## DECODING THE UNDERLYING PATHOLOGY OF EXERCISE-INDUCED

# ATRIAL FIBRILLATION

Atrial fibrillation (AF) is an increasingly common heart arrhythmia that is reaching epidemic proportions in Canada, mainly affecting those over 65 and tripling the risk of stroke. Two HSRLCE members have largely devoted their work to deciphering and addressing heart arrhythmias and, more specifically, the molecular underpinnings of exercise-induced AF.

For the past two decades, Dr. Paul Dorian, a scientist in the Keenan Research Centre of the Li Ka Shing Knowledge Institute and department director, Division of Cardiology, University of Toronto, and Dr. Peter Backx, director of HSRLCE's Transgenic Physiology Lab, have been studying cardiac arrhythmias. Bringing their combined expertise in cardiology, clinical pharmacology, molecular biology and animal physiology to bear on key emerging knowledge about exercise and AF, over the past two years the pair has been exploring the effects of intense exercise on cardiac remodelling using animal models of atrial fibrillation.

While exercise is generally viewed as a heart-healthy proposition, intense exercise has been shown to raise the risk of this heart rhythm disturbance in former athletes and current competitive middle-aged athletes. "Exercise is almost always protective on the heart's ventricles," explains Dr. Dorian. "However, there is a volume of exercise beyond which it starts to result in maladaptive remodelling of the atria, and is likely to lead to atrial fibrillation, at least in animal experiments." Their current investigation focuses on finding ways to better define the molecular mechanisms underlying this maladaptive change, and developing strategies to reverse it either by preventing inflammation and scarring or addressing them once they occur.

Dr. Backx and Dr. Dorian recently led a pivotal study examining how intense exercise leads to cardiac remodelling, which identified the role of tumor necrosis factor (TNF-alpha), an inflammatory cytokine in AF that seems to be activated by intense exercise. They subsequently co-authored and published their findings in the journal *Nature Communications*. This research has been instrumental in shedding new light on the mechanisms of maladaptive changes in the heart, and suggests a new therapeutic target as well as a possible role for TNF-inhibitors to prevent atrial structural remodelling while preserving the physiological benefits of exercise.

They are also embarking on exciting new research that involves the testing of antiarrhythmic drugs in combination in a brand new model using atrial stem cells and tissue. Dr. Dorian says that this area has not been well investigated to date, and that using human cardiac stem cells should yield some very useful insights.

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Dr. Paul Dorian