MELATONIN IN HEART FAILURE: WHAT IS NEW?

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Abstract:
Heart failure is a multifactorial clinical syndrome characterized by the inability of the heart to pump sufficient blood to the body. Despite recent advances in medical management, poor outcomes in patients with heart failure remain very high. This highlights a need for novel paradigms for effective, preventive and curative strategies. Substantial evidence supports the importance of endogenous melatonin in cardiovascular health and the benefits of melatonin supplementation in various cardiac pathologies and cardiometabolic disorders. Melatonin plays a crucial role in major pathological processes associated with heart failure including ischemic injury, oxidative stress, apoptosis, and cardiac remodeling. In this review, available evidence for the role of melatonin in heart failure is discussed. Current challenges and possible limitations of using melatonin in heart failure are also addressed. While few clinical studies have investigated the role of melatonin in the context of heart failure, current findings from experimental studies support the potential use of melatonin as preventive and adjunctive curative therapy in heart failure.

Keywords: Cardiac remodeling; cardioprotection; cardiomyopathy; fibrosis; heart failure; hypertension; ischemic heart disease; melatonin; metabolic syndrome.

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Introduction:

Melatonin is a hormone primarily released by the pineal gland at night and has been associated with control of the sleep–wake cycle. As a dietary supplement, it is often used for the short-term treatment of insomnia, such as from jet lag or shift work, and is typically taken by mouth. Evidence of its benefit for this use, however, is not strong. It was found that sleep onset occurred six minutes faster with use but found no change in total time asleep. The melatonin receptor agonist medication ramelteon may work as well as melatonin supplements, at greater cost but with different adverse effects, for some sleep conditions ***(1).***

Side effects from melatonin supplements are minimal at low doses for short durations. They may include somnolence (sleepiness), headaches, nausea, diarrhea, abnormal dreams, irritability, nervousness, restlessness, insomnia, anxiety, migraine, lethargy, psychomotor hyperactivity, dizziness, hypertension, abdominal pain, heartburn, mouth ulcers, dry mouth, hyperbilirubinemia, dermatitis, night sweats, pruritus, rash, dry skin, pain in the extremities, symptoms of menopause, chest pain, glycosuria (sugar in the urine), proteinuria (protein in the urine), abnormal liver function tests, increased weight, tiredness, mood swings, aggression and feeling hungover. Its use is not recommended during pregnancy or breastfeeding or for those with liver disease***(2).***

Melatonin is involved in synchronizing circadian rhythms, including sleep–wake timing and blood pressure regulation, and in control of seasonal rhythmicity including reproduction, fattening, moulting and hibernation. Many of its effects are through activation of the melatonin receptors, while others are due to its role as an antioxidant. In plants, it functions to defend against oxidative stress. It is also present in various foods ***(3)***.

Melatonin was discovered in 1958. It is sold over the counter in Canada and the United States; in the United Kingdom, it is a prescription-only medication. It is not approved by the US Food and Drug Administration (FDA) for any medical use. In Australia and the European Union, it is indicated for difficulty sleeping in people over the age of 54. In the European Union, it is indicated for the treatment of insomnia in children and adolescents. It was approved for medical use in the European Union in 2007 ***(4)***.

Biosynthesis:

Biosynthesis of melatonin occurs through hydroxylation, decarboxylation, acetylation, and a methylation starting with L-tryptophan. L-tryptophan is produced in the shikimate pathway from chorismate or is acquired from protein catabolism. First L-tryptophan is hydroxylated on the indole ring by tryptophan hydroxylase to produce 5-hydroxytryptophan. This intermediate (5-HTP) is decarboxylated by pyridoxal phosphate and 5-hydroxytryptophan decarboxylase to produce serotonin ***(5)***.

Serotonin is itself an important neurotransmitter but is also converted into N-acetylserotonin by serotonin N-acetyltransferase with acetyl-CoA. Hydroxyindole O-methyltransferase and S-adenosyl methionine convert N-acetylserotonin into melatonin through methylation of the hydroxyl group ***(5).***

In bacteria, protists, fungi, and plants, melatonin is synthesized indirectly with tryptophan as an intermediate product of the shikimate pathway. In these cells, synthesis starts with D-erythrose 4-phosphate and phosphoenolpyruvate, and in photosynthetic cells with carbon dioxide. The rest of the synthesizing reactions are similar, but with slight variations in the last two enzymes. It has been hypothesized that melatonin is made in the mitochondria and chloroplasts ***(6).***

Mechanism:

In order to hydroxylate L-tryptophan, the cofactor tetrahydrobiopterin (THB) must first react with oxygen and the active site iron of tryptophan hydroxylase. This mechanism is not well understood, but two mechanisms have been proposed**:**

1) A slow transfer of one electron from the THB to O2 could produce a superoxide which could recombine with the THB radical to give 4a-peroxypterin. 4a-peroxypterin could then react with the active site iron (II) to form an iron-peroxypterin intermediate or directly transfer an oxygen atom to the iron ***(7)***
2) O2 could react with the active site iron (II) first, producing iron (III) superoxide which could then react with the THB to form an iron-peroxypterin intermediate***(7)***

