

**Pandi-Perumal, Seithikurippu R. ; BaHammam, Ahmed S. ;  
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Tetyana ; Buttoo, Kenneth ; Dhandapany, Perundurai S. ;  
Brown, Gregory M. ; Cardinali, Daniel P.**

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## **Melatonin and Human Cardiovascular Disease**

Seithikurippu R. Pandi-Perumal<sup>1</sup>, Ahmed S. BaHammam<sup>1,CA</sup>, Nwakile I. Ojike<sup>2</sup>, Oluwaseun A. Akinseye<sup>3,4</sup>,  
Tetyana Kendzerska<sup>5</sup>, Kenneth Buttoo<sup>6</sup>, Perundurai S Dhandapany<sup>7-9</sup>, Gregory M. Brown<sup>10</sup>, Daniel P.  
Cardinali<sup>11,CA</sup>

<sup>1</sup>The University Sleep Disorders Center, Department of Medicine, College of Medicine, King Saud University, Riyadh, SAUDI ARABIA.

<sup>2</sup>Center for Healthful Behavior Change, Division of Health and Behavior, Department of Population Health, New York University Medical Center, 227 East 30th St, 10016 New York, NY, USA.

<sup>3</sup>Department of Internal Medicine, Icahn School of Medicine at Mount Sinai, Queens Hospital Center, 82-68 164th street, Jamaica, NY 11432, New York, USA.

<sup>4</sup>CUNY School of Public Health at Brooklyn College, New York, USA.

<sup>5</sup>Institute for Clinical Evaluative Science, Sunnybrook Health Sciences Center, Toronto, ON, CANADA.

<sup>6</sup>Sleep Disorders Center, 601 Harwood Avenue South, Ajax, ON L1S 2J5, CANADA.

<sup>7</sup>The Knight Cardiovascular Institute, <sup>8</sup>Departments of Medicine, Molecular and Medical Genetics, Oregon Health and Science University, Portland, Oregon, and <sup>9</sup>Centre for Cardiovascular Biology and Disease, Institute for Stem Cell Biology and Regenerative Medicine (inStem), Bangalore, India.

<sup>10</sup>Centre for Addiction and Mental Health, University of Toronto, 100 Stokes St., Toronto, ON M6J 1H4, CANADA.

<sup>11</sup>BIOMED-UCA-CONICET and Department of Teaching and Research, Faculty of Medical Sciences, Pontificia Universidad Católica Argentina, 1107 Buenos Aires, ARGENTINA.

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**Correspondence to:**

**1) Ahmed S. BaHammam**

Professor of medicine  
Director, University Sleep Disorders Centre,  
College of Medicine, King Saud University  
Box 225503, Riyadh 11324, Saudi Arabia  
Telephone: 966-1-467-1521  
Fax: 966-1-467-2558  
E-mails: ashammam2@gmail.com

**2) Daniel P. Cardinali, MD, PhD.,**

BIOMED-UCA-CONICET and  
Department of Teaching and Research,  
Faculty of Medical Sciences,  
Pontificia Universidad Católica Argentina, 1107  
Buenos Aires, Argentina.  
Phone: +54 911 44743547.  
E-mail: danielcardinali@fibertel.com.ar

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## **Abstract**

The possible therapeutic role of melatonin in the pathophysiology of coronary artery disorder (CAD) is increasingly being recognized. In humans, exogenous melatonin has been shown to decrease nocturnal hypertension, improve systolic and diastolic blood pressure, reduce the pulsatility index in the internal carotid artery, decrease platelet aggregation and reduce serum catecholamine levels. Low circulating levels of melatonin are reported in individuals with CAD, arterial hypertension and congestive heart failure. This review assesses current literature on the cardiovascular effects of melatonin in humans. It can be concluded that melatonin deserves to be considered in clinical trials evaluating novel therapeutic interventions for cardiovascular disorders.

**Key words:** blood pressure, cardioprotection, cardiovascular disorders, coronary artery disease, hypertension, platelets, melatonin.

## Background

Cardiovascular diseases (CVD) are the leading cause of death globally, with estimated 17.5 million deaths in 2012, representing 31% of all global deaths <sup>1</sup>. In the USA, about 1 in every 4 deaths are attributed to CVD with a direct cost of \$312.6 billion in the year 2011 <sup>2</sup>. While there is a documented improvement in mortality rate from CVD, the overall impact such as survival with disability, dependency and cost of care has significantly increased in the past decades <sup>3</sup>. There has equally been an extensive improvement in the knowledge and understanding of the pathophysiology of CVDs over the last years with advances in pharmacological and procedural interventions.

