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Abstract: Objective: Ketamine has been shown to be effective in treatment of episodes of major depressive disorder (MDD). This controlled study aimed to analyse the predictive and discriminative power of heart rate (HR) and heart rate variability (HRV) for ketamine treatment in MDD. Methods: In 51 patients, HR and HRV were assessed at baseline before and during ketamine infusion and 24 hours post ketamine infusion. Montgomery-Åsberg Depression Rating Scale (MADRS) was used to assess changes of depressive symptoms. A 30% or 50% reduction of symptoms after 24 hours or within 7 days was defined as response. A linear mixed model was used for analysis. Results: Ketamine infusion increased HR and HRV power during and after infusion. Responders to ketamine showed a higher HR during the whole course of investigation, including at baseline with medium effect sizes (Cohen’s d = 0.47–0.67). Furthermore, HR and HRV power discriminated between responders and non-responders, while normalized low and high frequencies did not. Conclusion: The findings show a predictive value of HR and HRV power for ketamine treatment. This further underlines the importance of the autonomous nervous system (ANS) and its possible malfunctions in MDD. Significance: The predictive power of HR and HRV markers should be studied in prospective studies. Neurophysiological markers could improve treatment for MDD via optimizing the choice of treatments.

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Predictive value of heart rate in treatment of major depression with ketamine in two controlled trials

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Ketamine as a fast-acting agent for treating major depressive disorder.
Neurophysiological markers such as electrocardiogram derived heart rate variability could be used to predict treatment outcome.
This work reveals the predictive power of heart rate and heart rate variability markers for the prediction of outcome to ketamine treatment.

Objective: Ketamine has been shown to be effective in treatment of episodes of major depressive disorder (MDD). This controlled study aimed to analyse the predictive and discriminative power of heart rate (HR) and heart rate variability (HRV) for ketamine treatment in MDD.

Methods: In 51 patients, HR and HRV were assessed at baseline before and during ketamine infusion and 24 hours post ketamine infusion. Montgomery–Åsberg Depression Rating Scale (MADRS) was used to assess changes of depressive symptoms. A 30% or 50% reduction of symptoms after 24 hours or within 7 days was defined as response. A linear mixed model was used for analysis.

Results: Ketamine infusion increased HR and HRV power during and after infusion. Responders to ketamine showed a higher HR during the whole course of investigation, including at baseline with medium effect sizes (Cohen’s d = 0.47–0.67). Furthermore, HR and HRV power discriminated between responders and non-responders, while normalized low and high frequencies did not.

Conclusion: The findings show a predictive value of HR and HRV power for ketamine treatment. This further underlines the importance of the autonomous nervous system (ANS) and its possible malfunctions in MDD. Neurophysiological markers could improve treatment for MDD via optimizing the choice of treatments.

1. Introduction

Since its usage in the first randomized controlled trial (Zarate et al., 2006) ketamine repeatedly has been shown to be effective in treatment resistant depression (TRD) (Han et al., 2016; McGirr et al., 2015). Despite the growing evidence of its efficacy, a recent consensus statement of the American Psychiatric Association (APA) clearly lines out that data is missing for selecting patients that might benefit from this treatment option (Sanacora et al., 2017).
Therefore, more knowledge on markers is needed to predict the outcome of ketamine treatment and inform therapeutic decisions.

Within the past few years, research has focused upon the characteristics of responders, indispensable for the selection of patients that could benefit from particular treatment (Zarate et al., 2013). There have been studies on genetic polymorphism predicting the outcome of ketamine infusion, that have stated an association between Val/Val brain-derived neurotrophic factor (BDNF) allele and better response to ketamine in mice (Liu et al., 2012) and later in human (Laje et al., 2012). A couple of functional neuroimaging studies using magnetoencephalography have revealed a correlation between baseline function in anterior cingular cortex and subsequent clinical improvement for ketamine treatment (Salvadore et al., 2009). Furthermore, H1-magnetic resonance spectroscopy (MRS) studies have revealed that baseline Glx/Glutamate ratio (a surrogate marker of glutamate) in the dorsomedial/dorsolateral prefrontal cortex is negatively correlated with the antidepressant effect of ketamine (Machado-Vieira et al., 2009; Salvadore et al., 2012). Few studies on predictive potential of pretreatment sleep architecture have proposed that baseline delta sleep ratio predicts ketamine response in depression (Duncan et al., 2013). Although these findings contribute to the understanding of possible neurobiological mechanisms of ketamine action, the gain for clinical implementation seems to be low. Further, regardless of a great recent interest in the topic (Nicu et al., 2014), objective clinical predictors to ketamine response remain elusive.

