A Functional-structural Model to Understand Cardiac Autonomic Nervous System (ANS) Dysregulation in Affective Illness and to Elucidate the ANS Effects of Antidepressive Treatment

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Abstract: Numerous studies provide evidence that major depression (MD) is associated with certain disorders of cardiac autonomic nervous system (ANS) function, in particular, with an autonomic neurocardiac imbalance characterized by a low cardiovagal modulation, a raised sympathetic nerve activity and a high resting heart rate. We assume that such MD-associated cardiac ANS disorders are mainly caused by functional-structural abnormalities within the central autonomic network (CAN), in particular, by well-defined abnormalities of hypothalamic structures in MD. In view of the well-known association between an autonomic neurocardiac imbalance and the risk for cardiac arrhythmias, we assume that MD-associated cardiac ANS disorders are at least partly responsible for the high cardiovascular mortality risk in MD. It is, however, still unclear whether antidepressive treatment will lower the risk for cardiovascular complications in MD. There is convincing evidence that a successful antidepressive treatment with electroconvulsive therapy, cognitive behavioral therapy, or pharmacotherapy with primarily non-antimuscarinergic antidepressants can improve an initially disturbed cardiac ANS function in MD. These studies correspond well to our findings that treatment with both, nefazodone or reboxetine, can induce a reduction of central sympathetic nerve activity and an increase of the initially lowered cardiovagal modulation depending on the improvement of depressive symptoms after treatment. Since both effects occured obviously independent from the primarily serotonergic or noradrenergic action of the antidepressants, our findings suggest the existence of a generally supraordinate and uniform mechanism underlying the ANS effects of antidepressive treatment with drugs inhibiting serotonin- or noradrenaline reuptake.

Key words: cardiac autonomic nervous system; antidepressive treatment

Introduction

Numerous epidemiological studies revealed a significant comorbidity between depressive and cardiovascular diseases. Depressive illnesses are also considered as predictors for a higher cardiovascular morbidity and mortality (summary in [29]). Various mechanisms have been discussed to explain the probably multicausal interaction between depressive and cardiovascular diseases [53]; one of these hypotheses focuses on disorders of the cardiac autonomic nervous system (ANS) in depressive patients [1].

Cardiac Autonomic Nervous System (ANS) Regulation within the Central Autonomic Network (CAN)

The ventromedial, prefrontal cortex including the anterior cingulum forms the primary supramedullary exchange for controlling and integrating emotions, cognition and ANS regulation within the central autonomic network (CAN). Numerous neural connections originate there that extend to the orbitofrontal cortex, the insular region, the limbic system with the central nucleus of the amygdala (CENA) and also to the nucleus tractus solitarii (Fig. 1). The CENA provides all subcortical projections to autonomic hypothalamic and brainstem regions. It also projects to the bed nucleus of the stria terminalis, which is thought to relay amygdalar influences on cardiovascular autonomic responses. The hypothalamus contains several regions that innervate autonomic nuclei of the brainstem and the spinal cord; these include the paraventricular nucleus (PVN), the dorsomedial nucleus and the lateral hypothalamic area. The PVN is a major site for integrating autonomic and neuroendocrine responses to stress and has been called the "master controller" of the ANS because it innervates all autonomic centers [13]. The connection between the subfornicial organ (SFO)
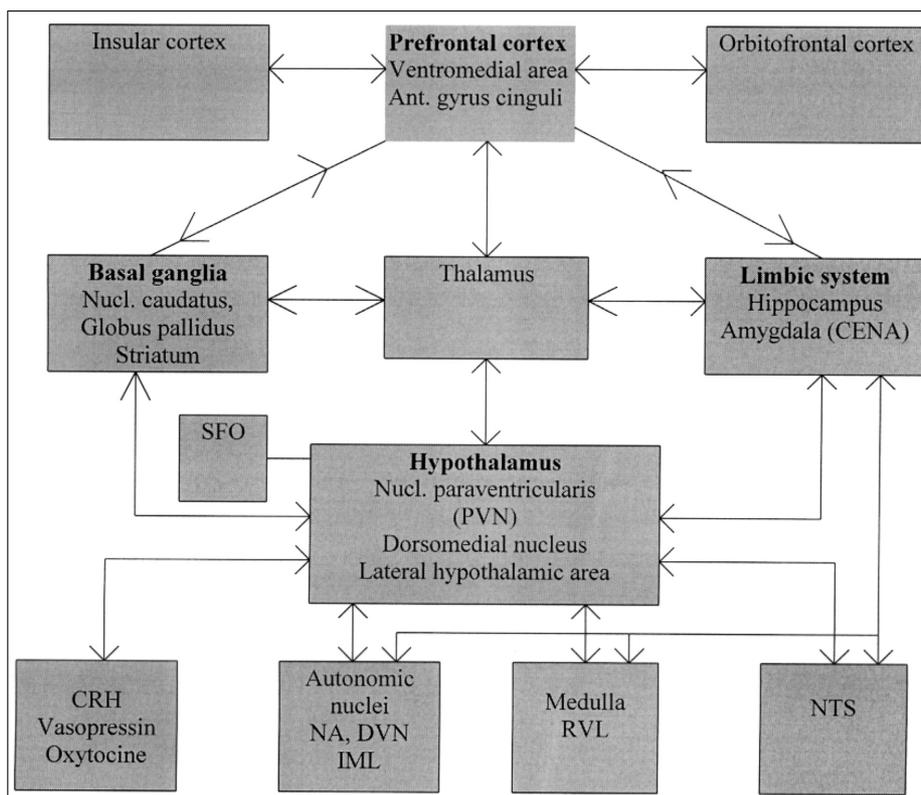
Fig. 1. The integration of behavioral, emotional and autonomic reactions occurs within the central autonomic network (CAN), whereby primarily neural connections between the orbitofrontal, insular and cingular cortex, as well as the thalamus, amygdala, hippocampus and hypothalamus participate. All these regions have direct or indirect connections with medullary and spinal neurons that are involved in the vagal and sympathetic modulation of heart action.
Abbreviations (alphabetical): CRH = corticotropin-releasing hormone; DVN = dorsal vagal nucleus; IML = intermediolateral cell column; NA = nucleus ambiguus; NTS = nucleus tractus solitarii; RVL = rostral ventral medulla; SFO = subfornicial organ

