The heartbreak of depression: 'Psycho-cardiac' coupling in myocardial infarction

Headrick, John P.; Peart, Jason N.; Budiono, Boris P; Shum, David H K; Neumann, David L.; Stapelberg, Nicolas J C

Published in:
Journal of Molecular and Cellular Cardiology

DOI:
[10.1016/j.yjmcc.2017.03.007](https://doi.org/10.1016/j.yjmcc.2017.03.007)

Licence:
CC BY-NC-ND

[Link to output in Bond University research repository.](#)

Recommended citation(APA):

Headrick, J. P., Peart, J. N., Budiono, B. P., Shum, D. H. K., Neumann, D. L., & Stapelberg, N. J. C. (2017). The heartbreak of depression: 'Psycho-cardiac' coupling in myocardial infarction. *Journal of Molecular and Cellular Cardiology*, 106, 14-28. <https://doi.org/10.1016/j.yjmcc.2017.03.007>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

For more information, or if you believe that this document breaches copyright, please contact the Bond University research repository coordinator.

The heartbreak of depression: ‘Psycho-cardiac’ coupling in myocardial infarction

John P. Headrick^{a,c*}, Jason N. Peart^{a,c}, Boris P. Budiono^a, David H.K. Shum^{b,c}, David L. Neumann^{b,c}, Nicolas J.C. Stapelberg^{b,c}

^aSchool of Medical Science, ^bSchool of Applied Psychology, and ^cMenzies Health Institute QLD, Griffith University, Southport QLD 4217, AUSTRALIA

Short Title: Depression and Myocardial Infarction

*Corresponding Author:

Prof. John Headrick
School of Medical Science
Griffith University, Gold Coast
Southport, QLD 4217
AUSTRALIA

Ph: (+61) 7 55528292

E-mail: j.headrick@griffith.edu.au

ABSTRACT

Ample evidence identifies strong links between major depressive disorder (MDD) and both risk of ischemic or coronary heart disease (CHD) and resultant morbidity and mortality. The molecular mechanistic bases of these linkages are poorly defined. Systemic factors linked to MDD, including vascular dysfunction, atherosclerosis, obesity and diabetes, together with associated behavioural changes, all elevate CHD risk. Nonetheless, experimental evidence indicates the myocardium is also directly modified in depression, independently of these factors, impairing infarct tolerance and cardioprotection. It may be that MDD effectively breaks the heart's intrinsic defense mechanisms. Four extrinsic processes are implicated in this psycho-cardiac coupling, presenting potential targets for therapeutic intervention if causally involved: sympathetic over-activity *vs.* vagal under-activity, together with hypothalamic-pituitary-adrenal (HPA) axis and immuno-inflammatory dysfunctions. However, direct evidence of their involvement remains limited, and whether targeting these upstream mediators is effective (or practical) in limiting the cardiac consequences of MDD is unknown. Detailing *myocardial* phenotype in MDD can also inform approaches to cardioprotection, yet cardiac molecular changes are similarly ill defined. Studies support myocardial sensitization to ischemic insult in models of MDD, including worsened oxidative and nitrosative damage, apoptosis (with altered Bcl-2 family expression) and infarction. Moreover, depression may de-sensitize hearts to protective conditioning stimuli. The mechanistic underpinnings of these changes await delineation. Such information not only advances our fundamental understanding of psychological determinants of health, but also better informs management of the cardiac consequences of MDD and implementing cardioprotection in this cohort.

Keywords: Cardioprotection; Chronic Stress; Major Depressive Disorder; Ischemic Heart Disease; Myocardial Infarction

1. Introduction

Major depressive disorder (MDD) shares a reciprocal relationship with coronary heart disease (CHD) (reviewed in [1-3]). This behavioral disorder places healthy individuals at increased risk of CHD [4-7], is strongly linked to CHD in those with or without existing cardiac disease [6,8-10], is an independent risk factor for cardiovascular mortality and morbidity [11-13], and is more prevalent in those who have suffered AMI [12,14]. As a CHD risk factor, MDD exerts an impact similar to conventional determinants (eg. smoking, elevated cholesterol, hypertension, diabetes) [15,16], and increases the risk of recurrent cardiac events and death in those with CHD by up to 4-fold [11,17,18]. The magnitude of CHD risk is also related to the severity of MDD, ranging from a 2-fold increase to up to 5-fold with more severe depression [7]. Depression thus appears as powerful a determinant of CHD risk and outcomes as more traditional risk factors, and its occurrence is significant: recent analyses indicate a lifetime prevalence of ~16% in the US [19], with varying estimates from other populations (and diagnostic criteria), for example ~11% in Canada [20], 4-7% in Singapore [21], 12% in a Scottish cohort [22], 18% in urban Ethiopians [23], and 5% in rural-to-urban Chinese workers [24]. Whether overall incidence is on the rise is questionable, with a perceived growing epidemic of MDD and anxiety disorders potentially reflecting population growth, among other factors [25]. Whether more extensive 'sub-threshold' depression influences CHD risk and outcomes is also unclear.

As opposed to most major CHD risk factors, the biological mechanisms linking depressive disorders and heart disease remain to be detailed. From a holistic perspective [reviewed in 2,26], depressive and chronic heart disorders share the same physiological network of mechanisms (thus risk factors). This Psycho-Immune-Neuroendocrine (PINE) network is predicated on key regulatory systems [26], including the autonomic nervous, immune and endocrine systems, and components of the central nervous system (Figs. 1 & 2). Perturbation of the regulatory PINE network may predispose an individual to both MDD and CHD, with onset of either disease (and manifestation of

one ahead of the other) influenced by hereditary and environmental factors [26] (Fig. 1).

Highlighted in Fig. 1, there is a high degree of bidirectional interconnectedness between CHD and MDD – common mechanistic elements are implicated in both scenarios, and pathologic outcomes of each exert positive feedbacks on the other. For example, MDD may promote cardiac dysfunction via intermediate pathological and physiological mechanisms: behavioral changes with MDD contribute to inactivity, in turn promoting obesity, dyslipidemia, type 2 diabetes and hypertension, while associated social isolation additionally worsens CHD risk and mortality. There is also evidence that disruption of the PINE network can physiologically promote risk of dyslipidemia, type 2 diabetes and hypertension, and thus CHD [26]. The same intermediary pathologies can equally contribute to MDD.

Although now a well-recognized and clinically important manifestation of psycho-cardiac coupling, and while the PINE network model provides a framework for understanding depression-dependent changes in CHD risk and outcomes [26], relatively few studies have investigated the molecular mechanistic basis of these interactions. In particular, *how the heart itself is intrinsically modified by depression remains to be fully detailed*. Certainly, co-morbidities associated with or promoted by MDD, including obesity, diabetes and aging, are known to negatively impact myocardial stress-resistance and cardioprotection [27-30]. However, experimental evidence reveals that chronic stress and MDD *directly impair myocardial capacity to withstand injury/infarction independently of these systemic factors*. This review focuses on these direct myocardial impacts of depression, specifically the heart's capacity to withstand damage with infarction and respond to protective intervention. Not only contributing to worsened CHD risk and outcomes, depression may simultaneously render the heart resistant to cardioprotective interventions. While Tako-Tsubo cardiomyopathy exemplifies the notion of a 'broken heart', evidence suggests depression may effectively break the heart's intrinsic defense mechanisms, thus ability to withstand cellular injury and death. Beyond accumulating epidemiological evidence, and development of frameworks with

which to test and unravel these interactions [2,26] (Fig. 1), the molecular bases of these myocardial changes await more detailed investigation (Fig. 2).

2. Impacts of depression on myocardial infarction

2.1 Pre-ischemic depression

It is only relatively recently that studies have examined the detrimental impacts of stress and MDD on the heart's response to ischemic insult or infarction. Data generated in the landmark Whitehall study revealed strong relationships between social stress and metabolic and cardiovascular health outcomes [31-33]. In terms of those at risk of AMI, the prevalence of depression is significant with approximately 1-in-5 patients referred for diagnostic catheterization and angiography suffering pre-existing MDD [8,34], confirming significant prevalence of the disorder in those at risk of AMI. Early investigations revealed that depression impairs heart rate variability and autonomic control in humans [35], and that chronic stress (inducing depressive symptoms) increases heart rate, sympathetic tone, and cardiovascular reactivity to stress in animals [36,37], suggesting enhanced cardiac vulnerability to arrhythmia and injury. Further investigations over the last 3 decades have largely relied on chronic stress models (*eg.* subjecting animals to physical restraint, social isolation, predation stress, forced swimming, environmental instability, and randomized series of such stressors), which exhibit symptoms of depression that may include anhedonia and decreases in sexual drive, aggression, investigative behavior and locomotion, together with circadian disruption, disordered sleep and weight loss [38,39] (models discussed below in section 4). These studies identify both ultrastructural disruption in otherwise healthy hearts [40,41] and substantial changes in myocardial injury responses [40,42-47]. However, they have not yet developed a mechanistic understanding of these cardiac outcomes. Most research to date has focused on key end-points, including cell death, infarction, arrhythmogenesis and stunning, with few delving into underlying molecular mechanisms.

Scheuer and Mifflin showed that experimental infarction in rats is significantly worsened by daily restraint stress [42]. These investigators had previously identified worsened infarction in response to chronically elevated corticosterone [43]. Subsequent work indicates that chronic emotional stress exaggerates infarction in rats in association with increases in markers of oxidative and nitrosative damage [44]. Ravingerova *et al.* found chronic stress also increases contractile dysfunction and risk of post-ischemic arrhythmias in normotensive rats, though stress somewhat paradoxically improved these parameters in hypertensive animals [45]. While emulating post-traumatic stress disorder (PTSD), a more recent study in a psychosocial predator-based animal model reports increases in contractile dysfunction and myocardial death following ischemia, though specifically in males and not females [46]. Delving into mechanistic elements, Rakhshan *et al.* found that chronic physical or psychological stress worsened myocardial damage during infarction, and that this effect was eliminated by chemical sympathectomy (without influencing corticosterone levels) [47]. While not assessing infarction per se, Xinxing *et al.* report an association between myocardial injury and shifts in adrenaline, noradrenaline, corticosterone and 5-HT in a rat model of chronic stress [40]. There is thus some support for sympathetic over-activity and HPA dysfunction in myocardial stress intolerance in depressive disorders, though the identities and roles of neurohumoral factors involved await confirmation (Fig. 2).

There is also relatively little information available regarding the myocardial molecular changes that underpin these reductions in ischemic tolerance, with data essentially limited to damage markers and expression of pro- and anti-apoptotic Bcl-2 family proteins (Fig. 2). An analysis of cardiac and nervous responses reveals induction of Bax and repression of Bcl-xl transcripts in a rodent model of depression, potentially predisposing to apoptosis [48]. Subsequent investigations from this group confirm shifts in both transcript and protein for apoptotic regulators, including increased myocardial Bax, Bcl-2 and Bax/Bcl-2 ratio without changes in caspase-3 in rodent models of depression either prior to [49] or following [50] infarction. This may evidence

differential activation of caspase-3 independent death pathways with depression: Bax and Bcl2 not only modulate caspase-3 dependent apoptosis, but influence mitochondrial respiration, membrane permeability, cytochrome *c* release, and caspase-3 independent death. How these proteomic and cell death responses arise remains to be determined, though reported elevations in oxidative and nitrosative damage [44] will certainly promote apoptosis and oncosis. Nonetheless, the bases of the latter molecular damage outcomes are also unknown – are processes of reactive oxygen or nitrogen species generation dysregulated, and/or are anti-oxidant and molecular detoxification and repair mechanisms impaired with depression? There is preliminary evidence myocardial anti-oxidants levels are suppressed [44] and injurious toll-like receptor 4 and NFkB signaling up-regulated [41] with chronic stress, whereas cardioprotective NOS and Akt signaling are only modified by chronic stress (crowding) in the hearts of hypertensive and not normotensive rats [45,51]. Further work examining shifts in pro-survival vs. pro-injury signaling pathways across a broader range of models may clarify the basis of intrinsically impaired infarct tolerance in depression.

Other unknowns include the impacts of differing types and durations of stress. For example, while several models of chronic stress detrimentally influence myocardial infarct tolerance, crowding stress reportedly fails to modify infarction in hypertensive rats [51], while acute forms of stress can be cardioprotective. The latter response, a form of hormesis, is exemplified in the broadly conserved pre-conditioning phenomenon - transient ischemia induces powerful protection against subsequent prolonged insult. This contrasts the generally detrimental effects of chronic psychological stress on myocardial phenotype [52]. Both acute and chronic stressors may influence intrinsic myocardial defense mechanisms: chronic metabolic disorders and aging dysregulate survival kinase signaling engaged by acute stressors, resulting in impaired infarct tolerance [53,54]. Physical stress (*eg.* wheel-running in naïve mice) induces cardioprotection via the same kinase signaling [55], and our recent unpublished findings suggest that psychological effects of environmental enrichment (placement of a locked running wheel in cages) may similarly boost

infarct tolerance in caged mice, coupled with phospho-regulation of the same survival and stress kinases (see preliminary data in Fig. 3). These intriguing observations of acute protection via simple environmental enrichment warrant further investigation, highlighting the importance of psychological state in dictating myocardial phenotype and also raising questions regarding behavioral status in ‘control’ caged rodents. Finally, it is relevant to note there is evidence that the impacts of differing types of stress may be sex-dependent, with a model of PTSD selectively exaggerating post-ischemic myocardial damage and dysfunction in males only [46], while in contrast other stress (eg. crowding, sleep deprivation) worsens ischemic outcomes in females and not males [51,56].