The focus of this review article is on the therapeutic potential of melatonin in CVDs. Melatonin (IUPAC name: N-[2-(5-methoxy-1H-indol-3-yl) ethyl] acetamide) is a natural methoxyindole first described as a pineal hormone and later shown to be present in most mammalian and non-mammalian cells <sup>4</sup>. Its effect is thought to be mediated through both receptor-mediated and receptor-independent mechanisms. The receptor-mediated actions of melatonin comprise membrane melatonergic receptors (MT1 and MT2) located throughout the vascular system including the heart (cardiomyocytes, left ventricle and coronary arteries) <sup>5,6</sup>. Melatonin may be also the natural ligand for the retinoid related orphan nuclear hormone receptor family (RZR/ROR) <sup>7</sup>.

MT1 melatonergic receptors mediate arterial vasoconstriction, inhibit neuronal firing and cell proliferation in cancer cells, and modulate reproductive and metabolic functions <sup>8,9</sup>. Activation of MT2 melatonergic induce vasodilation, phase shift circadian rhythms of neuronal firing in the suprachiasmatic nucleus, enhance immune responses and inhibit dopamine release in retina and leukocyte rolling in arterial beds. The receptor-independent mechanism of action of melatonin is achieved through its antioxidant and mitochondrial protecting effects <sup>7</sup>.

Melatonin has been shown to decrease nocturnal hypertension<sup>10</sup> reduce the pulsatility index in the internal carotid artery, decrease platelet aggregation<sup>11,12</sup>, and reduce serum catecholamine levels<sup>13</sup>. Moreover, decreased melatonin levels were reported in various pathological conditions including hypertension with non-dipper pattern<sup>14</sup>, congestive heart failure (CHF)<sup>15</sup>, ischemic heart disease<sup>16</sup> or in patients after acute myocardial infarction<sup>17</sup>. Figure 1 presents the functional pleiotropy of melatonin.

This paper provides a review of current literature on the cardiovascular effects of melatonin in humans. Medical literature was identified by searching databases including (MEDLINE, EMBASE), bibliographies from published literature and clinical trial registries/databases. Searches were last updated August 10, 2015.

### **Basic Aspects of Melatonin Physiology Relevant to Cardiovascular Physiopathology**

By employing specific melatonin antibodies, the presence of melatonin has been verified in multiple extrapineal tissues such as the brain, retina, lens, cochlea, Harderian gland, airway epithelium, gastrointestinal tract, liver, kidney, thyroid, pancreas, thymus, spleen, immune system cells, skin, carotid body, reproductive tract, and endothelial cells<sup>18</sup>. For further details, the reader is referred to a review by Acuña-Castroviejo et al<sup>18</sup>. Whether melatonin is produced in those tissues is a matter of debate because melatonin's amphiphilicity would allow an easy entry from circulation in most cases<sup>19</sup>. However, in some tissues melatonin concentrations exceed those in the blood<sup>20</sup>. Although the enzymatic machinery to produce melatonin is found in most of these locations<sup>18</sup>, circulating melatonin in mammals is derived exclusively from the pineal gland.

Melatonin effects on the vasculature depend on the specific receptor type activated. Animal studies reveal that vasoconstriction is mediated through MT<sub>1</sub> activation and vasorelaxation through MT<sub>2</sub>

activation, with the likely mechanism of action being via the modulation of the noradrenergic and/or nitric oxide effect <sup>21</sup>.

Melatonin is metabolized in the liver to 6-sulfatoxymelatonin (aMT6s), which is subsequently excreted in urine <sup>22</sup>. Melatonin that is produced outside the pineal gland generally does not reach the circulation, e.g. in case of the gastrointestinal tract, melatonin goes through a high pre-systemic hepatic elimination rate and therefore does not exert systemic effects <sup>23</sup>.

Reactive oxygen and nitrogen species are significant contributors to cardiac damage during ischemia-reperfusion injury after an acute coronary syndrome. The reported lower serum level of melatonin in this group of individuals (Table 1) worsens the possibility of further cardiac damage from ischemia-reperfusion injury because melatonin has been described as a direct free radical scavenger that protects against reactive oxygen and nitrogen species with high efficacy <sup>24</sup>. Melatonin also indirectly stimulates antioxidative enzymes such as superoxide dismutase, glutathione peroxidase, glutathione reductase and glucose-6-phosphate dehydrogenase, thereby lowering molecular damage under conditions of elevated oxidative stress such as acute coronary syndrome <sup>24</sup>.