Since the first studies on ketamine (CI 581) have been published after its first synthesis in 1962, the enormous impact on the activity of the autonomous nervous system (ANS) with increasing heart rate (HR) (Corssen and Domino, 1966) via a sympathetic pathway (Traber et al., 1970) and its anesthetic properties on the central nervous system (CNS) (Bergman, 1999) continually became clear. Due to this two-sided action and the fact, that ketamine blocks sensory event-related potentials in associative cortex but simultaneously preserves them in primary sensory regions it was soon called a dissociative anesthetic (Traber et al., 1970). Since heart rate and its associated measures reflect the activity of the ANS (Pomeranz et al., 1985) and are easily assessable in a clinical environment, this study aimed to evaluate the predictive power of heart rate and heart rate associated measures for ketamine treatment in MDD.

Specifically, reduced heart rate variability (HRV) in patients with depression reflects sympathovagal dysbalance accompanying the disorder. Meta-analyses have shown negative correlation between HRV and depression severity (Kemp et al., 2010). The impact of drugs for depression on HRV values was questioned in several studies. Clear evidence of further HRV reduction was only obtained in tricyclic drugs for depression, the impact of other medication remains controversial (Kemp et al., 2010; Licht et al., 2010). It was shown that baseline HRV changes in response to emotional stimuli were associated with the reduction in depressive symptoms after fluoxetine treatment (Fraguas et al., 2007). In detail, Low Frequency (LF) Power responses to sad stimuli and LF/High Frequency (HF) Power ratio triggered by happy stimuli were correlated to symptom decrease. Lower relative power of very low frequency (rLFV) HRV at baseline also predicted improvement during escitalopram treatment in a small pilot study (Jain et al., 2014). Analysis of ANS data from the large ISPOT-trial (Williams et al., 2011) showed in 598 patients that a significant increase of heart rate during resting condition, before the initiation of antidepressant treatment, was associated with a clinical response to a serotonin–norepinephrine reuptake inhibitor (SNRI) as compared to treatment with a selective serotonin–reuptake inhibitor (SSRI) (Olbrich et al., 2016). Summing up all these previous findings, it was hypothesized that an increased sympathetic tone as it can be reflected in higher HR, larger HRV power and larger Low Frequency power before, during and after infusion of a single dose of ketamine would be associated with a more pronounced decrease of symptoms.

2. Methods

Patients: Fifty-one patients were recruited into two consecutive controlled trials (EudraCT Number: 2009-010625-39; N = 27 and EudraCT Number: 2013-000952-17; N = 24) between 2010 and 2015. The first trial was double-blind (blinded for both participants and care providers) and randomized, using sealed envelopes and random permuted blocks (size of six) for a balanced group design and allocation of subjects for placebo/ketamine. The second trial had a controlled single-blind, one-arm, fixed sequence design without randomization, i.e. the sequence was the same for all participants: first infusion was placebo, second was ketamine. All participants were enrolled by the principal study investigator and subsequently assigned by the study assistant. Therefore, both, care providers and those assessing outcomes, were informed about the sequence. These studies aimed to identify clinical, electrophysiological, and biological predictors of response to a single intravenous dose of ketamine as treatment for depression (monotherapy or combination) in patients with MDD. More details have been published elsewhere (Sos et al., 2013). In both studies identical inclusion and exclusion criteria were applied. All patients were between 18 and 65 years old with MDD (recurrent or single episode) diagnosed according to DSM-IV criteria (APA 2006), confirmed using the Mini-International Neuropsychiatric Interview—M.I.N.I., Czech version 5.0.0 (Sheehan et al., 1998). Further main inclusion criteria were: Score 20 on the Montgomery-Åsberg Depression Rating Scale (MADRS), > 1 prior non-response to adequate antidepressant treatment in current major depressive episode (while in total 21 of the participants could be classified as TRD with > antidepressant trials during the current episode, see Supplement Table 1), and being on a stable dose of drugs for depressions for a minimum of four weeks prior to admission. Treatment augmentation by lamotrigine, lithium, antipsychotics and monoamine oxidase inhibitors was not allowed. Exclusion criteria were any suicidal risk assessed by clinical examination, current psychiatric comorbidity on Axis I and II, serious unstable medical illness or neurological disorder (e.g. epilepsy, head trauma with loss of consciousness) as well as lifetime history of psychotic symptoms and psychotic disorders in first- or second-degree relatives. Further, during the screening period, all patients underwent physical examination, routine blood tests, electrocardiogram, urinalysis, and urine toxicology before inclusion in the study, excluding patients with somatic diseases with a need of treatment, especially any cardiac condition including hypertension and medication for cardiac condition (e.g. beta-blockers). Patients continued their psychopharmacological treatment in unchanged dose over duration of the study. The study details were explained to all patients; a complete description was handed out before written informed consent was subsequently obtained. No changes to trial methods had been implied after trial commencement.

