Introduction

The introduction of a new medical diagnostic technique requires extensive validation of its true predictive value before it can be integrated into routine clinical use. Typically, the validation procedure includes two main phases: (i) extensive basic research in order to explore the scientific basis of the underlying physiological phenomenon, and (ii) validation of its diagnostic performance in large scale clinical trials.

The scientific basis of the HyperQ System is based on numerous research studies that have been published in leading cardiology journals during the last two decades. Extensive research efforts, including computer modeling[1], animal experiments[2] as well as dedicated studies in humans[3-5], provide a sound scientific basis for the ability to identify myocardial ischemia using analysis of the high-frequency components in the mid-QRS complex of the ECG. A comprehensive literature review and references can be found in BSP's White Paper 2.

The purpose of this review is to describe the clinical validation studies that have been performed using the HyperQ System.

Clinical Studies

In recent years the HyperQ System has been used in several clinical studies aimed at testing its clinical diagnostic value.

A large-scale clinical study aimed at evaluating the HyperQ System was conducted by cardiologists from Maccabi Healthcare Services, Israel 2nd largest HMO. In this study, the HyperQ System was evaluated during routine treadmill exercise testing to detect induced myocardial ischemia. Exercise myocardial perfusion SPECT was used as the gold standard for comparison. The study included 885 consecutive patients (643 men). The relative change in HyperQ intensity during exercise was adapted as an index of ischemia. Logistic regression was used to assess incremental diagnostic value of HyperQ data over conventional ECG analysis. The HyperQ index of ischemia was found to be more sensitive than conventional ST analysis (78% vs. 56%, p<0.01) with similar specificity (74% vs. 78%, p=ns). The HyperQ index offered a significant incremental diagnostic value over clinical symptoms and stress test data (see Fig 1). The results of this study were presented at scientific meetings[6,7] and a manuscript for a peer-reviewed cardiology journal is under preparation.

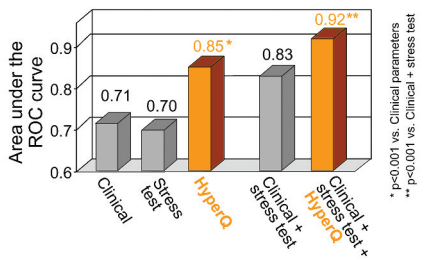

Figure 1: The area under the receiver operating characteristics (ROC) curve for various ischemia detection schemes, indicating the accuracy of detection. The HyperQ data provided marked improvement in diagnostic capability over (i) clinical parameters (Clinical), (ii) ST changes (not shown), and (iii) a sophisticated scoring approach of stress test results (Stress test).

A similar study was carried out at the C.A. Medical Center, West Virginia, by leading cardiologists and researchers from CAMC and Duke University. In this study HyperQ-based ischemia detection was compared with exercise myocardial perfusion SPECT in 133 patients. The HyperQ index of ischemia was found to be more sensitive than the conventional ST analysis (77% vs 43%, p<0.05) with comparable specificity (66% vs 57%). In women, HyperQ analysis resulted in improved specificity relative to conventional ECG (70% vs 33%, p<0.05).[8,9]

In a study performed at the Rabin Medical Center, Israel, 95 patients underwent exercise myocardial perfusion SPECT during which high frequency ECG was recorded. The HyperQ index was found to be markedly more sensitive than ST changes (76% vs 59%, p<0.01) and more specific (85% vs 57%, p<0.01).[9], Another important finding was that changes in the HyperQ signal were observable before ST changes were evident, indicating earlier detection of ischemia by the HyperQ.

On-going studies

Several clinical studies involving the HyperQ System are in the stage of data collection:

- Comparison between the performance of the HyperQ system and conventional ECG interpretation in consecutive patients referred for coronary angiography. All patients undergo exercise testing. Preliminary results indicate marked improvement in sensitivity of the HyperQ analysis compared to ST changes (71% vs. 27%) while achieving 85% specificity.[11]
- Analysis of HyperQ data obtained in consecutive subjects referred for routine screening ergometry. All participating subjects undergo stress echocardiography, which serves as the gold standard for comparison.
- Analysis of HyperQ data obtained in consecutive subjects referred for dobutamine stress echocardiography. This cohort of patients will allow examination of the HyperQ System in pharmacological stress testing.
- Comparing the performance of HyperQ with conventional ECG analyses in detecting acute ischemia in patients undergoing PTCA. Preliminary results indicate enhanced sensitivity of the HyperQ analysis in detecting ischemia, compared to ST analysis (86% vs. 48%).[12]
- Multi-center study aimed at comparing the positive predictivity of HyperQ analysis and ST changes in patients undergoing exercise testing in community clinics. More than 1200 patients have already been enrolled to the study, which is conducted by a leading Israeli HMO.[13]

References

1. Abboud S, Berenfeld O, Sadeh D. Simulation of high-resolution QRS complex using a ventricular model with a fractal conduction system. Effects of ischemia on high-frequency QRS potentials. Circ Res 1991;68:1751-1760.
2. Abboud S, Smith JM, Cohen RJ. Et al. High frequency electrocardiography of three orthogonal leads in dogs during a coronary artery occlusion. PACE 1989;12:574-581.
3. Abboud S, Cohen RJ, Friedman PL et al. Detection of transient myocardial ischemia by computer analysis of standard and signal averaged high frequency ECG in patients undergoing percutaneus transluminal coronary angioplasty. Circulation 1987;76:585-96.
4. Abboud S. High frequency electrocardiogram analysis of the entire QRS in the diagnosis and assessment of coronary artery disease. Prog Cardiovasc Dis 1993;35:311-328.
5. Pettersson J, Pahlm O, Wagner GS. Changes in high-frequency QRS components are more sensitive than ST-segment deviation for detecting acute coronary artery occlusion. J Am Coll Cardiol 2000;36:1827-34
6. Silber H, Sharir T. Diagnostic value of high frequency mid QRS analysis in the detection of exercise induced ischemia. Eur Heart J 2005;26 (Suppl):257.
7. Sharir T et al. Detection of Stress-Induced Myocardial Ischemia using Analysis of High-Frequency QRS Components. J Am Coll Cardiol 2006;47(4):132A
8. Lipton JA, Warren SG, Broce M, et al. High frequency QRS electrocardiogram analysis during exercise stress testing for detecting ischemia. Int J Cardiol [in press].
9. Toledo E, Almogy N, Lipton JA, et al. Improved Detection of Stress-Induced Ischemia Using Analysis of High-Frequency ECG Components. J Am Coll Cardiol 2007;49(9):110A
10. Zafrir N, Gadot M, Abboud S, Strasberg B. A New Technique for Detecting Stress-Induced Ischemia Using Analysis of the ECG Depolarization Phase. J Am Coll Cardiol 2007;49(9):21A
11. Reinsch N, Wieneke H, Erbel R. High Frequency QRS Analysis - An Effective Technique for the Diagnosis of Stress Induced Ischemia? Clin Res Cardiol 2006; 95 (Suppl) 7.
12. Herz I, Finkelstein A, George J et al. Analysis of high-frequency mid-QRS components is highly sensitive to myocardial ischemia caused by intra-coronary balloon occlusion. Eur Heart J 2006; 27 (Suppl):134.
13. Silber H, Shohat-Zabarski R, Shefer A et al. High frequency ECG – A novel tool for improving the diagnostic accuracy of exercise testing in the community setting. Eur Heart J 2007; 28 (Suppl):524.

The HyperQ™ Stress System received US FDA clearance (510K) and CE marking.