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The therapeutic use of the relaxation response in stress-related diseases

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Summary

The objective of this work was to investigate a possible (therapeutic) connection between the relaxation response (RR) and stress-related diseases. Further, common underlying molecular mechanisms and autoregulatory pathways were examined.

For the question of (patho)physiology and significance of RR techniques in the treatment of stress-related diseases, we analyzed peer-reviewed references only.

The RR has been shown to be an appropriate and relevant therapeutic tool to counteract several stress-related disease processes and certain health-restrictions, particularly in certain immunological, cardiovascular, and neurodegenerative diseases/mental disorders. Further, common underlying molecular mechanisms may exist that represent a connection between the stress response, pathophysiological findings in stress-related diseases, and physiological changes/autoregulatory pathways described in the RR. Here, constitutive or low-output nitric oxide (NO) production may be involved in a protective or ameliorating context, whereas inducible, high-output NO release may facilitate detrimental disease processes. In mild or early disease states, a high degree of biological and physiological flexibility may still be possible (dynamic balance). Here, the therapeutic use of RR techniques may be considered particularly relevant, and the observable (beneficial) effects may be exerted via activation of constitutive NO pathways.

RR techniques, regularly part of professional stress management or mind/body medical settings, represent an important tool to be added to therapeutic strategies dealing with stress-related diseases. Moreover, as part of 'healthy' life-style modifications, they may serve primary (or secondary) prevention. Further studies are necessary to elucidate the complex physiology underlying the RR and its impact upon stress-related disease states.

key words: **stress • allostasis • diseases • relaxation response • signaling pathways • nitric oxide • prevention**

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1. INTRODUCTION: STRESS, NITRIC OXIDE, AND THE RELAXATION RESPONSE

In recent studies, an association between stress and diseases has been examined [1–7]. Hence, this association apparently exists, yet, it is complex and specific clinical implications still have to be investigated further [3–5].

In general, stress has an impact upon the immune, circulatory, and nervous systems [3–5]. Therefore, stress may affect immunological [3], cardiovascular [4], and neurodegenerative diseases/mental disorders [5], and this may include both positive and negative aspects [3–7]. Thus, stress can either exert ameliorating or deleterious effects, depending on a multitude of factors (e.g, individual, endogenous, or exogenous elements) [2–7]. However, clinically – and with reference to actual medical settings – negative influences of stress upon health and disease processes seem to dominate [3–6]. This may especially be true in the 'western world', where stress-related health issues almost seem to have an increasingly epidemic character [2–5,8].

Stress describes the effects of psychosocial and environmental factors on physical or mental well-being [1–7]. Stressors and related stress-reactions are often distinguished [1,2]. Further, stress implies a challenge (stimulus) that requires behavioral, psychological, and physiological changes (adaptations) to be successfully met, therefore using a state of hyperarousal for the initiation of necessary counteracting reactions [1–5]. This state of hyperarousal involves physiological mechanisms that are known as the stress/emergency response or *fight-or-flight* response, a set of physiological changes that occur in stressful situations and that prepare the 'stressed' organism either to fight or to flee. The state of alertness had first been described by Walter Cannon – almost 100 years ago [9,10].

Recently, the concept of 'allostasis' has been introduced into the field of stress medicine/research by Sterling and Eyer [11], refined by McEwen [12]. Thereby, allostasis – literally meaning 'maintaining stability (or 'homeostasis') through change' [3,11,12] – describes the capacity to adapt or to constantly change, i.e, modify, physiological parameters in order to adjust to ever shifting environmental conditions [1,5,12]. Hence, we can also speak alternatively about maintaining a 'state of dynamic balance' alternatively [1,3–5]. Moreover, 'allostatic load' refers to the wear and tear that the body experiences due to repeated cycles of allostasis, i.e, allostatic stress responses, as well as the inefficient turning-on or shutting-off of these activated responses [3,12].

When the brain perceives/senses an experience or stimulus as stressful, physiologic and behavioral responses (→stress responses) are initiated, leading to allostasis and adaptation (→adaptive/allostatic stress responses) [1,12]. Thereby, the goal is to keep balance, self-organize, and maintain autonomy under challenge – and ultimately to survive [1]. As a result of this ongoing adaptation, over time, allostatic load can accumulate, and the overexposure to neural, endocrine, and immune stress mediators (see below) can have adverse effects on various organ systems, leading to the onset or progression of diseases [3–5,12].

Today, two molecules that play a major role in the (allostatic) stress response are thoroughly examined and their functions well-known. Each molecule represents one 'arm' of the response (the hypothalamic-pituitary-adrenal (HPA) axis and the sympathoadrenal medullary (SAM) system [13]). They are cortisol and norepinephrine (NE)/epinephrine [9,10,13,14]. More recently, other molecules involved have been detected, e.g, melatonin [15] and anandamide [16], and the connection of nitric oxide (NO) with the stress response has further been proposed [16–20].