with the PVN (Fig. 1) is critical for regulating vasopressin release and autonomic responses elicited by circulating angiotensin II and natriuretic peptides. Vagal preganglionic cardiomotor neurons are located in the nucleus ambiguus (NA) and the dorsal vagal nucleus (DVN). Vagal motor neurons receive various afferent inputs, mainly from the nucleus tractus solitarii (NTS), the location at which cardiovascular and respiratory afferents involved in cardiorespiratory reflexes terminate. Other important inputs arise from the medullary reticular formation, the raphe nuclei, the periaqueductal gray matter as well as from projections originating in the hypothalamus, amygdala and the insular cortex (Fig. 1). Vagal motor neurons are strongly excited by baroreceptor inputs via NTS and inhibited by hypothalamic and respiratory influences [13]. The inspiratory inhibition of cardiovagal activity, which involves activation of central muscarinic cholinergic receptors [27, 40], plays a substantial role in the appearance of respiratory sinus arrhythmia (RSA), although other mechanisms also appear to be involved. Cardiac ganglionic cells, into which preganglionic cardiovagal cells are converted, possess highly complex neural connections themselves; they receive catecholaminergic inputs from sympathetic collaterals in addition to cholinergic inputs. The "cardiac brain" hypothesis is based on these potentially complex neural interactions in the cardiac ganglia [63]. The postganglionic parasympathetic effects to the heart are mediated by acetylcholine through activation of the muscarinic m2-receptor subtype.

Sympathetic innervation of the heart arises from preganglionic neurons located in the intermediolateral cell column (IML) of segments T2-T5 of the spinal cord. These neurons receive important inputs from the hypothalamus, the rostral ventrolateral medulla (RVL) and periaqueductal gray matter (Fig. 1). Preganglionic fibers ascend to the paravertebral sympathetic chain and are converted into postganglionic fibers in the cervical and upper thoracic ganglia. Postganglionic sympathetic influences on the heart are mediated by norepinephrine acting through α- and β-receptors [13].

Respiratory sinus arrhythmia (RSA; tachycardia in inspiration, bradycardia in expiration) is a manifestation of functional integrity of the autonomic control of the heart and serves as an important clinical index of vagal innervation. In normal subjects there are rhythmic beat-to-beat oscillations of heart rate centered at two main frequencies: a low (LF-) component at approximately 0.1 Hz and a high frequency (HF-) component at approximately 0.25 Hz (summary in [75]). The HF-oscillation is considered a manifestation of RSA and therefore primarily reflects cardiovagal modulation of heart rate. The LF heart rate fluctuations are probably due to respiratory and non-respiratory mechanisms and may partly reflect sympathetic modulation. Standardized measurements of heart rate variability (HRV) including calculation of power spectral density permit an quantitative assessment of cardiovagal and with certain limitations also sympathetic modulation of the cardiac ANS [75]. It is a non-invasive procedure that does not place great demands on patient compliance and is therefore even well tolerated by patients with a severe psychiatric disease.

MAJOR DEPRESSION (MD) IS ASSOCIATED WITH AN AUTONOMIC NEUROCARDIAC IMBALANCE CHARACTERIZED BY A LOW CARDIOVAGAL MODULATION AND A HIGH RESTING HEART RATE

Numerous studies employing HRV or other neurophysiological and biochemical techniques showed alterations of cardiac ANS function with depressive patients compared to healthy individuals. These are characterized by a reduced cardiovagal modulation, a high sympathetic nerve activity or a combination of both mechanisms (summary in [4]), although few studies were not able to confirm such a pattern of findings [51, 85]. We recently found that patients with major depression (MD) showed a sympathetic-parasympathetic imbalance compared to healthy individuals. This included a reduction in cardiovagal modulation and a raised resting heart rate, whereby statistically significant differences were found for a subgroup of depressive patients with marked depressive symptoms (at least 25 points on the Hamilton Depression Rating Scale; HAMD) [2, 4]. Significant differences also persisted when additional variables known to alter HRV (e.g. age, sex, smoking, preceding treatment with antidepressants) were explicitly adjusted in the statistical calculations [2]. The most important finding from our studies was an inverse correlation between the severity of clinically depressive symptoms and the cardiovagal modulation of heart rate; the more intensely marked the depressive symptoms were, the lesser was the cardiovagal modulation. Such a pattern of findings was consistently reported both amongst subjects with unspecific depressive syndromes [36, 43] and amongst healthy [2, 4] or cardiologically diseased subjects with MD [73]. In addition, cardiovagal modulation seems to be lowered particularly amongst patients with a long duration of the depressive episode [4, 51]; the latter aspect corresponds well to the observation that no significant differences in HRV were found between healthy subjects and patients with only a short lasting depressive reaction [65].

PATHOPHYSIOLOGICAL MECHANISMS UNDERLYING MD-ASSOCIATED CARDIAC ANS DYSREGULATION

MD can be thought as a kind of "chronic stress disease". The mostly reproduced observation from psychobiological research studies of affective disorders is the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis amongst depressive subjects, that is associated with an increased release of corticotropin-releasing hormone (CRH), ACTH and cortisol (summary in [52]). Post-mortem studies showed both an increase of CRH [62] as well as of vasopressin and oxytocin expressing neurons in the paraventricular nucleus of the hypothalamus (PVN) in depressive patients [61], whereby vasopressin is known to potentiate the CRH-mediated ACTH release. The hyperactivity of the HPA axis at the hypothalamic level can be determined by changes in various neuromodula-

