

This Week's Citation Classic

Epstein S E, Robinson B F, Kahler R L & Braunwald E. Effects of beta-adrenergic blockade on the cardiac response to maximal and submaximal exercise in man. *J. Clin. Invest.* 44:1745-53, 1965.
[Cardiology Branch, National Heart Institute, Bethesda, MD]

The sympathetic contribution to the cardiac response to exercise was determined in man using propranolol, a beta-adrenergic blocking agent. Blocking sympathetic stimulation reduced heart rate, cardiac output, and mean arterial pressure during submaximal and maximal exercise, and diminished both maximum VO_2 and capacity for strenuous exertion. [The SC][®] indicates that this paper has been cited over 305 times since 1965.]

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April 29, 1980

"Eugene Braunwald and Richard L. Kahler had performed some interesting preliminary work in the early 1960s on oxygen debt occurring during strenuous exercise in patients with heart disease.¹ I joined Braunwald and Kahler in July, 1963 and Brian Robinson, from St. George's Hospital in London, began a two year fellowship with us later that year.

"As a result of the initial work, the four of us undertook a more systematic investigation of oxygen debt in an attempt to develop a reliable index of circulatory impairment, as well as a means of documenting therapeutic efficacy of various cardiovascular interventions. Over the next year we delved into the intricacies of exercise testing in normal subjects and in patients with heart disease. It soon became apparent that oxygen debt was neither a reliable means of assessing cardiovascular dysfunction nor of ascertaining the response of the cardiovascular system to interventions. Although our original goals

seemed thwarted, in the process we gained a considerable amount of expertise in exercise physiology. We also developed a deep interest in the mechanisms responsible for the profound circulatory changes occurring during exercise.

"There had been a great deal of interest in the role of the sympathetic nervous system in modulating this response. However, definitive studies were impossible to perform because of the inability to isolate the sympathetic component of the response. For example, most blocking drugs available had both anti-adrenergic and antiparasymphathetic effects. It so happened that Robinson, while in England, had worked with pronethalol, the first specific beta-adrenergic blocking agent developed. Shortly thereafter, propranolol, the successor to pronethalol, had become available. Thus, by mid-1964, we were in a fortunate situation: the laboratory had an intense interest in exercise physiology, and especially in the sympathetic component of the cardiovascular response to exercise; a specific beta-adrenergic blocking drug had recently been developed; and a large scale exercise-related effort the laboratory was engaged in had floundered, creating the time necessary to initiate what ultimately proved to be a fruitful investigation.

"The manuscript resulting from this study has been frequently cited mainly, I believe, for two reasons. First, the investigation was of interest to the physiologist exploring the basic mechanisms responsible for modulating the circulatory response to exercise. Second, beta-adrenergic blocking drugs were soon to become one of the more frequently used drugs in the therapy of various types of cardiovascular disorders. Clinicians and clinically oriented investigators therefore became vitally interested in the cardiovascular effects of beta-blocking agents and the effects these drugs have on exercise capacity."

1. Kahler R L, Thompson R H, Buskirk E R, Frye R L & Braunwald E. Studies on digitalis. VI. Reduction of the oxygen debt after exercise with digoxin in cardiac patients without heart failure. *Circulation* 27:397-413, 1963.