The stress response represents a common physiological pattern – molecular pathways that are activated in situations that require behavioral adjustments (challenging situations). As these physiological changes play a role in stress-related disease processes [3–6], so does the 'relaxation response'. The relaxation response (RR) is defined by a set of integrated physiological mechanisms and 'adjustments' that are elicited when a subject engages in a repetitive mental or physical activity and passively ignores distracting thoughts [21,22]. These behaviors – seen in meditation, certain forms of prayer, TaiChi/ /Qigong, Yoga, autogenic training etc. – are associated with instantly occurring physiological changes that include decreased oxygen consumption or carbon dioxide elimination (i.e, reduced metabolism), lowered heart rate, arterial blood pressure, and respiratory rate [21–26]. Herbert Benson, who first described and pioneered the initial research studies involved in the RR, identified it as the physiological counterpart of the stress or *fight-or-flight* response [21,22]. At the time of this discovery, the technologies and concepts revolving around NO did not exist. Today, we can thus envision how the RR may work via NO signaling, thereby partially substantiating Benson's original observations, which still hold. Hence, we surmise that the innate RR functions as a protective mechanism against excessive stress (and may therefore protect against stress-related disease processes), antagonizing the potentially harmful effects of the stress response [21,22,27–29].

It has been demonstrated that biological processes, because of their interdependencies, usually are in/aim at a state of (dynamic) balance [1,2]. This may also be true for stress and RR pathways. Therefore, we surmise – as noted earlier [17] – that the physiological functions involved in the RR are connected with similar if not the same molecular pathways observable in the stress response: In the RR, cortisol [30,31], NE/epinephrine [21–24,32], melatonin [33], and NO signaling [17] (preliminary data: Stefano) are also involved. For example, it has been demonstrated that the sensitivity to NE can be reduced by the regular use and elicitation of the RR, thereby decreasing the sympathetic nervous system reactivity during stressful events or to stressful stimuli [24,32]. Moreover, serotonin and dopamine levels apparently are also elevated during the use of RR-techniques, e.g, in meditation [34,35].

Recently, underlying pathophysiological patterns and common pathways of stress-related disease processes have been investigated [3–6,36]. In particular, NO pathways have been examined, since they seem to play a major role in the stress (patho)physiology [6]. Common mechanisms apparently exist that indicate a connection between pathophysiological findings in stress-related diseases and physiological pathways described in the RR. For example, NO is involved in many pathophysiological and physiological processes and it is produced/increased in stress and the RR. Immediate release of NO described in the RR presumably is of constitutive nitric oxide synthase (cNOS) origin [17]. Thereby, cNOS is a calcium-dependent enzyme (reliant on intracellular calcium transients) that is constitutively and permanently expressed – either in immune, endothelial (eNOS), or neuronal (nNOS) cells – and produces NO at a low levels [6]. This 'basal' NO can yet be increased for a short time via additional cNOS stimulation in response to certain signals [37]. The brief 'extra' cNOS-NO boost, though only in the nano-molar range, can exert lasting and profound physiological actions, still evident after NO returned to basal levels [37]. Hence, cNOS-derived NO release is part of acute response mechanisms that occur in many biological states and tissues mediating these states [16–19,37,38].

As the RR results in a decreased sympathetic nervous system responsivity, counteracts the activity of NE/epinephrine or cortisol, and opposes the stress response (see above), NO also counteracts NE activity and sympathetic responsivity directly [16–19,37,39]. Additionally, NO inhibits the release of other monoamine transmitter molecules [39,40]. In this regard, these autoregulatory pathways appear to involve different signaling molecules (like opiates and endocannabinoids), explaining the complexity of the response as well as the difficulty in uncovering its biochemical processes in the first place [16,37,40].

We surmise that 'balance' is a key feature in stress and NO (patho)physiology – as in the RR. As described above, the RR opposes the stress response, and NO counterbalances NE activity. Moreover, cNOS inhibits/balances inducible nitric oxide synthase (iNOS) activity [41]. Thereby, iNOS is a calcium-independent enzyme that is prevalent in many tissues, yet only expressed 'on demand' in specific situations and under the influence of various signaling molecules (like proinflammatory cytokines) [36,37,41]. Following its induction, iNOS produces NO at higher levels (in the micro-molar range) after a latency period, and this NO release lasts for an extended period of time [37]. However, there obviously exists a close interdependency between the two different types of NO production (cNOS or iNOS-related). NO may actually represent a 'double-edged sword' [6,42], since small quantities produced by constitutive enzymes may predominantly mediate physiological effects, whereas the expression of iNOS – or the hyperstimulation of NOS – may lead to larger quantities of NO, a situation that may be associated with cytotoxic and detrimental effects of NO observed in various disorders if evoked inappropriately or for extended periods of time [6,36,42].

Many beneficial effects of NO (especially cNOS-derived NO) have been described in the literature, but, in parallel, the significance of NO for negative pathophysiological states and disease processes is also known (overview in: [6,36,38,43,44]). Therefore, NO apparently has the potential to exert 'good' or 'bad', ameliorating or detrimental effects on health/disease outcome, and the actual/specific clinical differences may reflect a distinct amount of NO release, i.e, type of NO pathway activated (e.g, constitutive versus inducible), different affected disease states (specific points in time where NO action sets in and becomes vital for the further development), severity of disease, and varying capabilities of organisms to balance, shift, and terminate the underlying molecular pathways [6,36].