tors that exert excitatory or inhibitory effects on the PVN. As such, alterations in hippocampal mineralocorticoid and glucocorticoid receptors that are important for the feed-back regulation of the HPA axis were recently described with MD. Also, in post-mortem studies, morphological alterations in limbic, striatopallidal and thalamoprefrontal neural circuits have been verified that included reductions in neural number and/or size in the anterior cingular cortex and other prefrontal cortical areas (summary in [10]). Both, the prolonged activation of the HPA axis and the results of newer brain imaging studies (PET, SPECT, f-MRT) revealing raised perfusion and increased metabolism in certain neural circuits important for affective regulation (e.g. limbic system, basal ganglia, thalamus, ventromedial prefrontal cortex), point towards an inhibitory deficit and an excess of excitatory mechanisms with affective disorders [11]. This is supported by a deficit of inhibitory neuromodulators such as GABA-ergic neurons in the hippocampus or prefrontal cortex, or nitrous-oxide inhibitory neurons in the PVN [11]. Since a morphologically and functionally intact CAN is important for integrating emotional, neuroendocrine and autonomic function (Fig. 1), such alterations of the CAN, in particular, the hyperactivity of the HPA axis at the hypothalamic level and morphological alterations of the PVN, might play a key role for the existence of cardiac ANS dysfunction in MD. Neuroanatomic studies revealed a widespread distribution of CRH and CRH-receptors extending far beyond the hypothalamus with projections to numerous other brain areas responsible for cardiac ANS regulation including cholinergic, dopaminergic and noradrenergic neurons [68]. The locus coeruleus (LC) and the rostral ventral medulla (RVL) neurons are the main noradrenergic generators within the CAN. A bidirectional positive feed-back loop between the LC and the PVN (Fig. 2) has been implicated in the mechanisms of stress, including human depression [74]. Norepinephrine excites CRH neurons via a1-receptors in the PVN, whereas CRH markedly increases the firing of LC neurons. Together with the median raphe, the dorsal raphe provides the main source of ascending serotonergic innervation for almost the whole brain [84]. Both, the LC and the RVL, receive inhibitory serotonergic projections from the raphe nuclei [78] (Fig. 2). Animal experiments showed that CRH dose-dependently inhibits serotonergic neurotransmission [60]. Thus, an overexpression of CRH might result in a decreased inhibition of central sympathetic outflow. A decrease of the serotonergic neurotransmission in MD might not merely be functionally determined by an increase in CRH, but it might also be due to a numerically neuronal deficiency in the dorsal raphe in patients with primary affective disease [9]. An excess amount of CRH and CRH-containing neurons might be accompanied not just by a raised sympathetic activity, but also directly or indirectly by a reduced cardiovagal modulation. In animal experi-
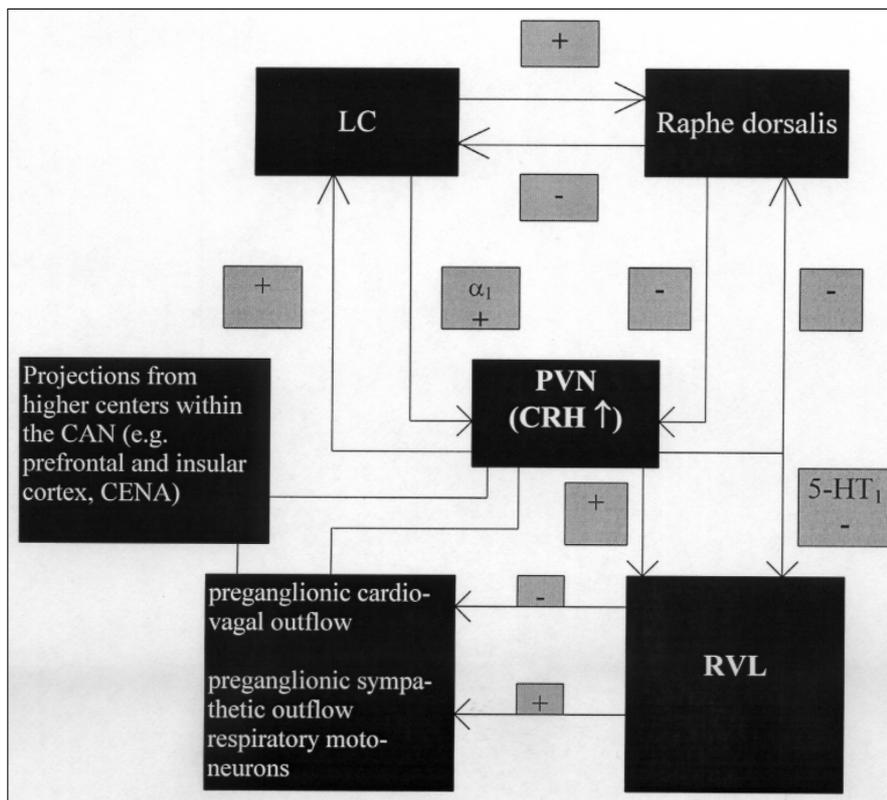
Fig. 2. The main noradrenergic generators within the CAN are the locus coeruleus (LC) and the rostral ventral medulla (RVL) neurons. The raphe nuclei provide the main source of ascending serotonergic innervation. The activity of the noradrenergic system depends on the activity of the serotonergic system, and vice versa, since both systems are connected to each other directly and indirectly via the paraventricular nucleus of the hypothalamus (PVN). Inhibitory serotonergic fibres project from the raphe nuclei to both the LC and the RVL. CRH dose-dependently inhibits serotonergic neurotransmission. The final result is a decreased inhibition of sympathetic nerve activity. A bidirectional positive feed-back loop between the LC and the PVN has been implicated in mechanisms of stress, including human depression.
Abbreviations (alphabetical): CENA = central nucleus of the amygdala; CRH = corticotropin-releasing hormone; LC = locus coeruleus; PVN = paraventricular nucleus of the hypothalamus; RVL = rostral ventral medulla

ments, intraventricularly applied CRH reduced baroreceptor-induced activation of cardiovagal motor neurons in a manner which was quantitatively similar to the effect induced by atropine [25]. Recently it was shown that intravenous application of CRH to healthy probands is followed by an increase in heart rate and a reduction of HRV at rest and during the RSA test; in contrast, an increase in HRV [58] was found under prednisolone, which via a negative feed-back loop inhibits CRH release. The activity of cardiovagal motoneurons is largely controlled by afferent inputs from the baroreceptor reflex via the NTS. Since the neural activity of the NTS (similar to that of the PVN) is in turn modulated by neural projections from supraordinate centers of the CAN (e.g. prefrontal cortex, amygdala) (Fig. 1), a disturbed neuronal activity at the level of the NTS might also participate in cardiac ANS dysfunction in MD. Both, parasympathetic and sympathetic nerve activity, are mediated via a multitude of diverse excitatory (e.g. noradrenaline, acetylcholine, glutamate, neuropeptide Y, substance P) or inhibitory (e.g. GABA, encephalin, vasopressin) trans-

mitters acting on the NTS, whereby both pressor and depressor effects have been confirmed for further transmitters such as serotonin and adenosine [13].

