



# Paradoxical strategy for treating chronic diseases where the therapeutic effect is derived from compensatory response rather than drug effect

Anthony J. Yun<sup>a,\*</sup>, Patrick Y. Lee<sup>a</sup>, Kimberly A. Bazar<sup>b</sup>

<sup>a</sup> Department of Radiology, Stanford University, 470 University Avenue, Palo Alto, CA 94301, USA

<sup>b</sup> San Mateo Medical Center, USA

Received 15 September 2004; accepted 17 September 2004

---

**Summary** Reversing chronic conditions remains an elusive goal of medicine. The modern medical paradigm based on blocking overactive pathways or augmenting deficient pathways offers symptomatic benefit, but tolerance to therapy can develop and treatment cessation can produce rebound symptoms due to compensatory mechanisms. We propose a paradoxical strategy for treating chronic conditions based on harnessing compensatory mechanisms for therapeutic benefit. Many current drugs may be repurposed for a paradoxical indication where the therapeutic effect is derived from compensatory response, rather than drug effect. For example, although exercise is associated with acute adrenergia, paradoxical downregulation of baseline sympathovagal ratio occurs as a remodeling response. For conditions that manifest chronic sympathetic bias such as cardiovascular diseases, judicious administration of adrenergic agonists may induce compensatory downregulation of baseline sympathovagal ratio. The concept may generalize to many other diseases, especially those involving pathways which exhibit strong homeostatic tendencies such as the neurologic, immune, and endocrine systems. Careful consideration of chronobiologic features is necessary to optimize dosing strategies for modulating compensatory responses, and eccentric dosing schedules, shorter-acting formulations, or pulsatile delivery may be desirable in some cases. To what extent the effect of desensitization to current therapy is mistaken for disease progression in conditions such as diabetes, myopia, depression, and hypertension warrants investigation. The merits of combining behavioral and drug therapies such as diet-insulin therapy for diabetes and exercise- $\beta$ -blockade for cardiovascular disease should be revisited since there is a risk for exacerbating the underlying dysfunction. The reduced dynamic range of various environmental experiences and the tendency to revert to the mean through medical intervention, thermoregulation, and other modern lifestyle changes may play under-recognized roles in human diseases. Perhaps alternating agonists and antagonist may exercise the entire dynamic range of pathways and improve health.

© 2004 Elsevier Ltd. All rights reserved.

---

## Hypothesis

Reversing chronic conditions remains an elusive goal of medicine. The modern medical paradigm based on blocking overactive pathways or aug-

---

\* Corresponding author. Tel.: +1 650 387 6667/248 8885; fax: +1 650 325 5028.

E-mail address: [ayun@stanford.edu](mailto:ayun@stanford.edu) (A.J. Yun).

menting deficient pathways offers symptomatic benefit, but tolerance to therapy can develop and treatment cessation can produce rebound symptoms due to compensatory mechanisms. Tolerance is defined as either a situation requiring dose escalation to maintain the therapeutic effect or a decreasing response to repeat similar dosing. A classic example is the use of  $\beta$ -blockers for hypertension, in which abnormally high sympathovagal ratio represents one of the therapeutic targets. With time, chronic sympathetic blockade with  $\beta$ -blockers may induce compensatory elevation of sympathovagal ratio, thereby creating higher dosing requirements and the potential for rebound hypertension upon cessation [1,2].

We propose a paradoxical strategy for treating chronic conditions based on harnessing compensatory mechanisms for therapeutic benefit. Our counterintuitive paradigm suggests that many current drugs may be repurposed for their paradoxical indication where the therapeutic effect is derived from the compensatory response they provoke, rather than the drug effect. For the purposes of discussion, we specifically focus on the potential use of sympathetic *agonists* for the treatment of diseases involving chronic sympathetic bias. The concepts of this specific case may generalize to many other areas of medicine.

## Evidence

### Autonomic dysfunction and diseases

Separately identifiable named medical conditions number in the thousands. However, the constitutional symptoms that manifest them are relatively few in number and typically involve the autonomic system [3]. Many diseases, including the compendium of conditions associated with aging, are associated with end-organ dysfunctions compatible with sympathetic bias [4]. Why adrenergic behavior emerges among end-organs is unknown, but withdrawal of central autonomic regulation leading to unmasking of intrinsic sympathetic bias in end-organs is one hypothesis [4]. Early evidence suggests that autonomic nerves may regress [4], relinquishing their regulatory hegemony over target organs [5]. Indeed, parasympathetic [5] and sympathetic receptor hypersensitivity [6–13] are common features of many diseases, especially those associated with aging, and may reflect upregulation of post-synaptic autonomic receptors in target organs as a compensatory adaptation to lost signal input.

The autonomic receptor hypersensitivity during aging and disease and the dysfunctional behavior of target organs that ensues are not unlike those seen in denervation injury [8,9]. Thus, the hyperadrenergic behavior of target organs during aging may reflect a regression to their intrinsic state after emancipation from central regulation. The hyperadrenergic behavior of all transplanted organs, which are initially electrically isolated from host autonomic regulation, supports this view [4]. From a teleologic perspective, it is intuitively appealing to speculate that target organ functions were acquired during evolution in their “agonal” state, with the central nervous system generally playing an inhibitory role. It is widely known that central nervous injury often manifests as peripheral hyperexcitation. Integrating these ideas, we postulate that regression of central autonomic control and simultaneous unmasking of end-organ hyperadrenergia accompanied by compensatory upregulation of autonomic receptors are emergent properties of many diseases, particularly those associated with aging.

Current treatment paradigms may need to be revisited in light of this framework. The important role of sympathetic overactivity in diseases is increasingly becoming recognized in many conditions including hypertension, acute coronary syndrome, and congestive heart failure. The dominant trend today in the treatment of such conditions is adrenergic blockade, typically with a  $\beta$ -blocker.  $\beta$ -Blockers have been shown to provide substantial clinical benefit in a number of large randomized clinical trials [14]. However, tolerance to therapy requiring dose escalation develops over time and patients can become refractory [15]. Furthermore, rebound hyperadrenergia occurs upon cessation of therapy [1,2]. These phenomena suggest that adrenergic blockade is far from the ideal solution.