From a cellular perspective, depression or chronic stress appears to impact all major cardiovascular elements. Studies to date support exaggerated cardiomyocyte apoptosis [40,49] and hypertrophy [57-59], together with myocyte abnormalities that include edema, myofibrillar damage and changes to mitochondria, nuclei and sarcoplasmic reticulum [40,41]. Myocyte contractile properties are also reportedly impaired, in association with depression of Ca^{2+} levels [59]. Exaggerated myocardial fibrosis, with increased transcripts for collagens, connective tissue growth factor and transforming growth factor- β 1 [57-59], implicate shifts in cardiac fibroblast phenotype/function. Coronary vascular function is also modified, with evidence of impaired coronary perfusion [45], while cardiac endothelial cells may also degenerate [41]. Chronic stress can also induce vascular stiffening [60], together with potentially adaptive NO generation and relaxation [61,62], though these outcomes have not been assessed specifically in coronary vessels. Thrombotic processes are also dysregulated, with evidence for involvement of circulating tissue factor (not vascular tissue factor, or platelet function) [63], although others report enhanced platelet aggregation [64]. Inflammatory and immune function is a key implicated element in the cardiovascular sequelae of MDD, and there is evidence for increased inflammatory cell infiltration and pro-inflammatory signaling in hearts of chronically stressed animals [41,58]. It thus appears all

major cellular elements of the heart, including myocytes, fibroblasts, endothelium and coronary vascular cells may be impacted in depression, together with invading or resident inflammatory/immune cells, and potentially platelets.

2.2 Post-Ischemic Depression

The occurrence of MDD after acute myocardial infarction (AMI) is well established, and is associated with both worsened quality of life [65] and higher mortality and rehospitalization [11,66, 67]. Up to 25% of patients suffer from depression post AMI, which is 2-4 times higher than the general population [8,34,68,69]. Though less well studied than the negative impacts of pre-existing depression, depression induced after AMI also appears to exaggerate cardiac apoptotic signaling and death [50] and tissue remodeling [70]. On the other hand, a recent study of post-infarction housing stress in rats found no significant effects on subsequent progression of heart failure [71]. Whether myocardial mechanisms underlying the effects of pre- vs. post-infarct depression are similar remains to be addressed, though Wang and colleagues find evidence of altered expression of apoptosis proteins in both scenarios [49,50].

3. Potential mediators of myocardial infarct intolerance in depression

There are 4 inter-related regulatory systems perturbed in MDD that plausibly give rise to myocardial intolerance to infarction (Figs. 1 & 2): sympathetic over-activity, vagal dysfunction, HPA axis abnormalities, and shifts in immune function and inflammation [2,26]. There is limited experimental support for involvement of the former neurohumoral mediators, while roles of immune and inflammatory processes have yet to be directly tested. The mechanistic roles of these 4 regulatory systems thus require more detailed investigation.

3.1 Sympathetic over-activity

The sympathetic nervous system is an important determinant of cardiovascular disease progression [72] and pathogenesis of AMI [73,74]. Individuals suffering depression exhibit increased sympathetic activity [74,75], including specifically elevated cardiac sympathetic tone [76]. This is also evidenced in reduced heart rate variability in psychological disorders including MDD [77-79]. Such autonomic dysfunction has been linked to increased risk of heart disease [80] and heart disease mortality and morbidity in MDD [35,81]. At a cellular level chronic sympathetic activation can increase oxidative stress and dysregulate apoptotic pathways to worsen myocardial injury [82]. Sustained release or sudden spikes in catecholamine levels also increase risk of cardiac complications such as arrhythmias and sudden cardiac death. Modulation of autonomic nervous activity has been shown to reduce myocardial ischemia-reperfusion injury [83-86], and β -blockade has been a mainstay in management of patients with CHD/AMI.

The myocardial effects of sympathetic over-activity are certainly consistent with involvement in the negative consequences of MDD (Fig. 2). Increased β -adrenergic receptor activity promotes both apoptosis and oncosis [87-90], with pro-death effects potentially involving NADPH oxidase activity [91,92], nitric oxide generation and nitrosative stress [93,94], and modulation of Bcl-2 protein expression profiles [90,95]. Oxidative stress with noradrenaline has also been linked to epigenetic repression of protective PKC ϵ (via NADPH oxidase-1 dependent oxidative stress) [96]. Additionally, increased β -adrenergic receptor activity enhances apoptotic death in response to immuno-inflammatory activation [95], in association with altered stress kinase signaling and Bcl-2 expression. These putative mechanisms are consistent with the elevations in myocardial oxidative and nitrosative stress [44], shifts in Bcl-2 proteins and execution of apoptosis [47-49], and inflammatory responses [41,58] observed in animal models of depression. Cardiac pathologies relevant to risk of and outcomes from AMI have also been linked to β -adrenergic receptor activity in models of chronic stress, including hypertrophy, fibrosis, diastolic dysfunction

and oxidative stress [58].

Although widely assumed, reflecting pro-infarct effects of sympathetic activity in other settings, the involvement of sympathetic over-activity in infarct intolerance in MDD has yet to be thoroughly tested. Furthermore, whether the degree and pattern of sympathetic activation in animal models of depression reflect changes and roles in human MDD is not at all clear. The recent report of Rakhshan *et al.* suggests reduced infarct tolerance in a rat model of chronic stress is blocked by chemical sympathectomy [47], consistent with involvement of sympathetic over-activity. Variable effects of sympathectomy on infarct tolerance [97-99] nonetheless raise questions regarding selectivity and the mechanistic basis of sympathectomy outcomes. That said, studies also confirm elevations in circulating noradrenaline and adrenaline in MDD [74-76], and Xinxing *et al.* recently report *in vitro* cytotoxicity in otherwise healthy cells subjected to changes in noradrenaline, corticosterone and 5-HT that mimic those in a rat model of chronic stress [40]. However, the involvement of these factors in stress-dependent myocardial changes *in vivo* has yet to be directly tested. For example, a reduction in 5-HT with chronic stress [40] might also promote cell survival given recent evidence of 5-HT receptor involvement in cardiac apoptosis and remodeling following adrenergic activation [100].

It is also important to note that effects of cardiac nerves on ischemic injury are complex, and adrenergic receptor sub-types exert distinct effects on myocyte survival vs. death. Regional ischemia activates the autonomic nervous system, reducing electrical stability and promoting arrhythmias, modifying cardiac O₂ supply/demand and worsening myocardial injury. However, disrupting extra-cardiac nervous system input can exert either protective [97,98,101] or injurious effects [102,103]. Indeed, it has been suggested that absence of cardiac nerve activity may impair cardiac functional recovery [104]. In terms of cardioprotection, the second (delayed) but not first (acute) window of protection with pre-conditioning may require cardiac nerve activity [105]. Others report that surgical denervation does not eliminate pre-conditioning in dogs, yet significantly

reduces infarction alone [101]. The cardiac α - and β -adrenergic receptor sub-types activated by noradrenaline and adrenaline also exert opposing effects on stress responses and cell death. Activation of β -adrenergic receptors can protect against or promote cell death [90], with β_1 activity contributing to both cardiac apoptosis [90,95,106] and cardioprotection via ischemic preconditioning [106-109], while β_2 receptor activity may contribute to myocyte survival, ischemic tolerance and preconditioning responses [90,110,111]. The α_1 adrenergic receptors also exert opposing effects, with the higher affinity α_{1A} receptor promoting myocyte survival and ischemic tolerance [112-114], contributing to delayed cardioprotection [115], and improved angiogenesis [116], remodeling and survival [117] post-infarction. The survival effects of α_{1A} receptor activity may involve modulation of Bcl-2 proteins implicated in the pro-apoptotic response to β -adrenergic receptor activity, providing a counterbalance to limit apoptosis with sympathetic over-activity. Conversely the lower affinity α_{1B} -adrenergic receptor may promote hypertrophy and contractile dysfunction [118], and as opposed to the longevity (and anti-cancer) effects of α_{1A} activity, appears to reduce lifespan [119]. Thus, sympathetic activation and HPA axis dysfunction may induce differential effects on cardiac death, remodeling processes and overall survival, governed by adrenergic receptor sub-type expression and activation patterns. These complexities, coupled with the limited analyses of sympathetic over-activity to date, indicate more direct and thorough assessment is needed to identify roles of sympathetic nervous and humoral signaling in reducing myocardial infarct tolerance in MDD (Fig. 2).

3.2 Vagal dysfunction

Major depressive disorder is associated with reduced vagal activity, with evidence of a causal relationship between vagal function and depression [3,120]. Importantly, vagal dysfunction is likely to impair myocardial infarct tolerance, and may also negate capacity to protect the heart of MDD patients via widely trialed pre-conditioning interventions (Fig. 1). Detailed below, vagal

stimulation and the primary vagal transmitter acetylcholine protect against cardiac and vascular injuries, and play an essential role in ischemic pre-conditioning responses (Fig. 2).

Early clinical studies identified the importance of autonomic function in mortality following AMI [121,122], with experimental studies establishing the role of vagal activity in limiting arrhythmogenesis and enhancing survival post-AMI [123-127]. Investigations subsequent to these analyses of electrical stability/arrhythmogenesis revealed that acetylcholine and muscarinic receptor agonists also protect mammalian myocardium from ischemic injury [128,129], initially implicating reactive oxygen species signaling and ATP-gated K^+ channel activity [130-133] together with nitric oxide [134].

Later studies established that vagal stimulation, confirmed to increase cardiac interstitial acetylcholine [135], also reduces ischemic damage and infarction [136-139], and improves post-infarct inflammation and remodeling [140]. The protective effects of vagal activity and acetylcholine are not limited to myocardial cells, extending to protection of coronary vascular cells [134] and reduction of peripheral vascular inflammation and injury [141] during infarction. Other work confirms essential involvement of vagal activity in cardioprotection via remote pre-conditioning [142,143], with evidence release of the protective factor (which induces protection via recruiting intrinsic cardiac ganglia) is dependent upon prior vagal activation [144].

Mechanistically, while initial studies focused on roles of reactive oxygen species, K_{ATP} channels and nitric oxide in the protection elicited by acetylcholine and muscarinic receptors, studies also support roles for improved Ca^{2+} handling [145,146], and the ‘cholinergic anti-inflammatory pathway’ (involving suppression of JAK-STAT and NF κ B signaling) appears key to the cardiac and vascular protection with vagal activity (Fig. 2). Acetylcholine modulates myocyte expression of inflammatory cytokines [147], and vagal stimulation reduces neutrophil invasion and inflammatory markers in post-ischemic myocardium [137], modifies TNF- α expression and differentially modulates protective *vs.* injurious TNF receptor sub-types[138,148], and inhibits

expression of injurious Il-17a during infarction [149].

Interestingly, more recent work in cultured cell models of hypoxia/reoxygenation injury supports beneficial effects of acetylcholine on autophagy [150], and mitochondrial biogenesis [151] and quality control via mitophagy [152]. Similarly, vagal nerve stimulation may limit myocardial injury by inhibiting mitochondrial dysfunction and associated apoptosis [139], though this study found protection was limited to intra-ischemic intervention while post-ischemic stimulation was ineffective. Other work supports vagal control of mitochondrial dynamics, likely promoting stress-tolerance and limiting cell death [153]. Inhibition of the mitochondrial unfolded protein response may additionally contribute to anti-apoptotic effects of acetylcholine, potentially via inhibition of mitochondrial oxidant generation [154]. Studies thus collectively reveal important roles for vagal activity in dynamic maintenance of mitochondrial phenotype and function. While neuronal autophagy appears dysregulated with depression, the effects of MDD or chronic psychological stress on cardiac fission, fusion and mitophagy await analysis.

Both muscarinic (M2, M3) receptors and nicotinic receptors may contribute to the protective effects of vagal activity and acetylcholine. Studies initially focused on muscarinic M2 receptors, with antagonism or knockdown confirming involvement in protection of cardiomyocytes [147,155]. Additionally, M3 agonism with choline is cardioprotective [146,156], and the M3 receptor is implicated in the anti-apoptotic effects of acetylcholine [154] and in vagally mediated protection [133]. Finally, nicotinic receptors may also participate, with the study of Calvillo *et al.* supporting involvement of the nicotinic pathway and inflammatory modulation in cardioprotection via vagal stimulation [137]. Activation of the $\alpha 7$ nACh receptor also substantially limits inflammation during myocardial ischemia-reperfusion [157], and may promote angiogenesis post-infarction [158] (Fig. 2).

Despite considerable evidence supporting cardiac protection via vagal activity in other settings, no study has yet demonstrated that reduced vagal activity underlies exaggerated

myocardial infarction in models of MDD. This is important if vagally targeted therapies were to be implemented. Clinically, vagal stimulation has been assessed in chronic heart failure, where it has been established as safe and efficacious [159-161]. Trials in myocardial infarction (or surgical ischemia) have yet to be undertaken. Among other unknowns, it is unclear whether detrimental impacts of sympathetic and vagal dysfunction on infarction and cardioprotective signaling are additive or potentially synergistic. It is thus unclear whether combined targeting of vagal and sympathetic pathways will be substantially more effective, practical or problematic, in terms of protecting against ischemic damage and infarction. We are unaware of studies assessing dual treatment via both parasympathetic agonism/nerve stimulation and sympathetic antagonism/nerve block. Although in a different setting, combined vagal stimulation and β -blockade has been shown to be more effective than either alone in preserving function in a model of chronic heart failure [162].

3.3 The HPA axis

The endocrine response to stress involves anterior hypothalamic release of corticotropin-releasing hormone, and pituitary secretion of adrenocorticotrophic hormone to stimulate adrenal cortex secretion of glucocorticoids such as cortisol [163]. Chronic stress results in over-secretion of glucocorticoids and downstream adrenal catecholamines [164]. Inflammatory dysfunction is an important element in MDD, and cytokines also stimulate the HPA axis, with IL-6 particularly important in axis activation during chronic stress [165]. Additionally, eicosanoids, platelet-activating factor and serotonin act as inflammatory mediators to stimulate the HPA axis [166]. Chronic activation of the HPA axis in depression may both directly and indirectly influence myocardial phenotype and stress-tolerance (Figs. 1 & 2).

