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REVIEW

Cardiac dysautonomia in depression – heart rate variability biofeedback as a potential add-on therapy

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Abstract: Depressive disorders are among the most important health problems and are predicted to constitute the leading cause of disease burden by the year 2030. Aside significant impact on quality of life, psychosocial well-being and socioeconomic status of affected patients, depression is associated with impaired cardiovascular health and increased mortality. The link between affective and cardiovascular disease has largely been attributed to dysregulation of the autonomic nervous system resulting in a chronic shift toward increased sympathetic and decreased parasympathetic activity and, consecutively, cardiac dysautonomia. Among proposed surrogate parameters to capture and quantitatively analyze this shift, heart rate variability (HRV) and baroreflex sensitivity have emerged as reliable tools. Attenuation of these parameters is frequently seen in patients suffering from depression and is closely linked to cardiovascular morbidity and mortality. Therefore, diagnostic and therapeutic strategies were designed to assess and counteract cardiac dysautonomia. While psychopharmacological treatment can effectively improve affective symptoms of depression, its effect on cardiac dysautonomia is limited. HRV biofeedback is a non-invasive technique which is based on a metronomic breathing technique to increase parasympathetic tone. While some small studies observed beneficial effects of HRV biofeedback on dysautonomia in patients with depressive disorders, larger confirmatory trials are lacking. We reviewed the current literature on cardiac dysautonomia in patients suffering from depression with a focus on the underlying pathophysiology as well as diagnostic workup and treatment.

Keywords: mood disorder, autonomic dysfunction, cardiovascular disease, brain-heart axis, biofeedback

Introduction

The burden of depression is high and on the rise globally: according to the World Health Organization, unipolar depressive disorder is predicted to be the leading cause of disease burden by 2030.[1] Affective disorders can cause people to bear daily activities as an enormous challenge and function poorly at work, at school and in their families. At its worst, it may culminate into suicide. It has been estimated that the prevalence of suicide among patients with affective disorders varies between 2.2% and 8.6%.[2]

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), the diagnosis of a Major Depression (MD) Episode requires five or more symptoms to be present within a 2-week period.[3] One of the symptoms should, at least, be either a depressed mood or anhedonia. The secondary symptoms

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are appetite or weight changes, sleep difficulties psychomotor agitation or retardation, fatigue or loss of energy, diminished ability to think or concentrate, feelings of worthlessness or excessive guilt and suicidality. These symptoms are rated in an all or none (0 or 1) fashion.[4] Beyond the human costs, mental diseases are placing an increasing load on the global economy.[5] Medical expenditures on depression scale similar to those on stroke and absenteeism its costs are higher than type 2 diabetes in the US.[6] The financial burden of major depressive disorder showed an increment of 21.5% from 2005 to 2010.[7] Depression represents a major economic challenge for Europe, as well. It was found the most costly brain disorder consuming up to 1% of the European overall GDP.[8] Since depression and cardiovascular disease were prognosed to be two of the three leading causes of global disease burden worldwide,[9–11] medical and socioeconomic concerns are assigned to their concurrence. In fact, patients with depression display impaired cardiovascular health which has been partially attributed to chronic dysregulation of the autonomic nervous system.

We aimed to review the current literature on cardiac autonomic failure in patients suffering from depression with a focus on the underlying pathophysiological mechanisms as well as diagnosis and treatment. We paid particular attention to cardiac autonomic function assessment via analysis of heart rate variability (HRV) and applied quality measures on the landscape of HRV studies based on the checklist of the recently published guidelines for HRV measurements in psychiatric investigations (GRAPH).[12] Lastly, we aimed to summarize current treatment options for impaired cardiac autonomic function in patients with depressive disorders with a focus on non-invasive biofeedback.

Search strategy

This is a narrative review. Literature research was undertaken using the Web of Science database, Medline via the PubMed and Ovid interface. The keywords "depressive symptoms", "depression", "major depressive disorder", "mood disorder" and "autonomic dysfunction", "heart rate variability", "baroreflex sensitivity", "heart rate variability biofeedback" with the use of the Boolean operators "AND" or "OR" were used to identify relevant studies and reports that examined the association between cardiac dysautonomia, depression and the effects of heart rate variability biofeedback (HRVB) in health and diseased states. In the initial literature search, we exclusively chose these keywords. In addition, we performed a second literature search using the same electronic database with more specific terms to ensure coverage of all aspects that our review focused on. For this purpose, we established a search strategy using the following terms and their combinations:

"economical burden", "brain-heart axis", "neurocardiac axis", "cardiovascular disease", "cardiovascular risk", "neuroimaging technique" AND "drug naive" OR "treated" AND "depression" OR "heart rate variability", "anxiety", "dysthymia", "impulse control disorder", "substance use disorder", "psychosis", "depression" AND "heart rate variability biofeedback"

We added every study that was relevant to our topic, which contained various study designs: randomized controlled studies, observational studies, meta-analyses, systematic reviews, and case reports published between 1969 and 2018. The relevance of the papers was assessed in light of our five core principles of this narrative review: 1) depression, 2) cardiovascular disease (CVD), 3) heart rate variability, 4) baroreflex sensitivity (BRS) and 5) heart rate variability biofeedback (HRVB). The included articles were all written in English. We reviewed the existing information on possible mechanisms linking depression and CVD and HRV as a measure for neurocardiac integrity. We summarized the results reported in depressive disorder on reduced HRV and BRS and excluded papers from our analysis if 4 or more recommendations of GRAPH were not fulfilled in them. Finally, HRVB as a treatment option was reviewed in psychiatric diseases, especially in depression aiming the restoration of physiological neurocardiac conditions.

Autonomic cardiac failure in depression

Depression and cardiovascular disease

Clinical depressive disorder is more than a substantial negative impact on mood and productivity. Pathophysiological connections were shown to exist between depression and somatic diseases, which is supported by observational and prospective clinical data.[13–17] The group of medical conditions that probably carries the highest overall health risk in this context are CVDs. Depressive disorder is an established risk factor for cardiovascular mortality and morbidity,[18–20] this entails coronary artery disease,[21,22] myocardial infarction,[23,24] congestive heart failure[25] and hypertension.[26] Primary and secondary associations have been described between depression and

increased cardiovascular risk.[22,27] A growing body of evidence shows that the brain-heart axis – including the autonomic nervous control of the heart – is disrupted by the functional and organic neural changes in depressive disorders. As for secondary causes, the behavioral constellation of the depressed person carries a complex obstacle in the way of primary and secondary prevention (lifestyle changes, compliance problems, poor adherence to medication).[28–30] The association between mood disorders and CVD was found to be independent of "classical" cardiovascular risk factors such as body mass index, physical activity, hypertension and hypercholesterolemia,[18,22,31,32] supporting a genuine disease-specific mechanism whereby depression compromises cardiovascular health. In line with this hypothesis, an independent association between depression and increased risk of developing coronary artery disease has been shown.[33] Based on cumulative data the American Heart Association has recommended that depression should be recognized as a risk factor for poor prognosis in patients with an acute coronary syndrome (ACS). The authors concluded that the preponderance of evidence had indicated that depression was associated with adverse medical outcomes after ACS.[13] Having this clinical perspective in mind, understanding underlying mechanisms mediating these comorbid disorders might help identify therapeutic targets.

Brain–heart axis – the site of autonomic disruption, linking depression and cardiovascular disease

The underlying pathological processes of the association of depression and CVD have been in the limelight of scientific research. Apart from numerous behavioral and lifestyle factors, the central mechanisms connecting mood and cardiovascular disorders appears to stem from a generalized autonomic dysregulation with hypothalamic-pituitary-adrenal activation.[27,34] This, in turn, has deleterious downstream effects, including the development of hypertension,[35] endothelial dysfunction,[36] inflammatory processes,[37] platelet activation[38] – which all have been hypothesized to contribute to impaired cardiovascular health in patients suffering from depression and thus lead to manifest CVD.

