Early Detection of Infection with Continuous Heart Rate Variability Analysis in Neutropenic Patients

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Hypothesis: Infection leading to organ failure kills more critically ill patients than any other cause. Early diagnosis of infection leading to timely antibiotics and resuscitation saves both patient lives and costs of care; however current techniques to diagnose infection are imprecise, insensitive and frequently late manifestations of infection. To address this problem, our aim is to uncover hidden information contained within cardiac interbeat-interval time series using advanced mathematical analysis rooted in complex systems science. Previous work has demonstrated altered heart rate variability (HRV) in patients with infection (more regular, less complex cardiac variation); not only is HRV altered with infection, the degree of HRV alteration also correlates with its severity. Building upon these results, our principal objective is to perform *continuous HRV monitoring* in adult patients at high risk for infection, and evaluate the hypothesis that change in HRV precedes traditional markers of infection.

Methods: In a consecutive observational trial, ambulatory patients undergoing bone marrow transplantation (BMT) for hematological malignancy underwent continuous Holter heart rate monitoring, starting the day prior to BMT and continuing until recovery. Demographic, clinical, microbiological data, daily symptoms and patient temperature were recorded; HRV analysis was performed and displayed with *continuous individualized variability analysis* (CIMVA) software that performs multi-parameter characterization of variability (including time-domain, frequency-domain, scale-invariant and complexity measures of variability), employing a smoothed, overlapping, iterative, interval-in-time analysis algorithm (interval & step size: 1200 & 200 heart beats).

Results: A total of 10 patients have completed this pilot investigation to date, undergoing monitoring for 12±3 days (range 5-15). All 10 patients became neutropenic, and all were diagnosed and treated for infection. The clinical diagnosis of infection was made due to fever (core temp > 38.0) in 8 patients, and due to symptoms in 2 (mucositis, diarrhea). Baseline HRV was defined as the average HRV during the first 24hr of observation (prior to BMT); reproducible reduction in baseline variability was present in all patients in association with infection (100%), as well as with severe symptoms (30%) such as recurrent diarrhea or vomiting. A 10% and 20% decrease in baseline HRV occurred 41±45 and 33±45 hours prior to antibiotic administration. No patient required ICU admission, and recovery of HRV was observed in 70% patients.

Conclusions: These descriptive preliminary data support feasibility of continuous HRV monitoring in ambulatory patients. Given that changes in HRV occur in association with symptoms and infection, and occur earlier than traditional clinical markers of infection, further investigation is warranted to define accuracy, sensitivity and specificity of change in variability as a tool for early detection of infection.

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