Glucocorticoids exert direct cardiovascular effects, including positive inotropism and increased blood pressure and cardiac output [167]. They also sensitize the cardiovascular system to

catecholamines, and prolong the actions of catecholamines at neuromuscular junctions [163].

Coupled with sympathetic over-activation, HPA axis dysfunction may exaggerate the pro-injurious actions of catecholamines. In addition, cortisol inhibits insulin and promotes lipolysis, modifying substrate metabolism and elevating blood glucose. Chronic stress also induces insulin-resistance, further promoting hyperglycemia, with both hyperglycemia and insulin-resistance known to impair infarct tolerance and cardioprotective signaling [27-30,168,169]. Similarly, elevations in serum fatty acids, particularly saturated forms, may induce myocardial dysfunction and apoptotic death, while polyunsaturated fats are protective [170,171]. Whether cortisol-dependent inhibition might also limit the cardioprotective action of insulin [89,172] has not been tested.

Stimulation of the HPA axis reduces production of thyroid-stimulating hormone and conversion of thyroxine to triiodothyronine (Fig. 2), which can lead to sick euthyroid syndrome [173], associated with cardiac dysfunction under normoxic and post-ischemic conditions [174]. It is less clear whether infarction is sensitive to this imbalance [175], although sick euthyroid syndrome is associated with greater in-hospital and long-term mortality in AMI patients undergoing percutaneous intervention [176]. Gonadal steroid secretion is also reduced with HPA axis activation [163], with evidence maintenance of testosterone levels reduces major adverse cardiovascular events and death [177], while protective effects of estrogen are well established [178]. Finally, prolonged activation of the HPA axis also inhibits growth hormone secretion and IGF-1 [179], with the growth hormone/IGF-1 axis known to reduce CHD risk and protect myocardium against infarction [180,181]. This spectrum of neuroendocrine outcomes with HPA axis dysfunction may collectively contribute to stress intolerance and other myocardial changes. In turn, HPA axis dysfunction has been extensively demonstrated in MDD [26] and other mental illness such as anxiety disorders [182,183]. While links between MDD and myocardial damage can be postulated in terms of mechanisms of autonomic and HPA axis dysregulation, their individual roles and contributions have yet to be detailed. Changes in HPA hormones have potential to modify cell death

processes [40], yet no study has confirmed involvement of HPA dysfunction in the effects of MDD on myocardial infarct tolerance.

3.4 Immuno-inflammatory function

Depression increases pro-inflammatory cytokine production and levels of acute-phase proteins, chemokines and adhesion molecules [184-189] (Figs. 1 & 2). Pro-inflammatory cytokines (eg. IL-1, IL-6, TNF α) promote fatigue, somnolence and withdrawal from social activity [189-191]. Moreover, endotoxin induces anhedonia in rats, coupled with somnolence and reduced exploratory and social behavior and food intake [191], and in humans induces anxiety, depressed mood and impaired memory function [192]. These symptoms have been termed ‘sickness behavior’ [191-195], and mirror the neuro-vegetative features of MDD. Importantly, sickness behavior symptoms induced with pro-inflammatory cytokines are reversed with anti-depressant medication [190,196].

Stress-dependent modulation of the immune response and pro-inflammatory cytokines also increases infection susceptibility [197,198], and in humans chronic stress is associated with susceptibility to viral infection, delayed wound healing, and impaired antibody responses to vaccination [199,200]. These changes are influenced, in turn, by other elements of the integrated network of mechanisms that can result in MDD [26] (Fig. 1). For example, both vagal activity and the HPA axis impact immune function and inflammation, and corticosteroids impair humoral immunity and increase autoimmune inflammatory responses [201] (Figs. 1 and 2). Long-term elevations in cortisol with chronic stress can thus promote autoimmune responses while limiting capacity to fight infection. In addition, myocardial apoptosis with endotoxemia appears to be promoted by β -adrenergic receptor activity [95], suggesting potential synergism between sympathetic activity, immune and inflammatory function in MDD.

Pro-inflammatory cytokines are known to exaggerate myocardial damage during infarction, although effects are complex with evidence of protective actions of transient elevations in cytokines

including TNF α [202], together with roles in promoting post-infarct healing [203-205]. Immune function is also a critical determinant of infarct outcomes and cardioprotection [206-209]. While no studies have effectively confirmed mechanistic involvement of perturbed inflammation and immune function in the impacts of MDD or chronic stress on infarct tolerance, there is evidence for inflammatory cell infiltration, activation of inflammatory signaling, and toll-like receptor 4 and NF κ B dependent myocardial injury in models of chronic stress [41,58]. Chronic stress also increases macrophage infiltration and growth and vulnerability of atherosclerotic plaques, in association with exaggerated infarct occurrence and injury [210].

4. Animal models of depression and their use in studies of infarct tolerance

Modeling human disease in animals poses a major challenge in examining mechanisms governing myocardial phenotype in depression. Issues include the perennial complication of species-specific biology, and questions regarding the nature of behavioral pathologies induced in different models. Importantly, while no single model replicates the range of physiological, psychological and social components of human depression, specific animal models do manifest important elements of the disorder [211]. As outlined by Willner [39], the validity of animal models is determined by 3 characteristics: the model should replicate the symptoms of human depression (face validity); model symptoms should involve neurophysiologic mechanisms corresponding to those in humans (construct validity); and pharmacological or other interventions should appropriately influence behavioral outcomes (predictive validity). Of course, it is problematic to ascertain the true construct validity of any animal model while the neurophysiological mechanisms underpinning human depression remain poorly defined. Limitations or complications relevant to all such models include evidence of significant strain- [212-216], sex- [46,51,217,218] and age-dependent [219-222] outcomes and responses to anti-depressants.

As the diversity of animal models, their pros, cons and relevance to human depression have

been reviewed in detail previously [211,223-225], they are addressed here in brief. Animal models of depression may be generally divided according to the means of induction of depressive behavior:

i) exposure to acute or sub-chronic stress, including the despair-based forced swimming and tail suspension test models. However, there are questions regarding the validity of these models, and they tend to produce limited and short-lasting depressive-like symptoms. On the other hand, the learned helplessness model (discussed below) does generate longer lasting behavioral and cognitive changes and appears a more valid model within this sub-set.

ii) chronic exposure to multiple 'mild' stressors, inducing depressive-like symptoms including anhedonia, reduced activity and changes in appetite and weight. It is important to recognize, however, that the key behavioral indicator of depressive state in these models - anhedonia-like behavior - is not specific to depression, arising in some other behavioral disorders.

iii) modulation of select physiologic processes to manifest depressive symptoms and examine the molecular pathogenesis of depression (eg. modulating HPA axis or immune function). However, considerable heterogeneity in behavioral outcomes may arise in such models, and outcomes may also not be specific to depression.

iv) genetic models [226-228] or surgical manipulations (eg. olfactory bulbectomy [220]) to modify phenotype and behavior, again more relevant in investigating specific pathophysiological elements of depressive disorders.

The three models most widely applied in pre-clinical research in recent years are the chronic mild stress, forced swim test, and learned helplessness models [224]. The former is most commonly applied in studying myocardial stress responses and infarct tolerance. Analyses of myocardial outcomes across a broader range of models are warranted, including effects of the forced swim test and learned helplessness models on infarct incidence and tolerance.

Chronic mild stress. The chronic mild stress model of depression was initially developed over 35 years ago [229,230], and has been adapted by investigators in studying multiple aspects of

depression including cardiac infarct intolerance [44,48-50]. Greater validity and manifestation of long-lasting depressive symptomatology are advantages [39]. The model triggers antidepressant-sensitive anhedonia-like behavior (assessed from reduced sucrose consumption and preference) and other depressive characteristics (reduced exploratory behavior and grooming), together with shifts in neurotransmitter signaling. These behaviors are induced over a 3-9 wk induction period in which differing stressors are applied in random/semi-random order, limiting capacity to adapt. However, widely varying durations of stress across studies may lead to differing outcomes, with the impact(s) of stressor duration yet to be adequately examined. The model is considered superior to the learned helplessness and forced swim test models in terms of the time-course and specific symptoms of depression, and also effects of anti-depressants. Disadvantages are in part practical – the method is highly labor intensive, the variety and durations of stress raise ethical concerns and may limit ethics approval, and importantly the model can be difficult to establish, with considerable variations in outcome despite use of similar protocols [39]. Additionally, repeated stressors (despite randomization) have the potential to induce resilient phenotypes, complicating interpretation. Commonly incorporated within chronic mild stress models, both crowding [231-233] and restraint [234,235] are also employed as individual stressors. However, it is possible resilience/adaptation arises, limiting their applicability. Studies do support a greater capacity to trigger depressive symptoms with unpredictable forms of stress rather than restraint alone [236], and there is also some evidence crowding stress does not alter infarct tolerance [51]. Social isolation as a sole stress has also not been examined for effects on myocardial infarct tolerance, though has been incorporated with other stressors in studies of chronic mild stress [48-50].

Forced swim test. In this model rodents are forced to swim in a partially fluid-filled cylinder in order to survive an inescapable situation. A pre-test swim of ~15 min is thought to induce behavioral despair, and is followed 24 hrs later by a brief 5 min session. Instances and duration of immobility are used as primary indicators of behavioral despair. Although the forced swim test is

widely employed in studies of depression, this is largely a reflection of its simplicity, low cost and short experimental duration rather than model validity, which remains questionable [237,238]. Indeed, the short induction period contrasts patterns of depression development in humans. Moreover, variations in parameters such as number of training sessions, testing durations and equipment dimensions can significantly impact outcomes. Nonetheless, the practical aspects of the model render it popular in high-throughput screening of anti-depressant responses [239]. The model has not yet been applied in studying potential shifts in cardiac infarct tolerance.

Learned helplessness. The learned helplessness model is increasingly employed, though yet to be applied in studying effects on cardiovascular phenotype and stress tolerance. Helplessness is a central feature of clinical depression, and is inducible in animal models. Learned helplessness reflects a failure to control unpleasant stimuli, and subsequently avoid stressful events. Unavoidable electrical shocks are used to induce helplessness in rodents, leading to development of 'escape failure' - a negative coping strategy in which animals no longer avoid stress. The model induces depressive symptoms, including anxiety-like behavior, and decreased exploratory behavior, locomotion and body growth [240-243]. Nonetheless, it is important to note that inescapable stress in humans induces short-term depressive-like symptoms not characteristic of clinical depression. Moreover, from a practical perspective relatively little is known regarding impacts of protocol variations on behavioral and other outcomes. Despite these limitations, together with the complexity of the protocol, need for specialized equipment and application of electrical shocks, learned helplessness is arguably one of the more valid animal models of depression [244]. While not yet studied for impacts on cardiac stress responses and infarct tolerance, the direct and indirect effects of unavoidable electrical shock were recently studied by Rakhshan and colleagues [47].

4.1. Application in studies of cardiac ischemic tolerance

Changes in myocardial responses to ischemia-reperfusion have only been assessed in a sub-

set of these depression models. Inhibitory effects on ischemic tolerance have been demonstrated in models of chronic mild stress that include: 20 day administration of stressors (daylight/darkness exposure, overcrowding, isolation, new hierarchy, cage tilting, restriction of water or food) [44]; or 21 days of randomized stressors (confinement to a small cage, restraint, water deprivation, food deprivation, isolation, flashing light, forced cold water swimming, group-housing in a soiled cage) [48-50]. Scheuer *et al.* tested the effects of chronic (1-2 hrs/day for up to 14 days) restraint stress [42], while crowding stress was assessed by Ravingerova *et al.* (living space reduced from 480 cm²/rat to 200 cm²/rat for 8 wks) [45] and Ledvenyiova-Farkasova *et al.* (living space reduced from 200 to 70 cm²/100 g body mass for 2 weeks) [51]. Rakhshan *et al.* employed a model of daily electrical shocks (over a 1 hr period/day for 1 wk) or witnessing shocks in communal housing [47], mimicking in part elements of the learned helplessness model. As detailed above, these forms of chronic stress increase both infarction and contractile dysfunction [42,47], or selectively influence contractile recovery [45,51]. Infarct intolerance is also evident in stress models reflective of other disorders, including sleep deprivation [56] and a predator/stress model of PTSD [46]. Interestingly, 2 weeks of crowding stress studied by Ledvényiová-Farkašová and colleagues [51] failed to influence infarct tolerance in normotensive animals, though selectively reduced contractile recoveries in female hearts (association with reduced NOS activity). This contrasts outcomes in models of restraint stress [42], chronic mild stress [40,44,48-50] and physical and psychological stress [47], suggestive of a lesser cardiac impact of crowding. Although it has been noted that chronic stress can yield mixed results in terms of myocardial infarct tolerance [52], this may reflect differing cardiovascular responses to metabolic vs. psychologic stressors. For example, both short-term and chronic hypoxic stressors are cardioprotective [245], as are brief and chronic caloric limitation [246] or physical exercise [247]. However, in the case of chronic ‘forced’ exercise, attendant psychological stress may contribute to cardiac detriment that is resistant to metabolic modulation [248].

A key limitation in a number of these investigations is failure to undertake behavioral assessment to confirm depressive states prior to myocardial insult. The studies in which behavioral responses were validated prior to ischemic injury include those of chronic mild stress by Wang *et al.* [48-50] and Xingxing *et al.* [40], and the work of Rorabaugh and colleagues in a model of PTSD [46]. No behavioral outcomes were assessed in other studies of the cardiac impacts of chronic mild stress [44], or chronic physical or psychological [47], restraint [43] or crowding [45] stress. Studies of other negative cardiovascular consequences of stress also fail to adequately assess associated behavioral changes [58].