Because of its highly lipophilic properties, melatonin crosses all cell membranes and easily reaches subcellular compartments, including mitochondria and nuclei, where it may accumulate in high amounts <sup>18,25</sup>. Melatonin counteracts lipid peroxidation <sup>26</sup> and DNA damage<sup>27</sup>. In particular, melatonin preserves normal mitochondrial function by reducing and preventing mitochondrial oxidative stress, thus curtailing subsequent apoptotic events and cell death <sup>18,25</sup>. Not only is melatonin itself a direct free radical scavenger, but metabolites that are formed during these interactions like N1-acetyl-N2-formyl-5-methoxykynuramine, which is deformed to N1-acetyl-5-methoxykynuramine, and cyclic 3-hydroxymelatonin, all of which are also free radical scavengers <sup>28</sup>. Thus, a cascade of metabolites of

melatonin may contribute to the efficacy of the parent molecule to protect against oxidative stress <sup>7</sup>. A major question to the view that antioxidants exert their health-protective effects by one-electron reactions with free radicals has been raised by Forman et al <sup>29</sup>. By kinetic constraints in vivo scavenging of radicals may be ineffective in antioxidant defense. Instead, enzymatic removal of nonradical electrophiles, such as hydroperoxides, in two-electron redox reactions could be the major antioxidant mechanism <sup>29</sup>. Indeed, the concept of radical avoidance was proposed by one of us to attempt to explain the protective effects of melatonin at the level of radical generation rather than detoxification of radicals already formed <sup>30</sup>. If melatonin is capable of decreasing the processes leading to enhanced radical formation, this might be achieved by low concentrations of the methoxyindole. The isoforms of NAD(P)H oxidases (Nox) and the mitochondria should be mentioned as main sources of free radicals. Moreover, reactive nitrogen species can secondarily give rise to the formation of reactive oxygen species (ROS), both in and outside mitochondria, so that levels of oxidants can be considerably decreased by limitation of nitric oxide (NO) formation. Melatonin down regulates NO synthesis and inhibits ROS formation in microglia exposed to amyloid-beta 1–42 by preventing the phosphorylation of the p47 Nox subunit <sup>31</sup>. Melatonin is also very effective to attenuate mitochondrial free radical formation. Therefore, radical avoidance by melatonin must be recognized as a highly complex phenomenon, which comprises the integrative, orchestrating role of this molecule with its numerous actions at different levels. It should be noted that concentrations of melatonin may be sufficient for relevant direct scavenging in melatonin-synthesizing organs, especially pineal gland and Harderian gland. Whether accumulation in mitochondria leads to effective concentrations may be debated, but is uncertain.

Melatonin displays a significant anti-inflammatory action and reduces the serum levels of oxidized low-density lipoprotein (LDL) responsible for atherogenic vascular formations <sup>32,33</sup>. Indeed oxidized LDL participates in the initiation and progression of atherosclerosis and contributes to endothelial

dysfunction and plaque destabilization through multiple mechanisms<sup>34</sup>. In vitro melatonin was found to inhibit oxidative LDL modification<sup>35</sup>, a process that may translate in reduced formation of atherogenic plaques in vivo. Melatonin also decreases the formation of cholesterol and reduces LDL accumulation in freshly isolated human mononuclear leukocyte<sup>36</sup>. However, not all studies have reported the LDL lowering effect of melatonin<sup>37</sup>.

Cyclophilin A is a ubiquitously expressed protein that has been highlighted as a major secreted oxidative stress induced factor in atherosclerosis. In a study evaluating the role of cyclophilin A in the early phase of atherosclerosis, the atheroprotective effect of melatonin was assessed<sup>38</sup>. Cyclophilin A expression increased and modulated inflammatory cell adhesion and interleukin-6 expression inducing vascular smooth muscle cell migration and inflammatory cell extravasation. All these effects were prevented by melatonin, indicating that melatonin treatment may represent a new atheroprotective approach that contributes to reducing the early phase of atherosclerosis<sup>39</sup>.

Melatonin inhibits several physiological processes in human platelets including the aggregation phenomenon, the release of ATP and serotonin (indexes of the platelet secretory mechanism), and the production of thromboxane B2<sup>11,12</sup>.