CLINICAL RELEVANCE OF CARDIAC ANS DYSREGULATION IN MD

Modern concepts on the pathophysiology of cardiovascular diseases assume that an imbalance between sympathetic and parasympathetic modulations significantly influences cardiac repolarization, and that it participates in bringing about cardiac arrhythmias [12, 34]. A relative excess of sympathetic influence on the heart might reduce the threshold for the occurrence of cardiac arrhythmias including ventricular fibrillation [22, 49, 81]. At the cellular level this effect might be associated with an increase in intracellular calcium concentration [15]. On the other side, vagal activity exerts a cardioprotective effect since it increases the threshold for ventricular arrhythmias both in animal experiments and man [12, 46, 47, 83]. An increased cholinergic stimulation might re-

duce the intracellular calcium concentration and might also indirectly reduce sympathetic nerve activity through interactions with both branches of the ANS [15]. In contrast, a low cardiovagal modulation (e.g. expressed as a decreased activity of the baroreceptor reflex or a reduction in HRV) is accompanied by a raised probability for the occurrence of cardiac arrhythmogenic events [12, 47, 87].

Since HRV reflects autonomic neurocardiac modulation to the heart, the pattern of HRV can predict the risk for the occurrence of ventricular arrhythmias [72]. For example, a major finding preceding ventricular fibrillation (sudden cardiac death) is a loss of HRV [71]. A reduced HRV is of predictive value for the probability of cardiovascular complications including sudden cardiac death not only with cardiovascular diseases [28, 37, 39], but also with other diseases such as diabetes mellitus [24] and alcoholism [33]. An autonomic imbalance with predominantly sympathetic activity to the detriment of cardiovagal modulation (e.g. expressed as a high LF/HF ratio in HRV spectral analysis) may precede the onset of ventricular tachycardia [45]. Moreover, an autonomic imbalance predicts cardiovascular complications and a raised mortality not only in patients with pre-existing heart disease [14, 41], but also in apparently healthy subjects [50].

For decades it has been known that mental stress and emotional excitement can trigger the occurrence of cardiac arrhythmias including ventricular fibrillation [47, 82, 72]. An MD is thought of as a "chronic stress disorder". Moreover, an MD is accompanied by functional and morphological alterations in well-defined brain structures of the CAN, which all have direct or indirect connections to medullary and spinal neurons that are involved in cardiac autonomic modulations. Considering these findings the presence of cardiac ANS dysregulation in MD is not surprising. In view of the well-known association between an autonomic neurocardiac imbalance and the risk for cardiac arrhythmias, we assume that such a cardiac ANS disorder - mainly an imbalance between sympathetic and parasympathetic modulation to the heart - are at least partly responsible for the high cardiovascular mortality risk in MD [1, 2].

DOES CARDIAC ANS DYSREGULATION REPRESENT A TRAIT OR STATE MARKER OF MD?

If not just functional, but possibly also structural brain alterations underlie the existence of MD associated disruptions in neurocardiac ANS regulation, it is possible that antidepressive treatment cannot improve such disturbances in cardiac ANS function. However, it is already well known from everyday clinical routine that even severe somatic symptoms of a vitalized MD dramatically improve after successful antidepressive treatment. Klieser (1990) found that a change in state of vegetative symptoms registered already during the early stages of antidepressive treatment (after 7 days) was positively correlated with therapeutic success upon completion of a 3-week pharmacotherapy, meaning that by considering clinical changes in vegetative complaints at an early timepoint of treatment, a later success or failure of treatment can be predicted [38].

Standardized measurements of HRV including spectral analysis represent a sensitive measurement procedure for evaluating cardiac ANS function. Using this technique it should be possible to quantitatively trace even small changes in autonomic modulation during the course of an antidepressive treatment. Two questions are of special clinical interest in this respect: 1.) Is clinical improvement of depressive symptoms followed by an improvement in cardiac ANS regulation, e.g. by a rise (reduction) in cardiovagal (sympathetic) modulation ? 2.) If so, is a successful antidepressive treatment followed by an always uniform improvement of ANS function, or alternatively, does the treatment-induced change of cardiac ANS function solely dependent on the type of the antidepressive treatment applied on an individual basis ?

METHODS

In an comprehensive Medline search we assessed studies evaluating the effects of antidepressive treatment on cardiac ANS function in MD by means of HRV. Our studies on this subject were also included [4, 7], the results of which are summarized and complemented by an explorative data analysis. We evaluated the effects of antidepressive treatment with nefazodone [4] or reboxetine [7] on cardiac ANS function in 50 patients with DSM-III R proven MD. The inclusion and exclusion criteria as well as the study conditions (e.g. time and place of HRV measurements, preparation of subjects, chief investigator, mode of communication with the patients) were identical in both studies; significant differences between the study populations were not evident. Standardized measurements of the 5-minute resting HRV including spectral analysis [5, 75] were taken before the onset of treatment, and after 2, 10 and 21 days of continuous treatment with nefazodone (200-600mg) or reboxetine (4-8mg). The clinical symptoms of depression were quantitatively recorded using the Hamilton Depression Rating Scale HAMD. As part of the explorative data analysis, Spearman correlation coefficients were computed between the differences in HAMD values (Day 0 - day 21), and the differences in the frequency domain HRV indices at the different measuring time-points (after 2, 10 and 21 days) with respect to the initial examination before treatment started (statistical procedure as described in [38]). The low- (LF-power, 0.04-0.15Hz) and high-frequency (HF-power, 0.15-0.40Hz) spectral components were computed in normalized units as proportions of the total power [5]. General consensus exists that the normalized HFnu-power reflects cen-

Table 1. Summary of HRV studies, which investigate the ANS effects of antidepressive treatment in patients with major depressive disorders (MD).