5. Relevance to clinical cardioprotection

Beyond reducing the risk and prevalence of CHD, a long-running and intractable challenge in cardiology has been the development of cardioprotective therapy to limit myocardial injury with AMI or ischemic surgery [28-30,249]. Early reperfusion remains the sole approach to salvage ischemic tissue, yet itself induces additional damage, and benefit remains variable and highly time-sensitive. There are few clinical scenarios in which outcome is so critically time-dependent: reperfusion is optimal within a 1.5-2 hr window that is rarely achieved in AMI - most Australians for example are reperfused >2.5 hrs from symptom onset, with less than 25% receiving 'timely' reperfusion [250]. Even optimally timed reperfusion yields highly variable outcomes [251]. As we and others argue [27-30], failure to clinically translate cardioprotection reflects in part failure to address the negative influences of aging, drugs and common co-morbid conditions (including atherosclerosis, obesity, diabetes, hypertension) on the myocardial defense mechanisms targeted by widely studied and trialed interventions. Though highly effective in young healthy hearts, many cardioprotective interventions appear less effective (if at all) in older hearts or in the presence of other co-morbid conditions. Depression is thus a key co-morbidity that has received even less attention than aging, obesity, diabetes or hypertension. Approximately 20% of CHD patients suffer

from MDD [8,34], while up to 25% of patients suffer depression post-infarction [252]. Thus, approaches to both acute protection against AMI and also later protection against delayed injury and remodeling may be significantly impacted.

The depressed CHD patient may pose a particularly problematic challenge. Protection via pre-conditioning may require cardiac nerve activity [105], although this remains contentious [101], and both vagal activity [142-144] and sympathetic signaling [106,107,253,254] have been implicated in ischemic pre- and post-conditioning responses. Thus, the sympathetic and vagal dysfunction potentially worsening infarct tolerance with depression may render these hearts less responsive to conditioning interventions. The effects of MDD and chronic stress on the expression and functionality of protective signaling pathways engaged by these stimuli, including the ‘reperfusion injury salvage kinase’ or RISK path [255], and the ‘survivor activating factor enhancement’ or SAFE path [202], are largely unstudied. To date only one investigation has directly tested the effects of depression on conditioning responses, supporting inhibition of ischemic post-conditioning in a rat model of chronic mild stress, potentially involving impaired post-ischemic activation of protein kinase B and STAT-3 [256]. Curiously, the study did not identify any impact of chronic mild stress on infarct size in non-preconditioned hearts, contrary to other reports of exaggerated cell death and infarction in similar models [40,44,48-50].

6. Myocardial effects of anti-depressants

Interactions between mood and cardiac phenotype are further evidenced by beneficial myocardial effects of anti-depressants [257], which can also improve AMI outcomes and CHD mortality [258]. However, it is important to highlight that to date no fully powered study has confirmed that anti-depressant (or psycho) therapy improves survival following AMI. Although consistent with the detrimental cardiac impacts of depression, interpretation of the above findings is complicated by pleiotropic cardioprotective effects of such agents [259,260]. Moreover, other

agents exhibiting cardioprotective actions also mediate anti-depressant effects (*eg.* resveratrol [261]), supporting a broad influence of cardiovascular health on depression. A detailed analysis of the cardioprotective effects of anti-depressants is needed, in particular identifying the molecular mechanisms of such effects, and whether these agents can act directly on the myocardium, independently of effects within the central nervous system.

7. Concluding remarks

In summary, studies to date indicate that models of depression worsen myocardial death and dysfunction following ischemia or infarction. However, there is a need to perform studies in a broader range of animal models (with behavioral outcomes confirmed), and the upstream mediators and molecular basis of myocardial changes remain to be detailed. In terms of neurohumoral mediators, there is some limited evidence for involvement of sympathetic over-activity [47], coupled with indirect evidence implicating catecholamines and 5-HT [40]. Further delineation of the roles of the major components of the PINE network - the autonomic nervous, immune and inflammatory systems, and the HPA axis - in inducing myocardial infarct intolerance with MDD is critical in understanding the reciprocal relationship between MDD and CHD. At the level of the myocardium itself, we also have a rather basic view of alterations in chronic stress models of MDD (or indeed MDD patients), with injury end-points primarily assessed to date. These studies support exaggerated oxidative and nitrosative damage [44], altered expression of Bcl-2 proteins and increased apoptosis and infarction [48-50], leaving the regulatory or signaling basis somewhat obscure: how are molecular oxidative and nitrosative damage exaggerated, Bcl-2 proteins and apoptosis pathways modified, and infarction worsened by MDD? Equally important - how does chronic stress or MDD influence the heart's intrinsic cytoprotective mechanisms and responsiveness to cardioprotective therapies. A single study indicates depression negates the ability of ischemic post-conditioning to limit infarction in rats [256], suggesting that depressive states may

be an additional factor in the inability of cardioprotective stimuli to limit infarction in those suffering CHD [29,30,249]. Identifying specific myocardial modifications underlying impaired infarct tolerance can facilitate development of approaches to improving cardiac phenotype and ischemic outcomes in this significant patient population.

Acknowledgements: There are no acknowledgements

Disclosures: None declared.

Funding: The work was supported by Griffith University and the Menzies Health Institute QLD.

References

1. Charlson FJ, Stapelberg NJ, Baxter AJ, Whiteford HA. Should global burden of disease estimates include depression as a risk factor for coronary heart disease? *BMC Med* 9 (2011) 47.
2. Stapelberg NJ, Neumann DL, Shum DH, McConnell H, Hamilton-Craig I. A topographical map of the causal network of mechanisms underlying the relationship between major depressive disorder and coronary heart disease. *Aust NZ J Psychiatry* 45 (2011) 351-369.
3. Stapelberg NJ, Hamilton-Craig I, Neumann DL, Shum DH, McConnell H. Mind and heart: heart rate variability in major depressive disorder and coronary heart disease - a review and recommendations. *Aust NZ J Psychiatry* 46 (2012) 946-957.
4. Jiang W, Krishnan RR, O'Connor CM. Depression and heart disease. *CNS Drugs* 16 (2002) 111-127.
5. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. *Am J Prev Med* 23 (2002) 51-61.
6. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med* 65 (2003) 201-210.
7. Goldston K, Baillie AJ. Depression and coronary heart disease: A review of the epidemiological evidence, explanatory mechanisms and management approaches. *Clin Psychol Rev* 28 (2008) 288-306.
8. Carney RM, Rich MW, Tevelde A, Saini J, Clark K, Jaffe AS. Major depressive disorder in coronary artery disease. *Am J Cardiol* 60 (1987) 1273-1275.
9. Rugulies R. Depression as a predictor for coronary heart disease. A review and meta-analysis. *Am J Prev Med* 23 (2002) 51-61.
10. Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, van Eijk JT, van Tilburg W. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry* 58 (2001) 221-227.

11. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med* 66 (2004) 802-813.
12. Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, Fauerbach JA, Bush DE, Ziegelstein RC. Prevalence of depression in survivors of acute myocardial infarction. *J Gen Intern Med* 21 (2006) 30–38.
13. Williams MS. Platelets and depression in cardiovascular disease: A brief review of the current literature. *World J Psychiatr* 2 (2012) 114-123.
14. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 99 (1999) 2192-2217.
15. Kuper H, Marmot M, Hemingway H. Systematic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of coronary heart disease. *Sem Vasc Med* 2 (2002) 267-314.
16. Bunker SJ, Colquhoun DM, Esler MD, Hickie IB, Hunt D, Jelinek VM, Oldenburg BF, Peach HG, Ruth D, Tennant CC, Tonkin AM. "Stress" and coronary heart disease: psychosocial risk factors National Heart Foundation of Australia position statement update. *Med J Aust* 178 (2003), 272-276.
17. van Melle JP, de Jonge P, Spijkerman TA, Tijssen JG, Ormel J, van Veldhuisen DJ, van den Brink RH, van den Berg MP. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis. *Psychosom Med* 66 (2004) 814-822.
18. Schulman J, Shapiro P. Depression and cardiovascular disease: what is the correlation. *Psychiatric Times* 25 (2008) 41.
19. Rosenström T, Jokela M. Reconsidering the definition of major depression based on collaborative psychiatric epidemiology surveys. *J Affect Disord* 207 (2017) 38-46.
20. Patten SB, Williams JV, Lavorato DH, Wang JL, McDonald K, Bulloch AG. Descriptive epidemiology of major depressive disorder in Canada in 2012. *Can J Psychiatry* 60 (2015) 23-30.

21. Picco L, Subramaniam M, Abdin E, Vaingankar JA, Chong SA. Gender differences in major depressive disorder: findings from the Singapore Mental Health Study. *Singapore Med J* (2016) doi: 10.11622/smedj.2016144. [Epub ahead of print].
22. Fernandez-Pujals AM, Adams MJ, Thomson P, McKechnie AG, Blackwood DH, Smith BH, Dominiczak AF, Morris AD, Matthews K, Campbell A, Linksted P, Haley CS, Deary IJ, Porteous DJ, MacIntyre DJ, McIntosh AM. Epidemiology and heritability of major depressive disorder, stratified by age of onset, sex, and illness course in generation Scotland: Scottish Family Health Study (GS:SFHS). *PLoS One* 10 (2015) e0142197.
23. Whittier AB, Gelaye B, Deyessa N, Bahretibeb Y, Kelkile TS, Berhane Y, Williams MA. Major depressive disorder and suicidal behavior among urban dwelling Ethiopian adult outpatients at a general hospital. *J Affect Disord* 197 (2016) 58-65.
24. Zhong BL, Liu TB, Chan SS, Jin D, Hu CY, Dai J, Chiu HF. Prevalence and correlates of major depressive disorder among rural-to-urban migrant workers in Shenzhen, China. *J Affect Disord* 183 (2015) 1-9.
25. Baxter AJ, Scott KM, Ferrari AJ, Norman RE, Vos T, Whiteford HA. Challenging the myth of an "epidemic" of common mental disorders: trends in the global prevalence of anxiety and depression between 1990 and 2010. *Depress Anxiety* 31 (2014) 506-516.
26. Stapelberg NJC, Neumann DL, Shum DHK, McConnell H, Hamilton-Craig I. Physiome to pathome: A systems biology model of major depressive disorder and the psycho-immune-neuroendocrine network. *Current Psych Rev* 11 (2015) 32-62.
27. Peart JN, Headrick JP. Clinical cardioprotection and the value of conditioning responses. *Am J Physiol Heart Circ Physiol* 296 (2009) H1705-H1720.
28. Przyklenk K. Efficacy of cardioprotective 'conditioning' strategies in aging and diabetic cohorts: the co-morbidity conundrum. *Drugs Aging* 28 (2011) 331-343.
29. Hausenloy DJ, Erik Bøtker H, Condorelli G, Ferdinandy P, Garcia-Dorado D, Heusch G,

- Lecour S, van Laake LW, Madonna R, Ruiz-Meana M, Schulz R, Sluijter JP, Yellon DM, Ovize M. Translating cardioprotection for patient benefit: position paper from the Working Group of Cellular Biology of the Heart of the European Society of Cardiology. *Cardiovasc Res* 98 (2013) 7-27.
30. Headrick JP, See Hoe LE, Du Toit EF, Peart JN. Opioid receptors and cardioprotection - 'Opioidergic conditioning' of the heart. *Br J Pharmacol* 172 (2015) 2026-2050.
31. Steptoe A, Feldman PJ, Kunz S, Owen N, Willemsen G, Marmot M. Stress responsivity and socioeconomic status: A mechanism for increased cardiovascular disease risk? *Eur Heart J* 23 (2002) 1757–1763.
32. Brunner EJ, Chandola T, Marmot MG. Prospective effect of job strain on general and central obesity in the Whitehall II study. *Am J Epidemiol* 165 (2007) 828-883.
33. Boehm JK, Peterson C, Kivimaki M, Kubzansky LD. Heart health when life is satisfying: evidence from the Whitehall II cohort study. *Eur Heart J* 32 (2011) 2672-2677.
34. Gonzalez MB, Snyderman TB, Colket JT, Arias RM, Jiang JW, O'Connor CM, Krishnan KR. Depression in patients with coronary artery disease. *Depression* 4 (1996) 57- 62.
35. Carney RM, Saunders RD, Freedland KE, Stein P, Rich MW, Jaffe AS. Association of depression with reduced heart rate variability in coronary artery disease. *Am J Cardiol* 76 (1995) 562-564.
36. Grippo AJ, Moffitt JA, Johnson AK. Cardiovascular alterations and autonomic imbalance in an experimental model of depression. *Am J Physiol Regul Int Comp Physiol* 282 (2002) R1333-R1341.
37. Strekalova T, Spanagel R, Bartsch D, Henn FA, Gass P. Stress-induced anhedonia in mice is associated with deficits in forced swimming and exploration. *Neuropsychopharmacology* 29 (2004) 2007-2017.
38. Willner P, Muscat R, Papp M. Chronic mild stress-induced anhedonia: a realistic animal model of depression. *Neurosci Biobehav Rev* 16 (1992) 525-534.
39. Willner P. Validity, reliability and utility of the chronic mild stress model of depression: a 10-

- year review and evaluation. *Psychopharmacology* 134 (1997) 1319-1329.
40. Xinxing W, Wei L, Lei W, Rui Z, Baoying J, Lingjia Q. A neuroendocrine mechanism of co-morbidity of depression-like behavior and myocardial injury in rats. *PLoS One* 9 (2014) e88427.
  41. Wang RP, Yao Q, Xiao YB, Zhu SB, Yang L, Feng JM, Li DZ, Li XL, Wu JJ, Chen J. Toll-like receptor 4/nuclear factor-kappa B pathway is involved in myocardial injury in a rat chronic stress model. *Stress* 14 (2011): 567-575.
  42. Scheuer DA, Mifflin SW. Repeated intermittent stress exacerbates myocardial ischemia-reperfusion injury. *Am J Physiol* 274 (1998) R470-R475.
  43. Scheuer DA, Mifflin SW. Chronic corticosterone treatment increases myocardial infarct size in rats with ischemia-reperfusion injury. *Am J Physiol* 272 (1997) R2017-R2024.
  44. Mercanoglu G, Safran N, Uzun H, Eroglu L. Chronic emotional stress exposure increases infarct size in rats: the role of oxidative and nitrosative damage in response to sympathetic hyperactivity. *Methods Find Exp Clin Pharmacol* 30 (2008) 745-752.
  45. Ravingerova T, Bernátová I, Matejíková J, Ledvényiová V, Nemčeková M, Pechánová O, Tribulová N, Slezák J. Impaired cardiac ischemic tolerance in spontaneously hypertensive rats is attenuated by adaptation to chronic and acute stress. *Exp Clin Cardiol* 16 (2011) e23–e29.
  46. Rorabaugh BR, Krivenko A, Eisenmann ED, Bui AD, Seeley S, Fry ME, Lawson JD, Stoner LE, Johnson BL, Zoladz PR. Sex-dependent effects of chronic psychosocial stress on myocardial sensitivity to ischemic injury. *Stress* 18 (2015) 645-653.
  47. Rakhshan K, Imani A, Faghihi M, Nabavizadeh F, Golnazari M, Karimian S. Evaluation of chronic physical and psychological stress induction on cardiac ischemia/reperfusion injuries in isolated male rat heart: the role of sympathetic nervous system. *Acta Med Iran* 53 (2015) 482-490.
  48. Wang Y, Xiao Z, Liu X, Berk M: Venlafaxine modulates depression-induced behaviour and the expression of Bax mRNA and Bcl-xl mRNA in both hippocampus and myocardium. *Hum Psychopharmacol* 26 (2011) 95-101.