Iron (IV) oxide from the iron-peroxypterin intermediate is selectively attacked by a double bond to give a carbocation at the C5 position of the indole ring. A 1,2-shift of the hydrogen and then a loss of one of the two hydrogen atoms on C5 reestablishes aromaticity to furnish 5-hydroxy-L-tryptophan ***(8).***

A decarboxylase with cofactor pyridoxal phosphate (PLP) removes CO2 from 5-hydroxy-L-tryptophan to produce 5-hydroxytryptamine. PLP forms an imine with the amino acid derivative. The amine on the pyridine is

protonated and acts as an electron sink, enabling the breaking of the C-C bond and releasing CO2. Protonation of the amine from tryptophan restores the aromaticity of the pyridine ring and then imine is hydrolyzed to produce 5-hydroxytryptamine and PLP ***(8).***

It has been proposed that histidine residue His122 of serotonin N-acetyl transferase is the catalytic residue that deprotonates the primary amine of 5-hydroxytryptamine, which allows the lone pair on the amine to attack acetyl-CoA, forming a tetrahedral intermediate. The thiol from coenzyme A serves as a good leaving group when attacked by a general base to give N-acetylserotonin ***(7).***

N-acetylserotonin is methylated at the hydroxyl position by S-adenosyl methionine (SAM) to produce S-adenosyl homocysteine (SAH) and melatonin ***(8).***

Regulation:

Melatonin secretion is regulated by activation of the beta-1 adrenergic receptor by norepinephrine. Norepinephrine elevates the intracellular cAMP concentration via beta-adrenergic receptors and activates the cAMP-dependent protein kinase A (PKA). PKA phosphorylates the penultimate enzyme, the arylalkylamine N-acetyltransferase (AANAT). On exposure to (day) light, noradrenergic stimulation stops, and the protein is immediately destroyed by proteasomal proteolysis. Production of melatonin is again started in the evening at the point called the dim-light melatonin onset ***(9).***

Blue light, principally around 460–480 nm, suppresses melatonin biosynthesis, proportional to the light intensity and length of exposure. Until recent history, humans in temperate climates were exposed to few hours of (blue) daylight in the winter; their fires gave predominantly yellow light. The incandescent light bulb widely used in the 20th century produced relatively little blue light ***(9).***

Light containing only wavelengths greater than 530 nm does not suppress melatonin in bright-light conditions. Wearing glasses that block blue light in the hours before bedtime may decrease melatonin loss. Use of blue blocking goggles the last hours before bedtime has also been advised for people who need to adjust to an earlier bedtime, as melatonin promotes sleepiness ***(9)***

Pharmacology:

Pharmacodynamics:

Melatonin is a full agonist of melatonin receptor 1 (picomolar binding affinity) and melatonin receptor 2 (nanomolar binding affinity), both of which belong to the class of G-protein coupled receptors (GPCRs). Melatonin receptors 1 and 2 are both Gi/o-coupled GPCRs, although melatonin receptor 1 is also Gq-coupled. Melatonin also acts as a high-capacity free radical scavenger within mitochondria which also promotes the expression of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase via signal transduction through melatonin receptors ***(5).***

Pharmacokinetics:

When used several hours before sleep according to the phase response curve for melatonin in humans, small amounts (0.3 mg) of melatonin shift the circadian clock earlier, thus promoting earlier sleep onset and morning awakening. Melatonin is rapidly absorbed and distributed, reaching peak plasma concentrations after 60 minutes of administration, and is then eliminated. Melatonin has a half-life of 35–50 minutes. 90% of orally administered exogenous melatonin is cleared in a single passage through the liver, a small amount is excreted in urine, and a small amount is found in saliva. The bioavailability of melatonin is between 10 and 50% ***(10).***

Melatonin is metabolized in the liver by cytochrome P450 enzyme CYP1A2 to 6-hydroxymelatonin. Metabolites are conjugated with sulfuric acid or glucuronic acid for excretion in the urine. 5% of melatonin is excreted in the urine as the unchanged drug. Some of the metabolites formed via the reaction of melatonin with a free radical include cyclic 3-hydroxymelatonin, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), and N1-acetyl-5-methoxykynuramine (AMK) ***(5).***

The membrane transport proteins that move melatonin across a membrane include, but are not limited to, glucose transporters, including GLUT1, and the proton-driven oligopeptide transporters PEPT1 and PEPT2. For research as well as clinical purposes, melatonin concentration in humans can be measured either from the saliva or blood plasma ***(10).***

Functions:

Circadian rhythm:

Melatonin plays an important role in the regulation of sleep–wake cycles. Human infants' melatonin levels become regular in about the third month after birth, with the highest levels measured between midnight and 8:00 am. Human melatonin production decreases as a person age. Also, as children become teenagers, the nightly schedule of melatonin release is delayed, leading to later sleeping and waking times ***(5).***