Author (year)	Subjects	Intervention / Therapy	Methods	Main results	Comment
Balogh (1993)	n = 17 MD	fluoxetine or desipramine over 4-8 weeks	5-min resting HRV	correlation between increase in cardiovagal modulation and improvement of depressive symptoms	pre-post comparison; no untreated or placebo group
Rechlin (1995)	n = 32 MD	randomized trial over 14 days doxepine (150mg), amitriptyline, (150mg), fluvoxamine (150mg), paroxetine (20mg)	5-min resting HRV + deep respiration	TCAs reduce cardiovagal modulation; no changes during SSRI treatment	pre-post comparison; no untreated or placebo group; no responder analysis
Rechlin (1995)	n = 30 MD	bright light therapy + TCAs	5-min resting HRV + deep respiration	increase of cardiovagal modulation in responders	pre-post comparison all patients under TCAs healthy control group
Tulen (1996)	n = 20 MD	randomized trial over 4 weeks mirtazapine or imipramine (individual dosage)	blood press. variability + HRV (resting + orthostatic reaction)	mirtazapine and imipramine both reduce cardiovagal modulation	pre-post comparison; no untreated or placebo group; no responder analysis
Schultz (1997)	n = 9 MD	electroconvulsive therapy (ECT); some patients received SSRIs	15-min resting HRV	reduction of cardiovagal modulation independent from response	pre-post comparison; no untreated or placebo group
Tucker (1997)	n = 17; MD, panic disorder, dysthymia	paroxetine (20mg) over 4 weeks	15-min resting HRV + standing	increase of cardiovagal and decrease of sympathetic modulations (LF/HF ratio)	pre-post comparison; no untreated or placebo group healthy control group
Agelink (1998)	n = 10 MD	electroconvulsive therapy (ECT)	5-min resting HRV	increase of cardiovagal modulation in responders	pre-post comparison; no untreated or placebo group
Roose (1998)	n = 81 MD with coronary heart disease (CHD)	randomized trial over 6 weeks paroxetine (20-40mg) oder nortriptyline (individual dosage)	24h-Holter HRV	transient increase in HRV after 2 weeks of paroxetine treatment; reduced HRV during nortriptyline	pre-post comparison; no untreated or placebo group; no responder analysis
Khaykin (1998)	n = 14 MD	randomized trial over 6 weeks fluoxetine (60mg) or doxepine (225mg)	24h-Holter HRV	increase of HRV in responders, decrease of HRV in non-responders	pre-post comparison; no untreated or placebo group
Carney (2000)	n = 30 MD with coronary heart disease (CHD)	cognitive behaviour therapy (CBT)	24h-Holter HRV	increase of cardiovagal imodulation and decrease of HRV after CBT	pre-post comparison; no untreated or placebo group; controls were non-depressed with CHD

Study	Patients	Intervention	HRV	Results	Comments
Nahshoni (2001)	n = 11 geriatric MD patients	electroconvulsive therapy; patients were on SSRIs or mianserine	5-min resting HRV	increase in cardiovagal and reduction in sympathetic modulation according to treatment response	pre-post comparison; no untreated or placebo group
McFarlane (2001)	n = 38 MD with previous myocardial infarction	randomized trial over 6 months sertraline (50mg) or placebo	24h-Holter HRV	increase of some cardiovagal HRV indices under sertraline compared to placebo	randomized, placebo-controlled study
Agelink (2001)	n = 25 MD	nefazodone (200-600mg) over 3 weeks	5-min resting HRV + deep respiration + Valsalva	reduction of sympathetic nervous outflow; correlation between cardiovagal modulation and improvement of depressive symptoms	pre-post comparison; no untreated or placebo group; healthy control group
Chambers (2002)	n = 16 MD	randomized trial using verum or placebo acupuncture over 8 weeks	8-min resting HRV	correlation between symptomatic improvement and increase of cardiovagal modulation	problem: how to define placebo-acupuncture
Agelink (2002)	n = 25 MD	reboxetine (4-8mg) over 3 weeks	5-min resting HRV + deep respiration + Valsalva	reduction of sympathetic nervous outflow; correlation between cardiovagal modulation and improvement of depressive symptoms	pre-post comparison; no untreated or placebo group

tral cardiovagal modulation, while the LFnu-power probably reflects modulations of both branches of the ANS (mainly sympathetic and to a lesser extent parasympathetic modulation). Correspondingly, the LF/HF ratio can be interpreted as an expression of the sympatho-vagal balance [75].

RESULTS

Table 1 summarizes the most important results from pharmacological and non-pharmacological studies evaluating the effects of antidepressive treatment on cardiac ANS function. Prospective studies on untreated MD patients, which compare HRV obtained during an acute depressive episode with those obtained after spontaneous remission, are lacking. An increase in HRV have been reported after successful antidepressive treatment of MD with electroconvulsive therapy [3, 54], adjuvant bright-light therapy [64], or cognitive behavioral therapy [17], although some conflicting results were also reported [70]. None of these studies used a placebo control. Another study found a significant correlation between a reduction in depressive symptoms and an increase in cardiovagal modulation amongst MD patients treated with acupuncture [19], a finding that would be entirely consistent with a "harmonization effect" of acupuncture on autonomic neurocardiac ANS control [6]. Numerous studies focused on the ANS effects of antidepressants. Since postganglionic vagal activity to the heart is mediated via acetylcholine on muscarinic m2-receptors, antidepressants with peripheral antimuscarinic effects can reduce HRV. Such a reduction of HRV has repeatedly been reported under tricyclic antidepressants (TCAs) [66]. Compared to imipramine, the tetracyclic mirtazapine has apparently weaker, but likewise significant antimuscarinic properties. A 4-week treatment with mirtazapine was not followed by a perceptible increase in global HRV despite a significant improvement of depressive symptoms [77]. However, an increase of central cardiovagal modulation might escape detection in this HRV study, because significant peripheral antimuscarinic effects of mirtazapine could have masked such an effect. Thus, two other studies revealed an increase in cardiovagal modulation after successful antidepressive treatment with primarily non-antimuscarinic antidepressants (e.g. SSRIs), and such findings were appraised as an indication for an improvement of cardiac ANS function after clinical improvement of depressive symptoms [8, 35]. Three more studies found evidence that treatment with paroxetine or fluoxetine coincided at least with a transient increase in HRV in MD patients with coronary heart disease [67], and improved or normalized the sympathovagal balance in depressed patients with dysthymia, panic- or posttraumatic stress-disorder [20, 76]. A placebo control was not included in any of these studies. The only placebo-controlled trial [48] found that sertraline facilitates the rate of recovery of some car-

Table 2. Correlation coefficients between clinical improvement of depressive symptoms (measured as the differences in the HAMD-scores after 3 weeks of antidepressive treatment compared to baseline before treatment started) and the changes in HRV (expressed as the differences of spectral power between baseline and follow-up examinations) after 2, 10 and 21 days during antidepressive treatment with nefazodone or reboxetine.