Tolerance and rebound associated with  $\beta$ -blocker use suggest a compensatory host response. Drug holiday between doses of  $\beta$ -blockers can resensitize patients to therapy in systemic hypertension and ocular hypertension [16–18]. The elements of the compensatory response are not fully understood, but increased sensitivity of the adrenergic pathway with or without downregulation of the parasympathetic pathway are likely culprits. The data supporting this view is somewhat controversial. While most authors have observed increased adrenergic sensitivity in response to  $\beta$ -blocker therapy [2], some have noted adrenergic downregulation after chronic exposure to  $\beta$ -blockers [19]. The discrepancy could be attributed to many factors including specific drug used and the chronobi-

ology of dose administration. Overall, while  $\beta$ -blockers provide objective clinical benefit in many diseases, they appear to elicit a compensatory response that may potentially exacerbate the underlying cause of the disease by further enhancing adrenergic hypersensitivity [2].

### Paradoxical use of adrenergic agonists for chronic sympathetic bias

We propose a paradoxical idea that judicious administration of sympathetic agonists may be useful in the treatment of conditions that manifest chronic sympathetic bias. The experimental pharmacologic evidence supporting our proposal is scant. How can we justify augmenting the sympathetic pathway when hyperadrenergia is the problem we are trying to correct? The justification lies in the recognition that chronic sympathetic bias in many diseases may be an intrinsic end-organ phenomenon accompanied by sympathetic receptor hypersensitivity [4,5]. Whereas  $\beta$ -blockers may induce further compensatory increase in chronic adrenergic hypersensitivity,  $\beta$ -agonists may induce a compensatory *decrease* in chronic adrenergic hypersensitivity and a compensatory *increase* in vagal function.

An intriguing piece of evidence is the additional benefit of administering a  $\beta$ -agonist during holiday periods between timolol doses in the treatment of ocular hypertension [17,18]. That such  $\beta$ -agonist administration augments the benefit of  $\beta$ -blockade could be attributed to the promotion of a compensatory vagal response by the  $\beta$ -agonist. Another interesting piece of evidence is the unexplained down-regulation of airway inflammation by the chronic administration of a long-acting  $\beta$ -agonist [20]. The pro-inflammatory effects of adrenergia are well-described elsewhere and aging is generally accompanied by both phenomena [4,21,22]. How can we reconcile these last two statements? The answer may lie in a subtle but important distinction between these scenarios. The chronic sympathetic bias of aging may be a post-synaptic, intrinsic end-organ phenomenon. One such end-organ system is the lymphoid system. The adrenergic behavior of the lymphoid system is the production of T helper (Th)2 pro-inflammatory cytokines [4,21,22]. The chronic administration of  $\beta$ -agonists, on the other hand, can be seen as a central pre-synaptic phenomenon. As such, chronic  $\beta$ -agonist administration may induce compensatory *downregulation* of the post-synaptic adrenergic receptor population and function in the end-organs. The decreased inflammation seen in chronic  $\beta$ -agonist administra-

tion may reflect the anti-adrenergic (or pro-vagal) remodeling of the lymphoid system.

### Evidence from exercise

The best supporting evidence for our paradigm comes from exercise. It is well-documented that enhanced efferent vagal activity increases heart rate variability (HRV) whereas sympathetic stimulation decreases HRV [23], and low HRV is associated with an increased risk of cardiac events and mortality [24,25]. Extensive evidence indicates that exercise strengthens vagal tone and increases HRV [26–28], suggesting that repeat sympathetic challenge may enable vagal rehabilitation and reduce sympathovagal ratio. Even a single episode of submaximal exercise appears to increase HRV and promote parasympathetic function [27]. While the possibility that exercise may lower sympathovagal ratio through pathways independent of the sympathetic stimulation cannot be excluded, the evidence supports the hypothesis that sympathetic activity of exercise may induce compensatory downregulation of baseline post-synaptic end-organ adrenergic function and relative upregulation of vagal function. Exercise exemplifies our biologic rehabilitation hypothesis, and we propose that the autonomic remodeling response to exercise may be similarly elicited by judicious therapeutic administration of agents that *promote* adrenergia to treat chronic disorders of sympathetic bias.

Potential safety issues related to acutely promoting adrenergia must be addressed [29]. Acute adrenergia plays a role in the precipitation of cardiovascular events including sudden death [29,30], especially in patients who have chronic sympathetic bias. Substantial controversy exists as to whether the use of  $\beta$ -agonists in asthma is independently associated with an increased risk of death [31,32]. To be safe, however, we believe that initiating therapy with a low dose of short-acting sympathetic agonists, then gradually building up the dose in crescendo fashion, may be prudent. The rationale is similar to starting with low-level exercise before advancing to more ambitious exertion in patients with a high-risk cardiovascular profile.

Our hypothesis has implications for the question of whether additional cardioprotective benefits accrue to patients who exercise while taking  $\beta$ -blockers [33,34]. Patients on  $\beta$ -blockers initially cannot raise their adrenergic response sufficiently to meet the cardiovascular demands during exercise and may fatigue quickly [35], an effect that can be reversed with atropine [36]. Patients in this group

