang J, Qin T, et al. Key player in cardiac hypertrophy, emphasizing the role of Toll-like receptor 4. Front Cardiovasc Med. 2020;7:579036.

114. Wan M, Yin K, Yuan J, Ma S, Xu Q, Li D, et al. YQFM alleviated cardiac hypertrophy by apoptosis inhibition and autophagy regulation via PI_3K/AKT/mTOR pathway. J Ethnopharmacol. 2022;285: 114835.
115. Sapia L, Palomeque J, Mattiazzi A, Petroff MV. Na^+/K^+-ATPase inhibition by ouabain induces CaMKII-dependent apoptosis in adult rat cardiac myocytes. J Mol Cell Cardiol. 2010;49:459–68.
116. Cong X, Kong W. Endothelial tight junctions and their regulatory signaling pathways in vascular homeostasis and disease. Cell Signal. 2020;66:109485.
117. Kawai T, Forrester SJ, O'Brien S, Baggett A, Rizzo V, Eguchi S. AT1 receptor signaling pathways in the cardiovascular system. Pharmacol Res. 2017;125:4–13.
118. Bunker J. Hypertension: diagnosis, assessment and management. Nurs Stand. 2014;28:50–9.
119. Dong X, Sumandea CA, Chen YC, Garcia-Cazarin ML, Zhang J, Balke CW, et al. Augmented phosphorylation of cardiac troponin I in hypertensive heart failure. J Biol Chem. 2012;287:848–57.
120. Haddad GE, Coleman BR, Zhao A, Blackwell KN. Regulation of atrial contraction by PKA and PKC during development and regression of eccentric cardiac hypertrophy. Am J Physiol Heart Circ Physiol. 2005;288:H695–704.
121. Carnevale D, Lembo G. PI3Kγ in hypertension: a novel therapeutic target controlling vascular myogenic tone and target organ damage. Cardiovasc Res. 2012;95:403–8.
122. Xu Q, Liu Y, Gorospe M, Udelsman R, Holbrook NJ. Acute hypertension activates mitogen-activated protein kinases in arterial wall. J Clin Invest. 1996;97:508–14.
123. Prasad AM, Morgan DA, Nuno DW, Ketsawatsomkron P, Bair TB, Venema AN, et al. Calcium/calmodulin-dependent kinase II inhibition in smooth muscle reduces angiotensin II-induced hypertension by controlling aortic remodeling and baroreceptor function. J Am Heart Assoc. 2015;4: e001949.
124. Loirand G, Pacaud P. The role of Rho protein signaling in hypertension. Nat Rev Cardiol. 2010;7: 637–47.
125. Shafiq M, Jagavelu K, Iqbal H, Yadav P, Chanda D, Verma NK, et al. Inhibition of mitogen-activated protein kinase (MAPK)-activated protein kinase 2 (MK2) is protective in pulmonary hypertension. Hypertension. 2021;77:1248–59.
126. Nakamura K, Miyoshi T, Yoshida M, Akagi S, Saito Y, Ejiri K, et al. Pathophysiology and treatment of diabetic cardiomyopathy and heart failure in patients with diabetes mellitus. Int J Mol Sci. 2022;23: 3587.
127. Boudina S, Abel ED. Diabetic cardiomyopathy, causes and effects. Rev Endocr Metab Disord. 2010;11: 31–9.
128. Ozturk N, Olgar Y, Ozdemir S. Trace elements in diabetic cardiomyopathy: an electrophysiological overview. World J Diabetes. 2013;4:92–100.
129. Belke DD, Swanson EA, Dillmann WH. Decreased sarcoplasmic reticulum activity and contractility in diabetic *db*/*db* mouse heart. Diabetes. 2004;53:3201–8.
130. Bockus LB, Humphries KM. cAMP-dependent protein kinase (PKA) signaling is impaired in the diabetic heart. J Biol Chem. 2015;290:29250–8.
131. Inoguchi T, Battan R, Handler E, Sportsman JR, Heath W, King GL. Preferential elevation of protein kinase C isoform beta II and diacylglycerol levels in the aorta and heart of diabetic rats: differential reversibility to glycemic control by islet cell transplantation. Proc Natl Acad Sci U S A. 1992;89: 11059–63.