	nefazodone (n = 23)	reboxetine (n = 21)
changes in LFnu-power		
after 2 days	r = 0.16	r = 0.01
after 10 days	r = 0.20	r = -0.21
after 21 days	r = 0.11	r = -0.22
changes in HFnu-power		
after 2 days	r = -0.21	r = -0.35
after 10 days	r = -0.35	r = -0.11
after 21 days	r = -0.43 *	r = -0.40 *
changes in LF/HF ratio		
after 2 days	r = 0.23	r = 0.32
after 10 days	r = 0.06	r = 0.07
after 21 days	r = 0.33	r = 0.33

*In both, the reboxetine and nefazodone treated group, we found a correlation between clinical improvement of depression and changes in relative HFnu-power after a 21-day antidepressive pharmacotherapy (r = -0.40-0.43; p = 0.05-0.07).

diovagal HRV indices within 6 months after a previous myocardial infarction. However, other studies failed to confirm the favorable effects of SSRI on cardiovagal modulation, and found either no changes or a dose-dependent decrease of HRV in fluvoxamine or paroxetine treated patients with MD or panic attacks [42, 66, 86]. These divergent results may be due to differences in treatment duration [66], or to dose-dependent antimuscarinic effects of some SSRIs as demonstrated for paroxe-

tine [42]. All these studies neither used a placebo control nor did they differentiate between treatment responders and non-responders.

We recently examined the effects of nefazodone or reboxetine on cardiac ANS function in otherwise healthy MD patients [4, 7]. Nefazodone (reboxetine) mainly influences the serotonergic (noradrenergic) neurotransmission; both antidepressants exhibit no significant anticholinergic properties. In both studies antidepressive treatment was followed by a clinical improvement of depressive symptoms measured as a reduction of the average HAMD scores after 3 weeks. In both studies, however, almost half of the patients still displayed a HAMD score of more than 17 points, meaning that in many cases no complete remission of the depressive symptoms could be achieved within the 21-days surveillance period. Therefore it is not surprising that we failed to detect any statistically significant increase of the mean values of cardiovagal HRV indices [4, 7]. However, if one considers the intraindividual degree of improvement of depressive symptoms (measured as the intraindividual decrease in HAMD score during the course of treatment), an inverse correlation results between symptomatic clinical improvement seen after 21 days of treatment and the changes in relative HF-power (Table 2). This was true for both, the nefazodone and reboxetine-treated group (r = -0.43 and r = -0.40; p = 0.05-0.07). This means that well improved patients (with the largest reductions in HAMD scores compared to the baseline examination) exhibit a larger increase in cardiovagal modulation compared to unimproved patients, and vice versa (Fig.3a, b). There was no significant correlation between mainly sympathetic HRV indices (LF-power, LF/HF) and therapeutic outcome. We also found that both antidepressants, i.e. the mainly "serotonergically" acting nefazodone and the mainly "noradrenergically" acting reboxetine, at least transiently reduced sympathetic nerve activity. The pattern of HRV findings, as previously discussed in detail, allow us to

Rank Diff-HFnu

Rank HAMD-Differences

r = -0.43
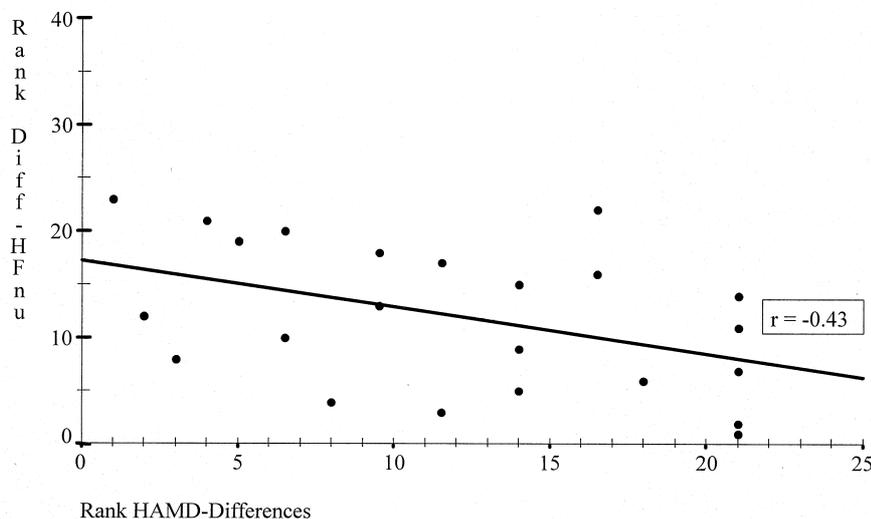
Fig. 3a, b. Relationship between the improvement of depressive symptoms (HAMD) and changes in cardiovagal modulation (HFnu-power) after 21 days of antidepressive treatment with nefazodone (*Fig. 3a*) or reboxetine (*Fig. 3b*) compared to the baseline examination before the start of treatment.
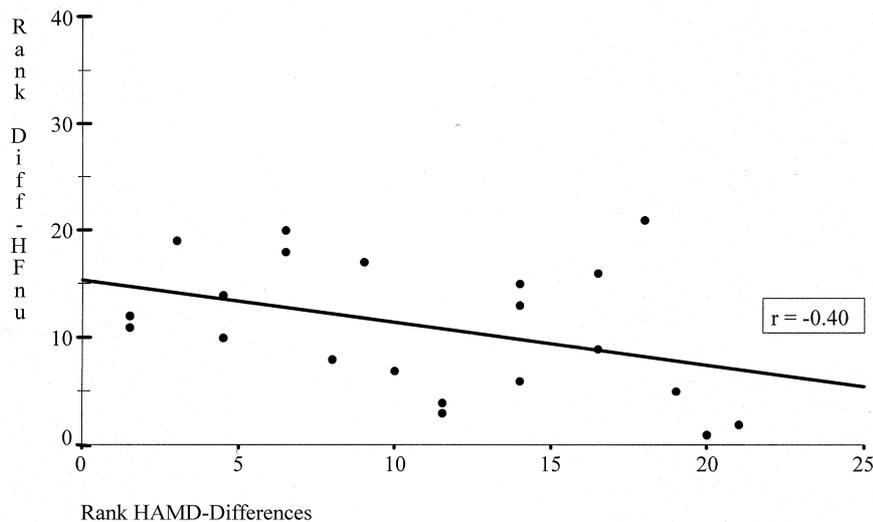
Fig. 3b.

assume a downregulation of sympathetic nerve activity at the level of the CAN [4, 7].