The studies were approved by the Ethical committee of Prague Psychiatric Centre/National Institute of Mental Health, Czech Republic and were performed in accordance with the ethical standards laid down in the Declaration of Helsinki 1975, revised Hong Kong 1989.

Ketamine Treatment/Infusion: A unilateral intravenous catheter was inserted into the subjects’ forearm for ketamine infusion. Racemic ketamine hydrochloride (Calypsol, Gedeon Richter Plc., Czech Republic) was administered using an infusion pump (ID 20/50, Polyomed medical CZ Ltd). Ketamine was dispensed in a loading dose of 0.27 mg/kg for the first 10 min, followed by an infu-
sion of 0.27 mg/kg within 20 min. Thus, total dose was 0.54 mg/kg within 30 min. These infusion rates were calculated with respect to the pharmacokinetics of ketamine (Hetem et al., 2000; Horacek et al., 2010). For placebo infusions, equal amount of saline (sodium chloride 0.9%) solution was administered via the infusion pump within an equal time period. All infusions were applied in clinical premises of Prague Psychiatric Centre, Czech Republic. Ketamine and norketamine blood levels were assessed via blood samples respectively 10 minutes and 30 minutes after starting the infusion.

Depression Rating: Severity of depressive symptoms was assessed using the MADRS. Ratings were obtained at baseline (before the infusion), and 24 h, 72 h and 7 days post infusion. Response to treatment often is defined as a reduction of at least 50% from baseline. In case of a fast-acting response to ketamine, we considered this criterion too stringent with a chance to omit a substantial number of patients who benefited from the treatment fast within 24 h but did not meet the 50% criterion. Further, the 50% response criterion yielded a too low number of responders for trustworthy statistical results. Thus, besides the 50% response criterion after 24 hours, a modified response criterion was used, defined as a decrease of depressive symptoms by means of MADRS > 30% at 24 h after infusion. Further analysis was done using > 30% and > 50% symptom decrease at any further assessment until day 7 after infusion.

Electrocardiogram Measurements, Heart Rate (HR) and Heart Rate Variability (HRV) Parameters: The HR is a measure of the autonomous nervous system (ANS) and reflects the interaction of the two involved branches, i.e. the sympathetic part (responsible for positive chronotropy) and the parasympathetic part (negative chronotropy). Parameters of the HRV yield more detailed information on the activity of the ANS: The HRV-power is derived from the spectral analysis of changes of consecutive ECG R-peaks in milliseconds. The involved frequency spectra include the Low Frequency spectrum from 0.04 to 0.15 Hz and are mainly driven by sympathetic activity while the high frequency range from 0.15 to 0.4 Hz is more influenced by the parasympathetic branch. Higher HRV power values are supposed to reflect increased parasympathetic tone and decreased sympathetic activity. The normalized units of the different spectra show the contribution of the two ANS branches to the total power. To calculate these parameters, electrocardiogram (ECG) recordings were acquired by a BrainScope digital amplifier (M&I, Prague, Czech Republic) with the subjects sitting in a semi-recumbent position, eyes closed in a maximal alert state in a sound attenuated room with subdued lighting. ECG was recorded from electrodes placed at the lowest left rib. The data sampling rate was 250 Hz (Study 1, N = 27) or 1000 Hz (Study 2, N = 24). The data of the second trial was downsampled to 250 Hz before analysis of the data. Recording took place before, during and in some cases 24 hours after infusion. Heart rate (HR) and heart rate variability (HRV) measures were assessed using Kubios software (Kubios HRV software Version 2.0, http://kubios. uku.fi/KubiosHRV/) while RR-peaks were detected using an automatic RR detection algorithm with visual inspection of the time series and consecutive correction, when necessary. To include similar length of intervals for all subjects, the baseline duration was limited to 5 minutes just before infusion onset. For all subjects 10 minutes of resting state were available at the beginning of the ketamine bolus infusion as well as 10 minutes at the end of infusion. 36 subjects underwent another 10 minutes ECG 24 hours later.