In an experimental study with an isolated perfused heart model in which the anterior descending coronary artery was temporarily ligated, infusion of melatonin (1–250 nM) during the ischemic and reperfusion episodes prevented the occurrence of arrhythmias including premature ventricular contraction and ventricular fibrillation which have been shown to occur on reperfusion without the infusion of melatonin<sup>40</sup>. Protective effects of melatonin shortly after coronary artery ligation and in the absence of ischemia reperfusion were also reported<sup>41</sup>. In a recent study using genetically engineered mice, it was demonstrated that nuclear melatonin receptor ROR $\alpha$  may serve as an endogenous defender

against ischemia reperfusion injury and may mediate the beneficial effect of melatonin on MI/R injury <sup>42</sup>. Likewise, the ex vivo pre-treatment with melatonin improved survival and function of adipose tissue derived mesenchymal stem cells in vitro as well as in vivo, and by using a rat model of myocardial infarction, it was found that melatonin pre-treatment enhanced the viability of engrafted stem cells, and promoted their therapeutic potency <sup>43</sup>.

In view of these experimental and observational cross-sectional studies, melatonin might exert a cytoprotective effect at the level of human heart.

### **Melatonin Levels in CVDs**

Individuals with elevated LDL / cholesterol levels have been reported to have low circulating levels of melatonin <sup>44</sup>, and low melatonin levels have been reported in patients with CAD (Table 1). In an observational cross-sectional study of 15 individuals with CAD vs. 10 healthy subjects, melatonin was significantly lower in the patients with CAD than in the healthy controls <sup>16</sup>. This is consistent with analysis of data from another observational cross-sectional study which reported that night-time urinary aMT6s levels were significantly lower in CAD patients than in the control group <sup>45</sup>. Significantly lower urinary aMT6s levels were reported in unstable angina patients or in patients with stable angina <sup>46</sup>. Yaprak et al reported that patients with CAD secreted less nocturnal melatonin at 02:00, 04:00 and 08:00 h than control subjects <sup>47</sup>. In another related study of 180 consecutive patients with a first ST elevation myocardial infarction that underwent percutaneous coronary intervention within 6 h from onset of symptoms, patients with angiographic no-reflow had lower intraplatelet melatonin levels compared to patients without no-reflow <sup>48</sup>. Intraplatelet melatonin levels were the only significant predictor of angiographic no-reflow after adjusting for potential confounders.

Low urinary aMT6s excretion was reported in CHF, a decrease that was observed regardless of  $\beta$ -adrenergic blocker. There were no significant differences in the low urinary aMT6s levels between chronic and acute CHF patients <sup>15</sup>.

Concerning hypertensive patients there were reports indicating the suppression of nocturnal melatonin secretion in non-dippers <sup>14,49</sup> and in an observational longitudinal study of 554 young women without baseline hypertension the relative risk for incident hypertension among women in the highest quartile of urinary melatonin was about half that in lowest quartile <sup>50</sup>.

### **Melatonin Effects on Arterial Blood pressure in Humans**

Numerous pharmacological and non-pharmacological procedures have been employed in the treatment of hypertension; however, the percentage of individuals with uncontrolled hypertension still remains unacceptably high <sup>51</sup>.

The effects of melatonin on cardiovascular function in healthy subjects are significant (Table 2).

Melatonin in comparison to placebo was able to reduce BP, vascular reactivity, the pulsatility index in the internal carotid artery and circulating catecholamines in healthy subjects<sup>13,52,53</sup>. In another related study comparing post-menopausal women with and without hormone replacement therapy (HRT), melatonin reduced internal carotid artery pulsatility index, systolic and diastolic BP and increased the nitric oxide level in HRT-treated women only, suggesting that several effects of melatonin may be modulated by gonadal steroids <sup>54</sup>. As shown by power spectral analysis of heart rate variability and BP monitoring, melatonin administration increased cardiac vagal tone and reduced plasma norepinephrine and dopamine levels in the supine position in awake healthy volunteers <sup>55</sup>. Although BP was reduced significantly, heart rate and burst rate of muscle sympathetic nerve activity (MSNA) did not change

significantly after melatonin<sup>56</sup>. However, in another study examining the sympathetic nerve responses to orthostatic stress the increase in MSNA was smaller in the melatonin treated group<sup>57</sup>.

Blunted decline in the physiological BP's nocturnal fall, the non-dipper pattern, is associated with hypertension-induced organ damage such as left ventricular hypertrophy, microalbuminuria, reduced arterial compliance and worse prognosis in terms of cardiovascular events<sup>58</sup>. As shown in Table 3, melatonin treatment can be useful in this kind of patients.

