Letter to the Editor

Usefulness of Heart Rate Variability (HRV) for Monitoring Clozapine Plasma Levels

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We would like to take this opportunity to discuss the recently published manuscript of Eschweiler et al. [3] and provide some additional relevant information on this subject.

Benzodiazepines and SSRIs were allowed as concomitant medication in the study. Both substances significantly influence HRV, as independent studies have shown.

The authors postulate that clozapine plasma concentrations (cpc) can be predicted by measuring HRV and, more specifically, that a 0.5 ($_{log}$CV) cutoff level for the coefficient of variation (where CV = 3.2%) is suitable for differentiating patients with "optimal" cps (> 350 ng/ml) from those with "suboptimal" cps (< 350 ng/ml). Fig. **1a** of their paper shows that 9 patients had optimal cpc, with all registering a $_{log}$CV below 0.5. Of the 24 cases with suboptimal cpc, the $_{log}$CV in 14 cases was above 0.5 and was below 0.5 in the other 10 cases. Thus, although a $_{log}$CV cutoff of 0.5 can encompass all patients with optimal cpc (sensitivity 100%), the specificity is low, since 10 of 24 patients with suboptimal cpc would be falsely identified as positive. A $_{log}$CV over 0.5 would appear to exclude an optimal cpc according to the pres-

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ented data, but the sensitivity for detecting a suboptimal cpc is low, since only 58.3 % of patients with suboptimal cpc were actually identified.

The authors postulate that HRV analysis might represent a tool for monitoring patient complicance in long-term clozapine treatment. This is only possible in a limited way, as the results of one of our own prospective case studies have shown. In 8 schizophrenic patients (5 female, 3male; mean age 35.7 ± 10.6 years), we measured HRV and cpc before treatment onset (baseline) and twice at weekly intervals during the dosing-up phase of clozapine treatment. The cpc increased during the course in all patients; the average cpc was 69.0 ± 23.4 (25 – 90) ng/ml and 164.1 ± 69.3 (76 – 285) ng/ml at the first and second dosing-up time points, respectively. The Figure **1** illustrates the $_{log}$CV values. As expected, clozapine reduced the overall HRV measured as a reduction in CV. However, it was remarkable that at the second dosing-up time (with the highest cpc), the largest reduction in CV compared to baseline was seen in only two cases (case 3 and 7); in 4 cases the CV at the first dosing-up time was even lower than it was at the second dosing-up time. Thus, despite the increasing cpc, a corresponding reduction of CV does not occur in all cases; instead, the CV even starts to reverse, a fact that would appear to limit the applicability of CV for monitoring cpc during long-term treatment. Analogous results were found for the remaining HRV indices (e.g., spectral power, not illustrated). The mechanisms underlying this clearly complex association between cpc and HRV are not known; one might presume that not only clozapine alters autonomic nervous system (ANS) function but that other factors such as the schizophrenic disease itself or the severity of schizophrenic systems also play a role. There is indeed evidence that the patient's psychotic states affect HRV, suggesting a relationship between cerebral cognitive activities and ANS function [5]. This thesis corresponds well to our observation that in patients responding well to haloperidol or clozapine, lower impairments of ANS function are seen compared to non-responders [1].

The authors found that the mean low-frequency (LF; 0.01 – 0.05 Hz) and mid-frequency (MF; 0.05 – 0.15 Hz) spectral powers were higher in olanzapine treated patients compared to clozapine-treated patients. They interpreted this pattern of findings as a confirmation of olanzapine's lower affinity to alpha-adrenergic receptors compared to clozapine. This is an oversimplification of the complex interactions between neuroleptics and HRV regulation. If one pursues the author's argument that the low-frequency spectral bands primarily reflect sympathetic modulation of HRV, clozapine must inhibit the sympathetic modulation of HRV stronger than olanzapine. However, biochemical investigations have shown an almost counter-regulatory increase in sympathetic nervous outflow reflected by an increase in plasma catecholamine concentrations during treatment with α-receptor-blocking neuroleptics. In humans, clozapine increases norepinephrine levels in both plasma and cerebrospinal fluid, suggested to be due to simultaneous α_1-, α_2-, and norepinephrine reuptake antagonism [2]. If a direct association exists between LF power and sympathetic nervous system outflow, than an increase rather than a reduction in LF power would be expected in response to clozapine. Kingwell et al. published an excellent study that has helped us to understand the complex regulation of HRV [4]. They stated that HRV, particularly the low-frequency power around 0.1 Hz, is not directly related to cardiac norepinephrine spillover and in fact represents a functional end-organ response that depends on multiple factors in addition to sympathetic nerve firing rates. These include cardiac adrenergic receptor sensitivity, postsynaptic signal transduction, electrochemical coupling, and multiple neural reflexes. Thus, an elevation in sympathetic nerve activity under clozapine is obviously not well translated into a functional end-organ response due to mechanisms that have not yet been elucidated.

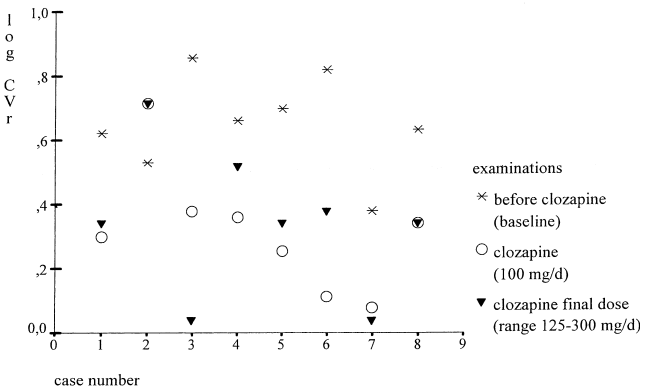

Fig. **1** The figure illustrates the individual coefficient of variation ($_{log}$CV) with respect to clozapine plasma concentrations in 8 cases.

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