Analysis: From R-peak to R-peak (RR)-intervals, heart rate (HR, measured as R-peak intervals) was computed as an overall estimator of the activity of the autonomous nervous system (ANS). The following parameters were extracted for assessment of parasympathetic and sympathetic activity (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996): Heart rate variability (0.04–0.4 Hz), normalized spectral power in the high frequency band (nHF; 0.15–0.4 Hz) as parameters for parasympathetic activity (Pomeranz et al., 1985) and normalized spectral power in the low frequency band (nLF; 0.04–0.15 Hz) as parameters for sympathetic activity (Malliani et al., 1991; Montano et al., 1994; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The normalized units of HRV frequency band power yield information about the sympathovagal balance and are reported in [%] of the total power. Thus, low and high normalized power values add up to 100%, so only low frequency values are reported to avoid redundancy.

Statistics: Data from the two controlled trials were pooled. Only data from the verum-cohorts were analysed since the main question here was whether HRV measures might predict antidepressant response. The sample size for both studies initially was calculated to detect the standardized mean difference of 0.8 or larger between ketamine and placebo in the primary endpoint (change in MADRS after 24 hours), given the alpha (type I error) was set at 0.05, 1-beta (power) at 0.90, and two-tailed paired t-test was used. The baseline clinical data of the groups of responders and non-responders were compared with an unpaired t-test or Fisher’s exact test as appropriate. Linear mixed models were used to examine differences between responders and non-responders by means of HR and HRV measures before, at beginning of infusion, at the end of infusion, and up to 24 hours after ketamine infusion as secondary outcome measures. The model included fixed effects for group (responders and non-responders), a repeated measures time factor, as well as a group by time interaction. Fixed and random intercepts were included in the model along with a random effect for participant. Schwarz’s Bayesian criterion was used to determine the best fitting covariance structure, which was diagonal. Additionally, gender and age served as covariates. Bonferroni corrected post hoc tests were used following significant effects and interactions. Cohen’s d was calculated using raw ECG parameters since no established method exists for calculating effect sizes for linear mixed models. SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) was used for calculations of all models. Since not all patients had an ECG recording after 24 hours, we performed a sensitivity analysis using only the first three ECG recording intervals (before, at the beginning and at the end of infusion). Further analysis included a logistic regression to calculate receiver operating curves (ROC) for significant parameters, including either only baseline HR parameter to obtain the predictive power or all available HR parameters.

3. Results

ECG data from 47 out of 51 (92%) subjects was used. No unintended effects or important harms occurred in neither of the trials. Both trials ended on schedule. Included subjects were aged 19–62 years (Mean 43.0, SD 12.3) with 20 (43%) males. Severity of depressive symptoms at baseline measured by MADRS was 24.0 ± 6.3. For further sociodemographic and clinical data see Supplement Table 1. Four ECGs had to be discarded due to missing or too short recording periods or artefacts so that the ECG data could not be processed (mean age 53.0, SD 7.3; 3 males; MADRS at baseline 2.0, SD 7.7, MADRS after 24 h 18.0, SD 9.0). For study 1, mean MDRS baseline scores was 20.4 (SD = 5.8) and MDRS score after 24 h was 13.9 (SD = 8.8); for study 2 mean MDRS baseline scores was 27.3 (SD = 4.8) and MDRS score after 24 h was 21.3 (SD = 7.1). The mean % change of MDRS scores showed no significant differences between the two studies (two-tailed T-test, T = 1.4, p = 0.18). Baseline demographic and clinical characteristics are
shown in Table 1. Sertraline and escitalopram (together 36%), venlafaxine (28%), and mirtazapine (17%) were the most frequently used drugs for depression in the study. After ketamine infusion, nine (19%) patients were rated as full responders (≥50% reduction in MADRS 24 h after infusion), nine were rated as remitted (MADRS score < 10 after 24 h) and 21 (45%) as responders when modified criterion (>30% after 24 h) was applied. Responders and non-responders were comparable in age, sex, baseline MADRS score and antidepressant treatment regimen together with drugs for depression dosage equivalent to fluoxetine according to (Hayasaka et al., 2015) (Table 1).