Central involvement of the brain-heart axis

Various studies have investigated the structures involved in modulating biobehavioral resources in emotion by flexibly adjusting physiological arousal in concert with changing situational demands.[39–41] To better understand this complexity, a model of interconnected neural elements has been introduced which is referred to as central autonomic network (CAN). In this model, autonomic, attentional and affective systems are integrated into a structural and functional network to interpret emotional regulation. The neural structures involved in the built-up of the CAN are the prefrontal cortex, insular cortex, the amygdala, hypothalamus, periaqueductal gray matter, parabrachial complex, nucleus tractus solitarii (NTS) and ventrolateral medulla, as well as the peripheral autonomic nervous system. The elements of this network were shown to be associated with various aspects of emotional and autonomic responses. Ventromedial prefrontal cortex is a key neural substrate of human social and affective function, central to the pathophysiology of mood and anxiety disorders. Neuroimaging studies in depression and anxiety suggest that it serves to regulate negative affect by top-down inhibition of brain regions involved in processing negative emotions – particularly the amygdala. Pathologically elevated negative affect in depression result from deficient prefrontal cortex-mediated inhibition of amygdala activity.[42,43] Prefrontal, orbitofrontal and insular areas of the cortex were found to gate emotionally entrained responses. Threat results in their withdrawn activity which involuntary, defensive behaviors of short latency. Long-term prefrontal cortex hypoactivity can manifest as poor habituation to novel stimuli, failure to recognize safety signals and poor affective information processing. In line with these data, reduced prefrontal activity can lead to hypervigilance and social isolation.[44] Beyond emotional regulation, patients with prefrontal cortex lesions also exhibited impaired cardiac autonomic responses.[45] Amygdala was described as a critical brain region for emotional fear.[46] Volume changes and increased metabolism of the amygdala was found in major depressive disorder.[47,48] The amygdala plays a pivotal role in integrating emotional content into appropriate cardiovascular responses that match the environmental challenges. Insular cortex is a site of multimodal integration, provides emotional related functions, conscious interoceptive awareness and mediates arousal-states in the autonomic divisions.[49] Neuroimaging studies revealed alterations in insular cortex activity in major depressive disorder.[50] Moreover, a positive correlation was found between dysfunction of the insular cortex and severity of depression.[51] Insular cortex lesions and impaired interconnection between

insular cortex, amygdala and hypothalamus were reported to induce arrhythmias.[52] In the CAN model, supramedullar structures converge to the NTS, as the final common pathway, through numerous feed-forward and feedback loops. The medullar segment of the brain stem receives and integrates afferent and efferent information crucial for autonomic regulation of the cardiorespiratory system. Cardiac and respiratory centers in the medulla are directly connected both physically and functionally. This allows them to elaborate complex afferentation and produce highly integrated efferent output.

Peripheral output and feedback of the brain–heart axis

Efferent parasympathetic and sympathetic fibers descend from the central nervous system to innervate – among others – the sinoatrial node and the vasculature in the cardiovascular system. Physiologically, sinoatrial node activity is under parasympathetic dominance, fluctuations in vagal efferent activity induce beat-to-beat changes in heart rate. Sympathetic innervation of the sinoatrial node affects heart rate to a lesser degree. However, the variation of elapsed time between two consecutive heartbeats is determined by the balance between the two antagonistic branches of the autonomic nervous system. Efferent autonomic activity mediates changes in heart rate and also total peripheral resistance. The resulting blood pressure alterations elicit cardiovascular feedback mechanisms such as the arterial baroreflex. The baroreflex includes conduction of sensory information from baroreceptor vessel walls (the aortic arch and carotid artery sinus) to the NTS. This information is further processed and integrated by the CAN with information from the cortical areas on the adequateness of the circulatory arousal. Eventually, the refined information propagates back to the cardiovascular system. According to human studies, the arterial baroreflex is responsible in 70% for the development of the cardiovagal tone.[53] Thus, the arterial baroreflex has a crucial role in the maintenance of the blood pressure regulation: acute increases in BP lead to a decrease in heart rate and a lowering of vessel tone via increased vagal and reduced sympathetic efferent activity whereas decreased blood pressure results in opposite changes.

HRV as a marker of neurocardiac function

HRV is considered a measure of neurocardiac function that reflects heart–brain interactions and autonomic nervous system dynamics. From this psychophysiological point of view, HRV may provide an insight into complex regulatory processes with an affective tincture.[54,55] The healthy heart is not a metronome, heart rate is varying slightly around a resting value within an interval due to autonomic, dominantly cardiovagal activity. Analysis of the HRV is suitable for assessing the magnitude of the cardiac efferent activity, mainly the parasympathetic activity.[56,57] An optimal level of HRV within an organism was found to reflect healthy function and an inherent self-regulatory capacity,[58] adaptability,[44] or emotional and stress resilience.[59,60] By contrast, reduced HRV has been linked to stress vulnerability. Higher resting HRV was shown to be associated with i) smaller negativity bias and ii) greater willingness to approach positive novel objectives. Moreover, the arterial baroreflex integrates cognitive and physiological aspects of emotion regulation. Afferent input from baroreceptors in the heart and the carotid-aortic arch contributes to visceroaffective integration, further highlighting the bidirectional link between autonomic and affective neural systems.[61,62] Conversely, functional magnetic resonance imaging (fMRI) studies have revealed that baroreceptor afferentation contributes to psychological factors, such as attention level, perception and the processing of certain emotions. At the time of baroreceptor activation, attenuation of pain evoked potentials, nociceptive motor and autonomic reflexes and perception of pain were present.[63,64] Periaqueductal grey matter activity mirrored negative emotional intensity ratings in concert with baroreceptor activity.[65] Baroreceptor activity also enhanced detection of threat signals and is associated with facilitation of "attentional blink" for fear. With other words, baroreceptor afferent signaling augmented the attribution of emotional salience to fear.[66]

Heart rate variability and baroreflex sensitivity

Each medical specialty selects a set of autonomic tests to characterize the most relevant aspects of autonomic function in the specific field. In human psychological and psychiatric research, the HRV is a widely used methodology for autonomic assessments. The range of available autonomic tests is listed in detail in Table 1.

Analysis of HRV is mostly based on ECG-recordings, from which the distance between two successive R-waves can be calculated. Based on time-RR-interval (RRI), series HRV parameters of time and frequency domain are

Table 1 Testing possibilities for autonomic function

Tests of autonomic cardiovascular reflexes	Valsalva maneuver, deep breathing, isometric handgrip test, cold pressor test, mental arithmetic, orthostatic test, head-up tilt test, baroreflex sensitivity testing, heart rate variability analysis
Measurements of neurotransmitter levels	Noradrenaline spillover test
Testing of cutaneous autonomic function	Thermoregulatory sweat test, sympathetic skin response SSR, quantitative sudomotor axon reflex test, Quantitative pilomotor axon reflex test, vasomotor test
Microneurography	Muscle sympathetic nerve activity, skin sympathetic nerve activity

Notes: Table of tests of autonomic functional integrity in cardiovascular, cutaneous and metabolic systems.

calculated. Usually, the following time domain measures are determined: standard deviation of normal RRIs (SDNN), root mean square of normal to normal interval differences, and the percentage of successive RRIs that differ by >50 ms (pNN50). The latter two parameters are indicative of the parasympathetic nervous system activity. In the frequency band, the most widely used indices are the very low (0.03–0.04 Hz), low (0.04–0.15 Hz) and high (0.15–0.4 Hz) power bands (LF and HF). Very low frequency power (VLF) describes sympathovagal balance and has unique characteristics that gained attention recently.[67] Normally, the respiration-related variability presents itself around 0.25 Hz frequency (15/min respiratory rate) and reflects parasympathetic nervous system effects (HF). The slower (6 cycles/min) fluctuations, observed in RRI, are presumably mediated by sympathetic and to a certain extent, parasympathetic nervous system activity (LF). By simultaneously assessing high and low-frequency HRV, information on the relative changes in sympathovagal balance can be gained (LF/HF). High variability of the heart rate indicates well-functioning parasympathetic nervous system regulation, reduced HRV is a consequence of deteriorated vagal and simultaneously increased sympathetic activity. Beyond that, HRV is a property of interdependent regulatory systems that operate on different time scales to help us adapt to environmental challenges. It is generated by heart–brain interactions and dynamic non-linear autonomic nervous system processes. Therefore, nonlinear HRV parameters represent a promising but not yet well-defined area of research. Due to the physiological and clinical importance of cardiovagal activity, numerous studies investigated the determining factors of the cardiovagal activity. The cardiac vagal motoneuron activity is largely influenced by the arterial baroreflex.[68] As a negative feedback loop, arterial baroreflex can minimize blood pressure fluctuations by influencing cardiac output and total peripheral resistance. From the complex efferentation, the cardiovagal branch of the reflex-the changes in blood pressure and heart rate can be well examined.[69] Cardiovagal BRS is a measure of the gain of the baroreflex and is defined as the change in RRI in milliseconds per unit change in blood pressure. To study the baroreflex function in humans, two approaches are widespread. The two methods investigate the reflectoric changes in RRI in response to i) pharmacologically induced blood pressure changes and ii) spontaneous fluctuations in blood pressure. The HRV and BRS methodologies are challenged to yield precise assessments in patient groups with low values; therefore, it is important to implement high-quality standards for such studies.[70]