With this work, we primarily want to examine the therapeutic suitability, applicability, and significance of RR techniques in reference to stress-related diseases: Does the implementation of RR techniques into stress management strategies and therapeutic medical settings (that are associated with stress-related diseases) represent a medically relevant strategy? Secondarily, we will investigate and discuss possible underlying molecular mechanisms and autoregulatory pathways that may be connected with the conceivable/proposed positive, i.e, beneficial or ameliorating, effects of RR techniques on the course of stress-related diseases. Are these possible common mechanisms part of the same superordinated (or: underlying) stress-related (patho)physiology – that either exerts positive or negative clinical effects and has been investigated recently (see above)? May the RR represent a tool that is able to preferably induce or facilitate the ameliorating capacities of stress-related molecular pathways? Do NO pathways in particular play an important role here?

2. THERAPEUTIC USE OF THE RELAXATION RESPONSE

2.1.Immunological diseases

Immunological diseases can be stress-related [3]. Further, they show a close connection with NO (patho)physiological pathways [6]. Moreover, RR techniques may be helpful in the treatment of immunological diseases, since significant (positive) therapeutic effects of the RR have already been demonstrated in association with disease processes that frequently occur in the immune system (see below).

2.1.1. Infectious diseases

The relevance of RR techniques, i.e, relaxation exercises or techniques that are able to elicit the RR, to fight immunological diseases has been shown in several studies (see below). In general, relaxation techniques are able to inhibit/reduce an acute (neurogenic, local) inflammation [45]. Moreover, meditation has been demonstrated to reduce harmful effects of stress (especially on the immune system) [46], since RR techniques counteract the stress response and decrease sympathetic nervous system responsivity [24,32], thereby opposing stress-related deleterious immunological processes [3,6,36]. The described capability of the RR to potential-

ly block NE action and increase (constitutive) NO may be crucial for its positive effects in this regard. In addition, Qigong, a combination of meditation, controlled breathing, and slow physical movement, is a RR technique that has been speculated to improve physical and mental health [30]. Here, immunological parameters may be important. Some of the responsible underlying mechanisms are already known, and they deal, in part, with different approaches to influence the immunological defense (e.g, they differ between stimulated and unstimulated conditions): Qigong is proposed to be capable of altering immunological functions, re-balancing cytokine production and cortisol levels, thereby counteracting stress-related deleterious hormone constellations [30] (also: see below). Taken together, the RR may represent a relevant therapeutic tool in certain immunological situations.

With specific reference to infectious diseases, evidence for the therapeutic relevance of RR techniques is still weak. However, these techniques are broadly in use, e.g, as a critical component of stress management or mind/body medical programs, and may especially be of importance for the treatment of various symptoms associated with infectious diseases [47,48]. In particular, the stress-related part of symptoms found in infectious diseases may represent a specific therapeutic focus for the application of the RR [3,6,48]. Hence, RR techniques are already in use in diverse therapeutic settings, e.g, medical symptom reduction (clinical) programs – derived from stress management programs [28,47–49] – to antagonize negative aspects of infectious diseases.

Stress may severely alter the onset and course of bacterial [50,51] or viral [52–55] infections, and this may be of particular significance in potentially deadly infectious diseases. Hence, stress is also of importance in acquired immune deficiency syndrome (AIDS) [55], as it, for example, further impairs memory deficits associated with the AIDS-related dementia complex by facilitating interleukin-1β (IL-1β) pathways [56]. Since the HIV infection is tied to the T cell population, to cytokine production and various anti-/proinflammatory processes connected with viral infection, stress-associated alterations in this area of the immune response may have a significant impact on AIDS itself [57].

The role of stress in infectious and parasitic diseases, though relevant for susceptibility, vulnerability, and progress of certain diseases [3,7,50,58], may not conceal the fact that an infectious agent or invader still has to be present. Yet, stress in combination with a predisposing and/or infectious environment may turn out to be deleterious in specific cases [55]. Further, chronic stress or imbalances in stress response pathways, for example, resulting from childhood traumatic events (like physical-emotional abuse) – not only increase the risk of getting depressed but also the odds of acquiring a sexually transmitted disease (like AIDS) later in life [59]. After all, RR techniques may be helpful here, since they, in general, counteract the detrimental effects that are related to an inadequate or deleterious activation of stress response pathways (see above).

In particular and in reference to HIV/AIDS, the relevance of the RR may primarily be linked to its ability to positively influence deteriorating symptoms, mental states, well-being, and disease-associated stress [60,61]. However, antiviral effects in relation to the known close connection between the stress response and the RR may also be considered, but detailed studies, especially those regarding such strong outcome parameters as survival, T cell count etc, are still missing. Yet, a possible connection between RR techniques, NO autoregulatory pathways that may become activated while the RR is elicited, and antiviral capacities of constitutive NO (involved in the RR) may represent an interesting field for future research [3,6,17].