Antioxidant:

Melatonin was first reported as a potent antioxidant and free radical scavenger. In vitro, melatonin acts as a direct scavenger of oxygen radicals and reactive nitrogen species including OH, O2, and NO In plants, melatonin works with other antioxidants to improve the overall effectiveness of each antioxidant. Melatonin has been proven to be twice as active as vitamin E, believed to be the most effective lipophilic antioxidant. Via signal transduction through melatonin receptors, melatonin promotes the expression of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase ***(11).***

Melatonin occurs at high concentrations within mitochondrial fluid which greatly exceed the plasma concentration of melatonin. Due to its capacity for free radical scavenging, indirect effects on the expression of antioxidant enzymes, and its significant concentrations within mitochondria, a number of authors have indicated that melatonin has an important physiological function as a mitochondrial antioxidant ***(11).***

The melatonin metabolites produced via the reaction of melatonin with reactive oxygen species or reactive nitrogen species also react with and reduce free radicals. Melatonin metabolites generated from redox reactions include cyclic 3-hydroxymelatonin, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), and N1-acetyl-5-methoxykynuramine (AMK) ***(11).***

Immune system:

While it is known that melatonin interacts with the immune system, the details of those interactions are unclear. An anti-inflammatory effect seems to be the most relevant. There have been few trials designed to judge the effectiveness of melatonin in disease treatment. Most existing data are based on small, incomplete trials. Any positive immunological effect is thought to be the result of melatonin acting on high-affinity receptors (MT1 and MT2) expressed in immunocompetent cells ***(12).***

In preclinical studies, melatonin may enhance cytokine production, and by doing this, counteract acquired immunodeficiencies. Some studies also suggest that melatonin might be useful fighting infectious disease including viral, such as HIV, and bacterial infections, and potentially in the treatment of cancer ***(12).***

Adverse effects:

Melatonin appears to cause very few side effects as tested in the short term, up to three months, at low doses. Several studies found no adverse effects of exogenous melatonin in several clinical trials and comparative trials found the adverse effects headaches, dizziness, nausea, and drowsiness were reported about equally for both melatonin and placebo. Prolonged-release melatonin is safe with long-term use of up to 12 months ***(13).***

Although not recommended for long term use beyond this, low-dose melatonin is generally safer, and a better alternative, than many prescriptions and over the counter sleep aids if a sleeping medication must be used for an extended period of time. Low doses of melatonin are usually sufficient to produce a hypnotic effect in most people. Higher doses do not appear to result in a stronger effect, but instead appear to cause drowsiness for a longer period of time. There is emerging evidence that the timing of taking exogenous melatonin in relation to food is also an important factor. Specifically, taking exogenous melatonin shortly after a meal is correlated with impaired glucose tolerance ***(13).***

Melatonin can cause nausea, next-day grogginess, and irritability. In the elderly, it can cause reduced blood flow and hypothermia. In autoimmune disorders, evidence is conflicting whether melatonin supplementation may ameliorate or exacerbate symptoms due to immunomodulation. Melatonin can lower follicle-stimulating hormone levels. Melatonin's effects on human reproduction remain unclear. In those taking warfarin, some evidence suggests there may exist a potentiating drug interaction, increasing the anticoagulant effect of warfarin and the risk of bleeding ***(13).***

Melatonin rich foods

No recommended dietary allowance (RDA) has been established for melatonin. When it comes to melatonin supplements, some experts recommend a dosage of around 0.5 to 3 milligrams for sleep-related issues. Higher doses may cause daytime drowsiness. Most food databases do not list the amount of melatonin in foods, but according to available research, these six foods are good sources of melatonin ***(14).***

Tart Cherries

Tart cherry juice is one of the best-known sleep aids. Researchers have found that it increases melatonin levels in the body and enhances sleep. Keep in mind that cherry juice is high in sugar. Drinking it nightly could significantly raise your intake of calories. Eating cherries instead of drinking their juice is a healthier way of getting melatonin.

Goji Berries
Produced by a plant native to China, goji berries have been touted for their anti-aging effects. They are also high in melatonin and may improve sleep.

Eggs
Among animal products, eggs are one of the best sources of melatonin. Eggs are also highly nutritious, offering protein and iron, among other essential nutrients ***(14)***

Milk
Warm milk is a traditional remedy for insomnia, so it is no surprise that it's high in melatonin. It could be a good option if you tolerate dairy.

Fish
Fish is a better source of melatonin than other meats. The best options are oily fish like salmon and sardines, which also provide valuable omega-3 fatty acids.