usually report improved tolerability to exercise over time as their body accommodates. It is plausible that accommodation occurs as a result of sympathetic upregulation to compensate for an insufficient adrenergic response during exercise. Confirming this view is the evidence that baseline serum norepinephrine levels may increase after initiating metoprolol in exercising patients [37], perhaps indicating sympathetic compensation to chronic blockade. Sympathetic compensation may also explain why the theoretical risk of administering  $\beta$ -blockers to asthmatic patients remains unsubstantiated empirically [38]. Chronic  $\beta$ -blocker use is associated with impotence, anxiety, worsening diabetes, and insomnia, which may be paradoxical indicators of vagal withdrawal and adrenergic excess [39–41]. Furthermore, exercising patients who are on  $\beta$ -blockers tend to have markedly elevated levels of natriuretic peptides as compared to those not on  $\beta$ -blockers [42]. The authors of the study concluded that the higher levels of natriuretic peptides constitute a protective mechanism [42], but the findings could also be interpreted as a signal that additional adrenergic stress may be present in the cardiovascular system. If this line of thinking holds, then withdrawing  $\beta$ -blockers from regularly exercising patients may unmask sympathetic hypersensitivity that had further increased in compensation during  $\beta$ -blockade. Health hazards of sympathetic overactivity are increasingly being elucidated [3], and ironically,  $\beta$ -blockers and exercise, which independently promote vagal tone, may exacerbate sympathetic hypersensitivity and pose greater health risks when combined in the same patient. Importantly, exercise-related ischemia in patients on  $\beta$ -blockers is a strong predictor of eventual fatal cardiovascular events [43].

### Other conditions associated with compensatory response to therapy

The concepts discussed in previous sections may generalize to many other areas of medicine. The opportunity is particularly intriguing in systems which exhibit substantial tolerance and tachyphylaxis during therapy. For reasons that are unclear, there is an interesting pattern among psychotropic medications to induce tolerance, and drug holidays are frequently required to counter compensatory mechanisms and reestablish sensitivity. Tolerance to baclofen occurs in the treatment for spasticity [44–46] and is thought to be related to a persistent occupation of  $\gamma$ -aminobutyric acid (GABA)<sub>B</sub> receptors by baclofen resulting in a decreased receptor

population [45,47,48], reduced sensitivity [48], or impaired interaction with other receptor systems [49]. Drug holiday appears to resensitize such patients [50]. Other examples where drug holiday has shown benefit include opioids for pain [51–54], L-dopa and bromocriptine for Parkinson's disease [55–59], selective serotonin reuptake inhibitors (SSRIs) for depression [60], haloperidol and chlorpromazine for schizophrenia [61,62], nitrates for hypertension [1,2,63–65], and anti-epileptic drugs for seizures [66], and tandospirone for the treatment of Machado-Joseph disease [67].

Immune and endocrine disorders also often exhibit strong compensatory responses, and drug holidays or pulsed dosing strategies, which generally involve high doses given in short bursts, are sometimes used to counter these effects [68]. Examples include prednisone, growth-hormone releasing hormone (GHRH), erythropoietin, and estrogen therapies [69–79]. Pulsed prednisone is used for various immune and oncologic disorders and may offer a superior efficacy or a decreased side effect profile compared to conventional administration [72–79]. Pulsed estrogen is used to mitigate the side-effects related to hormone replacement therapy [69,70]. Pulsed administration mirrors endogenous chronobiologic patterns that characterize many natural cellular and organismal functions. Examples include cyclical pulsatile secretion of insulin [80,81] and various hypothalamic hormones [82,83]. The importance of temporal resolution is reflected in the observation that pulsed administration can produce interesting, somewhat unexpected effects. For instance, pulsed estrogen has been proposed to reduce undesirable hormonal stimulation of breast and uterine tissue [69], but interestingly, such pulsing appears to increase stimulation of breast cancer cells [84]. Pulsed administration has been proposed to reduce bone demineralization associated with glucocorticoids, but substantial bone demineralization [73] and insulin resistance [74] still occur in these patients. Pulsed GHRH, which is thought to promote growth, can actually reduce growth rate in chickens [85]. Continuous parathyroid hormone (PTH) exposure, which occurs in conditions such as hyperparathyroidism, stimulates osteoclast formation and bone death while intermittent PTH stimulates osteoblast activity and bone growth. These findings suggest that careful considerations of chronobiologic dimensions to therapy are in order.

The differential response to acute and chronic therapy is similar to the paradoxical responses to acute and chronic endogenous stimuli. For instance, the immune response to sepsis behaves in opposing patterns during the acute phase, which

is associated with upregulation of tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1, IL-6, and interferon- $\gamma$  [86], and the chronic phase, which is associated with downregulation of immune function [87]. The hypothalamic-pituitary (HP) axis also shows differential response to acute versus chronic stress. The acute HP neuroendocrine response consists of activated anterior pituitary function with increased levels of hormones such as thyrotropin-releasing hormone, gonadotropin releasing hormone, and growth hormone releasing peptide [88] whereas chronic stress uniformly reduces pulsatile secretion of anterior pituitary hormones [88–90]. Notably, endocrine dysfunctions with the loss of hypothalamic feedback control, loss of pulsatility, HP axis downregulation, target-organ receptor downregulation, desensitization, and hormone resistance characterizes not only sepsis but also menopause, aging, and death [86–95]. Simply replacing a deficient hormone may not only fail to correct the problem, but may even cause deleterious effects [89]. Rehabilitating these pathways by restoring various HP and target organ functions in the proper temporal pattern and pulsatility represents a potentially exciting area of future research.

Chronic diseases which exhibit strong compensatory tendencies are compelling candidates for our paradoxical treatment model. Drugs which have the opposite function to current therapies may be tested for their ability to rally the compensatory response for therapeutic purposes. In most cases, the empirical pharmacologic evidence to support our hypothesis is very difficult to find, in part due to the counterintuitive nature of the idea. Further understanding of the temporal dimensions of physiology, cell biology, and molecular biology may yield new clues to the pathogenesis of diseases and treatment methodologies.