2.1.2. Autoimmune disorders

RR techniques are useful in autoimmune diseases. For example, TaiChi and meditation, in combination with traditional medications, appear to be beneficial for patients with arthritis: the affected individuals seem to live 'better lives' and may have better long-term clinical outcomes [62]. Further, progressive muscle relaxation training may generally improve health-related quality of life, reduce joint tenderness and be superior to dynamic muscle training (exercise) in improving muscle function of the lower extremities in patients with inflammatory rheumatic disease [63]. In systemic sclerosis, RR techniques have been recommended as a complementary therapy, e.g, due to its reported ability to shorten Raynaud attacks [64]. Finally, the use of iNOS-inhibitors (or possible cNOS-activators, including the RR) has already been discussed as a potential therapeutic tool to fight the progress of autoimmune diseases (since their use may decrease inflammation) [65–67]. Yet, some doubt has to be cast on that idea because of the inherent complexity of autoimmune diseases. Nevertheless, the RR may still represent a qualified tool (see above).

2.1.3. Cancer/neoplasms

RR techniques have also been shown to be useful in the treatment of cancer (and related symptoms). Women with breast cancer who were going through neoadjuvant chemotherapy, surgery, and radiotherapy improved their immunological setting via practicing relaxation techniques/guided imagery: IL-2-activated killer lymphocyte (LAK cell) activity was increased, higher absolute numbers and percentages of activated T cells and lower levels of circulating tumor necrosis factor-alpha (TNF-alpha) were observed after intervention (compared to control) [68]. Additionally, relaxation frequency and self-rated imagery quality were positively correlated with natural killer (NK) cell activity [68]. Thus, RR techniques are obviously able to produce (positive) immunological changes that may be clinically relevant – even under immunosuppression (due to the treatment of large or locally advanced tumors, i.e, chemotherapy, radiotherapy etc.) [68]. Further, meditation appears to be associated with increased levels of melatonin, a mechanism that may be related to a preventive or even therapeutic potential in breast and prostate cancer [69]. In this regard, meditation seems to

be capable of enhancing the melatonin production of the pineal gland [46,70].

Taken together, relaxation techniques may have a beneficial impact upon cancer survival [71], play an active role in combating malignant tumor growth [46,69], and may finally be effective in reducing the harmful effects of stress associated with the onset and progression of malignant tumors [46,72].

2.1.4. Others

For some diseases with great clinical importance whose definite etiology still remains unclear and/or whose placing within the immunological domain is controversially discussed, stress, NO pathways, and RR techniques are also considered relevant. Thus, atopic dermatitis, psoriasis, celiac disease, and ulcerative colitis/Crohn's disease are all presenting a close association with stress [3,45,73–78], and NO, parallel to situations already described, plays a significant role in coupled protective or ameliorating processes [6,73, 79,80]. However, as seen before, NO pathways may also turn out to be detrimental in sporadic or specific situations, and here, most often iNOS and related proinflammatory cytokine-driven processes are of importance [6,36,80–87]. Similar to diseases examined previously, RR techniques may, again, offer a practical tool for potential clinical applications [75,88–90]. In particular, meditation and autogenic training (AT, see below) have impressively been shown to exert beneficial effects [88–90].

2.2. Cardiovascular diseases

Similar to immunological diseases (described above), cardiovascular diseases can be stress-related as well [4]. Further, they also show a close connection with NO (patho)physiological pathways [4,6]. Moreover, RR techniques may be helpful in the treatment of cardiovascular diseases too, since significant (positive) therapeutic effects of the RR have already been demonstrated in association with disease processes that frequently occur in the circulatory system (see below).

2.2.1. Hypertension

Stress plays a significant role in cardiovascular diseases [4]. Particularly in hypertension, stress appears to be very powerful – in a negative context [4]. With regard to RR techniques, we find a significant number of studies pointing to the usefulness of the RR as a treatment option in hypertension [28,45,60,91,92]. In particular (and besides more unspecific methods to elicit the RR), yoga [93,94], (Buddhist) meditation [93,95,96], Transcendental Meditation (TM) [97–99], progressive muscle relaxation (PMR) [93], and autogenic training (AT) [88,89,100] have been shown to be effective. Thereby, AT describes a relaxation technique based on autosuggestions ('self-hypnosis') and the perception of 'natural' relaxing processes facilitating a calm basic attitude [89,100]. Further, TM is a well structured relaxation technique that is associated with the Maharishi Vedic Approach to Health [101]. In this context, TM has been demonstrated to have a beneficial impact upon cardiovascular functioning (including blood pressure regulation) at rest and during laboratory stress in adolescents at risk for hypertension [98]. Additionally, TM may reduce an overall (elevated) cardiovascular risk and decrease carotid atherosclerosis [98,99]. Finally, Buddhist meditation, while capable of eliciting the RR, not only decreases systolic and diastolic blood pressure, but also heart rate, serum cortisol levels, respiratory parameters, and reaction time (whereas it increases serum total protein levels) [96].

RR techniques reduce the reactivity to psychologic/mental challenges (stress) [102], and it may be because of this characteristic that 'stressed' individuals present lower blood pressures (compared to control) when trained to elicit the RR [45,102]. Moreover, the RR may even (immediately) lower stress levels associated with elevated blood pressure [95]. The RR has further been shown to have positive effects on blood pressures in postmyocardial patients [103] and to reduce complications related to hypertension [104]. A combination of RR techniques with stress management training may even be more effective [102,104–108], and positive results achieved here may last for several years [107]. Thereby, the effect size seen in the mentioned combinatorial treatment seems to be comparable with the potential outcome of weight loss or even conventional drug therapy – successful interventions that have been used in studies focusing on prevention and control of hypertension [105]. However, RR training alone, i.e, without combining it with broader stress management strategies, has also been demonstrated to be as effective as drugs in fighting hypertension under suitable circumstances [94,100,105], and therefore, it may be considered a first-line future therapeutic choice in qualified cases [105]. Finally, even a combination of various RR techniques, e.g, yoga and AT, may yet be more successful than one technique practiced alone [93].