49. Wang Y, Zhang H, Chai F, Liu X, Berk M. The effects of escitalopram on myocardial apoptosis and the expression of Bax and Bcl-2 during myocardial ischemia/reperfusion in a model of rats with depression. *BMC Psychiatry* 14 (2014) 349.
50. Wang Y, Liu X, Zhang D, Chen J, Liu S, Berk M. The effects of apoptosis vulnerability markers on the myocardium in depression after myocardial infarction. *BMC Med* 11 (2013) 32.
51. Ledvenyiova-Farkasova V, Bernatova I, Balis P, Puzserova A, Bartekova M, Gablovsky I, Ravingerová T. Effect of crowding stress on tolerance to ischemia-reperfusion injury in young male and female hypertensive rats: molecular mechanisms. *Can J Physiol Pharmacol* 93 (2015) 793–802.
52. Eisenmann ED, Rorabaugh BR, Zoladz PR. Acute stress decreases but chronic stress increases myocardial sensitivity to ischemic injury in rodents. *Front Psychiatry* 7 (2016) 71.
53. Przyklenk K, Maynard M, Greiner DL, Whittaker P. Cardioprotection with postconditioning: loss of efficacy in murine models of type-2 and type-1 diabetes. *Antioxid Redox Signal* 14 (2011) 781-790.
54. Peart JN, Pepe S, Reichelt ME, Beckett N, See Hoe L, Ozberk V, Niesman IR, Patel HH, Headrick JP. Dysfunctional survival-signaling and stress-intolerance in aged murine and human myocardium. *Exp Gerontol* 50 (2014) 72-81.
55. Budiono BP, See Hoe LE, Brunt AR, Peart JN, Headrick JP, Haseler LJ. Coupling of myocardial stress resistance and signalling to voluntary activity and inactivity. *Acta Physiol (Oxf)* 218 (2016) 112-122.
56. Zoladz PR, Krivenko A, Eisenmann ED, Bui AD, Seeley SL, Fry ME, Johnson BL, Rorabaugh BR. Sex-dependent effects of sleep deprivation on myocardial sensitivity to ischemic injury. *Stress* 19 (2016) 264-268.
57. Costoli T, Bartolomucci A, Graiani G, Stilli D, Laviola G, Sgoifo A. Effects of chronic psychosocial stress on cardiac autonomic responsiveness and myocardial structure in mice. *Am J*

Physiol Heart Circ Physiol 286 (2004): H2133-H2140.

58. Matsuura N, Nagasawa K, Minagawa Y, Ito S, Sano Y, Yamada Y, Hattori T, Watanabe S, Murohara T, Nagata K. Restraint stress exacerbates cardiac and adipose tissue pathology via β -adrenergic signaling in rats with metabolic syndrome. *Am J Physiol Heart Circ Physiol* 308 (2015) H1275-H1286.

59. Turdi S, Yuan M, Leedy GM, Wu Z, Ren J. Chronic social stress induces cardiomyocyte contractile dysfunction and intracellular Ca^{2+} derangement in rats. *Physiol Behav* 105 (2012): 498-509.

60. Goodson ML, Packard AE, Buesing DR, Maney M, Myers B, Fang Y, Basford JE, Hui DY, Ulrich-Lai YM, Herman JP, Ryan KK. Chronic stress and Rosiglitazone increase indices of vascular stiffness in male rats. *Physiol Behav* 172 (2017): 16-23.

61. Bernátová I, Púzserová A, Navarová J, Csizmadiová Z, Zeman M. Crowding-induced alterations in vascular system of Wistar-Kyoto rats: role of nitric oxide. *Physiol Res* 56 (2007): 667-669.

62. Puzserova A, Slezak P, Balis P, Bernatova I. Long-term social stress induces nitric oxide-independent endothelial dysfunction in normotensive rats. *Stress* 16 (2013): 331-339.

63. Stämpfli SF, Camici GG, Keller S, Rozenberg I, Arras M, Schuler B, Gassmann M, Garcia I, Lüscher TF, Tanner FC. Restraint stress enhances arterial thrombosis in vivo - role of the sympathetic nervous system. *Stress* 17 (2014): 126-132.

64. Matsuhisa F, Kitamura N, Satoh E. Effects of acute and chronic psychological stress on platelet aggregation in mice. *Stress* 17 (2014): 186-192.

65. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul Study. *JAMA* 290 (2003) 215–221.

66. Frasure-Smith N, Lesperance F. Recent evidence linking coronary heart disease and depression. *Can J Psychiatry* 51 (2006) 730-737.

67. Parashar S, Rumsfeld JS, Spertus JA, Reid KJ, Wenger NK, Krumholz HM, Amin A, Weintraub WS, Lichtman J, Dawood N, Vaccarino V. Time course of depression and outcome of myocardial infarction. *Arch Intern Med* 166 (2006) 2035–2043.
68. Hance M, Carney RM, Freedland KE, Skala J. Depression in patients with coronary heart disease : A 12-month follow-up. *Gen Hosp Psychiatry* 18 (1996) 61-65.
69. Aben, Verhey F, Strik J, Lousberg R, Lodder J, Honig A. A comparative study into the one year cumulative incidence of depression after stroke and myocardial infarction. *J Neurol Neurosurg Psychiatry* 74 (2003) 581-585.
70. Shi S, Liang J, Liu T, Yuan X, Ruan B, Sun L, Tang Y, Yang B, Hu D, Huang C. Depression increases sympathetic activity and exacerbates myocardial remodeling after myocardial infarction: evidence from an animal experiment. *PLoS One* 9 (2014) e101734.
71. Kop WJ, Galvao TF, Synowski SJ, Xu W, Can A, O'Shea KM, Gould TD, Stanley WC. Effects of environmental stress following myocardial infarction on behavioral measures and heart failure progression: The influence of isolated and group housing conditions. *Physiol Behav* 152 (2015): 168-174.
72. Malpas SC. Sympathetic nervous system overactivity and its role in the development of cardiovascular disease. *Physiol Rev* 90 (2010) 513–557.
73. Schomig A. Catecholamines in myocardial ischemia. Systemic and cardiac release. *Circulation* 82 (1990) II13-22.
74. Esler M, Turbott J, Schwarz R, Leonard P, Bobik A, Skews H, Jackman G. The peripheral kinetics of norepinephrine in depressive illness. *Arch Gen Psychiatry* 39 (1982) 295-300.
75. Veith RC, Lewis N, Linares OA, Barnes RF, Raskind MA, Villacres EC, Murburg MM, Ashleigh EA, Castillo S, Peskind ER, Pascualy M, Halter JB. Sympathetic nervous system activity in major depression. Basal and desipramine-induced alterations in plasma norepinephrine kinetics. *Arch Gen Psychiatry* 51 (1994) 411-422.

76. Barton DA, Dawood T, Lambert EA, Esler MD, Haikerwal D, Brenchley C, Socratous F, Kaye DM, Schlaich MP, Hickie I, Lambert GW. Sympathetic activity in major depressive disorder: identifying those at increased cardiac risk? *J Hypertens* 25 (2007) 2117-2124.
77. Dalack GW, Roose SP. Perspectives on the relationship between cardiovascular disease and affective disorder. *J Clinical Psych* 51(Suppl) (1990) 4–9.
78. Rechlin T, Weis M, Claus D. Heart rate variability in depressed patients and differential effects of paroxetine and amitriptyline on cardiovascular autonomic functions. *Pharmacopsychiatry* 27 (1994) 124-128.
79. Lehofer M, Moser M, Hoehn-Saric R, McLeod D, Liebmann P, Drnovsek B, Egner S, Hildebrandt G, Zapotoczky HG.. Major depression and cardiac autonomic control. *Biological Psychiatry* 42 (1997) 914-919.
80. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry* 55 (1998) 580-592.
81. Sloan RP, Shapiro PA, Bagiella E, Myers MM, Gorman JM. Cardiac autonomic control buffers blood pressure variability responses to challenge: a psychophysiologic model of coronary artery disease. *Psychosom Med* 61 (1999) 58-68.
82. Tachibana H, Naga Prasad SV, Lefkowitz RJ, Koch WJ, Rockman HA. Level of beta-adrenergic receptor kinase 1 inhibition determines degree of cardiac dysfunction after chronic pressure overload-induced heart failure. *Circulation* 111 (2005) 591-597.
83. Odenstedt J, Linderöth B, Bergfeldt L, Ekre O, Grip L, Mannheimer C, Andrell P. Spinal cord stimulation effects on myocardial ischemia, infarct size, ventricular arrhythmia, and non-invasive electrophysiology in a porcine ischemia-reperfusion model. *Heart Rhythm* 8 (2011) 892–898.
84. Linz D, Wirth K, Ukena C, Mahfoud F, Poss J, Linz B, Böhm M, Neuberger H-R. Renal denervation suppresses ventricular arrhythmias during acute ventricular ischemia in pigs. *Heart Rhythm* 10 (2013) 1525-1530.

85. Shinlapawittayatorn K, Chinda K, Palee S, Surinkaew S, Thunsiri K, Weerateerangkul P, Chattipakorn S, KenKnight BH, Chattipakorn N. Low-amplitude, left vagus nerve stimulation significantly attenuates ventricular dysfunction and infarct size through prevention of mitochondrial dysfunction during acute ischemia-reperfusion injury. *Heart Rhythm* 10 (2013) 1700–1707.
86. Sheng X, Chen M, Huang B, Liu J, Zhou L, Bao M, Li S. Cardioprotective effects of low-level carotid baroreceptor stimulation against myocardial ischemia-reperfusion injury in canine model. *J Interv Card Electrophysiol* 45 (2016) 131-140.
87. Colucci WS, Sawyer DB, Singh K, Communal C. Adrenergic overload and apoptosis in heart failure: implications for therapy. *J Card Fail* 6(2 Suppl 1) (2000) 1-7.
88. Remondino A, Kwon SH, Communal C, Pimentel DR, Sawyer DB, Singh K, Colucci WS. Beta-adrenergic receptor-stimulated apoptosis in cardiac myocytes is mediated by reactive oxygen species/c-Jun NH2-terminal kinase-dependent activation of the mitochondrial pathway. *Circ Res* 92 (2003) 136-138.
89. Yu QJ, Si R, Zhou N, Zhang HF, Guo WY, Wang HC, Gao F. Insulin inhibits beta-adrenergic action in ischemic/reperfused heart: a novel mechanism of insulin in cardioprotection. *Apoptosis* 13 (2008) 305-317.
90. Shin SY, Kim T, Lee HS, Kang JH, Lee JY, Cho KH, Kim DH. The switching role of β -adrenergic receptor signalling in cell survival or death decision of cardiomyocytes. *Nat Commun* 5 (2014) 5777.
91. Liang C, Rounds NK, Dong E, Stevens SY, Shite J, Qin F. Alterations by norepinephrine of cardiac sympathetic nerve terminal function and myocardial beta-adrenergic receptor sensitivity in the ferret: normalization by antioxidant vitamins. *Circulation* 102 (2000) 96-103.
92. Murdoch CE, Zhang M, Cave AC, Shah AM. NADPH oxidase-dependent redox signalling in cardiac hypertrophy, remodelling and failure. *Cardiovasc Res* 71 (2006) 208–215.
93. Hu A, Jiao X, Gao E, Koch WJ, Sharifi-Azad S, Grunwald Z, Ma XL, Sun JZ. Chronic beta-

- adrenergic receptor stimulation induces cardiac apoptosis and aggravates myocardial ischemia/reperfusion injury by provoking inducible nitric-oxide synthase-mediated oxidative stress. *J Pharmacol Exp Ther* 318 (2006) 469-475.
94. Li D, Qu Y, Tao L, Liu H, Hu A, Gao F, Sharifi-Azad S, Grunwald Z, Ma XL, Sun JZ. Inhibition of iNOS protects the aging heart against beta-adrenergic receptor stimulation-induced cardiac dysfunction and myocardial ischemic injury. *J Surg Res* 131 (2006) 64–72.
95. Wang Y, Wang Y, Yang D, Yu X, Li H, Lv X, Lu D, Wang H. β_1 -adrenoceptor stimulation promotes LPS-induced cardiomyocyte apoptosis through activating PKA and enhancing CaMKII and I κ B α phosphorylation. *Crit Care* 19 (2015) 76.
96. Xiong F, Xiao D, Zhang L. Norepinephrine causes epigenetic repression of PKC ϵ gene in rodent hearts by activating Nox1-dependent reactive oxygen species production. *FASEB J* 26 (2012) 2753-2763.
97. Jones CE, Beck LY, DuPont E, Barnes GE. Effects of coronary ligation of the chronically sympathectomized dog ventricle. *Am J Physiol* 235 (1978) H429-H434.
98. Jones CE, Devous MD Sr, Thomas JX Jr, DuPont E. The effect of chronic cardiac denervation on infarct size following acute coronary occlusion. *Am Heart J* 1978; 95: 738-746.
99. Barber MJ, Thomas JX Jr, Jones SB, Randall WC. Effects of sympathetic nerve stimulation and cardiac denervation on MBF during LAD occlusion. *Am J Physiol* 243 (1982) H566-H574.
100. Bharti S, Rani N, Bhatia J, Arya DS. 5-HT_{2B} receptor blockade attenuates β -adrenergic receptor-stimulated myocardial remodeling in rats via inhibiting apoptosis: role of MAPKs and HSPs. *Apoptosis* 20 (2015) 455-465.
101. Kingma JG, Simard D, Voisine P, Rouleau JR. Influence of cardiac decentralization on cardioprotection. *PLoS One* 8 (2013) e79190.
102. Lavalley M, Amano J, Vatner SF, Manders WT, Randall WC, Thomas JX Jr. Adverse effects of chronic cardiac denervation in conscious dogs with myocardial ischemia. *Circ Res* 57 (1985)

383–392.