Nuts
Most nuts have a good amount of melatonin. Pistachios and almonds are among the highest. Nuts also are an excellent source of many antioxidants, healthy omega-3 fats, and minerals ***(14)***

Figure (1): Melatonin rich foods

Melatonin & heart failure:
The role of melatonin (N-acetyl-5-methoxytryptamine) in human health and disease has become an important subject of investigation in cardiovascular research. Melatonin is a small indoleamine molecule mainly produced by the pineal gland upon the activation of the suprachiasmatic nucleus of the hypothalamus during the night under normal physiological conditions (for more details on melatonin secretion and localization). It exerts its traditional role as a chronobiotic or endogenous synchronizer regulating seasonal and circadian rhythms along with its sleep-inducing effects ***(3)***.
Also, as a multifunctional molecule, it induces numerous biological activities having potent antioxidant, anti-excitatory, anti-inflammatory, immunomodulatory, vasomotor, and metabolic proprieties (for more details). Of note, endogenous melatonin plays a critical role in various cardiovascular pathologies and metabolic disorders that may lead to HF ***(15).***
The influence of melatonin on the cardiovascular system is well established. Melatonin interacts with the heart and blood vessels indirectly via the nervous system and hormonal interactions, and directly, through its receptor-dependent and independent activities as a signaling molecule and a free radical scavenger, respectively. Melatonin receptors comprise membrane receptors type 1 (MT1 or Mel1A or MTNR1A) and type 2 (MT2 or Mel1B or MTNR1B) which are G-protein coupled receptors, and the retinoid-related orphan nuclear receptor (RZR/RORα) ***(16).***
These receptors mediate various regulatory activities of melatonin in the heart and the blood vessels. Their downstream signaling effector mechanisms include adenylate cyclase, protein kinase C (PKC), phospholipase C, phospholipase A2, potassium channels, guanylyl cyclase and calcium channels and mediate the anti-adrenergic effects of melatonin. In the context of HF, melatonin receptors play a significant role in the prevention of HF following myocardial infarction, and cardiomyopathy ***(3)***
Recent studies report the beneficial effects of melatonin treatment in various animal models of HF. In these models, melatonin reverses major

pathological processes associated with HF including oxidative stress, apoptosis, necrosis, fibrosis, and pathological remodeling. However, given the complex etiological aspects of HF, the role of melatonin in HF is not yet well understood. The present paper discusses available evidence on the role of melatonin in ischemic and non-ischemic HF. Considering the significant role of metabolic disorders in HF, the role of melatonin in metabolic syndrome-related HF is also summarized ***(3)***.

Melatonin and Heart Failure: Clinical Evidence:

Melatonin plays a crucial role in human cardiovascular health and disease. Several studies demonstrate the role of endogenous melatonin in cardiovascular health and the benefits of melatonin supplementation. Epidemiological studies show that pineal melatonin secretion as well as circulating melatonin levels are reduced in patients with acute and chronic HF. Emerging studies suggest serum melatonin levels as a useful marker for HF. It was found that serum melatonin levels negatively correlate with the levels of the N-terminal pro-brain natriuretic peptide (NT-pro-BNP), a well-known biomarker of HF ***(17).***

Also, melatonin levels predict the left ventricular remodeling after acute myocardial infarction and HF in patients with hypertensive cardiomyopathy. Interestingly, serum melatonin levels are also associated with reverse remodeling after cardiac resynchronization therapy in patients with HF and ventricular dyssynchrony, therefore supporting the essential role of endogenous melatonin in HF conditions ***(17).***

Melatonin treatment is considered to be a potential adjunctive chronotherapy in ischemic and hypertensive heart diseases. Administration of melatonin normalizes the circadian rhythm of blood pressure and ameliorates nocturnal hypertension in hypertensive men and women receiving antihypertensive treatment, even at very old age. Additionally, it improves the left ventricular function in HF patients with reduced ejection fraction ***(18).***

These findings demonstrate the benefits of melatonin in HF. Besides ischemic and hypertensive heart diseases, various cardiac pathologies such as cardiomyopathy, rheumatic heart disease, cardiopulmonary disease, and congenital heart disease, either alone or in concert with other risk factors, may also lead to HF. However, the clinical aspect of melatonin in these pathologies is still not yet explored ***(18).***

Melatonin and Non-Ischemic Heart Failure:

Non-ischemic HF refers to idiopathic dilated cardiomyopathy, myocarditis, alcoholic cardiomyopathy, cardiac dysfunction, and hypertensive heart disease. These arise due to various primary pathological causes/stimuli that include, among others, arterial hypertension, aortic stenosis, and pulmonary hypertension. If, for example, the primary pathological stimulus is arterial hypertension, it causes volume overload that leads to non-ischemic HF ***(19).***

Whereas, if pulmonary hypertension is the primary pathological stimulus, non-ischemic HF is initiated by pressure overload. The pressure overload increases ventricular afterload and induces concentric hypertrophy, and associates with fibrosis. Volume overload increases ventricular preload, induces eccentric hypertrophy and extracellular matrix degradation ***(19).***

The underlying mechanism of non-ischemic HF comprises neurohormonal activation, complex metabolic changes and increased production of reactive oxygen species and oxidative stress. Given its multiple regulatory functions with potent antioxidant properties, melatonin is considered to be a potential therapy in HF ***(20).***