Heart rate and ketamine infusion: In all patients we found a significant increase of HR from baseline recording to infusion, a further significant increase to post infusion and a normalization without a difference to baseline recording after 24 hours (all values p < 0.001, ANOVA with post hoc testing, Bonferroni corrected, see Fig. 1, left panel). For HRV power, there was only a significant increase during infusion compared to 24 hours post infusion (p < 0.009, Fig. 1, middle panel) while nLF power showed a significant increase directly post infusion compared to baseline (p < 0.035) and 24 hours post infusion conditions (p < 0.026, Fig. 1, right panel). The comparison between the two separate studies for all RR, HRV power and nLF power values at all time points did not show significant differences (two tailed T-tests, all p values < 0.16).

Mixed Linear Regression Model: When the traditional criterion of 50% decrease of symptoms after 24 h was applied with only 9 subjects classified as responders, the linear mixed model for HR showed no significant group effect (responders vs. non-responders; F = 0.05, df = 150.28, p = 0.83), a significant effect for covariate sex (F = 5.73, df = 162.30, p = 0.02, Table 2). For the 30% criterion after 24 h with 21 patient classified as responders, the linear mixed model for HR showed a significant group effect (responders vs. non-responders; F = 10.86, df = 147.65, p = 0.001) and significant effects for covariates sex (F = 5.83, df = 162.67, p = 0.017) and age (F = 4.24, df = 161.93, p = 0.041, Table 2). Cohen's d was 0.47 for all HR measures and 0.61 when only the baseline HR measures before infusion were considered. No significance was found for the effect of time (F = 2.58, df = 68.88, p = 0.061) or for the time × group interaction (F = 0.16, df = 67.33, p = 0.924). To figure out whether sex had a pivotal influence on the results, we performed the analysis separately for females and males with similar results concerning the group effects (e.g. F = 8.22, df = 34.20, p = 0.007 for males and F = 10.00, df = 89.79, p = 0.002 for the 30% criterion after 24 h).

The additional analysis with the response criterion (decrease of MADRS > 30% or 50% any time within up to 7 days) for the 30% criterion revealed a similar group effect for HR (F = 11.32, df = 149.05, p = 0.001) and significant effects for covariate sex (F = 7.59, df = 163.63, p = 0.007) but not for age (F = 2.80, df = 162.63, p = 0.10). For the 50% criterion, there was a group effect (responders vs. non-responders) for HR (F = 4.55, df = 144.63, p = 0.035) and a significant effect for covariate sex (F = 6.68, df = 162.56, p = 0.011).

Further analysis on specific HRV power revealed significant effects for group (responders vs. non-responders, 30%-24 h criterion; F = 6.65, df = 133.30, p = 0.011) and covariate age (F = 8.08, df = 81.52, p = 0.006) and time (F = 5.41, df = 93.10, p = 0.002), and no effect for sex (F = 3.00, df = 89.24, p = 0.087) and for time × group interaction (F = 0.75, df = 89.08, p = 0.97). The nLF analysis showed only a significant effect of time (F = 3.50, df = 63.20, p = 0.02) with no other significant effect or interaction (Fig. 2).

A sensitivity analysis was carried out since not all subjects had a fourth ECG recording after 24 hours. Therefore, only the first three measurements (before infusion, during infusion and directly after infusion) were considered for the linear mixed model. Results for the HR were a significant group– (F = 9.67, df = 131.65, p = 0.002) and time–effect (F = 3.71, df = 89.18, p = 0.028) and significant effects for covariates sex (F = 4.32, df = 131.59, p = 0.04) and age (F = 6.32, df = 131.59, p = 0.13). No significance was found for the time × group interaction (F = 0.24, df = 89.18, p = 0.79). Similar results were found for HRV parameters. Hence these results resampled the findings from the model with inclusion of all measurements.