## Embodiments

The concept of temporarily exacerbating an underlying dysfunction to ameliorate it long-term raises safety issues which must be addressed. The benefits of such a strategy must be weighed against the risk posed by compounding the underlying dysfunction. As is the case with exercise, however, short challenges in escalating doses can probably safely induce a paradoxical effect in the long term. Short-acting formulation, pulsed administration, and intermittent dosing may offer a better risk–benefit profile compared to chronic, long-acting dosing when it comes to paradoxical therapeutic strategies. The exact temporal pattern of adminis-

tration and withdrawal is likely to be critical, and the optimum pulsatility of administration as well as dose escalation and weaning tactics remain to be explored. For instance, the regular daily use of long-acting  $\beta$ -agonists has been shown to induce more compensatory tolerance than intermittent dosing [96]. Regular administration patterns should be compared with irregularly irregular patterns of pulses as to which can produce more robust and durable compensatory rehabilitation of a dysfunctional pathway. The latter eccentric pattern may be more successful in producing a balanced compensatory response. Sometimes, the ideal target for a compensatory response induction may reside in remote parts of the biologic feedback loop. For instance, using a therapeutic strategy to negatively regulate the feedback loop at the hypothalamic level may produce an augmented efferent response such as enhanced end-organ endocrine or autonomic output. Targeting such upstream centers of pathway regulation may be particularly desirable since the resulting compensatory output is more likely to exhibit a natural pulsatility and temporal profile. Another potential variation on the theme is alternating administrations of agonists and antagonists to fully exercise the entire dynamic range of the compensatory mechanism. The ideal parameters likely will vary by drug, the pathway being rehabilitated, and the individual patient, and will need to be determined by future research.

Given the potential need for more frequent dosing and possibly a more irregular pattern of dosing, patient compliance may emerge as an issue and may necessitate the development of novel drug-delivery methodologies. For instance, patches, depots, pumps, and automated drug delivery devices that can deliver drugs in selected patterns may be useful. In addition to varying the dosing schedule, it may be useful to vary the drug amount over time and to tailor the therapy to changing conditions. Closed-loop drug delivery systems that use software to adapt to measurable host parameters intelligently would provide additional advantages. For instance, a drug delivery device that can deliver a tailored dose of an appropriate  $\beta$ -agonist in response to a diagnostic measure of HRV may be useful.

## Implications

The concept of rehabilitating diseased pathways by harnessing intrinsic compensatory mechanisms may represent a fundamental paradigm shift in modern therapeutics. Many current drugs may be

repurposed for a paradoxical indication where the therapeutic effect is derived from the compensatory response, rather than the drug effect. The autonomic system was chosen as a model for discussion because tolerance and rebound are common phenomena associated with  $\beta$ -blockers and because autonomic dysfunction is increasingly implicated in the pathogenesis of a wide range of common disorders [4]. Beyond the autonomic system, many other potential applications of our paradigm are apparent. The opportunity is particularly beckoning in systems which exhibit tachyphylaxis such as the neurologic, endocrine, and immune systems. Could counterintuitive judicious use of antagonists to current therapies rehabilitate neurologic conditions such as Alzheimer's disease, schizophrenia, Parkinson's disease, and pain disorders? Could daytime administration of melatonin *antagonists* help treat nighttime insomnia? After all, daytime exposure to bright lights, which suppresses melatonin, appears to aid sleep at night, perhaps due to nighttime upregulation of melatonin in response to the daytime challenge [97–99]. Why certain pathways are particularly prone to tolerance and rebound is itself an interesting teleologic question. The adaptive purpose of the resiliency of neurologic and endocrine pathways in which the baseline is constantly reset by compensatory forces is unknown and could represent an epiphenomenon related to some other useful function. Compensatory forces in areas outside the neurologic and endocrine systems may also be harnessed to treat diseases. Could pro-inflammatory agents downregulate inflammation? Can  $\beta$ -blockers be used to treat asthma? Is there a way to use growth factors as *agonists* to fight cancers? Could myopia be treated with gradual hyperopic challenges rather than refractive correction, which offers short-term improvement in vision but may undermine compensatory mechanisms in the long run? Could hypertonic hydration, rather than a low-salt diet, paradoxically improve hypertension by reducing sympathetic tone [100]? While admittedly speculative, tinkering with such counterintuitive concepts may lead to surprising new methodologies to treat conditions.

The dynamic range of various environmental experiences has substantially dampened in modern times due to medical intervention, technologic innovation, and ecological changes. Reduced day–night light variation due to indoor living and electricity, reduced thermal range due to heat and air conditioning systems, reduced hunger–satiety oscillations from snacking and 24 h tube feeds, reduced visual focal length variation due to emergence of books and computers are among the

countless environmental features that have narrowed in dynamic range during modern times. To what extent the loss of dynamic range of physiologic functions plays a role in the pathogenesis and progression of diseases warrants further investigation. Perhaps the effect of desensitization to current therapy is mistaken for disease progression in conditions such as hypertension, depression, myopia, and diabetes. For example, SSRIs are widely used to treat depression, but biologic dependence is common and careful weaning is required to avoid discontinuation syndrome (DS), which is characterized by rebound depression, dizziness, and gastrointestinal disturbances [101–103]. Even patients remaining on therapy are at a risk for increased risk of suicide [104]. Could depression instead be treated with judicious administration of serotonin pathway *antagonists*? Earlier we discussed the possibility that combining exercise and  $\beta$ -blocker therapy may worsen adrenergic hypersensitivity and tachyphylaxis by inducing compensatory upregulation of the sympathetic system to meet the cardiovascular demands of exercise in a  $\beta$ -blocked state. Applying the same theory, does acute grief after tragedy adaptively upregulate the serotonin pathway and elevate baseline degree of happiness, and if so, does SSRI administration during tragedy undermine the compensatory benefits of acute grief and possibly further dampen baseline serotonin function? Are current diabetic management strategies *inducing* downregulation of  $\beta$ -cell function, which can be mistaken for disease progression? Does combining exercise with insulin therapy offset the compensatory response and possibly reduce baseline insulin sensitivity? Instead, could insulin *antagonists* be used to resensitize patients to insulin and treat diabetes?