Reduced heart rate variability and impaired baroreflex sensitivity in cardiovascular disease

Shifted sympathovagal balance toward the sympathetic branch leads to electric instability of the heart. Low HRV was associated with ventricular fibrillation after myocardial ischemia and infarction.[71,72] Reduced HRV was shown to be an independent risk factor for sudden cardiac death, while increased HRV was associated with reduced cardiac mortality.[72] Moreover, attenuation of HRV has been described in patients with chronic congestive heart failure and in those with hypertension and with dilatative cardiomyopathy.[73–75] Clinical significance of cardiac dysautonomia is, however, not limited to changes in HRV. A reduction in BRS was shown to be an independent risk factor for cardiovascular morbidity.[76] Impaired BRS has been linked to increase the risk for arrhythmias, hypertension,[77] heart failure,[78] myocardial infarction[79] and stroke.[80]

Combined reductions in HRV and BRS parameters were described in numerous diseased states. However, often there is no detectable, close relation between the indices of BRS and HRV, which can be probably explained by differences in their physiology. Therefore, it would be recommended to perform both HRV and BRS measurements simultaneously.[79]

Impairment of heart rate variability and impaired baroreflex sensitivity in depressive disorders

It appears from previous studies that autonomic disturbances in depressive disorders are present.[81–83] However, there is a considerable heterogeneity among studies concerning methods and ANS function testing. Based on our inclusion criteria (GRAPH), we have analyzed 21 studies in total, all presenting high methodological quality (Table 2). They were published between 2002 and 2017. In total, 967 patients with MD, 228 patients with history of depression, 591 patients with unipolar depression, 116 patients with bipolar disorder and 24 patients with posttraumatic stress disorder and MD were enrolled in these studies. Their results were compared to 1,050 healthy controls. Eighteen studies investigated autonomic nervous system function measured by HRV in depression, 14 (78%) studies have reported reduced variability of the heart rate. Seven studies determining BRS have described reduction in BRS in depressed patients compared to controls, however, one study showed only a tendency for BRS to be lower.

Attention has to be paid to the evaluation of this apparently convincing result. When relating autonomic dysfunction with depressive disorders many possible confounding factors have to be taken into account. Out of these, CVD/risk factors and (non-)pharmacological treatment are noteworthy. Only nine studies have reported CVD/risk profiles or exclusion criteria of this patient population. It is established that CVD is associated with autonomic disturbances, and in depressed patient populations, this prevalent comorbidity has to be accounted for when analyzing ANS function. There is an ongoing debate, if depression alone, antidepressive treatment or their combination result in autonomic abnormalities and reduced HRV. Out of investigations included in our review, eight studies enrolled medication-free patients. Seven of these studies (88%) published autonomic distortions in depressed patients compared to controls. This finding is in line with a meta-analysis,[82] which analyzed CVD-free, unmedicated depressed patients and found attenuated HRV which seemed to decrease with increasing depression severity. In contrast, two studies found that HRV parameters of depressed patients were not statistically significant from the values of healthy controls. Voss et al indicated, however, that BRS is reduced in depressed patients and concluded that BRS would mirror depression-related autonomic dysfunction more sensitively than HRV.

The effect of treatment on autonomic function in depression remains controversial. Treatment did not change HRV indices in the study of Brunoni et al and the authors concluded that reduced HRV could be a trait marker for depression. In three studies, however, treatment modified autonomic nervous system parameters, mostly worsened autonomic function was found. A prospective comparison indicated that the type of treatment may have different impacts on autonomic parameters (ie, tricyclic antidepressants reduced, SSRI did not change, repetitive transcranial magnetic stimulation increased them). It cannot be excluded that pharmacological treatment contributes to ANS dysfunction and indirectly to CVD risk in depression. However, it is also possible that sympathovagal imbalance is caused by depression severity, indexed by antidepressant use. In summary, since CVD is often associated with depression and autonomic parameters are largely influenced by CVD, in clinical assessment detailed CVD phenotyping and risk assessment should be performed and taken into account when autonomic functions are evaluated in patients suffering from depressive disorders.[27] It seems recommendable to involve CVD in the exclusion criteria or account for them statistically. Ideally, treatment-naïve populations should be targeted or each treatment modality must be adequately discussed and controlled for. Finally, BRS may represent a more sensitive marker of ANS dysfunction in depression. Therefore, it would be recommended to involve the measurement of this index when assessing ANS dysfunction in depression.

Understanding the brain–heart axis can imply therapeutic interventions in depressive disorders

Knowledge of psychophysiological mechanisms interconnecting affective, autonomic and cardiovascular regulation may also imply treatment possibilities when evidence of dysregulation is present. Currently, pharmacological interventions are considered effective, when a reduction of ≥50% on the Hamilton Depression Rating Scale (HAM-D) is achieved.[84] Below this ratio, the patients are held refractory to the specific treatment. Even the patients, who manage to respond adequately and fulfill the criterion, often continue to experience symptoms. Beyond this, the antidepressants are known to cause unpleasant side effects such as weight gain, which may also worsen the cardiovascular prognosis.[85] Moreover, when pharmacological therapy is discontinued, the patients frequently relapse. Non-pharmacological treatment options

Table 2 Studies in which HRV measures were calculated on a least one cohort with depression diagnoses

Study/year	Cohorts	Data	Parameters	Cardiovascular risk/treatment information	Results	Interpretation	Good practice checklist
Vasudev et al,[149] 2011	42 MD, 30 HC	BP and 10 mins ECG at rest	BP, LF, HF, TP, BS	Cardiovascular risk parameters included/ cardio-active and psychoactive drug use included	MD is an independent predictor for systolic orthostatic hypotension, low frequency HRV and BS	Autonomic abnormalities in late-life depression is associated with development of brain white matter hyperintensities	No information on R-R interval cleaning and artefacts
Wang et al,[150] 2013	53 MD, 53 HC	ECG over 24 hrs	SDNN, SDANN, RMSSD,pNN50, ratio of LF/HF	Some information on cardiovascular risk/all patients were receiving SSRIs treatment	In the depression group SDNN, SDANN, RMSSD, pNN50 and HF were lower, prevalence of supraventricular arrhythmia was significantly higher than in the control group	Depression is accompanied by dysfunction of the cardiac autonomic nervous system, depression severity is linked to severity of this dysfunction.	No information on artefact identification and cleaning methods
Johansson et al,[151] 2010	33 MD, 20 HC	30 mins ECG at rest and BP	HR, BS and BEI	Cardiovascular risk in exclusion criteria/ electroconvulsive therapy vs medical therapy	HR and BP were elevated in depressive patients before treatment compared with HC, whereas arterial BRS and BEI were reduced	The sensitivity and the number of times the arterial baroreflex is being active are reduced in MDD and this dysfunction may prevail long-term when depressive symptoms have improved	All items on checklist met
Hughes et al,[152] 2007	34 PTSD + MD, 28 PTSD, 16 MD, 46 HC	BP and IBI	BP, HR, BRS	No information on cardiovascular risk/ psychiatric and cardiovascular medication included	Women with PTSD (with or without MDD) exhibited significantly lower resting BRS than women without PTSD. BRS decreased during the anger recall task	PTSD is associated with reduced parasympathetic nervous system functioning	No information on artefact cleaning methods
Broadley et al,[153] 2005	36 treated recurrent MD, 39 HC	20 mins ECG and 10 mins BP at rest	HR, BRS	Some cardiac risk factors included/treatment with antidepressants	BRS was significantly lower in patients	BRS is impaired with depression and may contribute to increased cardiac risk	R-R interval calculation briefly discussed, artefact identification not included

(*Continued*)

Table 2 (Continued).