DISCUSSION

Our studies showed that a) cardiovagal modulation dependents on the severity of depressive symptoms and b) an increase in cardiovagal modulation correlates with clinical improvement of depressive symptoms upon completion of a 3-week antidepressive treatment with nefazodone or reboxetine. This pattern of findings suggests a direct association between depressive symptoms and cardiovagal modulation. It is probable that only a partial rise in cardiovagal modulation coincides with the clinical improvement, and that a normalization of cardiovagal modulation occurs never or at least never after a short duration of treatment, since despite successful antidepressive treatment, disease-immanent disorders of autonomic regulatory function may still persist [59]. The fact that we observed only a weakly significant correlation between cardiovagal modulation and clinical improvement might reflect such a temporal dynamic of improvement in ANS function after successful antidepressive treatment. A similar, only partial normalization of cardiovagal modulation and as such a pattern of findings consistent with our own was recently described after successful antidepressive behavioral therapy [17]. In summary, our findings correspond well with the results of other investigators who found an improvement in cardiac ANS regulation after successful antidepressive therapy with primarily non-antimuscarinic antidepressants, electroconvulsive therapy or cognitive behavior therapy (Table 1). Our data indicate that in MD patients treatment with non-antimuscarinic antidepressants can induce both, an increase of the initially lowered cardiovagal modulation and a reduction of sympathetic nerve activity [4, 7]. Both effects seem to be independent from the primary mechanism of action of the antidepressant (e.g. mainly serotonergic or noradrenergic).

DOES ANTIDEPRESSIVE TREATMENT UNIFORMLY AFFECT THE CAN CONTROLING CARDIAC ANS FUNCTION?

There is convincing evidence that a normalization of the initial hyperactivity of the HPA axis results after successful antidepressive treatment including electroconvulsive therapy and pharmacotherapy with various antidepressants such as TCAs, SSRIs or mirtazapine [23, 32, 55, 69, 79]. An improvement or normalization of the HPA function has been discussed as a major and supraordinate mechanism of action for antidepressive treatment [31]. Considering the structural-functional peculiarities of the CAN in MD we assumed that alterations within hypothalamic structures are at least partly responsible for cardiac ANS dysfunction in MD patients. Thus, the pattern of findings from our HRV studies - a reduction of sympathetic nerve activity combined with an increase in cardiovagal modulation after a successful antidepressive therapy - may be interpreted either as a side effect of the normalization of hypothalamic regulatory functions, or as a separate, supraordinate effect of antidepressive treatment with an as yet unknown mechanism. The correlation between the increase in cardiovagal modulation and clinical improvement of depression as shown in our study supports the first explanation, since an improvement of HPA axis function was also associated with clinical improvement of depressive symptoms [30]. Dampening of HPA axis hyperactivity has been suggested as a conditio sine qua non for successful improvement of psychopathology in MD [31]. Considering the close association between the hyperactivity of the HPA axis and a raised sympathetic nerve activity in MD (Fig.2), a normalization of HPA axis activity induced by antidepressive treatment might also be related to a reduction of sympathetic nerve activity induced by antidepressants. Such a decrease of sympathetic nervous system outflow has consistently been reported under treatment with reboxetine (selectively inhibits noradrenaline reuptake), desipramine

(mainly inhibits noradrenaline reuptake), and imipramine (inhibits both, noradrenaline and serotonin reuptake) (summary in [7]), and also under treatment with some SSRIs like paroxetine or fluoxetine [20, 76, 86]. The absence of a significant correlation between changes in mainly sympathetic HRV indices (e.g. LF power, LF/HF ratio) and an improvement of depressive symptoms in our study (Table 2) does not contradict this interpretation, since the interaction between the sympathetic and parasympathetic tree of the ANS does not follow a purely algebraic antagonism (i.e. an increase in cardiovagal modulation is not always followed by a quantitatively equal reduction in sympathetic modulation, and vice versa). Physiologically, this interaction occurs as part of a complex interplay between afferent and efferent nerve impulses, whereby sympathetic influences affect cardiovagal modulation via various pre- and postjunctional mechanisms, and vice versa, a situation underlying the term "accentuated antagonism" (summary in [13]). As a result, sympathetic influences are always involved in bringing about the measured "net effects" of cardiovagal modulation. In other words: the correlation between cardiovagal modulation and depressive symptoms always reflects sympathetic influences as well, even if no statistically linear correlation was found (as in our studies) between mainly sympathetic HRV indices and depressive symptoms.

Heuser (1998) suggested that the improvement of HPA axis function at the hypothalamic level induced by antidepressants might precede clinical improvement of depressive symptoms [30, 31]. In our studies we were not able to predict an improvement in psychopathology from early changes in autonomic modulation after 2 or 10 days of treatment (Table 2). Thus, our data do not support the certainly attractive hypothesis that therapeutic outcome of antidepressive treatment can be predicted with the help of short-term (within a few days) changes in autonomic modulation induced after application of a "test dose" of a mainly noradrenergic or serotonergic acting antidepressant.