103. Huang CH, Vatner SF, Peppas AP, Yang G, Kudej RK. Cardiac nerves affect myocardial stunning through reactive oxygen and nitric oxide mechanisms. *Circ Res* 93 (2003) 866-873.
104. Huang M-H, Ardell JL, Hanna BD, Wolf SG, Armour JA. Effects of transient coronary artery occlusion on canine intrinsic cardiac neuronal activity. *Integr Physiol Behav Sci* 28 (1993) 5-21.
105. Kudej RK, Shen YT, Peppas AP, Huang CH, Chen W, Yan L, Vatner DE, Vatner SF. Obligatory role of cardiac nerves and alpha1-adrenergic receptors for the second window of ischemic preconditioning in conscious pigs. *Circ Res* 99 (2006) 1270–1276.
106. Spear JF, Prabu SK, Galati D, Raza H, Anandatheerthavarada HK, Avadhani NG. beta1-Adrenoreceptor activation contributes to ischemia-reperfusion damage as well as playing a role in ischemic preconditioning. *Am J Physiol Heart Circ Physiol* 292 (2007) H2459-H2466.
107. Lochner A, Genade S, Tromp E, Podzuweit T, Moolman JA. Ischemic preconditioning and the beta-adrenergic signal transduction pathway. *Circulation* 100 (1999) 958-966.
108. Lange M, Smul TM, Blomeyer CA, Redel A, Klotz KN, Roewer N, Kehl F. Role of the beta1-adrenergic pathway in anesthetic and ischemic preconditioning against myocardial infarction in the rabbit heart in vivo. *Anesthesiology* 105 (2006) 503-510.
109. See Hoe LE, Schilling JM, Busija AR, Haushalter KJ, Ozberk V, Keshwani MM, Roth DM, Toit ED, Headrick JP, Patel HH, Peart JN. Chronic β 1-adrenoceptor blockade impairs ischaemic tolerance and preconditioning in murine myocardium. *Eur J Pharmacol* 789 (2016) 1-7.
110. Zhang Q, Xiang J, Wang X, Liu H, Hu B, Feng M, Fu Q. Beta(2)-adrenoceptor agonist clenbuterol reduces infarct size and myocardial apoptosis after myocardial ischaemia/reperfusion in anaesthetized rats. *Br J Pharmacol* 160 (2010) 1561-1572.
111. Bhushan S, Kondo K, Predmore BL, Zlatopolsky M, King AL, Pearce C, Huang H, Tao YX, Condit ME, Lefer DJ. Selective β 2-adrenoreceptor stimulation attenuates myocardial cell death and preserves cardiac function after ischemia-reperfusion injury. *Arterioscler Thromb Vasc Biol* 32

(2012) 1865-1874.

112. Rorabaugh BR, Ross SA, Gaivin RJ, Papay RS, McCune DF, Simpson PC, Perez DM.

alpha1A- but not alpha1B-adrenergic receptors precondition the ischemic heart by a staurosporine-sensitive, chelerythrine-insensitive mechanism. *Cardiovasc Res* 65 (2005) 436-445.

113. Huang Y, Wright CD, Merkwang CL, Baye NL, Liang Q, Simpson PC, O'Connell TD. An alpha1A-adrenergic-extracellular signal-regulated kinase survival signaling pathway in cardiac myocytes. *Circulation* 115 (2007) 763-772.

114. Shi T, Papay RS, Perez DM. α 1A-Adrenergic receptor prevents cardiac ischemic damage through PKC δ /GLUT1/4-mediated glucose uptake. *J Recept Signal Transduct Res* 36 (2016) 261-270.

115. Zhao X, Park J, Ho D, Gao S, Yan L, Ge H, Iismaa S, Lin L, Tian B, Vatner DE, Graham RM, Vatner SF. Cardiomyocyte overexpression of the α 1A-adrenergic receptor in the rat phenocopies second but not first window preconditioning. *Am J Physiol Heart Circ Physiol* 302 (2012) H1614-H1624.

116. Zhao X, Balaji P, Pachon R, Beniamen DM, Vatner DE, Graham RM, Vatner SF. Overexpression of cardiomyocyte α 1A-adrenergic receptors attenuates postinfarct remodeling by inducing angiogenesis through heterocellular signaling. *Arterioscler Thromb Vasc Biol* 35 (2015) 2451-2459.

117. Du XJ, Gao XM, Kiriazis H, Moore XL, Ming Z, Su Y, Finch AM, Hannan RA, Dart AM, Graham RM. Transgenic alpha1A-adrenergic activation limits post-infarct ventricular remodeling and dysfunction and improves survival. *Cardiovasc Res* 71 (2006) 735-743.

118. Vecchione C, Fratta L, Rizzoni D, Notte A, Poulet R, Porteri E, Frati G, Guelfi D, Trimarco V, Mulvany MJ, Agabiti-Rosei E, Trimarco B, Cotecchia S, Lembo G. Cardiovascular influences of alpha1b-adrenergic receptor defect in mice. *Circulation* 105 (2002) 1700-1707.

119. Collette KM, Zhou XD, Amoth HM, Lyons MJ, Papay RS, Sens DA, Perez DM, Doze VA.

- Long-term $\alpha 1B$ -adrenergic receptor activation shortens lifespan, while $\alpha 1A$ -adrenergic receptor stimulation prolongs lifespan in association with decreased cancer incidence. *Age (Dordr)* 36 (2014) 9675.
120. Rottenberg J. Cardiac vagal control in depression: a critical analysis. *Biol Psychol* 74 (2007) 200-211.
121. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 59 (1987) 256-262.
122. La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates and cardiovascular mortality among patients with a first myocardial infarction. A prospective study. *Circulation* 78 (1988) 816-824.
123. Kent KM, Smith ER, Redwood DR, Epstein SE. Electrical stability of acutely ischemic myocardium. Influences of heart rate and vagal stimulation. *Circulation* 47 (1973) 291-298.
124. Schwartz PJ, Stone HL. The role of the autonomic nervous system in sudden coronary death. *Ann NY Acad Sci* 382 (1982) 162-181.
125. Zuanetti G, De Ferrari GM, Priori SG, Schwartz PJ. Protective effect of vagal stimulation on reperfusion arrhythmias in cats. *Circ Res* 61 (1987) 429-435.
126. De Ferrari GM, Vanoli E, Stramba-Badiale M, Hull SS Jr, Foreman RD, Schwartz PJ. Vagal reflexes and survival during acute myocardial ischemia in conscious dogs with healed myocardial infarction. *Am J Physiol* 261 (1991) H63-H69.
127. Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS Jr, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. *Circ Res* 68 (1991) 1471-1481.
128. Lasley RD, Van Wylen DGL, Mentzer RM. Evidence for the role of Gi proteins in attenuating myocardial ischaemic damage. *Circulation* (1990) III-759.

129. Thornton JD, Liu GS, Downey JM. Pretreatment with pertussis toxin blocks the protective effects of preconditioning: evidence for a G-protein mechanism. *J Mol Cell Cardiol* 25 (1993) 311-320.
130. Yao Z, Gross GJ. Acetylcholine mimics ischemic preconditioning via a glibenclamide-sensitive mechanism in dogs. *Am J Physiol* 264 (1993) H2221-H2225.
131. Qian YZ, Levasseur JE, Yoshida K, Kukreja RC. KATP channels in rat heart: blockade of ischemic and acetylcholine-mediated preconditioning by glibenclamide. *Am J Physiol* 271 (1996) H23-H28.
132. Yao Z, Tong J, Tan X, Li C, Shao Z, Kim WC, vanden Hoek TL, Becker LB, Head CA, Schumacker PT. Role of reactive oxygen species in acetylcholine-induced preconditioning in cardiomyocytes. *Am J Physiol* 277 (1999) H2504-H2509.
133. Cohen MV, Yang XM, Liu GS, Heusch G, Downey JM. Acetylcholine, bradykinin, opioids, and phenylephrine, but not adenosine, trigger preconditioning by generating free radicals and opening mitochondrial KATP channels. *Circ Res* 89 (2001) 273-278.
134. Richard V, Blanc T, Kaeffer N, Tron C, Thuillez C. Myocardial and coronary endothelial protective effects of acetylcholine after myocardial ischaemia and reperfusion in rats: role of nitric oxide. *Br J Pharmacol* 115 (1995) 1532-1538.
135. Kawada T, Akiyama T, Shimizu S, Kamiya A, Uemura K, Li M, Shirai M, Sugimachi M. Detection of endogenous acetylcholine release during brief ischemia in the rabbit ventricle: a possible trigger for ischemic preconditioning. *Life Sci* 85 (2009) 597-601.
136. Katare RG, Ando M, Kakinuma Y, Arikawa M, Handa T, Yamasaki F, Sato T. Vagal nerve stimulation prevents reperfusion injury through inhibition of opening of mitochondrial permeability transition pore independent of the bradycardiac effect. *J Thorac Cardiovasc Surg* 137 (2009) 223-231.
137. Calvillo L, Vanoli E, Andreoli E, Besana A, Omodeo E, Gneccchi M, Zerbi P, Vago G, Busca

- G, Schwartz PJ Vagal stimulation, through its nicotinic action, limits infarct size and the inflammatory response to myocardial ischemia and reperfusion. *J Cardiovasc Pharmacol* 58 (2011) 500-507.
138. Kong SS, Liu JJ, Hwang TC, Yu XJ, Lu Y, Zang WJ. Tumour necrosis factor- α and its receptors in the beneficial effects of vagal stimulation after myocardial infarction in rats. *Clin Exp Pharmacol Physiol* 38 (2011) 300-306.
139. Shinlapawittayatorn K, Chinda K, Palee S, Surinkaew S, Kumfu S, Kumphune S, Chattipakorn S, KenKnight BH, Chattipakorn N. Vagus nerve stimulation initiated late during ischemia, but not reperfusion, exerts cardioprotection via amelioration of cardiac mitochondrial dysfunction. *Heart Rhythm* 11 (2014) 2278–2287.
140. Uemura K, Zheng C, Li M, Kawada T, Sugimachi M. Early short-term vagal nerve stimulation attenuates cardiac remodeling after reperfused myocardial infarction. *J Card Fail* 16 (2010) 689-699.
141. Zhao M, He X, Bi XY, Yu XJ, Gil Wier W, Zang WJ. Vagal stimulation triggers peripheral vascular protection through the cholinergic anti-inflammatory pathway in a rat model of myocardial ischemia/reperfusion. *Basic Res Cardiol* 108 (2013) 345.
142. Mastitskaya S, Marina N, Gourine A, Gilbey MP, Spyer KM, Teschemacher AG, Kasparov S, Trapp S, Ackland GL, Gourine AV. Cardioprotection evoked by remote ischaemic preconditioning is critically dependent on the activity of vagal pre-ganglionic neurones. *Cardiovasc Res* 95 (2012) 487-489.
143. Donato M, Buchholz B, Rodríguez M, Pérez V, Inserte J, García-Dorado D, Gelpi RJ. Role of the parasympathetic nervous system in cardioprotection by remote hindlimb ischaemic preconditioning. *Exp Physiol* 98 (2013) 425-434.
144. Pickard JM, Davidson SM, Hausenloy DJ, Yellon DM. Co-dependence of the neural and humoral pathways in the mechanism of remote ischemic conditioning. *Basic Res Cardiol* 111

(2016) 50.

145. Yang B, Lin H, Xu C, Liu Y, Wang H, Han H. Choline produces cytoprotective effects against ischemic myocardial injuries: evidence for the role of cardiac m3 subtype muscarinic acetylcholine receptors. *Cell Physiol Biochem* 16 (2005) 163–174.
146. Wang S, Han H, Jiang Y, Wang C, Song HX, Pan ZY, Fan K, Du J, Fan YH, Du ZM, Liu Y. Activation of cardiac M3 muscarinic acetylcholine has cardioprotective effects against ischemia-induced arrhythmias. *Clin Exp Pharmacol Physiol* 39 (2012) 343–349.
147. Li DL, Liu JJ, Liu BH, Hu H, Sun L, Miao Y, Xu HF, Yu XJ, Ma X, Ren J, Zang WJ. Acetylcholine inhibits hypoxia-induced tumor necrosis factor- α production via regulation of MAPKs phosphorylation in cardiomyocytes. *J Cell Physiol* 226 (2011) 1052–1059.
148. Katare RG, Ando M, Kakinuma Y, Arikawa M, Yamasaki F, Sato T. Differential regulation of TNF receptors by vagal nerve stimulation protects heart against acute ischemic injury. *J Mol Cell Cardiol* 49 (2010) 234–244.
149. Yi C, Zhang C, Hu X, Li Y, Jiang H, Xu W, Lu J, Liao Y, Ma R, Li X, Wang J. Vagus nerve stimulation attenuates myocardial ischemia/reperfusion injury by inhibiting the expression of interleukin-17A. *Exp Ther Med* 11 (2016) 171–176.
150. Zhao M, Sun L, Yu X, Miao Y, Liu JJ, Wang H, Ren J, Zang WJ. Acetylcholine mediates AMPK-dependent autophagic cytoprotection in H9c2 cells during hypoxia/reoxygenation injury. *Cell Physiol Biochem* 32 (2013) 601–613.
151. Sun L, Zhao M, Yu X, Wang H, He X, Liu JK, Zang WJ. Cardioprotection by acetylcholine: a novel mechanism via mitochondrial biogenesis and function involving the PGC-1 α pathway. *J Cell Physiol* 228 (2013) 1238–1248.
152. Sun L, Zhao M, Yang Y, Xue RQ, Yu XJ, Liu JK, Zang WJ. Acetylcholine attenuates hypoxia/reoxygenation injury by inducing mitophagy through PINK1/Parkin signal pathway in H9c2 cells. *J Cell Physiol* 231 (2016) 1171–1181.