Study/year	Cohorts	Data	Parameters	Cardiovascular risk/treatment information	Results	Interpretation	Good practice checklist
Moon et al,[154] 2013	34 MD, 27HC	5 mins ECG at rest	SDNN, RMSSD, VLF,LF, HF, TP, LF/HF	No cardiac risk factors mentioned/MD treated with SSRIs	Patients with MDD in the study had no significant main change in HRV	HRV is not sufficiently powerful to discriminate among various psychiatric illnesses	No information on artefact identification and cleaning methods
Dauphinot et al,[155] 2012	67 MD, 228 with history of MD	24 hrs ECG	SDNN, VLF, LF, HF, LF/HF, BRS	Some cardiac risk factors included/treatment with antidepressants in some cases	LF, VLF and LF/HF ratio were lower among subjects with depressive symptoms and history of depression, independently of antidepressant treatment	Depressive symptoms may be linked to autonomic nervous system lower performances	Artefact identification, data loss, cleaning not included
Udupa et al,[90] 2011	94 MD	resting ECG	SDNN, RMSSD, pNN50, TP, LF, HF, SVB	Treatment with: repetitive transcranial magnetic stimulation SSRIs and tricyclic antidepressants	Both time and frequency domain HRV measures showed increase with rTMS and decrease with TCAs; they remained virtually unchanged with SSRIs	The effects of antidepressant treatments on cardiac autonomic function abnormalities found in depression vary with the mode of treatment used	No information on extraction and cleaning of artefacts
Chang et al,[156] 2015	116 bipolar II depression, 591 unipolar depression, 421 HC	ECG recorded for 5 mins	VLF, LF, HF, LF/HF	Some cardiovascular risk factors included/all participants drug-naïve	Patients with BPII depression exhibited significantly lower mean R–R intervals, variance (total HRV), LF-HRV, HF-HRV but higher LF/HF ratio compared to those with UD	HRV may aid in the differential diagnosis of BPII depression and UD	No information on data analysis and cleaning, little information on demographics
Kemp et al,[157] 2014	98 MD	10 mins resting state ECG	R-R interval series, HRV mean square of successive squared differences and HF components	Treatment with: SSRI, SNRI, tricyclic antidepressant and other antidepressant, Cardiovascular risks: included	Tricyclic antidepressants, SNRIs and other antidepressants associated with increases in HR and decreases in its variability; depression did not display reductions in vagal activity	Mood disorders and antidepressants are increased risk for cardiovascular morbidity and mortality	All items on checklist met

(*Continued*)

Table 2 (Continued).

Study/year	Cohorts	Data	Parameters	Cardiovascular risk/treatment information	Results	Interpretation	Good practice checklist
Agelink et al,[158] 2002	25 MD	ECG and BP	HRV, RMSSDr, RMSSDd, LF, HF, LF/HF ratio	Treatment with reboxetine, no information on cardiovascular risk	Reboxetine treatment associated with decrease in absolute and relative LF power, in mean arterial pressure; significant decrease in average low- to high frequency ratio	Inhibition of brain NE reuptake by reboxetine resulted in an inhibition of central noradrenergic activity	Little information on demographics, no control group, R-R interval cleaning briefly discussed
Voss et al,[159] 2011	36 MD, 36 HC	30 mins ECG, BP	RMSSD, LF/HF ratio BPV, BRS	No treatment, no information on cardiovascular risk	Gender differences were detectable in HC showing predominant sympathetic modulation in males. These gender differences were abolished in patients suffering from MD, HRV was not different between patients and controls	BPV and BRS ares more sensitive to reveal depression-associated changes of autonomic function as compared to HRV	All items on checklist met
Terhardt et al,[160] 2013	41 MD, 28 HC	5 mins ECG and BP monitoring	LF, HF, LF/HF ratio, TP	Cardiovascular risk assessment not included, treatment with venlafaxine and mirtazapine	Depressed patients had increased heart rate and reduced HRV compared with non-depressed controls	Depression is related to reduced HRV, which might reflect sympathovagal imbalance; venlafaxine and mirtazapine led to further decline in HRV	Little information on data analysis, cleaning and demographics
Kikuchi et al,[161] 2009	15 MD,15 HC	ECG recorded for 5–10 mins	LF, HF and LF/HF ratio	No medication, no information on cardiovascular risk	MD group had a lower response to regular deep breathing in LF power and in LF/HF ratio	Reactivity to deep breathing revealed diminished cardiac autonomic reactivity in drug-naïve MD patients	No information on cleaning R-R intervals and artefacts
Brunoni et al,[162] 2013	118 MD, 118 HC	ECG for 15 mins	RMSSD, HF, HRV indices	Use of antidepressants included,risk factors for CVD assessed	Patients displayed decreased HRV relative to controls; HRV scores did not change following treatment with either a non-pharmacological or pharmacological intervention, nor did HRV increase with clinical response to treatment	Reduced HRV could be a trait-marker for MD	All items on checklist met

(*Continued*)

Table 2 (Continued).

Study/year	Cohorts	Data	Parameters	Cardiovascular risk/treatment information	Results	Interpretation	Good practice checklist
Hage et al,[163] 2017	64 MD	15 mins of ECG at rest	RSA, LF-HRV, and heart period (HP)	Maintenance on mood stabilizer and/or atypical antipsychotic throughout the study; no information on cardiovascular risk	MD subjects had significantly higher baseline RSA and LF-HRV in comparison to subjects with bipolar disorder	Reduced vagal tone and higher levels of inflammatory biomarkers may distinguish bipolar disorder from MD	All items on checklist met
Kemp et al,[164] 2014	72 MD, 94 HC	2 mins of ECG at rest	SDNN, RMSSD, LF, HF,PCSD1	All participants medication free, no information on cardiovascular risk	MDD patients with melancholia displayed significantly increased heart rate and lower resting-state HRV	MD patients with melancholia display robust increases in heart rate and decreases in HRV	No information on ECG used, no information on R-R interval cleaning and artefacts
Boettger et al,[165] 2008	18 MD, 18 HC	24 hrs ECG	SDANN, SDNN, RMSSD, AIF curve, VLF, LF, HF, TP	Cardiovascular risk not mentioned/free from medication	Power law slope was significantly reduced in patients for all intervals investigated and correlated with symptom severity	Decreased complexity of cardiac regulation in depressed patients	No information to rule out psychiatric disease in controls
Ha J et al,[166] 2015	30 MD, 30 HC	5-mins ECG	SDNN,RMSSD, NN50, pNN50, VLF, LF, HF, TP	Free from medication, little information on cardiovascular risks	In MD significantly lower VLF, LF, HF and TP; significantly smaller standard deviation of the NN, root mean square of the differences of the successive NN, and NN50/total number of all NNs	Low HRV may be an important predictor of both MD and CVD in elderly	No information on R-R interval cleaning and artefacts
Schulz et al,[167] 2010	57 MD, 57 HC	30 mins ECG and BP	SDNN, RMSSD, pNN50, Shannon entropy,BRS, LF, HF, LF/HF	Free of medication, no details on cardiovascular risk	Non-medicated depressed patients reveal a significantly changed short-term as well as long-term complexity of cardiovascular regulation	There are substantial changes in autonomic control probably due to a change of interactions between different physiological control loops in MD	Little information on recruitment and demographics

(*Continued*)

Table 2 (Continued).