The health merits of alternative medical practices, particularly those that expand the dynamic range of environmental experiences, can be reconsidered in light of our hypothesis. Hot sauna, sometimes alternating with cold baths, is a popular activity among Norwegian and other populations. Since thermal gradients, hot or cold, can acutely activate sympathetic activity [91,105], it is plausible that saunas and cold baths can “exercise” the autonomic system and strengthen it. Similarly, the benefits of acupuncture, meditation, yoga, and herbal therapies may in part be mediated through exercising the autonomic system. While chronic stress has many untoward health implications, popular activities that create an acute “adrenaline rush” including riding roller-coasters, watching horror movies, laughter, gambling [106], and ingesting caffeine may have beneficial health con-

sequences that remain to be explored. There may be a similar natural resonance to hunger–satiety oscillations, light–dark exposures, heat–cold variations, and sleep–wake cycles that optimally exercise various pathways. Yet there is a modern tendency to use technology to restore equilibrium, thereby reducing the dynamic range of biologic experience and possibly undermining the ability to respond to environmental disequilibria in the future. Modern medicine is largely built on this paradigm of pharmacologic reversion to the mean. The resulting tolerance to therapy that requires dose escalation and physiologic dependence do not serve as disincentives for drug companies. Patient compliance issues have led to a trend favoring extended-release formulations over short-acting formulations, but the resulting chronic intervention may be inconsistent with the subtle chronobiologic features of pathways and may even exacerbate the underlying system dysregulation. Our hypothesis portends a different trend in pharmacology: the development of drugs that require more innovative dosing, increase sensitization over time enabling dose reduction, and may cure the underlying chronic condition. Many current drugs may be repurposed for a paradoxical indication, possibly using shorter acting formulations that have previously been shunned due to patient compliance issues. Future research is needed to validate these and many other potential applications of our strategy.

## References

- [1] Tandon P, McAlister FA, Tsuyuki RT et al. The use of  $\beta$ -blockers in a tertiary care heart failure clinic: dosing, tolerance, and outcomes. *Arch Intern Med* 2004;164(7):769–74.
- [2] Brynne L, Paalzow LK, Karlsson MO. Mechanism-based modeling of rebound tachycardia after chronic l-propranolol infusion in spontaneous hypertensive rats. *J Pharmacol Exp Ther* 1999;290(2):664–71.
- [3] Yun AJ, Lee PY, Bazar KA. Many diseases may reflect dysfunctions of autonomic balance attributable to evolutionary displacement. *Med Hypotheses* 2004;62(6):847–51.
- [4] Yun AJ, Lee PY, Bazar KA. A new mechanism for diverticular diseases: aging-related vagal withdrawal. *Med Hypotheses* 2004, doi:10.1016/j.mehy.2004.07.010.
- [5] Golder M, Burtleigh DE, Belai A et al. Smooth muscle cholinergic denervation hypersensitivity in diverticular disease. *Lancet* 2003;361(9373):42–6.
- [6] Benowitz NL, Zevin S, Carlsen S, Wright J, Schambelan M, Cheitlin M. Orthostatic hypertension due to vascular adrenergic hypersensitivity. *Hypertension* 1996;28(1):42–6.
- [7] Araki K, Ueda Y, Kono I, Ookawara T, Kashima K. A case of neurogenic orthostatic hypertension. *Jpn J Med* 1991;30(5):446–51.
- [8] Kaplan NM. Two faces of sympathetic nervous activity: hypotension and hypertension. *Am J Med Sci* 1992;303(4):271–9.
- [9] Polinsky RJ, Kopin IJ, Ebert MH, Weise V. Pharmacologic distinction of different orthostatic hypotension syndromes. *Neurology* 1981;31(1):1–7.
- [10] Goldstein DS. Arterial baroreflex sensitivity, plasma catecholamines, and pressor responsiveness in essential hypertension. *Circulation* 1983;68(2):234–40.
- [11] Luck JC, Hoover RJ, Biederman RW, Ettinger SM, Sinoway UA, Leuenberger UA. Observations on carotid sinus hypersensitivity from direct intraneural recordings of sympathetic nerve traffic. *Am J Cardiol* 1996;77(15):1362–5.
- [12] Kenny RA, Traynor G. Carotid sinus syndrome—clinical characteristics in elderly patients. *Age Ageing* 1991;20(6):449–54.
- [13] Bunag RD, Tomita T, Krizsan D. Renovascular  $\beta$ -adrenergic hypersensitivity and hyperinsulinemia in rats with dietary-induced obesity. *J Pharmacol Exp Ther* 1990;255(1):325–32.
- [14] Yusuf S, Peto R, Lewis J, Collins R, Sleight P.  $\beta$ -Blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985;27(5):335–71.
- [15] Guirguis MS, Jamali F. Disease-drug interaction: reduced response to propranolol despite increased concentration in the rat with inflammation. *J Pharm Sci* 2003;92(5):1077–84.
- [16] Burnier M. Long-term compliance with antihypertensive therapy: another facet of chronotherapeutics in hypertension. *Blood Press Monit* 2000;5(Suppl. 1):S31–4.
- [17] Batterbury M, Harding SP, Wong D. Long-term drift and timolol therapy: possible role for pulsed therapy. *Int Ophthalmol* 1992;16(4–5):321–4.
- [18] Gandolfi SA. Restoring sensitivity to timolol after long-term drift in primary open-angle glaucoma. *Invest Ophthalmol Vis Sci* 1990;31(2):354–8.
- [19] De Blasi A, Pittana PL, Fratelli M, Garattini S. Reduction of  $\beta$ -adrenergic receptors can explain the lack of rebound effect after tertatolol withdrawal. *Am J Hypertens* 1989;2(11 Pt 2):257S–60S.
- [20] Abramson MJ, Walters J, Walters EH. Adverse effects of  $\beta$ -agonists: are they clinically relevant?. *Am J Respir Med* 2003;2(4):287–97.
- [21] Kassif Y, Rehany U, Rumelt S. Metoprolol responding uveitis. *Eye* 2004;18(1):41–3.
- [22] Gage JR, Fonarow G, Hamilton M, Widawski M, Martinez-Maza O, Vredevoe DL.  $\beta$ -Blocker and angiotensin-converting enzyme inhibitor therapy is associated with decreased Th1/Th2 cytokine ratios and inflammatory cytokine production in patients with chronic heart failure. *Neuroimmunomodulation* 2004;11(3):173–80.
- [23] Kollai M, Koizumi K. Reciprocal and non-reciprocal action of the vagal and sympathetic nerves innervating the heart. *J Auton Nerv Syst* 1979;1(1):33–52.
- [24] Tsuji H, Larson MG, Venditti Jr FJ. Impact of reduced heart rate variability on risk for cardiac events: The Framingham Heart Study. *Circulation* 1996;94(11):2850–5.
- [25] Tsuji H, Venditti Jr FJ, Manders ES. Reduced heart rate variability and mortality risk in an elderly cohort: The Framingham Heart Study. *Circulation* 1994;90(2):878–83.
- [26] Larsen AI, Gjesdal K, Hall C, Aukrust P, Aarland T, Dickstein K. Effect of exercise training in patients with heart failure: a pilot study on autonomic balance assessed