153. Xue RQ, Sun L, Yu XJ, Li DL, Zang WJ. Vagal nerve stimulation improves mitochondrial dynamics via an M3 receptor/CaMKK β /AMPK pathway in isoproterenol-induced myocardial ischaemia. *J Cell Mol Med*. 21 (2017) 58-71.
154. Xu M, Bi X, He X, Yu X, Zhao M, Zang W. Inhibition of the mitochondrial unfolded protein response by acetylcholine alleviated hypoxia/reoxygenation-induced apoptosis of endothelial cells. *Cell Cycle* 15 (2016) 1331-1343.
155. Miao Y, Zhou J, Zhao M, Liu J, Sun L, Yu X, He X, Pan X, Zang W. Acetylcholine attenuates hypoxia/ reoxygenation-induced mitochondrial and cytosolic ROS formation in H9c2 cells via M2 acetylcholine receptor. *Cell Physiol Biochem* 31 (2013) 189–198.
156. Zhao J, Su Y, Zhang Y, Pan Z, Yang L, Chen X, Liu Y, Lu Y, Du Z, Yang B. Activation of cardiac muscarinic M3 receptors induces delayed cardioprotection by preserving phosphorylated connexin43 and up-regulating cyclooxygenase-2 expression. *Br J Pharmacol* 159 (2010) 1217-1225.
157. Xiong J, Yuan YJ, Xue FS, Wang Q, Cheng Y, Li RP, Liao X, Liu JH. Postconditioning with $\alpha 7$ nAChR agonist attenuates systemic inflammatory response to myocardial ischemia-reperfusion injury in rats. *Inflammation* 35 (2012) 1357-1364.
158. Li XW, Wang H. Non-neuronal nicotinic alpha 7 receptor, a new endothelial target for revascularization. *Life Sci* 78 (2006) 1863-1870.
159. De Ferrari GM, Crijns HJ, Borggrefe M, Milasinovic G, Smid J, Zabel M, Gavazzi A, Sanzo A, Dennert R, Kuschyk J, Raspopovic S, Klein H, Swedberg K, Schwartz PJ; CardioFit Multicenter Trial Investigators. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. *Eur Heart J* 32 (2011) 847-855.
160. Schwartz PJ. Vagal stimulation for heart diseases: from animals to men. An example of translational cardiology. *Circ J* 75 (2011) 20–27.
161. Dicarlo L, Libbus I, Amurthur B, Kenknight BH, Anand IS. Autonomic regulation therapy for

the improvement of left ventricular function and heart failure symptoms: the ANTHEM-HF study. *J Card Fail* 19 (2013) 655–660.

162. Sabbah HN, Imai M, Zaretsky A, Rastogi S, Wang M, Jiang A. Therapy with vagus nerve electrical stimulation combined with beta-blockade improves left ventricular systolic function in dogs with heart failure beyond that seen with beta-blockade alone. *Eur J Heart Fail* 6(Suppl. 1) (2007) 114.

163. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Rev* 21 (2000) 55-89.

164. Eskandari F, Sternberg EM. Neural-immune interactions in health and disease. *Ann N Y Acad Sci* 966 (2002) 20-27.

165. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *J Psychosom Res* 53 (2002) 865-871.

166. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 332 (1995) 1351-1362.

167. Sambhi MP, Weil MH, Udhoji VN. Acute pharmacodynamic effects of glucocorticoids cardiac output and related hemodynamic changes in normal subjects and patients in shock. *Circulation* 31 (1965) 523-530.

168. Ansley DM, Wang B. Oxidative stress and myocardial injury in the diabetic heart. *J Pathol* 229 (2013) 232-241.

169. Angeli F, Reboldi G, Poltronieri C, Lazzari L, Sordi M, Garofoli M, Bartolini C, Verdecchia P. Hyperglycemia in acute coronary syndromes: from mechanisms to prognostic implications. *Ther Adv Cardiovasc Dis* 9 (2015) 412-424.

170. Sparagna GC, Hickson-Bick DL. Cardiac fatty acid metabolism and the induction of apoptosis. *Am J Med Sci* 318 (1999) 15-21.

171. Okere IC, Chandler MP, McElfresh TA, Rennison JH, Sharov V, Sabbah HN, Tserng KY, Hoit BD, Ernsberger P, Young ME, Stanley WC. Differential effects of saturated and unsaturated fatty acid diets on cardiomyocyte apoptosis, adipose distribution, and serum leptin. *Am J Physiol Heart Circ Physiol* 291 (2006) H38-H44.
172. Ji L, Fu F, Zhang L, Liu W, Cai X, Zhang L, Zheng Q, Zhang H, Gao F. Insulin attenuates myocardial ischemia/reperfusion injury via reducing oxidative/nitrative stress. *Am J Physiol Endocrinol Metab* 298 (2010) E871-E880.
173. Benker G, Raida M, Olbricht T, Wagner R, Reinhardt W, Reinwein D. TSH secretion in Cushing's syndrome: relation to glucocorticoid excess, diabetes, goitre, and the 'sick euthyroid syndrome'. *Clin Endocrinol* 33 (1990) 777-786.
174. Novitzky D, Cooper DK. Thyroid hormone and the stunned myocardium. *J Endocrinol* 223 (2014) R1-R8
175. Hsu RB, Huang TS, Chen YS, Chu SH. Effect of triiodothyronine administration in experimental myocardial injury. *J Endocrinol Invest* 18 (1995) 702-709.
176. Özcan KS, Osmonov D, Toprak E, Güngör B, Tatlısu A, Ekmekçi A, Kaya A, Tayyareci G, Erdinler İ. Sick euthyroid syndrome is associated with poor prognosis in patients with ST segment elevation myocardial infarction undergoing primary percutaneous intervention. *Cardiol J* 21 (2014) 238-244.
177. Anderson JL, May HT, Lappé DL, Bair T, Le V, Carlquist JF, Muhlestein JB. Impact of testosterone replacement therapy on myocardial infarction, stroke, and death in men with low testosterone concentrations in an integrated health care system. *Am J Cardiol* 117 (2016) 794-799
178. Deschamps AM, Murphy E, Sun J. Estrogen receptor activation and cardioprotection in ischemia reperfusion injury. *Trends Cardiovasc Med* 20 (2010) 73-78.
179. Burguera B, Muruais C, Penalva A, Dieguez C, Casanueva F. Dual and selective actions of glucocorticoids upon basal and stimulated growth hormone release in man. *Neuroendocrinology* 51

(2008) 51-58.

180. Colao A. The GH-IGF-I axis and the cardiovascular system: clinical implications. *Clin Endocrinol (Oxf)* 69 (2008) 347-358.

181. Troncoso R, Ibarra C, Vicencio JM, Jaimovich E, Lavandero S. New insights into IGF-1 signaling in the heart. *Trends Endocrinol Metab* 25 (2014) 128-137.

182. Stokes PE, Sikes CR. Hypothalamic-pituitary-adrenal axis in psychiatric disorders. *Annu Rev Med* 42 (1991) 519-531.

183. Jacobson L. Hypothalamic-pituitary-adrenocortical axis: neuropsychiatric aspects. *Compr Physiol* 4 (2014) 715-738.

184. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine* 9 (1997) 853-858.

185. Lanquillon S, Krieg J, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology* 22 (2000) 370-379.

186. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. *Am J Cardiol* 90 (2002) 1279-1283.

187. Danner M, Kasl SV, Abramson JL, Vaccarino V. Association between depression and elevated C-reactive protein. *Psychosom Med* 65 (2003) 347-356.

188. Alesci S, Martinez PE, Kelkar S, Ilias I, Ronsaville DS, Listwak SJ, Ayala AR, Licinio J, Gold HK, Kling MA, Chrousos GP, Gold PW. Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. *J Clin Endocrinol Metab* 90 (2005) 2522-2530.

189. Leff P, Hernández-Gutiérrez ME, Becerril LE, Martínez C, Téllez-Santillán C, Pérez-Tapia M, Salazar A, Antón B, Berlanga C, Pavón L. The interacting neuroendocrine network in stress-inducing mood disorders. *Open Neuroendocrinol J* 3 (2010) 180-207.

190. Anisman H, Merali Z. Cytokines, stress and depressive illness: brain-immune interactions. *Ann Med* 35 (2003) 2-11.
191. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 9 (2008) 46-56.
192. Reichenberg A, Yirmiya R, Schuld A, Schuld A, Kraus T, Haack M, Morag A, Pollmächer T. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry* 58 (2001) 445-452.
193. Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychol Rev* 105 (1998) 83-107.
194. Capuron L, Lamarque D, Dantzer R, Goodall G. Attentional and mnemonic deficits associated with infectious disease in humans. *Psychol Med* 29 (1999) 291-297.
195. Dantzer R. Cytokine, sickness behavior, and depression. *Immunol Allergy Clin North Am* 29 (2009) 247-264.
196. Pavón L, Sandoval-López G, Eugenia Hernández M, Loria F, Estrada I, Pérez M, Moreno J, Avila U, Leff P, Antón B, Heinze G. Th2 cytokine response in Major Depressive Disorder patients before treatment. *Neuroimmunol* 172 (2006) 156-165.
197. Bonneau RH, Sheridan JF, Feng N, Glaser R. Stress-induced modulation of the primary cellular immune response to herpes simplex virus infection is mediated by both adrenal-dependent and independent mechanisms. *J Neuroimmunol* 42 (1993) 167-176.
198. Glaser R, Kiecolt-Glaser JK. Stress-associated immune modulation: relevance to viral infections and chronic fatigue syndrome. *Am J Med* 105 (1998) 35S-42S.
199. Rozlog LA, Kiecolt-Glaser JK, Marucha PT, Sheridan JF, Glaser R. Stress and immunity: implications for viral disease and wound healing. *J Periodontol* 70 (1999) 786-792.

200. Vedhara K, Cox NK, Wilcock GK, Perks P, Hunt M, Anderson S, Lightman SL, Shanks NM. Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. *Lancet* 353 (1999) 627-631.
201. Correa SG, Maccioni M, Rivero VE, Iribarren P, Sotomayor CE, Riera CM. Cytokines and the immune-neuroendocrine network: What did we learn from infection and autoimmunity? *Cytokine Growth Factor Rev* 18 (2007) 125-134.
202. Lecour S. Multiple protective pathways against reperfusion injury: a SAFE path without Aktion? *J Mol Cell Cardiol* 46 (2009) 607-609.
203. Ren G, Dewald O, Frangogiannis NG. Inflammatory mechanisms in myocardial infarction. *Curr Drug Targets Inflamm Allergy* 2 (2003) 242-256.
204. Zhang M, Chen L. Status of cytokines in ischemia reperfusion induced heart injury. *Cardiovasc Hematol Disord Drug Targets* 8 (2008) 161-172.
205. Kleinbongard P, Heusch G, Schulz R. TNFalpha in atherosclerosis, myocardial ischemia/reperfusion and heart failure. *Pharmacol Ther* 127 (2010) 295-314.
206. Smith RM, Lecour S, Sack MN. Innate immunity and cardiac preconditioning: a putative intrinsic cardioprotective program. *Cardiovasc Res* 55 (2002) 474-482.
207. Arslan F, de Kleijn DP, Pasterkamp G. Innate immune signaling in cardiac ischemia. *Nat Rev Cardiol* 8 (2011) 292-300.
208. Arslan F, Keogh B, McGuirk P, Parker AE. TLR2 and TLR4 in ischemia reperfusion injury. *Mediators Inflamm* 2010 (2010) 704202.
209. Lin L, Knowlton AA. Innate immunity and cardiomyocytes in ischemic heart disease. *Life Sci* 100 (2014) 1-8.
210. Roth L, Rombouts M, Schrijvers DM, Lemmens K, De Keulenaer GW, Martinet W, De Meyer GR. Chronic intermittent mental stress promotes atherosclerotic plaque vulnerability, myocardial infarction and sudden death in mice. *Atherosclerosis* 242 (2015): 288-294.