Study/year	Cohorts	Data	Parameters	Cardiovascular risk/treatment information	Results	Interpretation	Good practice checklist
Bär et al,[168] 2004	18 MD, 18 HC	5 mins ECG	HRA, VLF, LF, HF, RMSSD, PLR	Examined once medicated and treatment-naive as well as after full clinical recovery/ no specification on cardiovascular risk	Treatment-naive MD patients differed significantly neither in heart rate parameters nor in parameters of the PLR from HC; after antidepressant treatment, parameters of heart rate analysis and PLR changed significantly and remained different after clinical recovery	The state of depression did not influence autonomic parameters significantly; treatment influenced autonomic function far more than the disease itself	All items on checklist met

Notes: Summary of ECG recordings, HRV measures, cardiovascular risk, treatment information and results are provided, in addition to their interpretation and adherence to the GRAPH checklist on the cohort.
Abbreviations: MD, major depression; HC, healthy control; BPII, bipolar disorder; UD, unipolar depression; BP, blood pressure; HR, heart rate; BS/BRS, baroreflex sensitivity; BEI, Baroreflex effectiveness Index; IBI, interbeat interval; SVB, sympathovagal balance; RSA, respiratory sinus arrhythmia; PCSD1, deviation of the Poincaré plot perpendicular to the line of identity; CVD, cardiovascular disease; HRA, heart rate assessment; CVC, cardiac vagal control; rTMS, repetitive transcranial magnetic stimulation; TCA, tricyclic antidepressant; PLR, pupillary light reflex; SVB, sympathovagal balance; AIF, autonomic information flow; PTSD, posttraumatic stress disorder; BPV, blood pressure variability; SDNN, standard deviation of NN-normal to normal R-R intervals; SDANN, standard deviation of the average NN-intervals; RMSSD (*r*/*d*), square root of the mean of the squares of the differences between adjacent NN intervals (resting/deep breathing); NN50, consecutive NN-intervals that differ by >50 ms; pNN50, proportion of consecutive R-R intervals that differ by more >ms; TP, total power; VLF, very low frequency power; LF, low frequency power; HF, high frequency power; LF/HF, low frequency to high frequency ratio.

carry clinical significance and are favored directions of psychiatric research. Neurocardiological interventions are likely to alleviate depressive symptoms, as well. Vagal stimulation, eg, was found to help patients with refractory depressive symptoms, however, its invasive nature and costliness mean significant limitation for its usability.[86] Deep brain stimulation of cingular areas has also been found to be effective in treatment severe resistant depression.[87,88] Further interventions targeting psychophysiological pathways are transcranial magnetic stimulation, psychotherapy and different biofeedback approaches with various evidence levels and grades.[89–91] Psychotherapy is, eg, well established and recommended as a treatment regimen in depressed patients in various national guidelines. Recently, it has been demonstrated that transcranial magnetic stimulation may be considered as a promising enhancement in treatment-resistant depression.[92] Whereas, HRVB represents a novel, experimental, non-pharmacological intervention to improve complex biobehavioral mechanisms that result in improvements in mood regulation, autonomic function and have possible positive impact on cardiovascular complications.

Heart rate variability biofeedback

Physiological background

HRVB is a biobehavioral clinical intervention that has been used in research studies in both psychological and somatic disorders. The technique has been shown to enhance vagal control of heart rate and affect the networks involved in neurocardiac regulations: the autonomic nervous system, the cardiovascular system, the respiratory system and biological substrates of emotion regulation.

At its discovery, it was observed that maximal oscillations in heart rate (up to 60/min!) were provoked by low respiratory rates.[93,94] The effects are based on resonance properties of the cardiovascular system. To be specific, breathing at the resonant frequency augments the earlier described respiratory sinus arrhythmia (RSA) and stimulates rhythmically the baroreflex that triggers large-amplitude reflectoric heart rate oscillations.[95] Thus, greatly amplified HRV develops at least partially due to increased baroreflex gain. This appears as augmented LF and LF/HF ratio in terms of HRV spectral parameters. The optimal breathing frequency individually varies (4.5–6.5/min) and averages around 5.5–6/min. Male gender and bigger height appear to be associated with lower resonant respiratory rate, the common physiological factor would be larger blood volume.[96] The higher the blood volume, the bigger is its inertia,

which leads to longer delay between baroreflex-elicited heart rate and blood pressure-and longer periodic time of resonant breathing.

Effects of heart rate variability biofeedback on autonomic cardiovascular regulation

The regular application of HRVB is thought to ameliorate autonomic functioning and restore autonomic homeostasis, important for cardiovascular health. Precise resonant frequency breathing plays a pivotal role in the beneficial effects of HRVB such as augmenting HRV parameters and reducing blood pressure in health.[97] HRVB has been found to reduce blood pressure in prehypertensive individuals and proved to be superior to slow abdominal breathing.[98] In another group of prehypertensive patients, beneficial effects on blood pressure and HRV parameters of HRVB were maintained when stressors were applied.[99] However, in an early study in mildly hypertensive patients, the HRVB has been found to be ineffective in reducing blood pressure values.[100] Larger, controlled studies are needed to detangle HRVB effects in hypertension. It seems reasonable to target subgroups within hypertensive patients, such as individuals with white coat hypertension or essential hypertension where stress is believed to be an important component of the pathology. HRVB seems a promising therapeutic add-on in patients with cardiac diseases, by reducing symptoms and increasing quality of life.[101] Del Pozo et al enrolled 63 patients with CAD and performed six sessions of HRVB with them coupled with daily practices at home.[102] A significant increment was observed in HRV parameters in this group of patients. In end-stage heart failure patients, HRVB has been shown to change the remodeling biology of the myocardium favorably.[103] Still, in heart failure patients, "6 mins walk test" performance was improved and perceived stress level was reduced by HRVB intervention.[104]

Another effect of HRVB mechanism is probably by influencing visceral afferent activity, which has complex upstream effects. This fits into a timely area of research regarding "peripheral emotion theories". It postulates that a feedback of bodily response is proposed to be the basis for emotional feelings and physiological change. Among these, there appears to be a primacy of cardiovascular feedback on the generation of biobehavioral phenomena. HRVB and the slow abdominal breathing during the intervention trigger central responses, primarily by increased baroreflex afferent (vagal) activity but also by subdiaphragmal vagal afferent stimulation.

HRVB increases the signal input intensity conveyed by vagal afferents. This effect is similar to the course of action of vagal nerve stimulation. Enhanced activity of vagal afferents conveyed via NTS and projected to cortical, paralimbic and limbic structures, known to be involved in emotion regulation and implicated in depression. The data originating from neuroimaging studies in vagal nerve stimulation, described substantial ipsi- or bilateral modifications of medial temporal regions such as hippocampus, parahippocampus or amygdala as well as orbito- and prefrontal cortical areas, all known to be involved in emotional processes.[86]

Deep brain stimulation of cortical areas, where vagal nerve projects, have been found also effective in treatment-resistant depression.[87,88]

Further evidence on these central effects come from Heartbeat Evoked Potential (HEP) studies. HEP in EEG recordings has been described to be altered by resonant breathing and attenuated by negative emotional stimuli.[105] HEP has also been found to be a marker of altered bodily awareness in depressed patients. Decreased interoceptive involvement of the insular cortex detected by fMRI was related to depression and somatic symptom severity in major depressive disorder.[106] It can be hypothesized that HRVB by altering cardiac afferent activity, improves interoceptive representation of the insular cortex, therefore reduces alexithymia and ameliorates decision-making in depression.[107]

Heart rate variability biofeedback assessment: conduction and practical aspects

In general, ECG or plethysmograph recording equipment is necessary for the application of HRVB. There are standardized, easily available HRV biofeedback systems for clinicians who wish to deliver HRVB (Stressball BioSign, Ottenhofen, Germany Mück-Weyman 1996, J&J Engineering, Poulsbo, WA, Stress Pilot, Biosoft, Germany). Ideally, the instrumentation provides real-time information on heart rate, respiration, low-frequency HRV power band and a running spectral chart to display average amplitude of heart rate fluctuations at each frequency. The original HRVB training protocol used to be 10-session long.[108] However, based on research data of the authors, it has been shortened and currently involves five visits with durations of 30–45 mins (Table 3.).[109]