LIMITATIONS

Our studies on the ANS effects of nefazodone or reboxetine [4, 7] did not employ a placebo group. This was for pragmatic reasons: a numerically sufficiently large sample of MD patients representative for everyday clinical life was to be studied. In this respect one justified criticism is that data from approval studies can not be transferred and generalized without reservations to treatment in everyday practice, for which reason the necessity of carrying out phase IV studies is stressed [44]. The only goal of our clinical phase IV study was to evaluate the ANS effects of two antidepressants (the effectiveness of which was proven and which had already been approved for marketing). If the objective of our study would have been to evaluate the clinical efficacy of these drugs, then a pla-

cebo control would have been indispensable. If one considers the declared intention of our study, however, it would appear to be highly dubious for ethical reasons to with-hold an efficacious therapy from 50 patients with severe depressive symptoms. Therefore, a placebo controlled study with the sole purpose of studying ANS effects of two antidepressants could hardly be realized in most European countries, and particularly in Germany, where the span between ethical justification and the clinical necessity of placebo-controlled studies is anchored deeply in the consciousness of both, the medical profession and the psychiatrically ill patients. As such most studies on the ANS effects of antidepressants also refrained from recruiting a placebo group (Table 1). Our patients all had to be treated in a hospital because of the severity of their depressive symptoms. As such a 3-week placebo treatment was just as obsolete for economic reasons as an absolute renunciation of therapy (untreated control group). If we had included outpatients with less marked depressive symptoms, it could not have been reliably guaranteed (unlike treatment under hospital conditions) that all patients would have taken their medication. Compliance with intake of prescribed medication represents a major problem particularly with psychiatrically ill patients. We are not aware of any HRV longitudinal study involving a large number of untreated depressive patients; in one of our own case series we found no significant spontaneous changes in the 5-minute resting HRV amongst 6 MD patients, and a good reproducibility of the HRV indices within an observation period of 24-48 hours [2]. These findings are consistent with numerous other studies which confirm a sufficient reproducibility of HRV [75], although conflicting findings have occasionally been reported [16]. Whether a good reproducibility of HRV would also exist during placebo treatment of an MD, remains yet to be tested. Interestingly, positron emission tomography (PET) studies on the effects of pain stimuli in patients treated with opiates or placebo were able to show that even after application of placebo there was a demonstrable alteration in cerebral blood flow in the prefrontal cortex including the anterior cingulate [57]. This means that a placebo treatment in some indications is able to induce functional changes in well-defined brain areas of the CAN known to be involved in controlling cardiac ANS function (Fig.1).

We assumed that MD-associated abnormalities in cardiac ANS function are mainly caused by functional-structural abnormalities of the CAN, particularly within hypothalamic structures. The results of our HRV studies [2, 4, 7] are consistent with this hypothesis. Future studies, which should combine measurements of HRV with biochemical determinations of hormones of the HPA axis, might further strengthen the hypothesis between improvement in HPA axis function and corresponding changes in cardiac autonomic modulation induced by antidepressants. Never-

theless, some methodological limitations regarding HRV studies should not be overlooked. HRV can only reflect autonomic neurocardiac modulation at the end-organ level, and therefore, represent the combined outcome of autonomic modulations generated within the CAN and their modification by peripheral ANS structures. This is, however, a general (and unavoidable) problem for most biochemical and neurophysiological studies in man that attempt to gain information on CNS regulatory mechanisms on the basis of measurements of peripheral parameters as physiological endpoints of a feedback loop (e.g. plasma catecholamines, hormones, skin conductance level). In order to guarantee a certain differentiation between central and peripheral mechanisms of ANS modulation, the activity of cardiac autonomic nerves would have to be measured separately at their central and peripheral levels. With our current state of knowledge such a procedure would be practically impossible in man. It might be helpful to complement HRV data with direct measurements of cardiac sympathetic nerve activity (e.g. cardiac norepinephrine spillover) [80]. Since this is, however, a quite invasive technique, a broad application of this procedure will not be possible, and the realization of such studies will be limited to small case numbers in the hands of a few specialized laboratories.

PERSPECTIVES AND FUTURE NEED FOR STUDY

The mechanisms underlying antidepressive treatment-induced changes in cardiac ANS require further clarification. Since not only the HRV, but also the ability to stimulate or inhibit HPA axis function (dexamethasone / CRH stimulation test) can vary quite considerably between individual MD patients, combined measurement of HPA axis function and HRV are urgently needed for strengthening the hypothesis of an association between improvement in HPA axis function and corresponding changes in cardiac autonomic modulation induced by antidepressants. A study on this subject is currently being carried out in cooperation with the University of Duesseldorf; it examines the effects of antidepressive treatment with repetitive transcranial magnetic stimulation on HPA axis function and cardiac ANS regulation. In addition, combined studies of HRV together with newer imaging procedures such as functional MRI (f-MRI), SPECT or PET might be helpful for acquiring new information regarding the mechanisms of ANS dysregulation in MD. Studies on the antidepressive effects of the vagal stimulation technique (VNS) appear to be of special interest in this regard [26]. VNS causes immediate and long term changes in brain regions with vagal innervation (e.g. the orbito-frontal cortex, the thalamus and the limbic system), that have also been implicated in the pathophysiology of affective disorders [18]. For example, an increase in glucose metabolism could be shown after a multimonth treatment with VNS in the orbitofrontal cortex, the anterior

cingulum, and in the left insular region [26], whereby these brain structures are parts of the CAN (Fig.1). Intraoperative stimulation studies in man demonstrated that the left insular region primarily controls cardiovagal activity, while the right insular region controls sympathetic nerve activity [56]. These findings are consistent with the results of HRV studies on patients with structural lesions of the insular cortex: compared to normal individuals only patients with lesions of the left insular region revealed a higher heart rate and a reduced HRV including a reduction in HF-power (i.e. a pattern of HRV allowing a reduced cardiovagal modulation to be presumed). Against this background a recently conducted f-MRI study on the CNS effects of the antidepressant venlafaxine (a combined noradrenaline-serotonin reuptake inhibitor) may be of special interest: In this study, serial f-MRI scans were prepared during presentation of affect-stimulating or affect-neutral images to 12 untreated MD patients and 5 controls, whereby the results of the baseline examination were compared with those obtained after antidepressive treatment with venlafaxine [21]. Significant group by time inter-actions in response to the negative vs. neutral stimuli were found in the left anterior cingulum and in the left insular cortex. Considering that the left insular is primarily involved in the supramedullary control of cardiovagal modulation [56], this finding might be related to changes in cardiovagal modulation following venlafaxine treatment. Overall, these examples suggest an association between changes in emotion and cognition induced by antidepressive treatment and corresponding changes in cardiac ANS function at the level of the CAN. Therefore, future imaging studies on the CNS effects of antidepressive treatment, in particular on the CNS effects of VNS, should also investigate cardiac ANS function. Because surgical intervention is required to institute VNS, a predictable outcome of therapeutic success would be more desirable than would be the case when applying medication. Therefore, such studies should not only examine the influence of VNS on cardiovagal modulation of heart rate, but should also investigate the predictive value of cardiovagal modulation for the therapeutic outcome of antidepressive treatment with VNS.

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