132. Lei S, Li H, Xu J, Liu Y, Gao X, Wang J, et al. Hyperglycemia-induced protein kinase C β_2 activation induces diastolic cardiac dysfunction in diabetic rats by impairing caveolin-3 expression and Akt/eNOS signaling. Diabetes. 2013;62:2318–28.
133. Dhalla NS, Ganguly PK, Bhullar SK, Tappia PS. Role of catecholamines in the pathogenesis of diabetic cardiomyopathy. Can J Physiol Pharmacol. 2019;97:815–9.

134. Erickson JR, Pereira L, Wang L, Han G, Ferguson A, Dao K, et al. Diabetic hyperglycaemia activates CaMKII and arrhythmias by *O*-linked glycosylation. Nature. 2013;502:372–6.
135. Daniels L, Bell JR, Delbridge LM, McDonald FJ, Lamberts RR, Erickson JR. The role of CaMKII in diabetic heart dysfunction. Heart Fail Rev. 2015;20:589–600.
136. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation. 2007;115:3213–23.
137. Fujio Y, Nguyen T, Wencker D, Kitsis RN, Walsh K. Akt promotes survival of cardiomyocytes *in vitro* and protects against ischemia-reperfusion injury in mouse heart. Circulation. 2000;101:660–7.
138. Palomer X, Salvadó L, Barroso E, Vázquez-Carrera M. An overview of the crosstalk between inflammatory processes and metabolic dysregulation during diabetic cardiomyopathy. Int J Cardiol. 2013;168:3160–72.
139. Wang S, Ding L, Ji H, Xu Z, Liu Q, Zheng Y. The role of p38 MAPK in the development of diabetic cardiomyopathy. Int J Mol Sci. 2016;17:1037.
140. Poller W, Dimmeler S, Heymans S, Zeller T, Haas J, Karakas M, et al. Non-coding RNAs in cardiovascular diseases: diagnostic and therapeutic perspectives. Eur Heart J. 2018;39:2704–16.
141. Lu P, Ding F, Xiang YK, Hao L, Zhao M. Noncoding RNAs in cardiac hypertrophy and heart failure. Cells. 2022;11:777.
142. Wong LL, Rademaker MT, Saw EL, Lew KS, Ellmers LJ, Charles CJ, et al. Identification of novel microRNAs in the sheep heart and their regulation in heart failure. Sci Rep. 2017;7:8250.
143. Matsa E, Burridge PW, Wu JC. Human stem cells for modeling heart disease and for drug discovery. Sci Transl Med. 2014;6:239ps6.
144. Burridge PW, Li YF, Matsa E, Wu H, Ong SG, Sharma A, et al. Human induced pluripotent stem cell–derived cardiomyocytes recapitulate the predilection of breast cancer patients to doxorubicin-induced cardiotoxicity. Nat Med. 2016;22:547–56.
145. Noor N, Shapira A, Edri R, Gal I, Wertheim L, Dvir T. 3D printing of personalized thick and perfusable cardiac patches and hearts. Adv Sci (Weinh). 2019;6:1900344.
146. Gao L, Kupfer ME, Jung JP, Yang L, Zhang P, Da Sie Y, et al. Myocardial tissue engineering with cells derived from human-induced pluripotent stem cells and a native-like, high-resolution, 3-dimensionally printed scaffold. Circ Res. 2017;120:1318–25.
147. Prieto-Avalos G, Cruz-Ramos NA, Alor-Hernández G, Sánchez-Cervantes JL, Rodríguez-Mazahua L, Guarneros-Nolasco LR. Wearable devices for physical monitoring of heart: a review. Biosensors (Basel). 2022;12:292.
148. Moshawrab M, Adda M, Bouzouane A, Ibrahim H, Raad A. Smart wearables for the detection of cardiovascular diseases: a systematic literature review. Sensors (Basel). 2023;23:828.
149. Attia ZI, Kapa S, Lopez-Jimenez F, McKie PM, Ladewig DJ, Satam G, et al. Screening for cardiac contractile dysfunction using an artificial intelligence–enabled electrocardiogram. Nat Med. 2019;25:70–4.
150. Ashley EA. Towards precision medicine. Nat Rev Genet. 2016;17:507–22.
151. Weldy CS, Ashley EA. Towards precision medicine in heart failure. Nat Rev Cardiol. 2021;18:745–62.