- by heart rate variability. *Eur J Cardiovasc Prev Rehabil* 2004;11(2):162–7.
- [27] Pober DM, Braun B, Freedson PS. Effects of a single bout of exercise on resting heart rate variability. *Med Sci Sports Exerc* 2004;36(7):1140–8.
- [28] Jurca R, Church TS, Morss GM, Jordan AN, Earnest CP. Eight weeks of moderate-intensity exercise training increases heart rate variability in sedentary postmenopausal women. *Am Heart J* 2004;147(5):e21.
- [29] Eisner MD, Abramson M, Bailey M et al. Inhaled  $\beta$ -agonists and death from asthma: revisiting the controversy. *Am J Respir Crit Care Med* 2001;163(6):1502.
- [30] Yun AJ, Lee PY, Bazar KA. Acute coronary syndrome and heart failure may reflect maladaptations of trauma physiology that was shaped during pre-modern evolution. *Med Hypotheses* 2004;62(6):861–7.
- [31] Crane J, Pearce N, Flatt A et al. Prescribed fenoterol and death from asthma in New Zealand 1981–1983: a case control study. *Lancet* 1989;1(8644):917–22.
- [32] Abramson MJ, Bailey MJ, Couper FJ et al. Are asthma medications and management related to deaths from asthma?. *Am J Respir Crit Care Med* 2001;163(1):12–8.
- [33] One on one. The  $\beta$ -blocker I take has slowed my heart rate, making it difficult to achieve my target heart rate when I exercise. Does this mean the exercise isn't doing me any good? *Mayo Clin Womens Healthsource* 2004;8(9):8.
- [34] Simon HB. I am a 46-year-old man with hypertension. I recently started taking Inderal for my blood pressure. I feel fine and my pressure is way down, but I can no longer get my pulse up when I work out on my treadmill or bike. Does that mean I won't benefit from exercise anymore?. *Harv Mens Health Watch* 1999;4(3):8.
- [35] Wonisch M, Hofmann P, Fruhwald FM et al. Influence of  $\beta$ -blocker use on percentage of target heart rate exercise prescription. *Eur J Cardiovasc Prev Rehabil* 2003;10(4):296–301.
- [36] Munagala VK, Guduguntla V, Kasravi B, Cummings G, Gardin JM. Use of atropine in patients with chronotropic incompetence and poor exercise capacity during treadmill stress testing. *Am Heart J* 2003;145(6):1046–50.
- [37] Blanchet M, Ducharme A, Racine N et al. Effects of cold exposure on submaximal exercise performance and adrenergic activation in patients with congestive heart failure and the effects of  $\beta$ -adrenergic blockade (carvedilol or metoprolol). *Am J Cardiol* 2003;92(5):548–53.
- [38] Glaab T, Weiss T. Use of  $\beta$ -blockers in cardiovascular diseases and bronchial asthma/COPD. *Internist (Berl)* 2004;45(2):221–7.
- [39] Silvestri A, Galetta P, Cerquetani E et al. Report of erectile dysfunction after therapy with  $\beta$ -blockers is related to patient knowledge of side effects and is reversed by placebo. *Eur Heart J* 2003;24(21):1928–32.
- [40] Yamada Y, Shibuya F, Hamada J, Sawada Y, Iga T. Prediction of sleep disorders induced by  $\beta$ -adrenergic receptor blocking agents based on receptor occupancy. *J Pharmacokinet Biopharm* 1995;23(2):131–45.
- [41] Bell DS. Advantages of a third-generation  $\beta$ -blocker in patients with diabetes mellitus. *Am J Cardiol* 2004;93(9A):49B–52B.
- [42] Marie PY, Mertes PM, Hassan-Sebbag N et al. Exercise release of cardiac natriuretic peptides is markedly enhanced when patients with coronary artery disease are treated medically by  $\beta$ -blockers. *J Am Coll Cardiol* 2004;43(3):353–9.
- [43] Marie PY, Mercennier C, Danchin N et al. Residual exercise SPECT ischemia on treatment is a main determinant of outcome in patients with coronary artery disease treated medically at long-term with  $\beta$ -blockers. *J Nucl Cardiol* 2003;10(4):361–8.
- [44] Penn RD, Kroin JS. Long-term intrathecal baclofen infusion for treatment for spasticity. *J Neurosurg* 1987;66(2):181–5.
- [45] Coffey JR, Cahill D, Steers W et al. Intrathecal baclofen for intractable spasticity of spinal origin: results of a long-term multicenter study. *J Neurosurg* 1993;78(2):226–32.
- [46] Meythaler JM, Steers WD, TuelS M, Cross LL, Haworth CS. Continuous intrathecal baclofen in spinal cord spasticity: a prospective study. *Am J Phys Med Rehabil* 1992;71(2):321–7.
- [47] Abel NA, Smith RA. Intrathecal baclofen for treatment of intractable spinal spasticity. *Arch Phys Med Rehabil* 1994;75(1):54–8.
- [48] Wallace M, Yaksh TL. Long-term spinal analgesic delivery: a review of the preclinical and clinical literature. *Reg Anesth Pain Med* 2000;25(2):117–57.
- [49] Hara K, Saito Y, Kiriara Y, Yamada Y, Sakura S, Kosaka Y. The interaction of antinociceptive effects of morphine and GABA receptor agonist within the rat spinal cord. *Anesth Analg* 1999;89(2):422–7.
- [50] Vidal J, Gregori P, Guevara D, Portell E, Valles M. Efficacy of intrathecal morphine in the treatment of baclofen tolerance in a patient on intrathecal baclofen therapy (ITB). *Spinal Cord* 2004;42(1):50–1.
- [51] Lorenz M, Hussein S, Verner L. Continuous intraventricular clonidine infusion in controlled morphine withdrawal-case report. *Pain* 2002;98(3):335–8.
- [52] Breitfeld C, Eikermann M, Kienbaum P, Peters J. Opioid "holiday" following antagonist supported detoxification during general anesthesia improves opioid agonist response in a cancer patient with opioid addiction. *Anesthesiology* 2003;98(2):571–3.
- [53] Lenz KL, Dunlap DS. Continuous fentanyl infusion: use in severe cancer pain. *Ann Pharmacother* 1998;32(3):316–9.
- [54] Mercadante S, Villari P, Ferrera P, Arcuri E. Local anesthetic switching for intrathecal tachyphylaxis in cancer patients with pain. *Anesth Analg* 2003;97(1):187–9.
- [55] Corona T, Rivera C, Otero E, Stopp L. A longitudinal study of the effects of an L-dopa drug holiday on the course of Parkinson's disease. *Clin Neuropharmacol* 1995;18(4):325–32.
- [56] Rascol O. Medical treatment of levodopa-induced dyskinesias. *Ann Neurol* 2000;47(4 Suppl 1):S179–88.
- [57] Nutt JG, Carter JH, Woodward WR. Effect of brief levodopa holidays on the short-duration response to levodopa: evidence for tolerance to the antiparkinsonian effects. *Neurology* 1994;44(9):1617–22.
- [58] Kenny AM, Schneider MB, Baden DR, Pfeiffer RF, Murrin LC. Bromocriptine holiday: effects on dopamine receptors and turning behavior in rats. *Neurology* 1986;36(3):400–44.
- [59] Direnfeld LK, Feldman RG, Alexander MP, Kelly-Hayes M. Is L-DOPA drug holiday useful?. *Neurology* 1980;30(7 Pt 1):785–8.
- [60] Rothschild AJ. Selective serotonin reuptake inhibitor-induced sexual dysfunction: efficacy of a drug holiday. *Am J Psychiatry* 1995;152(10):1514–6.
- [61] Hershey LA, Gift T, Atkins RW, Rivera-Calimlim L. Effect of a drug holiday on plasma chlorpromazine levels in chronic schizophrenic patients. *Psychopharmacology (Berl)* 1981;73(4):355–8.
- [62] Newton JE, Cannon DJ, Couch L et al. Effects of repeated drug holidays on serum haloperidol concentrations, psy-