Table 3 Shortened protocol for heart rate variability biofeedback training

Visit 1	First, the client is introduced to the basics of HRVB mechanism and technique. Especially for patients with psychiatric disorders, it is important to deliver a psychoeducation for the intervention. It increases compliance; adherence and comfort of the patient if he is prepared for the course of action. The operator should explain well the background of the method and follow the described regimen carefully. Furthermore, it is necessary to put the results of HRVB into perspectives, namely, that the individual with affect disorders may short-and long-term improve emotion self-regulation by practicing precisely and regularly the breathing technique. When the patient is equipped with the sensors, the appearing signals on the computer screen have to be defined for the subject. During the first (or second) visit, the optimal, resonant respiratory rate is determined. The patient ought to be informed briefly on the cardiorespiratory resonance phenomenon and the role of baroreflex in it. It can be helpful, if both thoracic and abdominal breathing sensors are attached, that allow the assessment of thoracic versus abdominal components in breathing. The determination of the optimal breathing frequency starts with paced breathing around the adult average value, 0.1 Hz – 5.5–6/min respiratory rate. The clients are coached to breath evenly and not too deeply for several minutes. The clinician detects patient's well-being and observes the coherence between respiration and HRV. Lehrer et al provided a worksheet to be filled out at each respiratory frequency (6.5–6.0–5.5–5.0–4.5) and the combination of measures and characteristics to estimate the resonant frequency. Then, the patient is informed on his optimal breathing frequency. The resonant frequency may have to be retested during the second visit. Notably, the patient's resonance frequency will change while practicing HRVB regularly. The first visit usually appears as stressor for the patients that can influence the resonant frequency. Biofeedback can be delivered during the first visit; however, most often it is part of the second or third visit. In the end of the first visit, there is homework for the patient. With the help of a watch or a custom-made computer program/mobile application, the patient is supposed to practice breathing at resonant frequency at home for 20 mins daily. It is important gain to draw the patients attention to the beneficial effects of HRVB when applying regularly and mastering it precisely. At any stage of HRVB training, give the patient the opportunity to ask.
Visit 2	Trainees practice abdominal breathing at resonant frequency and adjacent frequencies when needed, in order to clarify the optimal breathing frequency. Patients are instructed to maintain exhalation for a longer time period that inhalation duration. Also, the subject should exhale with pursed lips, which makes exhalation less effortful. The patients are asked to practice at home the extended methodology for breathing. They should be aware of the symptoms of hyperventilation and how to avoid it. Calm the patient if at any point of the learning curve he experiences stress.
Visit 3	Abdominal breathing is further practiced if the patient was unable to learn it. The most important event of the third session is usually the introduction of HRVB to the patients. After a brief training with paced breathing, the client is asked to use their cardiotachometer line displayed in front of them. The line represents their continually changing heart rate. Ideally, the monitor displays also the respiratory activity. The patient is then instructed to breathe in phase with the heart rate while maximizing HRV. As a homework, the subject has to practice resonance frequency breathing technique with abdominal, pursued lips breathing with a clock, computer breath pacer or mobile application as mentioned earlier, then practice with a home breathing trainer when available for 20 mins, two times daily. The goal would be to achieve the maximum in smoothness of the curve and the amplitude of HRV oscillations. For the evaluation of HRVB, the conventional HRV parameters are used. LF was found especially responsive to HRVB, probably due to triggered baroreflex.
Visit 4–5	During the last sessions, the review of the breathing technique, fine tuning of the resonant frequency, supervised practice of HRVB by the client takes place. The therapist should focus on reinforcing the HRVB home practices by emphasizing its clinical gains. Any concerns, questions, doubts of the patient should be addressed.

Notes: The table provides an exemplary protocol of HRV biofeedback training which has been applied in clinical practice and some research studies. However, no consensus exists on the optimal settings and protocol.
Abbreviations: HRV, heart rate variability; HRVB, heart rate variability biofeedback.

Utility of heart rate variability biofeedback in clinical practice

HRVB has been shown to enhance psychophysiological functioning in both health and disease. In healthy individuals, HRVB practicing has been shown to improve control over autonomic responses when encountering negative stimuli.[110] Furthermore, merely the acquired skill of HRVB enabled the participants to better reduce heart rate in emotionally challenging situations.[111] HRVB appears to reduce anxiety and improve coping with stressors,112 although large randomized-controlled trials are lacking to confirm these findings. Highly anxious college[113] students have achieved decreases in anxiety and negative mood with the help of a HRVB protocol. Profession-associated stress was addressed by a study with quasi-experimental research design, who investigated HRVB effects on psychophysiological stress markers in correctional

officers.[114] They have found improvements of laboratory stress marker levels and reduced psychological distress which would mean a health-care cost difference of 1,179 USD/year/person. A recent review has concluded that HRVB is a safe, easy-to-learn method for athletes and coaches to apply in order to increase sports performance.[115] Competitional stress and recital excitement is often a profound source of anxiety in dancers and musicians, which may undermine their performance. HRVB has benefitted the both the dance and musical performance.[116,117] In a systematic review HRVB has been also described as a feasible, adjuvant, health-promoting stress management tool for peripartum women.[118] According to the two studies[119,120] analyzed in this review, stress levels of peripartum women with HRVB intervention were reduced compared with participants who did not receive HRVB. Furthermore, HRVB has also been shown to decrease depressive symptoms (measured by a significant decrease in total Edinburgh Postnatal Depression Scale score) by reducing anxiety or difficulties in sleeping in postpartum women.[119] To our knowledge, there is no information on the effectiveness of HRVBF on psychological stress in the first and early second trimester of pregnancy. It is also unclear, whether stress reduction via HRVB has beneficial effect on preterm labor. Recently, a study with open trial design has found significant decrease in impaired ability to tolerate normal stressors and dysphoric mood by a 4-week HRVB treatment in young individuals with clinically high risk for developing psychosis.[121] Promising trends in reducing self-reported anxiety were also reported. However, randomized-controlled trial would be necessary to assess the efficacy of HRVB in this group of individuals.

Beneficial effects of HRVB have been shown in somatic and psychiatric diseases, as well. It is known that HRV correlates negatively with age in adults and biofeedback effects on cardiovascular variability attenuate with declining age.[122,123] In contrast with this observation, Lehrer et al have shown that age-related attenuation effect of biofeedback does not affect significantly the usability of HRVB for treating asthma in older patients.[124] HRVB has been found a useful add-on therapy in chronic obstructive pulmonary disease, improving quality of life and 6 min walk test.[125] Another study has investigated the effects of HRVB on subjects with chronic neck-shoulder pain, who experienced after a 10-week session improvements in perceived health and showed ameliorated HRV profile.[126] Patients with unexplained medical symptoms can represent unique challenge to physicians, HRVB may represent a useful method to alleviate their somatic symptoms and improve their functional status.[127]

Furthermore, potential efficacy of HRVB is indicated by a growing number of studies in mental disorders. In a pilot study in patients with posttraumatic stress disorder in veterans, HRVB together with conventional therapy has elevated diminished HRV and reduced their symptoms, whereas conventional therapy alone had no significant effect on either HRV or symptom profile.[128] HRVB was also found to attenuate dysfunctional eating behaviors and reduce food craving, eating and weight concerns food craving. Interestingly, the intervention was not accompanied by long-term increase in HRV parameters.[129] By reducing craving and anxiety accompanying abstinence HRVB represents a useful adjunct therapeutic option in substance use disorders.[130] In a mixed group of alcohol or drug addict men, HRVB proved to be an efficient add-on therapy for reducing craving.[131] Reduced HRV parameters in this group of patients appeared to predict increases in craving by the end of the conventional treatment. Improved HRV, vasomotor function and reduced anxiety in response to HRVB intervention was also seen in alcohol-dependent patients.[132] After 1-year follow-up, the rate of abstinence tended to be higher in patients who underwent HRVB intervention.[133]

However, while these findings are quite promising, large well-designed confirmatory studies are needed to form a basis for potential translation of the technique into standard clinical care. Moreover, a publication bias with non-reporting of negative studies is to be anticipated, particularly as the majority of available studies have small sample sizes.

Studies of heart rate variability biofeedback as add-on therapy in depression

To our best knowledge, there have been four studies enrolling patients diseased by depression disorders alone.[134–137] Details of these studies are found in Table 4 and they are discussed below in chronological order.

