SUMMARY AND CONCLUSION

- Treatment of rats with isoproterenol dose-dependently caused myocardial damage. Pre-treatment of rats with melatonin protected the cardiac tissue in a dose-dependent manner. Increased activities of SGOT, LDH and LDH 1 indicate myocardial ischemia and tissue injury following treatment of rats with ISO. Isoproterenol-induced myocardial injury was due to induction of oxidative stress as is evident from an enhanced level of lipid peroxidation and a reduced level of cardiac tissue GSH, the two bio-markers of oxidative stress. All these changes were ameliorated when the rats were pre-treated with melatonin. The continuation of melatonin treatment for two and four more day post-ISO treatment period brought back these parameters of cardiac damage and oxidative stress to near normal.

- Treatment of rats with ISO at a dose of 25mg/kg BW caused alterations in the activities and protein levels of the key cardiac antioxidant enzymes. Pre-treatment of rats with melatonin at a dose of 10mg/kg BW significantly ameliorated the ISO induced changes in the activities and protein levels of these enzymes. In addition, when the melatonin treatment was continued for 2 and 4 more days after discontinuation of the ISO treatment, activities of the antioxidant enzymes were found to be almost near control values.

- Treatment of rats with ISO caused tissue injury as evident from our histological studies. These were further supported by studies on tissue collagen through Sirius red staining and confocal microscopy. The tissue morphology was also studied through scanning electron microscopy. All these changes observed in the cardiac tissue following ISO treatment was found to be ameliorated when the rats were pre-treated with melatonin. Continuation of melatonin treatment for another two and four day after
the discontinuation of the ISO treatment caused further improvement in the recovery from tissue injury.

- Treatment of rats with ISO was found to generate reactive oxygen species like superoxide anion free radicals and hydroxyl free radicals which were found to be reduced to almost basal levels when the rats were pre-treated with melatonin. Continuation of melatonin treatment for further 2 and 4 days after discontinuation of the ISO treatment was found to further reduce the level of superoxide anion free radicals.

- Treatment of rats with ISO caused alterations in the activities of the mitochondrial Kreb's cycle enzymes and the enzymes of mitochondrial respiratory chain. These changes in the activities of the enzymes were ameliorated when the rats were pre-treated with melatonin.

- Treatment of rats with ISO also caused alterations in the levels of proteins associated with apoptosis and stress signaling pathways which were found to be ameliorated when the rats were pre-treated with melatonin.

- Treatment of rats with ISO increased the total DNA and RNA content of the cardiac tissue along with increasing the number of apoptotic nuclei as was evident from the DAPI stained sections of the tissue. Pre-treatment of rats with melatonin for 2 days was able to reduce the total DNA and RNA content to that observed in the control animals but was unable to decrease the number apoptotic nuclei. However, continued melatonin treatment in rats for 2 and 4 more days after the discontinuation of the ISO treatment led to decrease in the number of DAPI-stained apoptotic nuclei that were found similar to the control rats.

- Treatment of rats with ISO caused changes in the cardiac hemodynamic parameters which were found to be partially but significantly ameliorated
when the rats were treated with melatonin. However, when the melatonin treatment was continued for 2 and 4 more days after the discontinuation of ISO treatment, the cardiac hemodynamic parameters improved further and cardiac function was maintained at the level observed in the control rats.

Thus, our studies clearly indicate, that isoproterenol, a β-adrenergic agonist, at a dose of 25mg/kg BW, s.c., causes myocardial ischemia in rats, as is evident from the changes in the myocardial tissue morphology and the biomarkers of cardiac damage. That isoproterenol-induced cardiac injury is caused by the induction of oxidative stress is also evident from our studies. Melatonin, a naturally available tryptophan derivative, when applied at a dose of 10mg/kg BW i.p. is capable of ameliorating the ISO-induced changes to the biochemical and morphological parameters of the cardiac tissue. This small indole plays a role in protecting the myocardium from ISO-induced damage through its direct as well as indirect antioxidant activity. It also plays a role in the recovery of the rat heart after ISO-induced damage.

Cardiovascular disorders are fast becoming a principal cause of concern in the modern world. Most of the available drugs for the treatment of cardiovascular disorders have severe side-effects when their long-term use is necessary. The therapeutic role of melatonin against cardiovascular disorders is currently getting well documented in various experimental and clinical situations. Our studies additionally indicate that melatonin, a ubiquitously available natural amphiphilic molecule, not only has the potential to play an important role as a cardio-protective antioxidant and a future therapeutic agent against myocardial ischemia but may also be effective as an agent that may be useful in the recovery process after ischemic shock. However, more concerted and thorough studies need to be carried out in respect of melatonin’s efficacy as a cardioprotective agent both individually and as a co-therapeutic.