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**FOR IMMEDIATE RELEASE – January 26, 2005**

**CITATION:** “Chronic Nicotine in Hearts with Healed Ventricular Myocardial Infarction Promotes Atrial Flutter That Resembles Typical Human Atrial Flutter,” *American Journal of Physiology: Heart and Circulatory Physiology*,” Published online Jan. 2005.

**HIGHLIGHTS:** Despite the evidence that cigarette smoking is a major cause of coronary heart disease, more than 46 million Americans continue to smoke cigarettes or use over the counter nicotine products to satisfy their nicotine addiction. In a recent animal study, researchers at Cedars-Sinai Medical Center and the University of California, Los Angeles have found that chronic nicotine ingestion after a heart attack significantly increases the incidence of cardiac fibrosis and causes electrical remodeling of the heart. This reaction promotes a kind of rapid heart rhythm that has many similarities to typical human atrial flutter, a potentially life-threatening condition that affects approximately a quarter-million Americans each year.

#### **ANIMAL STUDY SHOWS LINK BETWEEN NICOTINE AND ATRIAL FLUTTER**

**LOS ANGELES (Jan. 26, 2005)** — In a recent animal study, researchers from the Division of Cardiology at Cedars-Sinai Medical Center, in collaboration with the University of California, Los Angeles, have found that over time, the absorption of nicotine after myocardial infarction (MI) significantly increases the incidence of cardiac fibrosis in canine hearts. This reaction promotes a kind of rapid heart rhythm that has many similarities to typical human atrial flutter, a potentially life-threatening condition that affects approximately a quarter million Americans each year.

In an article published online in the January issue of the *American Journal of Physiology: Heart and Circulatory Physiology*, researchers report a study that tested the effects of nicotine on hearts with healed myocardial infarction. Numerous studies have shown that smoking promotes coronary heart disease and myocardial infarction and is a major cause of chronic obstructive pulmonary disease, an independent predictor of atrial flutter. These findings have raised the possibility that a causal link might exist between nicotine and atrial flutter in patients with myocardial infarction.

Atrial flutter is a type of rapid heart rate caused by the upper chambers of the heart (the right and left atria). The resulting rhythm is so rapid (about 400 beats/min) that the atria are not able to fully empty their contents into the ventricles, and the “left behind” blood stagnates, increasing the risk of thromboembolism and stroke. Fibrosis is an abnormal condition in which fibrous connective tissue spreads over or replaces smooth muscle; it is most common in the heart, lung, peritoneum and kidney.

“Although there were anecdotal reports, this hypothesis had not been previously tested systematically as to the reaction between nicotine and disease in promoting cardiac arrhythmias,” said Hrayr Karagueuzian, Ph.D., senior research scientist in the Division of Cardiology at Cedars-Sinai and senior author on the study. “We knew a significant portion of patients with heart disease had an increased incidence of atrial flutter, but there

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weren't any explanations as to the mechanistic basis or the need for concomitant disease.”

Myocardial infarction, or heart attack, occurs when the supply of blood to the heart is suddenly and severely reduced or cut off, causing the muscle to die from lack of oxygen. In the study, the condition was created surgically in anesthetized lab animal hearts by permanent occlusion of the left anterior descending coronary artery. Nicotine was administered for one month using osmotic mini-pumps with a dose similar to that absorbed by heavy smokers. An osmotic pump is a tiny implantable device that functions somewhat like an intravenous tube, delivering agents (in this case, nicotine) through a semi-permeable membrane.

The study included four groups. Those with only an MI and surgery experienced no flutter. Similarly, those that underwent surgery and received nicotine, but had no MI, also did not experience any flutter; nor did those that did not have surgery or nicotine. The final group, however, which had an MI, along with surgery and nicotine, did experience atrial flutter.

“Nicotine caused a significant increase in atrial interstitial fibrosis (a two-fold increase in the left atrium and a 10-fold increase in the right atrium) in the myocardial infarction group but only a two-fold increase in the right atrium in the non-MI group,” according to Karagueuzian. Furthermore, “chronic nicotine caused a kind of atrial electrical remodeling (change) that encourages the maintenance of a single stable wavefront allowing the atrial flutter to be sustained unperturbed” added Karagueuzian. The scientists were able to replicate the findings in computer simulations.

According to the American Heart Association, people who smoke a pack of cigarettes a day have more than twice the risk of heart attack than people who've never smoked; and smokers who have a heart attack have less chance of surviving than nonsmokers. The Centers for Disease Control and Prevention reports that cigarette smoking results in a two-to-three fold risk of dying from coronary heart disease. From 1995 to 1999, an average of 442,398 Americans died each year of smoking-related illnesses; 33.5 percent of these deaths were cardiovascular-related.

“We were surprised to find that nicotine induced a considerable increase in atrial interstitial fibrosis in the dogs with myocardial infarction but only a mild increase in the dogs with no MI,” Karagueuzian said. “These differential effects on atrial fibrosis occurred despite the fact that nicotine blood levels were similar in both groups and within the range seen in smokers.”

According to Karagueuzian, “To the extent that this animal model may be representative of human atrial flutter, our findings may be valuable in determining the pathogenesis of human typical atrial flutter and eventually helping to identify a therapeutic target for preventing fibrosis and atrial flutter.”

More immediately, Karagueuzian hopes the study will give smokers a better understanding of the mechanisms of nicotine-induced heart disease and that they will take a second look at reducing their habit or stopping it entirely and permanently.

The study was funded in part by the University of California-Tobacco Related Disease Research Program (11RT-0058), the AHA National Scientist Development Grant (0131017N) and Cedars-Sinai Electrocardiographic Heartbeat Organization.

One of only four hospitals in California whose nurses have been honored with the prestigious Magnet designation, Cedars-Sinai Medical Center is one of the largest nonprofit academic medical centers in the Western United States. For 17 consecutive years, it has been named Los Angeles' most preferred hospital for all health needs in an independent survey of area residents. Cedars-Sinai is internationally renowned for its diagnostic and treatment capabilities and its broad spectrum of programs and services, as well as breakthroughs in biomedical research and superlative medical education. It ranks among the top 10 non-university hospitals in

the nation for its research activities and was recently fully accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP). Additional information is available at [www.cedars-sinai.edu](http://www.cedars-sinai.edu).

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