First, an open-label study with 11 patients with major depressive disorder.[134] The middle-aged patients were dominantly females, similar to the other three studies, discussed later. There was no control arm in this investigation. All subjects were diagnosed in accordance with DSM-IV. Depression severity was assessed by HAM-D and Beck Depression Inventory (BDI)-II. Anxiety and dysthymic disorders as comorbidities were allowed as long as the primary diagnosis was MD. Detailed exclusion

Table 4 Details of the studies investigating HRV biofeedback intervention in major depressive disorders

Study	N(f)	Subgroups	Age1	Dx and psychological measures	Comorbidity/ medications	Excluded if:	Restrictions	HRVB protocol	HRV indices	Other highlights:	Findings
Karavidas et al. [134]	MD:11(7) No control group	None	45(10.8)	DSMIV, HAM-D, BDI-II	Anxiety, dysthymic disorder, on active treatment but only 3 maintained it during the study	Primary axis I or II diagnosis for other than major depression, report of current substance abuse, cognitive impairment, non-psychiatric medications, history of psychosis, mental deficiency, CKD, CHF, heart disease, HT, chronic low BP, cardiac arrhythmias.	None reported	Lehrer 2000 with home practices	SDNN, VLF, LF, HF, pNN50	None	Increases in SDNN, pNN50, LF, HF during sessions, returned back to baseline in the end of protocol, improved depression symptoms, no correlation between the two findings
Siepmann et al. [135]	MD:14(13) HC (24(12)	HC 12: active treatment HC 12 HRVB	MD and HC together: 28(7.3)	DSMIV, BDI, STAI major depression, bipolar disease, dysthymia, recurrent depressive disorder, moderate/mild depressive episode	No information on comorbidities, on medication(antidepressant, psychotherapy, anxiolytic medication)	History of psychosis, mental deficiency, CAD,CHF, CKD,HT, hypertension, chronic low BP, cardiac arrhythmia	Hx positive for alcoholism, regular caffeine	6 sessions in 2 weeks	pNN50, VLF, LF, HF, LF/HF	Vasoconstrictory response of cutaneous blood vessels (VR)	Baseline-during HRVB-follow up after 2 weeks reduced heart rate and pNN50 at follow-up, spectral HRV variables tended to improve, unchanged VR, BDI and STAI: reduced scores during HRVB and follow up
Caldwell et al. [137]	MD:20 (20); 10 (10)	MD: 10 HRVB + psychotherapy; 10 only psychotherapy-(TAU)	Reported for subgroups: HRVB 20.09 (1.81); TAU: 20.20(1.47); HC 20.64 (1.29)	MINI, BDI-II	None reported	Age <18 or over 25 years, use of vasoactive drugs, CVD, alcohol or drug abuse, any physiological or neurological disorders, history of electroconvulsive therapy, had injury	Exercise, caffeine, tobacco 3 hrs prior testing	Lehrer 2013, home practices	SDNN, LF, HF, LF/HF	None	Post-treatment comparisons: HRVB group showed the greater decline in depressive symptoms, SDNN, HF and LF/HF showed significant changes, relation between SDNN and depressive symptom changes
Hartogs et al. [136]	MD:7(6) No control group	None	46.4(14)	DSMIV, BDI-II, daily diary, Happiness Index, Positive Outcome List (POL)	Avoidant and dependent personality traits, current medication for 3 patients	Neuropsychiatric disorder, personality disorder, substance dependence and mental retardation	None reported	HRVB Stress Relief Program: 30	None	Heart coherence	POL recovery in 2 patients, BDI-II and POL improvement in one patient, POL in one patient deteriorated

Abbreviations: N(f), number of patients (number of female patients in brackets); Age1, age expressed as mean ± standard deviation; MD, major depression; HC, healthy controls; BDI, Beck Depression Inventory; HAM-D, Hamilton Depression Rating Scale; CKD, chronic kidney disease; CHF, chronic heart failure; HT, hypertension; BP, blood pressure; POL, positive outcome measure; SDNN, standard deviation of normal to normal R-R intervals; pNN50, proportion of consecutive R-R intervals that differ by >50 ms; VLF, very low frequency power; LF, low frequency power; HF, high frequency power; LF/HF, low frequency to high frequency ratio; HRVB, heart rate variability biofeedback; STAI, state-trait anxiety inventory; CAD, coronary artery disease; Dx, diagnosis; Hx, history; TAU, therapy as usual; MINI, Mini-International Neuropsychiatric Interview.

criteria were applied which also included CVDs. The training manual of Lehrer et al was followed when performing HRVB. They have implemented home-practice as part of the training routine. This is an essential component of the method, since HRV biofeedback relies on self-management that is not controlled by therapeutic supervision following few initial supervised training sessions. However, the lack of control over this might impair the evaluation of efficacy. The determined HRV parameters were in line with international guidelines. It was observed that depressive symptoms were improved during HRVB treatment and there were also increases in SDNN, pNN50, LF and HF. However, no correlation was detected between the two findings. Improved HRV indices tended to return back to baseline by the end of the protocol. Complete and partial clinical remissions were reported in 6 and 3 patients, respectively. The authors have emphasized that especially the neurovegetative components of the disorder (sleep hygiene, fatigue, concentration) showed partial recovery. The study was a preliminary, uncontrolled investigation, which does not lead to definitive conclusions. Further limitation that the sample was Caucasian, dominantly female and the home-practice was not standardized.

Shortly after, another open-label trial was performed and recruited 14 patients with MD and 24 healthy controls.[135] Half of the controls received HRVB intervention. The participants were young adults; the majority of them were female. Anxiety and depression severity was assessed by BDI and state-trait anxiety inventory. Patients already receiving antidepressant and/or anxiolytic medication and/or psychotherapy were included. Exclusion criteria were elaborated in detail and they have controlled for CVD, similarly to the first study. HRVB protocol and the calculated HRV parameters were in line with protocols. Additionally, the authors have also assessed vasoconstrictory response of cutaneous blood vessels (VR). The depressive symptoms were improved during HRVB treatment, at the end of the intervention and at 2 weeks follow-up. The latter highlights the possible long-term efficacy of the intervention, as well as the fact that a chronic disease requires constant care. Reduced heart rate and pNN50 was described at follow-up. By contrast, there was no change noted in healthy controls receiving biofeedback. VR was unchanged. However, vasomotor tone is influenced by the baroreflex, that is known to be triggered by HRVB technique.[138] The authors concluded that HRVB appears to be a useful adjunct for the treatment of depression, associated with increases in HRV. Major limitation of the study was the small sample size, the absence of an active control group in depressed patients. Longer follow-up period also would have been recommended.

The third study was conducted with a replicated single-subject study.[136] Seven participants with MD completed the full protocol, there were no healthy controls. The patients were middle-aged, mostly (6) women. CVD did not form a part of the exclusion criteria. Diagnosis of MD was based on DSM-IV. Avoidant and dependent personality traits were allowed, three patients were on medication. Psychological measures included BDI-II, happiness index and positive outcome list. The authors applied a conceptually different technique, the Stress Relieving Program which included HRVB. HRVB sessions were extended by induction, remembrance of positive emotions and turning negative feelings into positive. The authors have also not reported conventional HRV variables, but assessed heart coherence. It was described as a harmonious ordered heart rhythm pattern and reflects a regular, sine-wavelike pattern in HRV. This study did not show significant reduction of the depressive symptoms and increases in heart coherence as the effect of their Stress Relieving Program. The authors explain their findings by the backdraft phenomenon: inducing positive emotions such as self-compassion in depressed patients may cause an eruption of negative emotions towards themselves. Similarly to the previous publications, small size, female dominance, uncontrolled disease duration represent limitations.

In a randomized-controlled study, the participants received conventional psychotherapy with or without HRVB training.[137] Thirty female college students were enrolled, 20 with MD and 10 healthy controls. Strict age-restrictions were applied (18–25 years) in this study. The participants were asked to refrain from exercise, caffeine or tobacco consumption 3 hrs prior to the testing. Only one of them reported current use of medication, the others were free of treatment. MINI and BDI-II were used in this study for psychological measurements. Guidelines of HRVB intervention and HRV determination were followed. Similarly to the first open-label study, the authors have implemented uncontrolled home-practice as part of the training routine. The HRVB group showed the greatest decline in depressive symptoms and SDNN, HF and LF/HF showed vagal activity increment in this group of patients. They have also demonstrated that depressive symptom improvement seen in HRVB group was partially driven by improvement in HRV (SDNN). Small sample

size, narrow age-range and female exclusivity represent limitations. Furthermore, HRVB was studied with psychotherapy only, HRVB combined with antidepressant therapy is lacking. There was no group that received only HRVB treatment.

