THE HEART RATE RESPONSE TO ADENOSINE AS A PREDICTOR OF ADVERSE CARDIAC OUTCOMES IN THE DETECTION OF ISCHEMIA IN ASYMPTOMATIC DIABETICS STUDY

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Background: The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study demonstrated an overall low 5-year hard cardiac event rate of 2.7%. We hypothesized that a blunted heart rate response (HRR) to adenosine infusion, a marker of cardiac autonomic neuropathy, might identify within DIAD a cohort at higher cardiac risk.

Methods: Of 1,123 DIAD participants, 518 were randomized to screening with adenosine myocardial perfusion imaging (MPI) and had available data. HRR was calculated as maximum percent change in heart rate from baseline during adenosine infusion. A HRR <20% was considered abnormal. The cohort was divided into 3 HRR groups: <20% (n=79, 15%), 20-39% (n=182, 35%), and ≥40% (n=257, 50%). Since participants with small MPI defects had similar outcomes as those with normal MPI, these participants were combined and compared to participants with moderate/large MPI defects. The primary end point was a composite of nonfatal myocardial infarction and cardiac death.

Results: Follow-up was 4.7±0.9 years during which 15 (3%) participants experienced the primary outcome. The mean HRR was lower in those who had a cardiac event vs. those who did not (27±23% vs. 42±22%, p=0.004). Participants with a lower HRR experienced more events than those with higher HRR (8%, 3%, 1%, for HRR <20%, 20-39% and ≥40%, respectively, p=0.01). In a Cox proportional regression model that included MPI abnormalities and HRR, both were independently associated with cardiac events (p for model <0.001). HRR <20% was associated with 9-fold increased risk (HR 9.0, p=0.007) and moderate/large abnormal MPI was associated with nearly 6-fold increased risk (HR 5.7, p=0.004). There was no interaction between HRR and MPI abnormalities for the prediction of events. Participants with abnormal MPI and HRR <20% (n=8) were at highest risk for cardiac events (38%) whereas those with HRR ≥40%, irrespective of MPI abnormalities (n=234), were at lowest risk (≤1%, log-rank p<0.001).

Conclusions: In DIAD, abnormal HRR to adenosine infusion is an independent predictor of cardiac events. This marker of cardiac autonomic neuropathy identifies asymptomatic patients with diabetes at increased risk, particularly when associated with abnormal MPI.