- chiatric symptoms, and movement disorders in schizophrenic patients. *J Clin Psychiatry* 1989;50(4):132–5.
- [63] Azevedo ER, Schofield AM, Kelly S, Parker JD. Nitroglycerin withdrawal increases endothelium-dependent vasomotor response to acetylcholine. *J Am Coll Cardiol* 2001;37(2):505–9.
- [64] Hebert D, Lam JY. Nitroglycerin rebound associated with vascular, rather than platelet, hypersensitivity. *J Am Coll Cardiol* 2000;36(7):2311–6.
- [65] Marsh N, Marsh A. A short history of nitroglycerine and nitric oxide in pharmacology and physiology. *Clin Exp Pharmacol Physiol* 2000;27(4):313–9.
- [66] Laowattana S, Abou-Khalil B, Fakhoury T, Ashmead D. Brief antiepileptic drug withdrawal prolongs interval to next seizure. *Neurology* 1999;53(8):1736–41.
- [67] Takei A, Fukazawa T, Hamada T, Yabe I, Tashiro K. 'Drug holiday' effects of tandospirone in a patient with Machado-Joseph disease. *Psychiatry Clin Neurosci* 2003;57(6):607–8.
- [68] Gaylor ML, Duvic M. Generalized pustular psoriasis following withdrawal of efalizumab. *J Drugs Dermatol* 2004;3(1):77–9.
- [69] Kenemans P, Genazzani AR, Palacios S, Schneider HP. Pulsed estrogen exposure selectively modulates tissue response: a hypothesis. *Gynecol Endocrinol* 2004;18(3):159–64.
- [70] Genazzani AR, Bernardi F. Estrogen effects on neuroendocrine function: the new challenge of pulsed therapy. *Climacteric* 2002;5(Suppl 2):50–6.
- [71] Ferrario E, Ferrari L, Bidoli P et al. Treatment of cancer-related anemia with epoetin alfa: a review. *Cancer Treat Rev* 2004;30(6):563–75.
- [72] Oshitani N, Kamata N, Oiso R et al. Outpatient treatment of moderately severe active ulcerative colitis with pulsed steroid therapy and conventional steroid therapy. *Dig Dis Sci* 2003;48(5):1002–5.
- [73] Haugeberg G, Griffiths B, Sokoll KB, Emery P. Bone loss in patients treated with pulses of methylprednisolone is not negligible: a short term prospective observational study. *Ann Rheum Dis* 2004;63(8):940–4.
- [74] Dessein PH, Joffe BI, Stanwix AE, Christian BF, Veller M. Glucocorticoids and insulin sensitivity in rheumatoid arthritis. *J Rheumatol* 2004;31(5):867–74.
- [75] Sundel RP, Baker AL, Fulton DR, Newburger JW. Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. *J Pediatr* 2003;142(6):611–6.
- [76] Kropff MH, Lang N, Bisping G et al. Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (HyperCDT) in primary refractory or relapsed multiple myeloma. *Br J Haematol* 2003;122(4):607–16.
- [77] So LK, Lau AC, Yam LY et al. Development of a standard treatment protocol for severe acute respiratory syndrome. *Lancet* 2003;361(9369):1615–7.
- [78] Girdhar A, Chakma JK, Girdhar BK. Pulsed corticosteroid therapy in patients with chronic recurrent ENL: a pilot study. *Indian J Lepr* 2002;74(3):233–6.
- [79] Hedlund-Treutiger I, Henter JI, Elinder G. Randomized study of IVIg and high-dose dexamethasone therapy for children with chronic idiopathic thrombocytopenic purpura. *J Pediatr Hematol Oncol* 2003;25(2):139–44.
- [80] Buchanan TA. Pancreatic  $\beta$ -cell loss and preservation in type 2 diabetes. *Clin Ther* 2003;25(Suppl B):B32–46.
- [81] Polonsky KS, Sturis J, Van Cauter E. Temporal profiles and clinical significance of pulsatile insulin secretion. *Horm Res* 1998;49(3–4):178–84.
- [82] Schurmeyer TH, Schulte HM, Avgerinos PC et al. Pharmacology of ovine and human CRH. *Horm Metab Res Suppl* 1987;16:24–30.
- [83] Martinez-Fuentes AJ, Hu L, Krsmanovic LZ, Catt KJ. Gonadotropin-releasing hormone (GnRH) receptor expression and membrane signaling in early embryonic GnRH neurons: role in pulsatile neurosecretion. *Mol Endocrinol* 2004;18(7):1808–17.
- [84] Mueck AO, Seeger H, Wallwiener D. 'Pulsed' estradiol action can stimulate breast cancer cell proliferation. *Clin Exp Obstet Gynecol* 2004;31(1):23–4.