A double-blind, placebo-controlled study demonstrated that melatonin given orally (2.5 mg per day) for 3 weeks to patients with essential hypertension significantly reduced both systolic and diastolic BP<sup>59</sup>.

Non-dipper hypertensives have also been found to have a missing surge of melatonin production at nighttime compared to hypertensives who had an appropriate reduction in BP at nighttime (Table 1)

14,49.

In a meta-analysis performed on the effect of melatonin on nocturnal BP, the combination of controlled-release melatonin and antihypertensive treatment was found effective and safe in ameliorating nocturnal hypertension, whereas fast-release melatonin was not<sup>60</sup>. The data differed from a former report indicating that the evening administration of melatonin induced an increase of BP and heart rate in hypertensive patients well controlled by nifedipine<sup>61</sup>. These discrepancies underline the necessity of further studies on the matter.

It has been suggested that the reduction of nocturnal BP by repeated melatonin intake at night is attributable to its curing effect on the circadian output of the suprachiasmatic nucleus<sup>62</sup>. The normalization of circadian pacemaker function in the regulation of BP by melatonin treatment has thus been proposed as a potential strategy for the treatment of essential hypertension.

The vasoregulatory actions of melatonin are complex and may involve both central and peripheral mechanisms<sup>63,64</sup>. The responses elicited by activation of MT1 (vasoconstriction) and MT2 (vasodilation) are dependent on circadian time, duration and mode of exposure to endogenous or exogenous melatonin, as well as of functional receptor sensitivity.

### **Potential Use of Melatonin in Pulmonary Hypertension**

Oxidative stress has been proposed as one of the major mechanisms leading to the development of pulmonary hypertension<sup>65,66</sup>. Therefore, it is reasonable to explore the effect of antioxidant therapy in pulmonary hypertension. As discussed above, melatonin has a potent antioxidant activity, which can reduce antioxidant damage in cardiovascular tissues.

Three recent animal studies have suggested that melatonin may be beneficial in hypoxic pulmonary hypertension. In one study performed in new-born sheep gestated, born, and raised at 3600 meters melatonin reduced pulmonary artery pressure and resistance for the first 3 days of treatment, and significantly improved the vasodilator function of small pulmonary arteries, reduced pulmonary oxidative stress markers and increased enzymatic and non-enzymatic antioxidant capacity<sup>67</sup>.

In another study performed in Sprague Dawley rats exposed to intermittent chronic hypoxia for 4 weeks to induce hypoxic pulmonary hypertension<sup>68</sup> melatonin administration attenuated the elevation of right ventricular pressure, and reduced the pulmonary vascular structure remodeling. In line with these findings, a third study assessed the effect of melatonin as a curative or preventive therapy of pulmonary hypertension in Long Evans rats in which pulmonary hypertension had been induced by injecting monocrotaline. Melatonin was administered 5 days prior to or 14 days after the injection of monocrotaline. The study showed that both curative and preventive treatment improved right ventricular functional and plasma oxidative stress parameters and reduced cardiac interstitial fibrosis<sup>69</sup>.

Therefore, melatonin seems to confer beneficial effects in pulmonary hypertension via anti-oxidant, anti-inflammatory and antiproliferative mechanisms. Clinical investigation of the effects of melatonin on right ventricle hemodynamic and function in patients with pulmonary hypertension are warranted.

### **Melatonin dose and safety**

The majority of clinical trials on the therapeutic usefulness of melatonin in different fields of medicine have shown very low toxicity of melatonin over a wide range of doses <sup>70</sup>. Doses of melatonin that considerably exceed those used in cardiovascular disorders have been found to be safe. In the treatment of amyotrophic lateral sclerosis patients who received either 60 mg / day orally for up to 13 months <sup>71</sup>, or enteral doses of 300 mg / day for up to 2 years <sup>72</sup>. In a phase I dose escalation study in healthy volunteers to assess the tolerability and pharmacokinetics of 20, 30, 50, and 100 mg oral doses of melatonin, no adverse effects after oral melatonin, other than mild transient drowsiness with no effects on sleeping patterns, were seen <sup>73</sup>. Therefore, further clinical trials using dosages of melatonin in the range of 50 to 100 mg / day appear to be reasonable and are warranted. The priorities for populations, outcomes, and durations of these studies must be defined.

### **Conclusion**

The possible therapeutic role of melatonin in CVDs is increasingly apparent, especially with potential benefits in the reduction of ischemia-reperfusion injury and decreasing nocturnal BP. The data suggest that preserving endogenous melatonin levels, or the use of melatonin supplements, may be beneficial in CVDs.