2.2.2. Atherosclerosis, endothelial dysfunction

Stress is associated with endothelial dysfunction and atherosclerosis in many ways [4]. For example, stress is capable of deteriorating endothelial functioning [4]. Similar to other (common) pathophysiological pathways described in stress-related diseases, NO also plays a crucial role in atherosclerosis and endothelial dysfunction [4,6,36].

RR techniques have been demonstrated to be helpful in the treatment and prevention of atherosclerosis and endothelial dysfunction. For example, Transcendental Meditation has been shown to reduce oxidative stress and lower serum levels of lipid peroxides, thereby reducing the risk of developing atherosclerosis [109]. Other studies have found a similar correlation by using different techniques [110–112]. Thus, RR techniques may be considered therapeutically relevant in atherosclerosis, and here (as illustrated), predominantly ameliorating NO pathways may be involved [6] (also: see 2.2.3.).

2.2.3. Coronary artery disease

In general, coronary artery disease (CAD) describes a special form of atherosclerosis that manifests itself in the coronary arteries. Thus, both fields overlap and what has been demonstrated for atherosclerosis may almost be transferred and adopted here. Yet, these common aspects will not be particularly focused upon in the following. Instead, some specific facts will be examined. However, expectedly, stress is also strongly associated with CAD [13,113,114].

RR techniques are successfully applied to the treatment of CAD. They help against angina pectoris episodes/ /symptoms or other complications of CAD [88,112, 115–117] and may also provide a greater sense of spiritual well-being that may, in turn, be important for the prevention or regression (slow-down) of CAD [118]. Effects may last over an extended period of time [118].

In a recent long-term study, Transcendental Meditation (TM) has been demonstrated to increase exercise tolerance, maximal workload, to delay the onset of ST-segment depression (test findings), and to significantly reduce the CAD patients' rate-pressure product [119]. Further, long-term yoga/'yogic lifestyle' seems to reduce even severe coronary atherosclerosis (coronary angiogram results) and to improve symptomatic status (reduction of angina episodes, decrease in the need of revascularization procedures), exercise capacity, and risk factor profile (reduction in body weight, serum total cholesterol, LDL, triglyceride levels – accompanied by an increase in HDL) [112,120]. Additionally, TaiChi training has been shown to facilitate better cardiorespiratory outcome/cardiac function following coronary artery bypass surgery: oxygen consumption (physical capacities) and peak work rate were improved [121]. Finally, medical stress management programs (including RR techniques) have also been described to be beneficial for CAD patients in the long-term, because these programs may reduce their risk for cardiovascular events, improve their risk factor profile, decrease atherosclerosis, and may be generally more effective than exercise training alone [99,108,122,123]. Moreover, stress management may also be capable of reducing the severity of mental stress-induced ischemia in CAD patients [122].

With regard to the positive outcome of stress reduction on CAD, RR techniques appear to be strongly relevant. Hence, TM has been shown to reduce 'stress' (that is, negative effects of stress) and decrease CAD risk factors, as well as cardiovascular mortality [99,119], and yoga may further prevent adverse consequences of coronary disease by improving resistance to stress [112,120,124].

2.2.4. Myocardial infarction

Myocardial infarction (MI) describes an ischemic event that is following an acute interruption of a sufficient coronary blood supply, usually going along with CAD, coronary spasm, thromboembolism, arrhythmia, trauma etc. [125,126]. Beyond doubt, stress has the potential to actively trigger this threatening cardiac event [127–129], and here, mental stress appears to be exceptionally potent [4,129–132]. In addition, mental stress obviously has a profound impact upon long-term cardiac events and outcome as well [4,122].

Since RR techniques, by nature, elicit the relaxation response and thereby counteract negative effects of activated stress responses, they may be helpful in the treatment of MI too (see above). In fact, RR techniques have – over time – increasingly and successfully been administered to MI patients and now have become a useful therapeutic tool in MI as well. Thereby, positive effects have been described for short- and long-term outcome [88,107,133], and the RR has further been shown to enhance the physical and psychic status of patients after rehabilitation (following MI) [134,135]. After all, relaxation therapy consequently appears to improve the cardiovascular long-term prognosis: it decreases future ischemic events and fatal MI [107].

2.3. Neurodegenerative diseases, mental disorders

Neurodegenerative diseases and mental disorders may – under particular circumstances – be related to the stress (patho)physiology [5]. This relationship may be of direct or indirect nature [5]. Further, these pathological states may show a connection with NO (patho)physiological pathways [6], and RR techniques may be helpful in the treatment of these diseases, since significant (positive) therapeutic effects of the RR have already been demonstrated in association with disease processes that are relevant to neurodegenerative diseases and mental disorders (see below).

