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SUDEP and Heart Rate Variability

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Sudden Unexplained Death in Epilepsy (SUDEP); Heart Rate Variability (HRV)

We read with interest the important article by Surges et al. regarding their case-controlled study of heart rate variability **(HRV)** and sudden unexplained death in epilepsy **(SUDEP)** (Surges et al 2009). Surges retrospectively examined multiple measures of HRV in a group of seven SUDEP victims and seven age-matched controls. To the authors' surprise, differences in HRV measures were not significant.

However, when one carefully reviews the HRV data, specifically measures of high-frequency HRV (**RMSSD and High Frequency Spectral Power**), it is clear that there are substantial numerical differences between the two groups (Surges et al 2009). High-frequency HRV is important to consider because it is associated with vagus nerve/parasympathetic control of the heart, and low values indicate dysfunctional central nervous system control of the cardiac rhythm (Stein et al 1993; Kleiger et al 1987). In data gathered from 4:00 – 5:00 p.m., mean values of both RMSSD and High Frequency Spectral Power were noticeably lower in the SUDEP group than in the control group (Surges et al 2009). For example, the SUDEP group showed a mean RMSSD of 38 msec (SD 12 msec), while the control group had a mean of 46 msec (SD 23 msec). For High Frequency Spectral Power the magnitude of the difference and standard deviation were even higher. The SUDEP group had a mean of 297 $msec^2$ (SD 178 $msec^2$) versus a mean HFSP of 500 $msec^2$ (SD 449 $msec^2$) for the control group. This represents a 40% difference between the groups. With the small sample size and the large standard deviations in both measures, it is not surprising that a significant difference could not be detected. Surges et al. admit, “The inter-individual variability of HRV parameters is relatively large…” and “…Our failure to detect any difference in inter-ictal HRV in SUDEP and control patients could therefore be due to small sample size” (Surges et al 2009).

Further, given that many control subjects had risk factors for SUDEP (poorly controlled epilepsy, long duration of epilepsy, and multiple AED's), there is reason to believe that the control subjects may eventually die of SUDEP given sufficient follow-up, as Surges et al. rightly point out (Surges et al 2009; Walczak et al 2001).

If this study is interpreted incorrectly, a potential biomarker of SUDEP may be overlooked. HRV is a measure of the beat-to-beat variability of the heart. (Stein et al 1993). It is heavily dependent on the vagus nerve, which modulates heart rate in response to inspiration, expiration,

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wake and sleep state, and levels of activity (Stein et al 1993). Low HRV is strongly predictive of increased mortality in heart disease, and is associated with an increased risk of lethal arrhythmias and sudden cardiac death. (Kleiger et al 1987; Hartikainen et al 1996; Ponikowski et al 1994) There is growing evidence low HRV may be a risk factor for SUDEP (Ansakorpi et al 2002; Mukherjee et al 2009). HRV is reduced in people with poorly controlled epilepsy, who are at higher risk for SUDEP (Ansakorpi et al 2002; Mukhergee et al 2009). Recently in this journal, Mukherjee et al found that 31 subjects with poorly-controlled epilepsy (at risk for SUDEP) had significantly lower measures of high-frequency HRV than 30 subjects with well-controlled epilepsy (114 vs. 397, p=0.013) of HRV. The authors conclude that abnormal autonomic regulation, evidenced by low HRV "…might be a predisposing factor for SUDEP." This confirms data from Ansakorpi et al who also found significantly reduced HRV in subjects with poorly controlled temporal lobe epilepsy compared with well-controlled subjects and normal controls.

Recently, we evaluated the relationship between HRV and the risk for SUDEP. We assembled a weighted seven-item inventory of SUDEP risk factors prospectively validated by Walczak et al (Walczak et al 2001). We then correlated HRV measures with the total score, and found a highly significant inverse correlation between high-frequency HRV (RMSSD) and risk for SUDEP (DeGiorgio et al 2009). The results strongly suggest that high-frequency measures of HRV may be associated with the risk of SUDEP.

We applaud Surges et al. for exploring this difficult topic, and for their intellectual honesty and willingness to point out the limitations of this study. When evaluated closely, their data actually indicate a trend toward low values of high-frequency HRV in victims of SUDEP. If confirmed in a larger cohort, this would provide important evidence that HRV is indeed a biomarker of SUDEP.

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