Melatonin is available in pharmacologically pure form, is relatively inexpensive, is absorbed when administered via any route, and its toxicity is remarkably low. Considering that CVDs are the leading cause of death globally <sup>1</sup>, the fact that melatonin has been found to be cardioprotective and possess low

toxicity could have important clinical implications. Therefore, more extensive, large size clinical trials are needed to evaluate melatonin's efficacy as a novel therapeutic intervention in CVDs.

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**Table 1. Reduction of melatonin secretion in CVD patients.**

Study design	Population characteristics, sample size	Melatonin measurement	Results	Ref.
Observational cross-sectional study	15 coronary heart disease (CHD) patients, 10 healthy controls	Serum melatonin concentrations was measured by radioimmunoassay at night (02:00 h) and afternoon (14:00 h)	Melatonin was significantly lower in the patients with CHD than in healthy controls (median 7.8 [interquartile range 6.5-11.8] vs. 36.2 [32.2-42.5] pg/mL, $p < 0.0001$ ). Melatonin was undetectable in the afternoon	<sup>16</sup>
Observational cross-sectional study	48 male patients with severe CHD, 24 of them were taking $\beta$ -blockers daily in therapeutic dosages. Eighteen age-matched healthy men served as controls	6-sulfatoxymelatonin (aMT6s) was measured by radioimmunoassay (RIA) in overnight urine	Nighttime urinary aMT6s levels were significantly lower in CHD patients than in the control group ( $F=16.8$ , $P<0.001$ ) $\beta$ -adrenoceptor blocker treatment had no significant influence in these patients ( $F=0.052$ )	<sup>45</sup>
Observational cross-sectional study	24 healthy subjects; 32 patients with chronic, stable, coronary disease; 27 patients with unstable angina	Nocturnal excretion of aMT6s in urine collected from 18:00 to 06:00 h. aMT6s was measured by a specific RIA	Urinary aMT6s was significantly lower in unstable angina patients than in healthy subjects or in patients with stable angina. It correlated negatively with age in healthy subjects, but not in coronary patients. aMT6s in patients treated with $\beta$ -adrenoceptor blockers did not differ significantly from coronary patients not receiving $\beta$ -blockers.	<sup>46</sup>

Observational cross-sectional study	33 hospitalized patients with congestive heart failure (CHF) vs. 146 healthy ambulatory controls	Nocturnal excretion of aMT6s in urine collected from 18:00 to 06:00 h. aMT6s was measured by a specific RIA	-aMT6s levels were lower in CHF patients than controls (median 2.6 vs. 6.02 $\mu\text{g}$ , $p < 0.0001$ ). This decrease was observed regardless of $\beta$ -adrenergic blocker treatment. There were no significant differences in urinary aMT6s levels between chronic and acute CHF patients. A significant decrease in aMT6s excretion occurred with age.	15
Observational cross-sectional study	16 elderly patients with essential hypertension, Patients were defined as either dippers (DIP, n = 8) or non-dippers (NDIP, n = 8) according to the nocturnal change in the mean arterial pressure	aMT6s was determined by ELISA in two separate urine collections, one in the daytime and one during the night.	Daily aMT6s excretion was comparable in DIP ( $3.28 \pm 0.87 \mu\text{g}/12 \text{ h}$ ) and NDIP ( $2.31 \pm 0.68 \mu\text{g}/12 \text{ h}$ ) ( $p = 0.39$ ). While DIP presented the physiological nocturnal increase in urinary aMT6s ( $8.19 \pm 1.68 \mu\text{g}/12 \text{ h}$ ), this surge of melatonin production was missing in NDIP.	14
Observational cross-sectional study	16 patients with angiographically documented CAD vs. 9 healthy controls	Blood samples were collected every 2 h between 22:00 and 08:00 h. Melatonin levels were measured by RIA.	Patients with CAD secreted less nocturnal melatonin at 02:00, 04:00 and 08:00 h than control subjects ( $P = 0.014$ , $P = 0.04$ and $P = 0.025$ , respectively). Peak and delta melatonin (peak-lowest melatonin) were significantly lower in patients with CAD ( $P = 0.006$ and $P = 0.002$ , respectively). Peak time of melatonin secretion was observed earlier in patients with CAD.	47
Observational cross-sectional study	190 primary hypertensive patients exhibiting a dipping and non-dipping BP profile (88 men and 102 women)	Plasma melatonin was measured at the middle of the daytime and nighttime by RIA.	When patients were divided into dippers and non-dippers on the basis of mean arterial or diastolic BP a lower ratio of night/day melatonin concentration was found in non-dippers than in dippers. There was a blunted night/day difference in plasma melatonin concentrations in hypertensive patients with the non-dipping profile in diastolic BP.	49