At a cellular level, the main mechanistic hallmarks of non-ischemic HF include extracellular matrix deposition and fibrosis, adverse changes in contractile proteins, and alterations in cardiac mitochondrial metabolic pathways. In the context of cardiac fibrosis, Hu and co-workers describe how effector cells are activated and cause extracellular matrix (ECM) deposition (glycosaminoglycan and collagen) in the myocardium. If this deposition is moderate, it can aid in post-injury cardiac recovery, but if the deposition is excessive, it promotes myocardial scarring and HF ***(21).***

Currently, there is no effective anti-fibrotic treatment. Interestingly, several studies show that melatonin protects the failing heart by reducing extracellular matrix deposition and fibrosis. Melatonin reduces cardiac fibrosis by reducing the concentration and content of insoluble/total cardiac collagen. This anti-fibrotic effect may be mediated via an angiotensin-II, growth factors and an angiotensin receptor pathway. Therefore, by modulating the underlying mechanism of extracellular matrix deposition and fibrosis, melatonin directly stunts non-ischemic HF ***(19).***

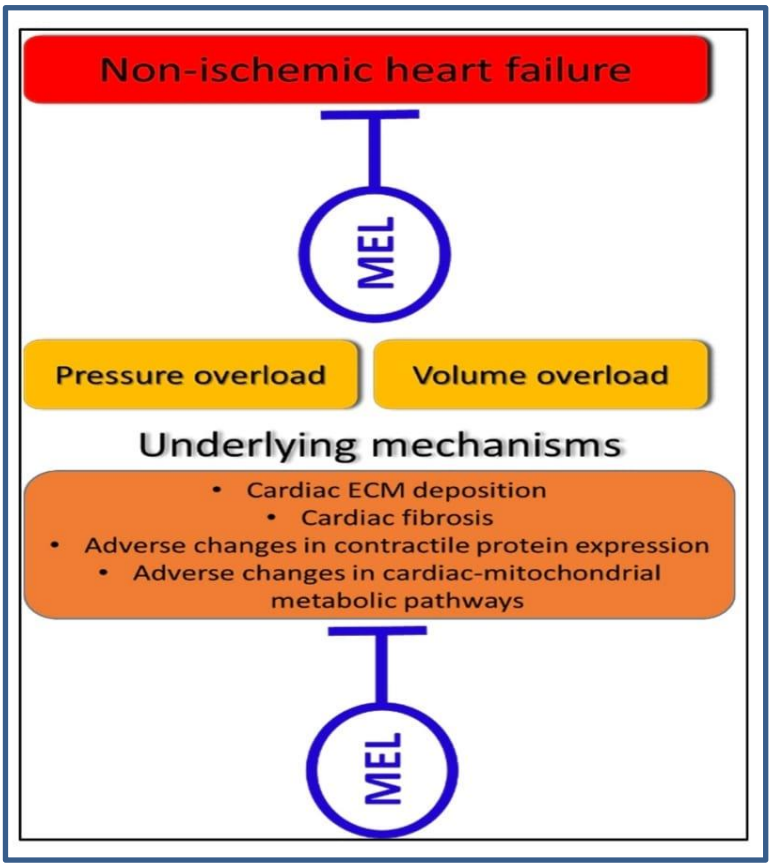

Figure (2): A representation of the two types of non-ischemic HF (pressure overload and volume overload), and their underlying mechanisms ***(19)***

Besides fibrosis and ECM deposition in non-ischemic HF, the expression of contractile protein myosin heavy chain (MHC) changes from the alpha to the beta isoform, and this promotes non-ischemic HF. Melatonin upregulates the expression level of α-myosin heavy chain and downregulates the expression level of the β-myosin heavy chain in non-ischemic HF. Thus, this action of melatonin slows the deterioration of cardiac contractile function caused by permanent pressure overload ***(22).***

These improvements in contractile protein expression are also associated with reduced left ventricular ejection fraction, fractional shortening, and interventricular septal thickness in diastole. Consequently, melatonin directly ameliorates cardiac contractile protein expression that results in improved non-ischemic HF despite a permanent pathological stimulus ***(22).***

Currently, mitochondrial function is regarded as a promising therapeutic target in HF. The changes in cardiac-mitochondrial metabolic pathways, together with the changes in mitochondrial function and biogenesis contribute to non-ischemic HF. In diseases such as pulmonary hypertension, the myocardium is exposed to lower than usual oxygen that causes a shift in cardiac metabolic pathways. In this regard, cardiac metabolism shifts from oxidative phosphorylation to glycolysis, with the latter being unable to sustain cardiac functional demands during progressed cardiac disease ***(23).***

In the transverse aortic constriction model, the failing myocardium displays a reduced fatty acid oxidation and increased glycolysis pathways, and, in the pulmonary artery banding model, it displays an impaired glucose oxidation and a decreased energy reserve, with a subsequent insufficient energy supply. Melatonin is known to improve cardiac-mitochondrial function and metabolism. However, the effect of melatonin in such metabolic pathways in non-ischemic HF remains poorly described ***(16).***