Receiver Operating Curves: To demonstrate the discriminative power of the HR and HRV measures for the outcome of ketamine infusions in major depression, we performed a logistic regression analysis. When considering only HR and HRV measures from the baseline condition for predictive reasons, i.e. parameters obtained before infusion, the area under the curve was 0.68 with a sensitivity of 72% and a specificity of 64% (Fig. 3). Here, mainly pre infusion Heart Rate (Wald = 4.42) and to a smaller degree also pre infusion Total HRV Power (Wald = 2.25) contributed to the results.

When logistic regression was performed on all available HR and HRV measures (thus including HR, HRV power and nLF power from all four recordings) and response groups, the area under the curve increased to 0.96 with a sensitivity of 94% and a specificity of 93%. The highest contribution to this result was made by total HRV power during ketamine infusion (Wald = 1.94) and normalized Low Frequency after infusion (Wald = 2.26). However, including all available measures, i.e. also parameters after the first infusion, has no predictive value. The area under the curve for the 50% decrease criterion after 24 h was 0.53 for both conditions, the baseline parameters and for all available parameters over time.

Correlation of heart rate measures and ketamine/norketamine blood levels: To clarify the relationship between heart rate measures and ketamine/norketamine levels, the correlation analysis revealed several significant associations. In general, ketamine and norketamine levels were positively correlated with heart rate and negatively correlated with total HRV power. No clear trend was seen with correlations with normalized low frequency power. Only the negative correlations between ketamine levels after 30 min post infusion and total HRV power after 24 h survived Bonferroni correction (see Table 3).

Table 1
Sociodemographic and clinical properties of responders and non-responders (30% criterion after 24 h).

|                      | All N = 47 | Responders N = 21 | Non-responders N = 26 | p value |
|----------------------|------------|-------------------|------------------------|---------|
| Age (yrs)            | 43.0 ± 12.3 | 41.3 ± 13.3       | 44.2 ± 11.5            | 0.44<sup>1</sup> |
| F/M                  | 27/20      | 13/8              | 14/12                  | 0.77<sup>1</sup> |
| MADRS baseline       | 24.0 ± 6.3 | 23.0 ± 7.1        | 24.7 ± 5.6             | 0.36<sup>1</sup> |
| AD mono/comb         | 13/34      | 6/15              | 7/19                   | 1.00<sup>1</sup> |
| FLX equi. (mg)       | 54.1 ± 24.5 | 54.9 ± 25.3       | 53.5 ± 24.3            | 0.85<sup>1</sup> |

MADRS: Montgomery–Åsberg Depression Rating Scale.
AD: antidepressant.
FLX equi. (mg): dosage equivalent to fluoxetine in milligram.
4. Discussion

This study shows that the profile of the autonomous nervous system activity, namely the heart rate and its associated measures, differ for responders and non-responders to ketamine infusion treatment in major depressive disorder. This held true with a response criterion of 30% MADRS decrease after 24 h or a 30%/50% decrease within 7 days. The baseline HR parameters obtained before infusion yielded significant medium effect size differences between responders and non-responders, suggesting a predictive value. The simple measure of a high heart rate was associated with a positive treatment effect. These findings show that HR and HRV are potentially useful clinical biomarkers for treatment outcome.