Observational cross-sectional study	180 consecutive patients with a first ST-elevation myocardial infarction who underwent primary percutaneous coronary intervention within 6 hours from onset of symptoms	Intraplatelet melatonin levels were measured in platelet-rich plasma using an enzymatic immunoassay procedure	Patients with angiographic no-reflow had lower intraplatelet melatonin levels compared to patients without no-reflow (12.32±3.64 vs. 18.62±3.88 ng/100,000 platelets, p < 0.0001). After adjusting by potential confounders, binary logistic regression analysis indicated that intraplatelet melatonin levels were the only significant predictor of angiographic no-reflow (odds ratio 1.58, P < 0.0001)	48
Observational longitudinal study	554 young women without baseline hypertension	First morning urine melatonin levels	During 8 years of follow-up, a total of 125 women developed hypertension. The relative risk for incident hypertension among women in the highest quartile of urinary melatonin (>27.0 ng per mg creatinine) compared to the lowest quartile (<10.1 ng per mg creatinine) was 0.49 (95% CI, 0.28-0.85; P<0.001).	50

**Table 2. Effects of melatonin on cardiovascular function in healthy humans.**

<b>Study design</b>	<b>Population</b>	<b>Experiment</b>	<b>Results</b>	<b>Ref.</b>
Placebo-controlled study	12 young women	Melatonin 1 mg oral tablet between 14:30 and 17:30 h, 90 min before investigation	The administration of melatonin significantly reduced BP, the pulsatility index in the internal carotid artery, and catecholamines levels.	<sup>52</sup>
Placebo-controlled study	17 young, healthy, early follicular-phase women	Melatonin 1 mg oral tablet between 14:30 and 17:30 h, 90 min before investigation	The administration of melatonin significantly reduced BP, the pulsatility index in the internal carotid artery, and catecholamines levels.	<sup>53</sup>
Randomized, double-blind, placebo-controlled study	14 normal healthy young men	Melatonin 1 mg oral tablet between 14:30 and 17:30 h, 90 min before investigation	The administration of melatonin significantly reduced BP, the pulsatility index in the internal carotid artery, and catecholamines levels. The effect of melatonin on pulsatility index was related to baseline values, being greater in men with higher baseline values	<sup>13</sup>
Randomized, double-blind placebo controlled study	23 postmenopausal women of which 12 were on the estrogenic phase and 11 were under hormone replacement therapy (HRT) and of with continuous transdermal estradiol plus cyclic medroxy-progesterone acetate	Melatonin 1 mg oral tablet between 14:30 and 17:30 h, 90 min before investigation	In untreated postmenopausal women, melatonin treatment was ineffective, while in HRT-treated women, studied during the estrogenic phase, melatonin reduced, within 90 min, systolic ( $-8.1 \pm 9.9$ mmHg; $P = 0.054$ ), diastolic ( $-5.0 \pm 7.0$ mmHg; $P = 0.049$ ) and mean ( $-6.0 \pm 6.6$ mmHg; $P = 0.037$ ) BP. Norepinephrine but not epinephrine levels, were also reduced. Similarly, resistance to blood flow in the internal carotid artery was decreased by melatonin .	<sup>54</sup>
Placebo-controlled	26 healthy men	Melatonin (2 mg). Power spectral analysis of	Compared with placebo, melatonin administration	<sup>55</sup>

study		heart rate variability (HRV) and BP monitoring were recorded in the supine position before and 60 min after melatonin administration and in the standing position 60 minutes after administration. Plasma catecholamine levels were also measured.	increased R-R interval, the square root of the mean of the squared differences between adjacent normal R-R intervals, melatonin decreased the low-frequency to high-frequency ratio and BP in the supine position (P <0.01). Plasma norepinephrine and dopamine levels in the supine position after melatonin administration were significantly lower than in placebo.	
Observational study	5 healthy male subjects	3 mg of melatonin was given and the BP, heart rate and muscle sympathetic nerve activity (MSNA) were recorded continuously for 80 min	BP was reduced significantly, while heart rate and burst rate of MSNA did not change significantly.	<sup>56</sup>
Placebo-controlled study	11 healthy subjects	Fifty min after receiving a 3 mg tablet of melatonin or placebo (in different days) sympathetic nerve responses to orthostatic stress (MSNA), arterial BP, heart rate, forearm blood flow and thoracic impedance were measured	During the placebo trial, MSNA increased by $33 \pm 8$ and $251 \pm 70$ % during -10 and -40 mmHg, respectively, but increased by only $8 \pm 7$ and $111 \pm 35$ % during -10 and -40 mmHg with melatonin, respectively (P< 0.01). Arterial BP and forearm vascular resistance responses to orthostatic stress were unchanged by melatonin	<sup>57</sup>