2.3.1. Alzheimer's disease

In neurodegenerative disorders, similar combinations of detrimental influences of stress, NO-related (patho)physiological pathways, and possible benefits from RR techniques apparently exist [3,5,6]. The potential underlying mechanisms and interconnections may eventually resemble those found in other diseases (described above: immunological [3,6] or cardiovascular diseases [4,6]).

Stress, particularly chronic stress, obviously plays a (predominantly negative) role in neurodegenerative diseases, e.g, in Alzheimer's disease (AD) [5]. Therefore, we can expect to find positive effects of RR techniques – counteracting stress – in the scientific literature.

Positive and protective effects of RR techniques in neurodegenerative disorders have been documented. Besides directly counteracting the stress response (and thereby altering its possible deleterious impact upon neurons/neurodegenerative disorders), the RR may have further implications. It activates areas in the brain responsible for attention, motivation, and memory (e.g, anterior cingulate, hippocampal formation) and may also regulate other critical structures (e.g, amygdala) or facilitate the control of the autonomic nervous system, whereas the general brain activity/metabolism is decrea-

sed [136,137]. This specific pattern of activation may exert protective effects on the brain, although still a speculative prospect. However, such a protective mechanism could be related, for example, to a generally decreased production of metabolism-derived harmful by-products, i.e, oxidative stress. Finally, the RR seems to be effectively capable of improving concentration and cognitive function, e.g, memory [138]. We now also know that stress may reduce neurogenesis in the adult hippocampus [5,139,140]. Thus, the RR – and the reduction of stress with the RR – may be clinically relevant in AD and other neurodegenerative disorders.

2.3.2. Anxiety, depression

The possible association of anxiety and depression with stress has been discussed recently [5]. Further, NO pathways may also be involved in the (patho)physiology of anxiety/depression [5,6]. Again, a combination of stress and common underlying mechanisms – that include NO activity – seems to represent one possible road leading to detrimental disease processes. Here, RR techniques might qualify for therapeutic use (see below).

With reference to anxiety/depression, RR techniques appear to be highly recommendable. Many studies have been conducted that have shown a positive clinical outcome of the RR in connection with either anxiety [28,134,141,142] or depression [60,141–143]. In particular (regarding specific techniques), AT has been demonstrated to be effective in the treatment of anxiety [88,89,144] or depression [89]. Further, (mindfulness) meditation seems to be helpful in the treatment of anxiety as well [142,145], and meditation may also enhance melatonin levels – an effect that may lead to positive, health promoting results (as shown, for example, in depression) [70,146]. Additionally, Taoist meditation ('orientation') seems to be associated with less depression and hopelessness [147], and yoga may reduce levels of anxiety as well [61]. Moreover, yoga has been discussed as an effective alternative to drugs – even in certain kinds of depression [148]. Finally, TM has also been described to be helpful in the treatment of anxiety/depression [115,149,150]. Here, anxiolytic effects of TM may occur by promotion of an inhibitory (GABAergic = gamma aminobutyric acidergic) tone in specific areas of the brain [149]. Thereby, NO and endocannabinoid pathways may also be involved [16].

3. Discussion

The objective of this work has been to investigate a possible (therapeutic) connection between the RR and stress-related diseases. Further, common underlying molecular mechanisms and autoregulatory pathways have been examined. Hence, for the question of (patho)physiology and significance of RR techniques in the treatment of stress-related diseases, we have only analyzed peer-reviewed references.

Stress-related diseases are very common – and their number and dissemination are still increasing, especially in the 'western world' [2,7,151,152]. Hence, life-style, i.e, avoidable or self-inflicted/-controlled environmental and behavioral (challenging) stimuli, may play a significant role in stress-related diseases [2,7,123]. For example, according to latest evaluations, more than 80% of coronary heart disease and about 70% of colon cancer cases are potentially preventable by life-style modifications [123]. Thus, stress and life-style are of growing importance in the medical field [2,123,152], and therefore, it appears to be of particular interest to develop alternative or supplementary therapeutic strategies for the treatment of stress-related diseases – since present (previous) strategies obviously were unable to stop the mentioned negative trend. Such new approaches, aiming at beneficial life-style modifications or stress management, have been developed recently and are now part of professional stress management or mind/body medical programs [47,123]. RR techniques are an inherent, regular part of these programs [47].

Stress, i.e, (allostatic) stress responses, and a related secretion of norepinephrine, cortisol apparently cause or exacerbate many different disease processes [2–7,12,14]. Further, the relaxation response describes an innate response that acts as a physiological counterpart of the stress response (see above). Moreover, NO appears to be of importance for both (patho)physiological response pathways, and recently, first studies have been conducted that examined the actual connection between (constitutive) NO and the RR [17] (also: see above, Figure 1). Together with preliminary, unpublished observations (Stefano), these studies suggest that constitutive NO levels are increased in subjects who evoke the RR. Thus, beneficial NO pathways may help to explain why the RR has been demonstrated to be useful in the treatment of a large variety of stress-related disorders, since constitutive NO possesses many ameliorating and/or protective capacities [6] (Figure 1). However, NO is released in the RR and stress likewise and further has detrimental capacities itself, and these seem to be predominantly associated with higher NO levels and longer periods of elevated NO concentrations, both conditions that may be obtained by iNOS expression (described above). This inducible form of NO production may therefore represent an immanent part of possibly hazardous stress response pathways (Figure 1). Yet, in contrast, NO that potentially is produced as a result of an elicitation of the RR presumably is of cNOS-origin, i.e, constitutive NO, since its release appears almost immediately after the start of the RR exercise (see above; unpublished data).