The increase of HR after infusion of ketamine is in line with the literature and with the expected effect of ketamine and its increase of sympathetic activity (Corry and Domino, 1966; Traber et al., 1970). Ketamine induces sympathomimetic cardiovascular and respiratory effects such as increased heart rate and blood pressure as well as bronchodilation with evidence for direct interaction of ketamine with alpha-1 and beta-2-adrenoceptors of the autonomous nervous system (Bevan et al., 1997). The dissociative syndrome at higher ketamine dosage refers to a functional and electrophysiological separation of contradictory nervous system activity (Haas and Harper, 1992) and is defined by a decrease of central nervous system (CNS) arousal, whereas the activity of the autonomous nervous system (ANS) is kept at high levels or even increases. When trying to figure out the mode of function of ketamine in MDD, one has to bear in mind that MDD has been associated with a hyperarousal by means of EEG wakefulness regulation (Hegerl et al., 2011; Olbrich et al., 2012) or sleep latency (Rotenberg et al., 2002). Thus, the antidepressant effect of kata-
mine in parallel with reduction of CNS arousal might be compared to the impact of sleep deprivation as one of the most effective treatment forms in MDD. Orozco-Solis et al. (Morgan, 2017; Orozco-Solis et al., 2017) showed common gene expression changes for ketamine treatment and sleep deprivation in the anterior cingulate cortex of mice, further underlining this argumentation line. Also, Duncan et al. (Duncan et al., 2017) were able to delineate the association of ketamine antidepressant action and circadian timekeeping. In the presented study a high ANS arousal was predictive for ketamine treatment outcome. This may be reflecting an overall hyperarousal of the ANS and CNS in those patients being responders. The presence of a high arousal before ketamine treatment would allow a larger change with decrease of arousal over the course of treatment. The reason why ANS arousal is even increased during treatment in parallel with an improvement of symptoms might be found in oppositional effects of ketamine on ANS and CNS. However, the latter cannot be proven by our study and must be focus of further investigations.

Some evidence exists for decreased HRV in MDD (Brunoni et al., 2013; Kemp et al., 2012; Yeh et al., 2016; van Zyl et al., 2008) with a dysfunctional parasympathetic system and increased sympathetic activity (Chen et al., 2017). Further, the change of HR and HR associated measures following treatment with several drugs for depression has been analysed in detail, showing that some drugs, such as agomelatine, increase the parasympathetic tone (Yeh et al., 2016) while tricyclic drugs for depression seem to decrease it (Kemp et al., 2010). Other treatment options, such as electro convulsive therapy (ECT), showed no effect on HRV measures (van Zyl et al., 2008). The presented results show that ketamine increases heart rate and HRV power in depressive patients and that these parameters have a predictive power for treatment response.

![ROC-Curve](image)

**Fig. 3.** Left panel: The receiver-operating curves (ROC, blue) for HR and HRV parameters obtained only before infusion, i.e. at baseline, reflecting the predictive value of autonomous nervous system (ANS)-activity in ketamine infusion for major depressive disorder (MDD). The right panel shows the ROC of all available parameters consisting of heart rate (HR), heart rate variability (HRV) power and normalized low frequency power from all four conditions (baseline, start, end of infusion and 24 h post infusion) for differentiation between responders (N = 21) and non-responders (N = 26) but without predictive value (right panel).

**Table 3**

Correlations between Heart Rate and Heart Rate Variability measures during the different assessment points and the ketamine and norketamine blood levels after infusion.

| HR and HRV parameters | Ketamine Blood Levels [ng/ml] | Norketamine Blood Levels [ng/ml] |
|-----------------------|-----------------------------|-----------------------------|
|                       | 10 min post Infusion | 30 min post Infusion | 10 min post Infusion | 30 min post Infusion |
| Baseline              | HR                     | 0.131                     | 0.245                     | 0.337*                     | 0.269                     |
|                       | HRV                   | -0.223                    | -0.198                    | -0.193                    | -0.134                    |
|                       | nuLF                  | -0.145                    | 0.049                     | -0.18                     | -0.004                    |
| Start Infusion        | HR                     | 0.1                      | 0.186                     | 0.337*                     | 0.174                     |
|                       | HRV                   | -0.211                    | -0.157                    | -0.233                    | -0.161                    |
|                       | nuLF                  | -0.089                    | 0.085                     | -0.18                     | -0.123                    |
| Post Infusion         | HR                     | 0.171                    | 0.199                     | 0.375*                     | 0.159                     |
|                       | HRV                   | -0.357*                   | -0.357*                   | -0.17                     | -0.191                    |
|                       | nuLF                  | -0.009                    | 0.113                     | -0.313                    | -0.267                    |
| 24 h post Infusion    | HR                     | 0.371                    | 0.409*                    | 0.398*                     | 0.498***                  |
|                       | HRV                   | -0.475*                   | -0.594**                  | -0.29                     | -0.454*                   |
|                       | nuLF                  | -0.042                    | 0.161                     | -0.332                    | -0.13                     |