**Table 3. Effect of melatonin in hypertensive patients**

Study design	Population	Experiment	Results	Ref.
Double-blind crossover study	47 mild to moderate essential hypertensive outpatients taking nifedipine 30 or 60 mg as a monotherapy at 08:30 h for at least 3 months	melatonin 5 mg at 22:30 h. A 24 h noninvasive ambulatory blood pressure monitoring was recorded from each patient	The evening administration of melatonin increased BP and heart rate (HR) throughout the 24 h period (Delta SBP = + 6.5 mmHg, P < 0.001; Delta DBP = + 4.9 mmHg, P < 0.01; Delta HR = + 3.9 beats min <sup>-1</sup> , P < 0.01). The increase in DBP as well as HR was particularly evident during the morning and the afternoon hours.	61
Double-blind, placebo-controlled, crossover study	16 men with untreated essential hypertension	2.5mg of oral melatonin given as a single and repeated (daily for 3 weeks) dose 1 hour before sleep. 24-hour ambulatory blood pressure and actigraphic estimates of sleep quality	Repeated melatonin intake reduced systolic and diastolic blood pressure during sleep by 6 and 4 mm Hg, respectively. Heart rate was not affected. A single dose of melatonin had no effect on blood pressure. Repeated doses of melatonin also improved sleep P<0.05.	59
Randomized, double-blind, placebo controlled study	38 treated hypertensive patients (22 males) with confirmed nocturnal hypertension (mean nighttime systolic BP >125	Controlled release-melatonin 2 mg or placebo 2 h before bedtime for 4 weeks. 24-Hour ambulatory blood pressure monitoring	Melatonin treatment reduced nocturnal systolic BP significantly from 136+/-9 to 130+/-10 mm Hg (P=.011), and diastolic BP from 72+/-11 to 69+/-9 mm Hg (P=.002), whereas placebo had no effect on nocturnal BP. The reduction in nocturnal systolic BP was significantly greater with melatonin than with placebo (P=.01), and was most prominent between 2:00 AM and 5:00 AM	60

	mm Hg), according to repeated 24-hour ambulatory blood pressure monitoring		(P=.002)	
Combined analysis of controlled clinical trials	Post hoc analysis of pooled antihypertensive drug-treated subpopulations from four randomized, double-blind trials.	Prolonged-release melatonin (PRM) (2 mg) for 3 weeks or 28 weeks. Measured the efficacy (by Leeds Sleep Evaluation Questionnaire scores of quality of sleep and alertness and behavioral integrity, sleep latency and Clinical Global Impression of Improvement) and safety of PRM for primary insomnia in patients aged 55 years and older who were treated with antihypertensive drugs	Compared to placebo, PRM had significantly improved quality of sleep and behavior following awakening (P < 0.0008). Sleep latency (P = 0.02) and CGI-I (P = 0.0003) also improved significantly. No differences were observed between PRM and placebo groups in daytime blood pressure at baseline and treatment phases. The rate of adverse events normalized per 100 patient-weeks was lower for PRM (3.66) than for placebo (8.53).	74
Randomized, double-blind, placebo-controlled, parallel-group design	16 hypertensive patients (age 45-64 yr; 9 women) treated with the beta-blockers atenolol or metoprolol	Melatonin 2.5 mg nightly for 3 weeks Sleep quality measured by polysomnography	Melatonin supplementation for 3 weeks significantly increased total sleep time (+36 min; P = 0.046), increased sleep efficiency (+7.6%; P = 0.046), decreased sleep onset latency to Stage 2 (-14 min; P = 0.001), increased Stage 2 sleep (+41 min; P = 0.037) when compared to placebo. The sleep onset latency remained significantly shortened on the night after discontinuation of melatonin administration (-25 min; P = 0.001), suggesting a carry-over effect.	75

## Figures legends

**Figure 1:** Functional pleiotropy of melatonin