Role of Prostanoids in Inflammatory Tachycardia: A Reply to the Letter of Dr. Eugene Nalivaiko

Dr. Nalivaiko discussed the role of the sympathetic nervous system in inflammatory tachycardia, tachycardia observed under inflammatory conditions, citing our recent study (4) as a reference. In fact, inflammatory tachycardia has long been thought to result from increased sympathetic activity brought by inflammatory signals. However, we presented another novel mechanism leading to inflammatory tachycardia in mice: PGF2α and thromboxane A2 (TXA2) play mediatory roles in the phenomenon (4). In short, these prostanoids increased beating rates of isolated atria in a concentration-dependent manner via their respective receptors, the FP and TP. In addition, the inflammatory cytokine-induced increase in beating rate of isolated atria was totally dependent on both the FP and TP, indicating that inflammatory cytokines stimulated local production of PGF2α and TXA2 and thus induced tachycardia. Furthermore, LPS, a potent inducer of systemic inflammation through the production of inflammatory cytokines, failed to induce tachycardia in mice lacking both the FP and TP, confirming the in vivo role of PGF2α and TXA2 in inflammatory tachycardia.

In our model of LPS-induced tachycardia, a β-adrenergic blocker significantly reduced heart rate by 100 beats/min, but failed to affect the biphasic pattern of tachycardia itself, indicating that the prostanoids have a distinctive role in inflammatory tachycardia independent of the sympathetic nervous system. This result presents an important suggestion to evaluate the effect of beta blockers on tachycardia. Because the sympathetic nervous system is a main constituent determining basal and demand-dependent heart rate, any beta blocker would usually reduce heart rate under various situations, as seen also in our model. Therefore, it seems important to observe the pattern of tachycardia after the administration of beta blockers to properly evaluate their effects. In this mean, previous studies might have failed to detect the factors mediating inflammatory tachycardia other than the sympathetic nervous system due to an apparent inhibitory effect of beta blockers on heart rate at a single observation time point. In another aspect, it would be very difficult to demonstrate increased sympathetic discharge leading to tachycardia by use of beta blockers because they inhibit basal sympathetic tone in addition to the increased tone under inflammatory conditions.

Dr. Nalivaiko indicated the difference in the dose of LPS used between in his rabbit study (3) and in our mouse study (4), and suggested that the sympathetic nervous system and the prostanoids may participate in inflammatory tachycardia differently according to an extent of inflammation. It is noteworthy, however, that rabbits show the highest sensitivity to LPS but mice show the lowest one. Therefore, to discuss the difference in dose dependent effects of LPS between rabbits and mice is difficult, and further studies using a single species would be required to clarify the issue.

We found that a pattern of LPS-induced tachycardia in mice lacking the PGE2 receptor EP3 [these mice showed a defective febrile response to LPS (5)] was nevertheless similar to that in wild-type mice. This result clearly indicates that febrile response and inflammatory tachycardia are independent events mediated by the different prostanoids and that fever itself could not induce tachycardia, which is in sharp contrast with a previous idea. The effect of nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and indomethacin, on heart rate results from a reduction in sympathetic tone caused by their antipyretic action. Interestingly, there are two pioneering human studies reporting a potent suppressive effect of NSAIDs on both inflammatory tachycardia and febrile response under inflammatory conditions (1, 2). Considering an independence of inflammatory tachycardia and febrile response found in mice, these reports suggest that the prostanoids play a role in inflammatory tachycardia also in humans. However, roles of the prostanoids and sympathetic nervous system in inflammatory tachycardia in humans remain to be clarified in future studies.

REFERENCES