211. Czéh B, Fuchs E, Wiborg O, Simon M. Animal models of major depression and their clinical implications. *Prog Neuro-Psychopharmacol Biol Psychiatry* 64 (2016) 293-310.
212. Lucki I, Dalvi A, Mayorga AJ. Sensitivity to the effects of pharmacologically selective antidepressants in different strains of mice. *Psychopharmacology (Berl)* 155 (2001) 315-322.
213. Pothion S, Bizot JC, Trovero F, Belzung C. Strain differences in sucrose preference and in the consequences of unpredictable chronic mild stress. *Behav Brain Res* 155 (2004) 135-146.
214. Crowley JJ, Blendy JA, Lucki I. Strain-dependent antidepressant-like effects of citalopram in the mouse tail suspension test. *Psychopharmacology (Berl)* 183 (2005) 257-264.
215. Ibarguen-Vargas Y, Surget A, Touma C, Palme R, Belzung C Multifaceted strain-specific effects in a mouse model of depression and of antidepressant reversal. *Psychoneuroendocrinology* 33 (2008) 1357-1368.
216. Yalcin I, Belzung C, Surget A. Mouse strain differences in the unpredictable chronic mild stress: a four-antidepressant survey. *Behav Brain Res* 193 (2008) 140-143.
217. Dalla C, Pitychoutis PM, Kokras N, Papadopoulou-Daifoti Z. Sex differences in animal models of depression and antidepressant response. *Basic Clin Pharmacol Toxicol* 106 (2010) 226-233.
218. Page GG, Opp MR, Kozachik SL. Sex differences in sleep, anhedonia, and HPA axis activity in a rat model of chronic social defeat. *Neurobiol Stress* 3 (2016) 105-113.
219. Abel EL. Ontogeny of immobility and response to alarm substance in the forced swim test. *Physiol Behav* 54 (1993) 713-716.
220. Slotkin TA, Miller DB, Fumagalli F, McCook EC, Zhang J, Bissette G, Seidler FJ. Modeling geriatric depression in animals: biochemical and behavioral effects of olfactory bulbectomy in young versus aged rats. *J Pharmacol Exp Ther* 289 (1999) 334-345.
221. Martinez-Mota L, Ulloa RE, Herrera-Perez J, Chavira R, Fernandez-Guasti A. Sex and age differences in the impact of the forced swimming test on the levels of steroid hormones. *Physiol*

Behav 104 (2011) 900-905.

222. Mitchell NC, Koek W, Daws LC. Antidepressant-like effects and basal immobility depend on age and serotonin transporter genotype. *Genes Brain Behav* 14 (2015) 543-549.

223. Pollak DD, Rey CE, Monje FJ. Rodent models in depression research: classical strategies and new directions. *Ann Med* 42 (2010) 252-264.

224. Yin X, Guven N, Dietis N. Stress-based animal models of depression: Do we actually know what we are doing? *Brain Res* 1652 (2016) 30-42.

225. Carnevali L, Montano N, Statello R, Sgoifo A. Rodent models of depression-cardiovascular comorbidity: Bridging the known to the new. *Neurosci Biobehav Rev* (2017) doi: 10.1016/j.neubiorev.2016.11.006. [Epub ahead of print].

226. Cryan JF, Mombereau C. In search of a depressed mouse: utility of models for studying depression-related behavior in genetically modified mice. *Mol Psychiatry* 9 (2004) 326-357.

227. Wegener G, Mathe AA, Neumann ID. Selectively bred rodents as models of depression and anxiety. *Curr Top Behav Neurosci* 12 (2012) 139-187.

228. Barkus C. Genetic mouse models of depression. *Curr Top Behav Neurosci* 14 (2013) 55-78.

229. Katz RJ, Roth KA, Carroll BJ. Acute and chronic stress effects on open field activity in the rat: implications for a model of depression. *Neurosci Biobehav Rev* 5 (1981) 247-251.

230. Roth KA, Katz RJ. Further studies on a novel animal model of depression: therapeutic effects of a tricyclic antidepressant. *Neurosci Biobehav Rev* 5 (1981) 253-258.

231. Armario A, Ortiz R, Balasch J. Effect of crowding on some physiological and behavioral variables in adult male rats. *Physiol Behav* 32 (1984) 35-37.

232. Bugajski J, Borycz J, Glod R, Bugajski AJ. Crowding stress impairs the pituitary-adrenocortical responsiveness to the vasopressin but not corticotropin-releasing hormone stimulation. *Brain Res* 681 (1995) 223-228.

233. Sgoifo A, Koolhaas J, De Boer S, Musso E, Stilli D, Buwalda B, Meerlo P. Social stress,

- autonomic neural activation, and cardiac activity in rats. *Neurosci Biobehav Rev* 23 (1999) 915-923.
234. Purdy RH, Morrow AL, Moore PH Jr, Paul SM. Stress-induced elevations of gamma-aminobutyric acid type A receptor-active steroids in the rat brain. *Proc Natl Acad Sci USA* 88 (1991) 4553-4557.
235. Resstel LB, Tavares RF, Lisboa SF, Joca SR, Correa FM, Guimaraes FS. 5-HT_{1A} receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. *Br J Pharmacol* 156 (2009) 181-188.
236. Zhu S, Shi R, Wang J, Wang JF, Li XM. Unpredictable chronic mild stress not chronic restraint stress induces depressive behaviours in mice. *Neuroreport* 25 (2014) 1151-1155.
237. Bogdanova OV, Kanekar S, D'Anci KE, Renshaw PF. Factors influencing behavior in the forced swim test. *Physiol Behav* 118 (2013) 227-239.
238. Su J, Hato-Yamada N, Araki H, Yoshimura H. Test-retest paradigm of the forced swimming test in female mice is not valid for predicting antidepressant-like activity: participation of acetylcholine and sigma-1 receptors. *J Pharmacol Sci* 123 (2013) 246-255.
239. Petit-Demouliere B, Chenu F, Bourin M. Forced swimming test in mice: a review of antidepressant activity. *Psychopharmacology* 177 (2005) 245-255.
240. Chourbaji S, Zacher C, Sanchis-Segura C, Dormann C, Vollmayr B, Gass P. Learned helplessness: validity and reliability of depressive-like states in mice. *Brain Res Brain Res Protoc* 16 (2005) 70-78.
241. Li B, Yang CJ, Yue N, Liu Y, Yu J, Wang YQ, Liu Q, Wu GC. Clomipramine reverses hypoalgesia/hypoesthesia and improved depressive-like behaviors induced by inescapable shock in rats. *Neurosci Lett* 541 (2013) 227-232.
242. Li H, Zhou C, Chen D, Fang N, Yao Y, Li L. Failure to protect against myocardial ischemia-reperfusion injury with sevoflurane postconditioning in old rats in vivo. *Acta Anaesthesiol Scand* 57 (2013) 1024-1031.

243. Jia M, Smerin SE, Zhang L, Xing G, Li X, Benedek D, Ursano R, Li H. Corticosterone mitigates the stress response in an animal model of PTSD. *J Psychiatr Res* 60 (2015) 29-39.
244. Vollmayr B, Gass P. Learned helplessness: unique features and translational value of a cognitive depression model. *Cell Tissue Res* 354 (2013) 171-178.
245. Kolár F, Jezková J, Balková P, Breh J, Neckár J, Novák F, Nováková O, Tomášová H, Srbová M, Ost'ádal B, Wilhelm J, Herget J. Role of oxidative stress in PKC-delta upregulation and cardioprotection induced by chronic intermittent hypoxia. *Am J Physiol Heart Circ Physiol* 292 (2007) H224-H230.
246. Rohrbach S, Aslam M, Niemann B, Schulz R. Impact of caloric restriction on myocardial ischaemia/reperfusion injury and new therapeutic options to mimic its effects. *Br J Pharmacol* 171 (2014) 2964-2992.
247. Starnes JW, Taylor RP. Exercise-induced cardioprotection. *Med Sci Sports Exerc* 39 (2007) 1537-1543.
248. Mancardi D, Tullio F, Crisafulli A, Rastaldo R, Folino A, Penna C, Pagliaro P. Omega 3 has a beneficial effect on ischemia/reperfusion injury, but cannot reverse the effect of stressful forced exercise. *Nutr Metab Cardiovasc Dis* 19 (2009) 20–26.
249. Heusch G, Rassaf T. Time to give up on cardioprotection? A critical appraisal of clinical studies on ischemic pre-, post-, and remote conditioning. *Circ Res* 119 (2016) 676-695.
250. Huynh LT, Rankin JM, Tideman P, Brieger DB, Erickson M, Markwick AJ, Astley C, Kelaher DJ, Chew DP. Reperfusion therapy in the acute management of ST-segment-elevation myocardial infarction in Australia: findings from the ACACIA registry. *Med J Aust* 193 (2010) 496-501.
251. Miura T, Miki T. Limitation of myocardial infarct size in the clinical setting: current status and challenges. *Basic Res Cardiol* 103 (2008) 501-513.
252. Smolderen KG, Spertus JA, Reid KJ, Buchanan DM, Krumholz HM, Denollet J, Vaccarino V, Chan PS. The association of cognitive and somatic depressive symptoms with depression

- recognition and outcomes after myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2 (2009) 328–337.
253. Banerjee A, Locke-Winter C, Rogers KB, Mitchell MB, Brew EC, Cairns CB, Bensard DD, Harken AH. Preconditioning against myocardial dysfunction after ischemia and reperfusion by an alpha 1-adrenergic mechanism. *Circ Res* 73 (1993) 656-670.
254. Kitakaze M, Hori M, Morioka T, Minamino T, Takashima S, Sato H, Shinozaki Y, Chujo M, Mori H, Inoue M, Kamada T. Alpha 1-adrenoceptor activation mediates the infarct size-limiting effect of ischemic preconditioning through augmentation of 5'-nucleotidase activity. *J Clin Invest* 93 (1994) 2197-2205.
255. Hausenloy DJ, Yellon DM. New directions for protecting the heart against ischaemia-reperfusion injury: targeting the Reperfusion Injury Salvage Kinase (RISK)-pathway. *Cardiovasc Res* 61 (2004) 448-460.
256. Zhuo C, Wang Y, Wang X, Wang Y, Chen Y. Cardioprotection by ischemic postconditioning is abolished in depressed rats: role of Akt and signal transducer and activator of transcription-3. *Mol Cell Biochem* 346 (2011) 39-47.
257. Grippo AJ, Beltz TG, Weiss RM, Johnson AK. The effects of chronic fluoxetine treatment on chronic mild stress-induced cardiovascular changes and anhedonia. *Biol Psychiatry* 59 (2006) 309-316.
258. Banankhah SK, Friedmann E, Thomas S. Effective treatment of depression improves post-myocardial infarction survival. *World J Cardiol* 7 (2015) 215-223.
259. Paraskevaidis I, Parissis JT, Fountoulaki K, Filippatos G, Kremastinos D. Selective serotonin re-uptake inhibitors for the treatment of depression in coronary artery disease and chronic heart failure: evidence for pleiotropic effects. *Cardiovasc Hematol Agents Med Chem* 4 (2006) 361-367.
260. Lee SM, Hutchinson M, Staikopoulos V, Saint DA. Amitriptyline pharmacologically preconditions rat hearts against cardiac ischemic-reperfusion injury. *Int J Cardiol* 190 (2015) 353-

359.

261. Liu D, Xie K, Yang X, Gu J, Ge L, Wang X, Wang Z. Resveratrol reverses the effects of chronic unpredictable mild stress on behavior, serum corticosterone levels and BDNF expression in rats. *Behav Brain Res* 264 (2014) 9-16.

FIGURES

Fig. 1. Directional network map highlighting the pathways linking chronic stress and MDD to multiple mechanisms of cardiac pathology. Biological systems (boxes) which are nodes in the network are depicted in different colors (endocrine mechanisms, purple; autonomic activity, yellow; inflammatory mechanisms, green; mechanisms relating to both cardiac tissues and function, red). Arrows are colored according effects on target nodes (promotes = blue; inhibits = red).

Inputs potentially influencing cardiac phenotype are highlighted. Not shown are CNS feedbacks (eg. vagal/sensory afferents, HPA activation by cytokines/inflammation)

Fig. 2. Potential signaling governing myocardial stress phenotype in MDD. Within myocardium MDD/stress impairs infarct tolerance and cardioprotection, in association with

exaggerated nitrosative/oxidative damage, altered expression of apoptotic mediators and increased apoptosis. The basis of these direct myocardial changes remains unclear. MDD (and chronic stress models of MDD) are associated with sympathetic activation *vs.* vagal suppression, HPA axis dysfunction, inflammation and immunomodulation. The HPA axis dysfunction: elevates adrenal glucocorticoid (*eg.* cortisol) secretion via hypothalamic corticotropin release hormone (CRH) and anterior pituitary adrenocorticotrophic hormone (ACTH) release; suppresses gonadal hormone production (testosterone, estrogen) via reduced hypothalamic gonadotropin releasing hormone (GnRH) and pituitary gonadotropin (LS, FSH) secretion; and suppresses thyroid thyroxine (T4) and circulating triiodothyronine (T3) levels, and hepatic insulin-like growth factor-1 (IGF-1) release via reductions in pituitary thyroid-stimulating hormone (TSH) and growth hormone (GH) secretion, respectively. Vagal activity directly impacts the heart, and modifies stress responses/remodeling via the cholinergic anti-inflammatory reflex (including inhibition of macrophage/inflammatory cell cytokine generation via $\alpha 7$ nicotinic receptors - $\alpha 7$). Sympathetic activity also directly impacts the heart while influencing cytokine/substance P release from inflammatory cells, B cell antibody production, and acetylcholine (ACh) release from choline acetyl-transferase expressing T cells. Cytokines/inflammation in turn signal to the central nervous system via vagal and sensory afferent fibers (not shown). Metabolic changes with altered cortisol, catecholamines, T3 and GH include insulin-resistance, hyperglycemia, lipolysis and elevated circulating free fatty acids (FFAs). Which of this array of neurohumoral, inflammatory and immune factors are key in inhibiting myocardial stress resistance remains to be established.

Fig. 3. Environmental enrichment may mimic the cardioprotection with physical exercise in mice. These unpublished data show effects of environment enrichment (initial placement of a locked running wheel in the cage for 2 days) compared with 7 days of voluntary wheel running in Langendorff perfused hearts isolated from these mice [54]: phospho-activation of myocardial AKT (pro-survival); phospho-inhibition of GSK3 β (pro-injury); and functional recovery from 25 min global ischemia and 45 min reperfusion (% recovery of left ventricular pressure development, LVDP). Note the similar signalling and cardioprotective outcomes with both active wheel-running and simple environment enrichment. Data are means $\pm$ SEM ($n=6-7$).