Therefore, future studies could investigate the impact of melatonin on cardiac-mitochondrial metabolic pathways in non-ischemic HF. These metabolic pathways can be assessed with high-resolution respirometry that can assess the capacity of cardiac-mitochondrial electron transfer system, proton leakage, and electron transfer system-complex activities. Such investigations can make essential contributions to the body of knowledge regarding the role of melatonin in non-ischemic HF ***(16).***

Mitochondrial biogenesis plays a crucial role in non-ischemic HF. Non-ischemic HF induced by pulmonary artery banding or transverse aortic constriction is associated with a reduction in cardiac-mitochondrial biogenesis. Primary

pathological stimuli in non-ischemic HF alter critical proteins that result in a downregulation of cardiac-mitochondrial biogenesis. This mechanism is believed to contribute to the failing myocardium ***(16).***

Zhai and co-workers were the first to investigate the effects of melatonin on cardiac-mitochondrial biogenesis in non-ischemic HF. Using an in vivo transverse aortic constriction-induced pathological cardiac hypertrophy model, they demonstrated that melatonin upregulates the expression of peroxisome proliferator-activated receptor gamma coactivator-1 beta (PGC1-β, a proxy for mitochondrial biogenesis) in non-ischemic HF ***(22).***

These results suggest that even in non-ischemic HF, where the primary pathological stimulus is permanent, melatonin can promote cardiac-mitochondrial biogenesis. It is, therefore, likely that in this model, melatonin stimulates an adaptive response to the primary pathological stimulus. This comprises the upregulation of cardiac-mitochondrial biogenesis as reflected by the increased expression of PGC1-β. The increased number of mitochondria may aid the failing myocardium in producing sufficient energy to maintain cardiac energy requirements in HF ***(16).***

These findings support the argument that melatonin directly and beneficially upregulates cardiac-mitochondrial biogenesis, to improve non-ischemic HF. The role of mitochondria in the protective effects of melatonin may be explained by the highest concentration of melatonin in the mitochondria as compared to the other subcellular compartments, and the recently discovered production and secretion of melatonin by mitochondria ***(24)***.

Role of melatonin in heart failure related to the metabolic syndrome:

Features of the metabolic syndrome include high blood pressure, insulin resistance, lipid abnormalities, diabetes, and obesity. These features and related diseases such as obstructive sleep apnea, are highly prevalent in HF patients and play a critical role in the progression from subclinical to clinical ventricular dysfunction and ***(25)***.

Multiple molecular and cellular responses including neurohormonal activation, complex metabolic changes and increased production of reactive oxygen species, and oxidative stress contribute to the development of HF in metabolic syndrome. Melatonin has recently received attention as a potential therapy in obesity and related cardiometabolic abnormalities. Its role in metabolic syndrome is reported in both animal and human studies ***(25).***

In pre-diabetic animal models, short-term melatonin treatment (4 mg/kg per day for three weeks) protects the hearts of diet-induced obese rats, independent of body weight and fat mass. Whereas long-term melatonin administration reverses the metabolic abnormalities associated with insulin resistance and dyslipidemia and protects the hearts of the obese rats. In these animals, melatonin treatment (4 mg/kg per day for six weeks) also increases basal and insulin-stimulated glucose uptake by cardiomyocytes isolated from the hearts of obese, insulin-resistant rats, supporting the insulin-sensitizing effect by melatonin ***(26).***

Impairment of insulin-stimulated glucose uptake is considered the most consistent change that develops early in insulin-resistant hearts. It also associates with increased oxidative stress and cardiomyopathy. Interestingly, a recent study in the DahlS.Z-Lepr(fa)/Lepr(fa) (DS/obese) rat model of metabolic syndrome, shows that melatonin receptor agonist, ramelteon treatment at either low (0.3 mg/kg per day) or high (8 mg/kg per day) dose attenuates body weight gain, left ventricular fibrosis, and diastolic dysfunction, as well as cardiac oxidative stress and inflammation ***(27).***

Similar beneficial effects on cardiac hypertrophy and fibrosis are also reported in pre-diabetic obese (ob/ob) mice treated with melatonin (100 mg/kg per day in drinking water) for 8 weeks (from 5 weeks of age). In this model, melatonin induces its beneficial effects by reversing the mitochondrial and metabolic defects in the hearts. These findings support the importance of melatonin and the potential use of melatonin receptor agonists in HF-related metabolic syndrome ***(16)***.

In a diabetic rat model, melatonin also ameliorates metabolic risk factors including lipid abnormalities, insulin resistance, modulates apoptotic proteins, and protects the heart against diabetes-induced apoptosis and cardiomyopathy. This finding suggests the use of melatonin as a preventive approach against HF in patients with the metabolic syndrome. This beneficial effect of melatonin in diabetic rats is also reported in other diabetic models, and it is further supported by recent clinical studies ***(28)***.