**significant with p < 0.05 after Bonferoni correction**

**significant with p < 0.05**

HR: Heart Rate
HRV: Heart Rate Variability
nuLF: normalized units Low Frequency
In a small sample of 33 unmedicated subjects a higher heart rate was predictive for response to SSRI or mirtazapine treatment (S. Olbrich et al., 2012). Also, the results of the International Study to Predict Optimized Treatment for Depression (iSPOT-D) showed an increasing heart rate over time in resting position being predictive for response to SNRI treatment (Olbrich et al., 2016). Thus, the presented findings of elevated levels of ANS activity in responders to ketamine might be non-specific to ketamine but mark a general susceptibility for treatment effects. The higher HR levels over the course of ketamine infusion in responders in comparison to non-responders might be carry-on effects of an initially increased sympathetic or decreased parasympathetic tone. The specificity of the found effect of HR and HRV on ketamine response should be focus of study protocols that include several different treatment options.

There was a correlation between HR measures and ketamine/nonketamine levels. Thus, one might speculate that the presented findings with increased HR in responders just reflect a higher blood level of the drug in responders and therefore, response was only dosage dependent. However, there was no significant difference by means of dosage between responders and non-responders and, even more importantly, HR was already elevated in responders even before the treatment started, i.e. before ketamine had an influence on the HR. Hence it can be said that subjects that are more sensitive to a sympathetic enhancement and that show higher excitability of the ANS before treatment, also yield a larger response by means of HR acceleration in parallel with decrease of depressive symptoms. Still, it remains unknown whether the higher heart rate in responders is a trait or a state. Increased sympathetic tone just before the start of the infusion might be reflecting the excitement before an experimental treatment (state) and not a higher sympathetic tone in general (trait). It should be the focus of following study protocols to compare HR data from ECGs that has been derived days or probably weeks before ketamine treatment to differentiate between state and trait aspects.

It is noteworthy that patients were under drugs for depression in this study. Thus, a possible influence and merged effects of drugs for depression and ketamine on ANS activity cannot be disentangled. Still, this setting is close to a real-world scenario where treatment resistant patients suffering from MDD are likely to have several medications in parallel.

Furthermore, it is important to note that response prediction with a single parameter is a rather limited approach and might miss clinical relevance. A whole set of biomarkers for different treatment approaches needs to be identified with consecutive assessment of response-probabilities for each individual biomarker profile.

As a limitation it must be mentioned that the response criterion with 50% decrease of MADRS after 24 h did not yield significant group differences between responders and non-responders for HRV measures. This might be due to the very low response rate of 9 subjects out of 47 that showed a 50% decrease of symptoms after 24 h. When lowering the threshold to 30% decrease after 24 h or increase the time for response to 7 days, the results remained significant with more subjects showing responsiveness, thus increasing the power of the analysis. It is still noteworthy that all parameters changed into the same direction for the 50% and the 30% criteria. A second limitation can be found in the fact that data from two different studies with slightly different designs, e.g. the blinding procedures, has been pooled for this analysis. Since the HRV analysis was not the primary outcome of neither of these studies, the combination of the data to reach sufficient group sizes seemed justified for an ex-post explanatory analysis. Further, we decided not to include the analysis of the placebo group since data quality especially in the single blinded trial was not always sufficient. To differentiate between a marker for a ketamine-specific response and an unspecific response, placebo analysis is needed from further trials. A third limitation is that suicidality was an exclusion criterion for the studies, thus lowering the possibility for generalization for all depressed patients.

5. Conclusion

These results encourage further research on autonomous nervous system regulation for determining pathophysiological subgroups for ketamine treatment response. The usefulness of a fast treatment or augmentation strategy in patients with an electrophysiological profile indicative for response to that approach should be tested in prospective studies for individualizing treatment in MDD.

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Conflict of Interest

Torsten Meyer declares that he has no relevant or material financial interests that relate to the research described in this paper.

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Erich Seifritz declares that he has no relevant or material financial interests that relate to the research described in this paper.

Sebastian Olbrich declares that he has no relevant or material financial interests that relate to the research described in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.01.030.

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