Stressful stimuli that lead to the secretion of NE (and glucocorticoids, NO) may impede our evolutionarily developed natural healing capacities. Nevertheless, activation of the allostatic stress response (→sympathetic nervous system and HPA axis activation) still represents a primarily adaptive mechanism in appropriate situations (like acute disease processes and biological challenges), i.e, allostasis/dynamic balance. In chronic processes, however, a detrimental accumulation of allostatic load may occur (Figure 2). Thus, in more severe or chronic states of diseases, a more rigid and non-flexible regiment may take over (→'linear regulation'

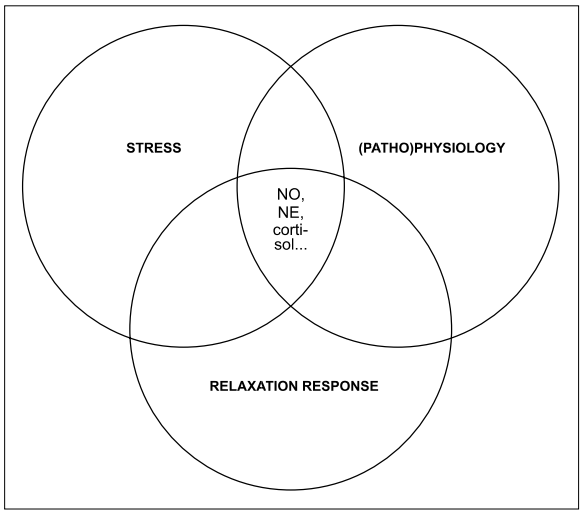

Figure 1. Stress, i.e, activated stress responses, and the relaxation response (RR) are associated with alterations in nitric oxide (NO), norepinephrine (NE), and cortisol levels. Other signaling molecules and autoregulatory components (e.g, corticotropin releasing hormone, serotonin, dopamine) also seem to play a role. Further, the RR counteracts the stress response, e.g, it decreases NE responsivity, presumably involving (constitutive) nitric oxide pathways. Thereby, the RR may positively influence stress-related pathophysiological disease processes. On a molecular basis, the impact of the RR upon NE and cortisol (re)activity (decrease), and a possible stimulation of constitutive NO release, may represent a crucial step for ameliorating effects described in connection with the therapeutic use of RR techniques. References: [3–6] (also: see text).

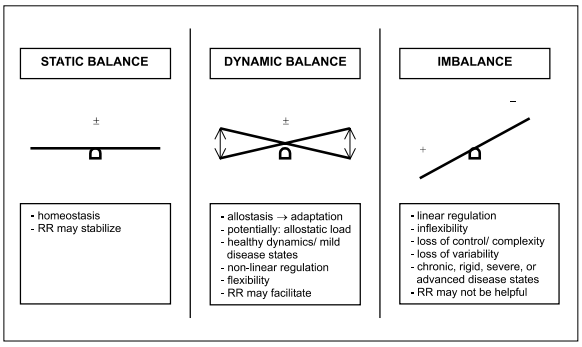

Figure 2. Balance is 'key' in stress (patho)physiology, including associated nervous system activity and nitric oxide signaling, and relaxation response (RR) pathways. Left: In a state of static balance (homeostasis), no adaptations are necessary. Thus, allostatic load can not accumulate. RR techniques may stabilize this state, although, it rather represents a theoretic construct, since life and biological processes related to life usually are not of a static nature. Middle: In a state of dynamic balance, homeostasis (here: a 'steady state') is possible as well, but it is achieved via activation of allostatic (stress) response pathways, leading to adaptation. The system is characterized by a high degree of flexibility, as seen in healthy subjects or mild disease states. However, successful adjustments may still yield/promote allostatic load. Acute disease processes or acute stress (bearable/adequate amount of 'challenge') may successfully be processed, and RR techniques may facilitate this state. Right: In a state of imbalance, linear or non-flexible 'dynamics' may have taken over. This state usually is related to severe, advanced, or chronic diseases. Homeostasis is impossible. Yet, organisms may nonetheless – and unsuccessfully – try to adjust, eventually leading to a strong, i.e, disastrous, accumulation of allostatic load (possible: vicious circle). RR techniques may not be sufficient anymore to reverse deleterious, pathophysiological disease processes or re-balance the system. However, RR techniques may still be capable of reducing symptoms or decreasing negative by-effects of a disease or its treatment. References: see text.