As the underlying mechanism, melatonin alleviates cardiac remodeling and dysfunction in the diabetic heart by upregulating autophagy and limiting apoptosis while modulating mitochondrial integrity and biogenesis. These effects are mediated by various intracellular signaling pathways including Mst1/silent

information regulator 3 (Sirt3), dynamin-related protein 1 (Drp1)/Sirt1 and spleen tyrosine kinase (Syk) ***(16).***

Clinical studies show that reduced melatonin secretion levels are associated with a higher risk of incident myocardial infarction in women with increased body mass index. These findings suggest that melatonin may be an effective therapy in obesity-related abnormalities that may predispose patients to ischemic HF. For example, melatonin supplementation (5 mg/day, two hours before bedtime, for two months) improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome ***(16).***

It is well-known that the presence of diabetes per se adversely affects long-term survival and risk of hospitalization in patients with acute and chronic HF. Interestingly, in a randomized, double-blind, placebo-controlled trial involving 60 diabetic patients with coronary heart diseases melatonin (10 mg once a day for 12 weeks) exerts its beneficial effects by ameliorating serum C-reactive protein levels, glycemic control, and high-density lipoprotein-cholesterol. Given the high prevalence of diabetes in HF patients, the promising beneficial effects of melatonin should be explored for future effective therapy in HF patients with metabolic syndrome ***(28).***

Current challenges and perspectives in the use of melatonin in heart failure:

Even though the use of animals has provided more insight into the pathophysiological mechanisms of HF and the development of new therapies, the complex etiology of HF still makes it challenging to study HF using animal models. Melatonin was suggested as a preventive and curative therapy against various forms of the cardiac disease. However, in the context of HF, there are a few important things to consider ***(29)***

A reciprocal relationship exists between the anatomic changes of the myocardium and the initial pathological stimulus (e.g., pulmonary hypertension). This means that treatment with melatonin may directly modulate the primary pathological stimulus (local effects) or can be released into circulation (systemic effects) where it affects the remodeled myocardium. In a rat model of pulmonary hypertensive rats, melatonin confers cardiac protection and stunts non-ischemic HF ***(16)***

Even in this model, the protective effects of melatonin may either be due to its direct effect on the remodeled myocardium or the primary pathological stimulus; it is likely that melatonin simultaneously induces beneficial effects against the primary pathological stimulus and on the remodeled myocardium. This is especially relevant in studies where melatonin treatment is administered via drinking water or oral pills formations. In such models, melatonin is released into systemic circulation and may thereby have beneficial effects on the remodeled myocardium and the initial pathological stimulus ***(30).***

In most models of non-ischemic HF, it is challenging to determine whether melatonin can directly interfere with the non-ischemic HF process. If one wants to delineate the effects of melatonin on the actual cardiac remodeling/HF process, a more appropriate model would be transverse aortic constriction or pulmonary artery banding. With this model, a silk suture is permanently placed on the aorta, or an occluding hemoclip is permanently placed on the pulmonary artery trunk ***(31)***

Thus, there is an artificial primary pathological stimulus that cannot be changed or altered by melatonin, yet non-ischemic HF remains present. Such models would authenticate a claim that melatonin can interfere (beneficially) with the non-ischemic HF process. In line with this notion, the effects of melatonin were recently studied in an in vivo model of transverse aortic constriction-induced HF ***(16).***

Despite the permanent silk suture (unchangeable artificial, primary pathological stimulus); melatonin stunted non-ischemic HF. This observation confirms that melatonin can, in fact, stunt the HF process, even when the permanent pressure overload caused by the suture remains permanent/unchanged ***(22).***

In the context of metabolic syndrome, melatonin secretion levels are low in patients with insulin resistance and impaired glucose tolerance, and mutations in MTNR1B gene are associated with an increased risk of diabetes. Moreover, the nuclear melatonin receptor RORα is downregulated in the diabetic heart, and its deficiency aggravates the diabetic cardiomyopathy and HF. While administration melatonin or RORα agonist reduces cardiomyocyte hypertrophy and fibrosis and improves cardiac function, a direct need for an exploration of the benefits of melatonin for the prevention of HF in diabetic states warrants further studies ***(16).***

Hypothetically, given the potent antioxidant and anti-inflammatory properties of melatonin, its administration may be beneficial in diabetic people with HF. However, previous reports on the role of melatonin on glucose homeostasis are inconsistent, and mutations in MTNR1B in diabetic patients may further worsen the deleterious effect of melatonin on glucose

tolerance in humans. This observation requires a careful consideration for eventual personalized use of melatonin in HF patients with diabetes ***(32).***

Melatonin treatment is also beneficial in other models of HF-related cardiomyopathies that are not explicitly described in this paper. For example, it protects against cardiomyopathy induced with ovariectomy, radiation, hyperthyroidism, chemotherapies, aluminum phosphide, lipopolysaccharides and sepsis, and chronic Chagas disease ***(16).***

Thus far, melatonin is not yet studied in animal models of peripartum cardiomyopathy, another type of non-ischemic HF. Future study in this regard may uncover exciting results given the involvement of prolactin in the pathology of the peripartum cardiomyopathy, and the interference of prolactin and melatonin in the processes responsible for the development and maintenance of pregnancy ***(33)***.