In summary, the patients were dominantly females, which have been listed as limitation of the studies; however, the depressive disorder affects women more. All subjects were diagnosed in accordance with the DSM-IV. Treatment-wise, there is large heterogeneity between types of medications and dosing regimens. In each study, there were patients who discontinued the study protocols. Exclusion criteria were not concordant throughout the studies, CVD was not part of them in two studies. Two studies did not enroll control arms in their investigation.[134,137] As for the design of the studies, the only randomized-controlled study was performed in the latest study.[137] Three studies followed the protocol of HRVB and HRV guidelines. All studies, except for one, could show significant reduction of the depressive symptoms and increases in HRV parameters as the effect of HRVB sessions. It seems the HRVB technique produces a reduction in depressive symptomatology and its effects may last beyond the direct time frame of the experiment (2 weeks after). Furthermore, it would also be of interest if remission is achieved. To improve the precise assessment the use of exact questionnaires can be suggested, especially those monitoring anxiety. Comorbid anxiety and anxiety symptoms were described as a confounder when investigating HRV in depression.[139] Favorable changes in HRV parameters, however, are less conclusive. Two studies have found wide range of HRV parameters to improve as an effect of HRVB, one of them described that by the end of the 10th session, the parameters tended to return back to baseline values.[135,137] It seems likely that the cumulative time spent practicing HRVB correlates with the improvement of neurocardiac function; therefore it may be advisable to include this value to assess a "dose–response" relationship. One study reported changes only in pNN50 and heart rate, however, these changes were also observed at 2-week follow-up.[136]

Unfortunately, the standard antidepressant and psychotherapy seem not to increase HRV to physiologic levels.[82,140] The effective treatment of depression might not reduce stress physiology which contributes to decreased HRV. Reducing stress levels early and adequately with the HRVB could increase the motivation of patients to adhere to the therapy and cooperate. The correlation between the improvement of HRV and reduced depressive symptoms means a further question for this research area. The first study reported no significant relationship between the two findings, whereas the last study found that improved HRV accounted partially for positive changes in mood. A possible explanation for these mixed findings could be that HRV improvements are related more closely to specific depression symptoms such as sadness, crying and poor sleep.[141]

Studies in different pathologies with depressive symptoms

In an open-label study with 12 female fibromyalgia patients (18–60 years), HRVB improved the overall functioning and the depressive symptoms by the end of the 10 sessions and later at the 3 months follow-up.[142] Immediate, after-session HRV values showed increment, but HRV and BRS measures did not differ among sessions and at follow up. Small sample size and the lack of control group are major limitations of the study.

The prevalence of heroin use has increased dramatically lately, serious comorbidities such as depression have to be taken also in account. Heroin users exhibiting depressive symptoms were enrolled in the following study with counterbalanced, within-subject experimental design.[143] HRVB technique was applied during six sessions, only nine abusers completed all the sessions which was found to improve HRV parameters. Depression severity also showed amelioration; however, it was not statistically significant.

The following three papers investigated HRVB effects in CVDs and surgery complicated with depression. As outlined earlier, CVDs are independently associated with depression and stress, as well as impaired cardiovagal control of heart rate. Their promising results indicate that this novel neurocardiac intervention facilitates psychological-emotional coping and also improves cardiovagal regulation. Therefore, adding HRVB may represent a low-risk therapeutic tool in rehabilitation and postoperative risk reduction programs for patients with CVDs.

Post-stroke depression is one of the common complications of cerebrovascular events.[144] Li et al recruited 13 poststroke patients (mean age: 55 years, dominantly females) for a randomized controlled trial and trained them in line with the 10 session-long HRVB protocol. Another group of 11 poststroke patients (mean age: 60 years, dominantly males) received treatment as usual only. Improvements in sleep disturbance and daytime

dysfunction have been observed. Furthermore, gains in certain HRV parameters were also found. Although there has been a significant drop in several depression severity scores, an overall clinical remission (≥50% improvement at HAM-D) was not achieved. It is hypothesized that the specific characteristics and pathogenesis of post-stroke depression have caused an altered effectiveness of HRVB in this setting. It seems possible that selecting patients based on their baseline HRV would characterize a group more responsive to HRVB treatment.

Nolan et al have conducted a randomized-controlled study in 46 patients with coronary heart disease and associated depression who were randomly assigned to an HRVB performing and an active control group.[145] HRVB improved psychological adjustment, indicated by reduced scores of Perceived Stress and Centre for Epidemiologic Studies in Depression Scales and augmented vagal regulation, measured by increased HF, were reported. Above this, the two beneficial findings were found to be associated.

Finally, Patron et al in a randomized controlled study aimed to apply HRVB in 26 patients (mean age: 61 years) after cardiac surgery in order to increase their cardiovagal activity – expressed as RSA – and reduce their depressive symptoms.[146] Amplified RSA and a drop of depression scores were described, the changes were inversely related to each other from pre to post training.

Clinical implications of heart rate variability biofeedback

HRVB has shown encouraging results so far. Certain conditions, such as anxiety, stress, mood fluctuations are highly related to modern lifestyles. When lacking appropriate coping-supportive solutions that reduce vulnerability and increase the sense of control, they may culminate into mental illness and impair cardiovascular functions. In-lab training sessions withdraw liberty of the individuals, and may not be enough for the complete understanding of how HRVB works or for mastering physiological improvements at aim of the technique. There are PC-compatible breath tracers, mobile applications, home breathing tracers available to help and promote the acquisition of the breathing technique. Furthermore, HRV spectral analysis feature for biofeedback purposes has also been implemented into smartphone application, which could bring this intervention closer to the general population. The present review did not aim to summarize all these approaches; however, some examples are provided here. First, in an earlier study, a system was created containing a wireless monitoring belt (Zephyr BioHarness) to gather HRV and breathing frequencies.[147] Ubiquitous smartphone was used to process and display real-time information for biofeedback. In 2014, United States Patent was issued for a system called Mobile Wellness Device. It was reported to acquire ECG signals and transmit them to a server via a mobile device offering accurate HRVB measurement which is portable. In a preliminary efficiency study, a smartphone solution for cardiac coherence training was presented.[148] It was based on a photopletysmographic imaging through the smartphone camera. This sensor-less technology allows controlling biofeedback exercise through simplified HRVB algorithm. Further validation with existing computer-based technologies such as Freeze Framer or Symbioline would be necessary. As a further application, pattern recognition might be used to alert and predict acute and chronic psychophysiological events. When combined with other platforms, like actigraphy, sleep characteristics could be assessed. Adherence to treatment and compliance of the patients with depression could also be improved by a reliable home-monitoring device.

Conclusion

Depressive disorders represent a devastatingly common, recurring disease with immense financial burdens. Therefore, there is a definitive need for more adequate prevention and treatment amelioration. Better understanding of pathophysiological processes involved in depression could be to assistance to that. Recent advances in neuroscience indicate pathophysiological interconnections between affective, autonomic and cardiovascular regulations. In line with this, reduced HRV and BRS – widely accepted measures of the autonomic functions – are established independent risk factors for CVDs. Furthermore, diminished HRV and BRS have also been shown in depression. Comprehensive approach that addresses mood disorder, autonomic dysfunction and cardiovascular dysregulation may plead gainful. Recent therapies for depression do not target autonomic dysfunction or even worsen it. HRVB is an available, easy of attainment method, which aims to restore autonomic homeostasis and cardiovascular function. Enteroceptive regulation can be improved by this self-management technique to a clinically relevant extent. Recent investigations reported that HRVB application alleviated anxiety and improved mood in psychiatric diseases, including depression.

Implementation of HRVB into depression treatment strategies and home-monitoring techniques may ameliorate patient compliance and treatment adherence. The effective treatment of depression might not reduce stress physiology which contributes to decrease HRV. An early reduction in stress levels with the HRVB could increase motivation of patients to adhere to the therapy and cooperate. However, clinical utility of this method is still a question and larger clinical trials are necessary to explore the therapeutic potential of HRVB.

Limitations

The present review has been written in a narrative review format in order to provide comprehensive and up-to-date summary of available research findings. Similarly to systematic reviews, the search methodology was described in detail, in order to assure reproducibility. However, our exclusion criteria did not involve study designs or article types, compared to systematic reviews, our sample of articles represent a broader group with a higher risk for bias. The pathological processes linking depression, CVD to autonomic nervous system are, in part, hypothetical, future research would have to address its further investigation. When selecting papers for cardiac dysautonomia in depression, two authors have reviewed them (AP and SzSz) and applied the GRAPH guideline in order to include studies that were performed at high methodological standards. Still, not all checkpoints were always fulfilled in the included articles. Furthermore, the diverse patient characteristics (duration, severity of the disease, pharmacological and/or non-pharmacological treatment), comorbidity issues, which were often not reported, differing design characteristics weaken the strength of the conclusions drawn here.

It has to be emphasized, that HRVB is a somewhat promising, non-pharmacological intervention, but it is experimental. Large-scale clinical trials are mandatory to investigate its clinical efficacy in diseased states. There is still very limited data available that investigates the effects of HRVB in depression. The patient characteristics and study design heterogeneity, especially at this low amount of data, represents a considerable bias and limits the merit of their discussion.

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