- [85] Moellers RF, Cogburn LA. Pulsatile infusion of growth hormone-releasing factor depresses growth of young broiler chickens. *Comp Biochem Physiol Comp Physiol* 1994;107(4):665–72.
- [86] Kox WJ, Volk T, Kox SN, Volk HD. Immunomodulatory therapies in Sepsis. *Intens Care Med* 2000;26(Suppl. 1):S124–8.
- [87] Monneret G, Debarb AL, Venet F et al. Marked elevation of human circulating CD4+CD25+ regulatory T cells in sepsis-induced immunoparalysis. *Crit Care Med* 2003;31(7):2068–71.
- [88] Van den Berghe G. Endocrine evaluation of patients with critical illness. *Endocrinol Metab Clin North Am* 2003;32(2):385–410.
- [89] Van den Berghe G. Endocrinology in intensive care medicine: new insights and therapeutic consequences. *Verh K Acad Geneesk Belg* 2002;64(3):167–87.
- [90] Van den Berghe GH, De Zegher FE. A senescent pattern of pituitary function during critical illness and dopamine treatment. *Verh K Acad Geneesk Belg* 1996;58(4):383–411.
- [91] Yun AJ, Lee PY, Bazar KA. Temporal variation of autonomic balance and diseases during circadian, seasonal, reproductive, and lifespan cycles. *Med Hypotheses* 2004;63(1):155–62.
- [92] McDonald IR, Lee AK, Than KA, Martin RW. Failure of glucocorticoid feedback in males of a population of small marsupials *Antechinus swainsonii* during the period of mating. *J Endocrinol* 1986;108(1):63–8.
- [93] Schroeder S, Wichers M, Klingmuller D et al. The hypothalamic-pituitary-adrenal axis of patients with severe sepsis: altered response to corticotropin-releasing hormone. *Crit Care Med* 2001;29(2):310–6.
- [94] Briegel J, Schelling G, Haller M, Mraz W, Forst H, Peter K. A comparison of the adrenocortical response during septic shock and after complete recovery. *Intens Care Med* 1996;22(9):894–9.
- [95] Rosenfield RL. Current concepts of polycystic ovary syndrome. *Baillieres Clin Obstet Gynaecol* 1997;11(2):307–33.
- [96] Anderson SD, Brannan JD. Long-acting  $\beta$ -2-adrenoceptor agonists and exercise-induced asthma: lessons to guide us in the future. *Paediatr Drugs* 2004;6(3):161–75.
- [97] Partonen T, Vakkuri O, Lamberg-Allardt C. Effects of exposure to morning bright light in the blind and sighted controls. *Clin Physiol* 1995;15(6):637–46.
- [98] Olofsson K, Alling C, Lundburg D, Malmros C. Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. *Acta Anaesthesiol Scand* 2004;48(6):679–84.
- [99] Wakamura T, Tokura H. Influence of bright light during daytime on sleep parameters in hospitalized elderly patients. *J Physiol Anthropol Appl Human Sci* 2001;20(6):345–51.
- [100] Yun AJ, Lee PY, Bazar KA. Clinical benefits of hydration and volume expansion in a wide range of illnesses may be

- attributable to reduction of sympathovagal ratio. *Med Hypotheses* 2004, doi:10.1016/j.mehy.2004.07.014.
- [101] Michelson D, Fava M, Amsterdam J et al. Interruption of selective serotonin reuptake inhibitor treatment. *Br J Psychiatry* 2000;176:363–8.
- [102] Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: A randomized clinical trial. *Biol Psychiatry* 1998;44(2):77–87.
- [103] Stahl MM, Lindquist M, Pettersson M et al. Withdrawal reactions with selective serotonin re-uptake inhibitors as reported to the WHO system. *Eur J Clin Pharmacol* 1997;53(3–4):163–9.
- [104] Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove E, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004;363(9418):1341–5.
- [105] Kinugasa H, Hirayanagi K. Effects of skin surface cooling and heating on autonomic nervous activity and baroreflex sensitivity in humans. *Exp Physiol* 1999;84(2):369–77.
- [106] Desai RA, Maciejewski PK, Dausey DJ, Caldarone BJ, Potenza MN. Health correlates of recreational gambling in older adults. *Am J Psychiatry* 2004;161(9):1672–9.

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