Additional challenges and limitations to the use of melatonin in cardiovascular diseases were recently summarized somewhere else. As previously highlighted, the current challenge for using melatonin is mostly its dosage, low bioavailability, and unknown long-term effect of high doses. The use of melatonin as a nutritional supplement is widely accepted. The dietary melatonin and phytomelatonin represent an alternative for effective melatonin preventive treatment ***(2).***

However, the lack of standardized methods to determine melatonin concentration in foods or in plants, together with the low melatonin bioavailability following oral administration in humans (approximately 15%) with, moreover, a short maximal half-life, makes hard to attribute some of the observed benefits to the dietary melatonin. Most of the melatonin-rich foods might also have other cardioprotective ingredients. Nevertheless, the increase in circulating melatonin following the consumption of melatonin-rich food may be itself a good indication of the potential effects of melatonin ***(16)***.

Despite multiple cardiovascular benefits of melatonin supplementation, it is worth mentioning that due to various reasons few studies do not demonstrate the protective effect of melatonin in HF, such as in a rat model of isoproterenol-induced left ventricular hypertrophy and a rabbit model of myocardial infarction. This observation is consistent with the recent clinical studies conducted in the context of myocardial ischemia/reperfusion injury where the effect of melatonin administration is neutral with unexpected detrimental effect favoring ventricular remodeling ***(34)***.

Most of the unexpected findings are due to methodological issues including, mainly, the severity of cardiac damage, dosages, time, and mode of administration of the treatment, the type of animal models, age, and comorbidities. Nevertheless, all of these studies confirm the safety of melatonin treatment. Accordingly, better-designed studies are needed to delineate the role of melatonin in HF and related conditions ***(34)***

In addition, besides the well-documented safety of melatonin, other reports show that circulating melatonin levels are high in some HF patients, and its supplementation may also be detrimental. These data suggest that melatonin should be used with caution in humans. However, in view of the multiple cardiovascular benefits of melatonin, these studies present a very little substantive evidence to support any significant adverse effects of melatonin at the level of the heart ***(16)***.

Melatonin is an endogenously produced molecule and is also consumed in edible plants and other foodstuffs, and its safety is well documented. As recently stated, its multiple benefits at the cost of very few side effects may exceed those of some drugs much more widely used for cardiac protection ***(35)***.

The exploration of the role of melatonin in HF is clinically relevant. Melatonin is currently prescribed for the regulation of sleep patterns such as in the jet lag and sleep disorders. However, very few clinical studies have thus far investigated the beneficial effects of melatonin supplementation in patients with HF ***(16)***.

Considering the correlation between circulating melatonin levels and the well-established biomarkers of HF such as NTpro-BNP, high-sensitivity C-reactive protein, and lipid peroxidation in HF patients, further studies are needed. These studies could determine the pathogenic as well as the prognostic importance of melatonin alterations in patients with chronic HF ***(28).***

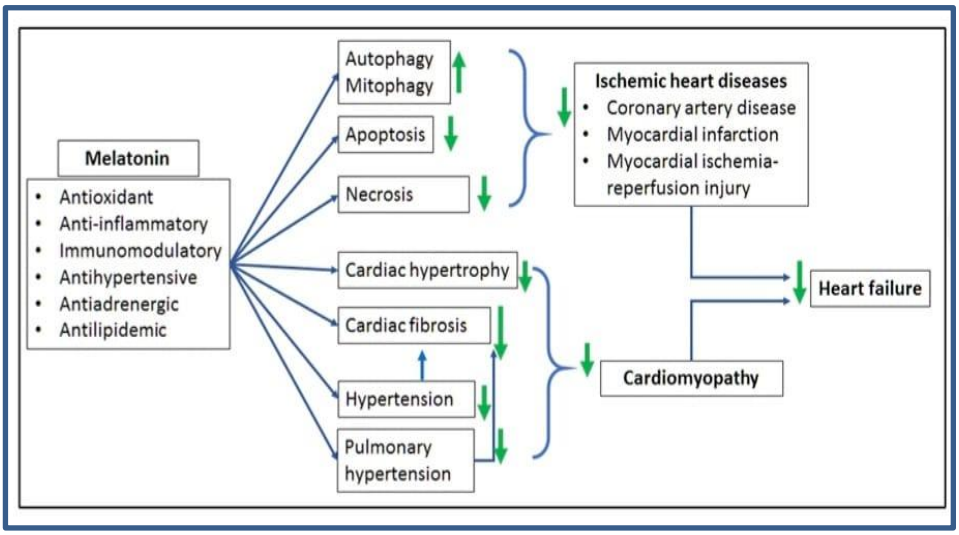

Figure (31): Summary of the beneficial effect of melatonin in cardiac pathologies associated with the development of heart failure ***(16)***

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