[153,154]). NO may be involved, but here, the detrimental effects of (inducible) NO may play a more significant role than the ameliorating capacities [6]. Additionally, in more chronic situations, an organism may become more vulnerable or susceptible to negative aspects of activated stress response pathways, and a healthy state of (dynamic) balance may be 'out of sight' [1,6,17]. In contrast, in less rigid, less severe, earlier disease states, flexibility may still be possible and NO may eventually be helpful, predominantly via its constitutive pathways [6] (→'non-linear regulation', physiological complexity [153,154]). This state may be facilitated via RR techniques (Figure 2). Interestingly, recent studies seem to underline this concept:

The effects of RR techniques on immunological parameters differ between stimulated and non-stimulated conditions [30]. That is, in accordance to the 'need' of the organism/cell culture, RR techniques may be able to increase or decrease the immune or stress response, thereby keeping/facilitating balance. In unstimulated cultures of peripheral blood cytokine-secreting cells, Qigong practice (of the blood donor) has been demonstrated to lower the immunological reactivity, whereas in lipopolysaccharide-stimulated cultures, immunological pathways (here: type 1 cytokine production) have been shown to be activated [3,30]. Further, RR techniques may be able to decrease blood levels of the stress hormone cortisol in healthy subjects, and here, concomitant changes in numbers of cytokine-secreting cells may also occur [30,96]. Thus, in moderate disease states (or in healthy subjects), RR techniques may facilitate balance-orientated protective functions. Yet, under severe conditions, the RR may not serve as a suitable therapeutic tool or decrease symptoms to a certain degree only (Figure 2). Therefore, RR techniques may be particularly of importance in association with primary (or secondary) prevention.

Taken together, the RR has been shown to be an appropriate and relevant therapeutic tool to counteract several stress-related disease processes and certain health-restrictions, particularly in immunological, cardiovascular, and neurodegenerative diseases/mental disorders (observed here). Further, shared – i.e, analogous – underlying molecular mechanisms apparently exist that may represent a functional connection between the stress response, pathophysiological findings in stress-related diseases (especially regarding NO pathways),

and physiological changes/autoregulation described in the RR [3–6] (also: Figure 1). Here, constitutive or low-output NO production may be involved in a protective or ameliorating context, whereas inducible, high-output NO release may enhance detrimental disease processes [6]. NO therefore may hold ambivalent capacities: Small quantities and pulsatile releases produced by cNOS may mediate physiological effects, whereas iNOS expression (or a 'chronic'/static overstimulation of cNOS) may lead to large quantities or constantly and pathophysiologically elevated levels of NO, a situation that may be associated with cytotoxic or negative NO effects detectable in various disorders [6,36,42]. Stress response and NO activity/pathways have to be coordinated and balanced [6] (also: Figure 2). Hence, RR techniques may support/be dependent upon the low-output NO pathways, since these techniques seem to facilitate constitutive NO production, thereby possibly initiating beneficial functions to counteract stress-related diseases and re-balance autoregulatory signaling processes. Further, regular elicitation of the RR may stabilize once obtained/achieved positive results (Figure 2). However, the proposed link between RR techniques and ameliorating, i.e, constitutive, NO pathways – beneficial in stress-related disease processes – still is of a more speculative nature. Future studies will additionally have to examine this relationship to confirm the (patho)physiological bridge, stated here, between stress-related diseases states and the undoubtedly relevant therapeutic capacities of RR techniques in the treatment of these conditions. Such studies will eventually be able to further elucidate the question, which other signaling molecules may be of importance in this complex setting: A participation of melatonin, serotonin, dopamine, and endocannabinoid signaling has already been detected or discussed in stress/RR (see above). Particularly the latter autoregulatory molecule(s) may eventually help to better understand and complete the (patho)physiological picture drawn by phenomena observed in the RR and their therapeutic use in stress-related diseases [16,17].

4. Conclusions

In this speculative review, we primarily examined the therapeutic suitability, applicability, and significance of RR techniques in reference to stress-related diseases. Clearly, the implementation of RR techniques into stress management strategies and therapeutic medical settings associated with stress-related diseases represents a clinically relevant strategy. Further, possible underlying molecular mechanisms and autoregulatory pathways that may be connected with the positive effects of RR techniques on the course of stress-related diseases may, for example, involve cNOS-derived NO pathways. Moreover, certain (patho)physiological analogies amongst various stress-related diseases – and effects described in the RR – may prevail. Hence, the RR may be capable of facilitating the ameliorating capacities of physiological (stress-related) molecular pathways and, in particular, constitutive NO pathways apparently play an important role here.

In more severe or chronic states of diseases, NO also is involved. However, a more rigid regimen may have taken over. Here, the detrimental effects of iNOS-derived NO may play a more significant role than the ameliorating capacities. In less rigid, less severe, and earlier states of diseases, however, flexibility of biological processes may still be possible to a greater degree, and NO effects/pathways may predominantly be helpful, i.e, by stimulation of their constitutive components. This latter state may specifically – or generally – be facilitated and supported via the RR. Yet, when chronic stress or an overwhelming acute stressor/stimulus occurs, and further, when an underlying deteriorating predisposition becomes important, a loss of balance or control may lead to more deleterious processes – or even to a disease-promoting vicious circle. Here, the RR may not be effective anymore. After all, cNOS-derived NO may represent a crucial and common molecular component that may underlie the beneficial therapeutic influences exerted by RR techniques on the course and treatment of stress-related diseases. Future studies will provide us with a more detailed and specific knowledge.

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