HEALTH AND STRESS

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HOW REDUCING STRESS CAN PREVENT HEART ATTACKS

KEYWORDS: Ebers Papyrus, William Harvey, William Osler, Stewart Wolf, Sisyphus Syndrome, Walter Cannon, "Voodoo Death", Ray Rosenman, Uffe Ravnskov, Kilmer McCully, coronary plaque microabscess, Kevin Tracey, "anti-inflammatory reflex", Prince Sultan Cardiac Center "The Heart as King of Organs" Saudi Arabia conference

A lecture I was invited to give at the Leo Award Ceremony in Sweden was recently published in a special edition of the *Scandinavian Cardiovascular Journal*. I had been asked to review the origins and evolution of the lipid hypothesis of coronary heart disease to expose the faulty premises on which it is based and the deception and chicanery used to perpetuate it by powerful vested interests. My presentation was based on numerous Power Point slides that could not be utilized since they were in color. And because of space constraints, all the speakers were asked to submit an abbreviated version emphasizing the highlights of the lecture and strictly limiting the number of black and white illustrations and diagrams.

ALSO INCLUDED IN THIS ISSUE

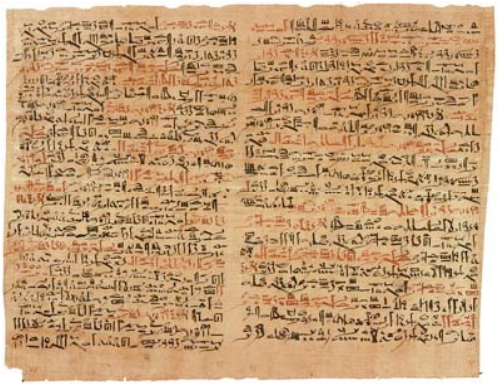
The title of my published condensed article was also changed to "Why lowering cholesterol does not prevent heart attacks in contrast to reducing stress". While the first claim could be easily supported, I received several requests for more proof about the second. Most of my commentary on this had been omitted since it was not pertinent to the main theme, and should have been explained in more detail.

A relationship between stress, sudden death and heart disease has been recognized since antiquity. However, it has only been in recent decades that

scientific proof of such relationships has confirmed what many previously considered to be old wives' tales or unsubstantiated anecdotal reports.

The Evolution Of Stress - Heart Relationships And Coronary Prone Behavior

The appreciation that emotional factors can have a powerful influence on the heart, and the acknowledgment of some intimate, but poorly understood, heart-mind connection, is certainly not new. The Yellow Emperor's Canon of Internal Medicine, dating back 40 or more centuries, states that, "The heart is the root of life and causes the versatility of the spiritual faculties."



Ebers Papyrus Book of Hearts Chapter

The 35-century-old Ebers Papyrus explains that the heart is the center of the blood supply to every part of the body and is responsible for mental, emotional and physical complaints. Emotional disorders like depression discussed in a Book of Hearts chapter suggest that the early Egyptians considered mind and body to be inseparable and made no distinction between mental and physical disorders.

Similar beliefs are expressed in the Upanishads and other ancient Hindu scriptures and Eastern philosophies. Aristotle, and later Virgil, actually taught that the heart rather than the brain was the seat of the mind and emotions. Twenty centuries ago, the Roman physician Celsus, who first described the four cardinal signs of inflammation (heat, redness, swelling and pain) wrote, "Fear and anger, and any other state of the mind may often be apt to excite the pulse." William Harvey, who published his discovery of how the blood circulated through the body in 1628, was also aware that the heart was much more than a mechanical pump, and similarly noted, "Every affection of the mind that is attended either with pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart."

John Hunter, who during the 18th century elevated surgery from a mechanical trade to an experimental science, suffered from angina and a bad temper. Being a keen observer, he complained, "My life is in the hands of any rascal who chooses to annoy or tease me." This proved to be an accurate prophecy, since he died suddenly during a violent argument with a colleague over a rather trivial matter. Jean-Nicholas Corvisart, Napoleon's physician, wrote that **heart disease was due to the "passions of the mind"**, among which he included anger, fear, madness, terror, jealousy, love, despair, joy, avarice, stupidity, and aggressive ambition.

We still use "heart" in numerous phrases and expressions to describe feelings, emotions, character or temperament, such as: heart of gold (warm hearted or generous), heart of stone (cruel or cold hearted), broken hearted, heartache, take to heart or eat one's heart out (have sorrow or longing dominate one's emotion), lighthearted (be carefree), set my heart at rest (relieve anxiety), does my heart good (gives happiness), to my heart's content (be fully satisfied), set one's heart on (wish for intensely) stout hearted or take heart (have or regain courage) take to heart (to think seriously about or to be overly concerned), put your heart and soul into something (be most enthusiastic), lose your heart (fall in love with), wear your heart on your sleeve (display your feelings or fall in love too easily), in my heart of hearts (innermost feelings or beliefs), cross my heart (tell the absolute truth), have a heart (be compassionate), from the bottom of my heart or heartfelt (with complete sincerity), had my heart in my mouth (be extremely fearful or anxious), know something by heart (word for word). The core, or center and most important part of any proposal, idea or object comes from *cor*, the Latin word for heart. We go the core or heart of anything to learn its true essence, significance or meaning, such as the heart of the matter or the heart of the city.

Theodur Von Dusch, a German physician. cited excessive involvement in work and very loud speech as the major characteristics of people who later developed coronary disease in his 1868 textbook on the heart. Two decades later, the French cardiologist Henry Huchard, wrote that angina was caused by spasm of the coronary vessels due to emotional excitement. He coined the term "tobacco angina", which he ascribed to arteriosclerosis of the coronary arteries. In his 1897 *Lectures on Angina Pectoris and Allied States*, Sir William Osler described the coronary patient as, “not the delicate neurotic but the robust, the vigorous in mind and body, the keen ambitious man, the indicator of whose engine is always full speed ahead.” He later wrote that he could make the diagnosis of angina based on the appearance, demeanor and mannerisms of the patient in the waiting room, and how he entered the consultation room.

In 1936, the Menninger brothers, psychiatrists who were pioneers in mind/body medicine, observed that coronary patients characteristically had very aggressive and hostile behaviors. A decade later, Flanders Dunbar who had introduced the term "psychosomatic" into American medicine, wrote that coronary patients tended to be authoritarian with an intense drive to achieve unrealistic goals. Around the same time, Charles Kemple noted the frequency of fierce ambition and a compulsive desire to achieve power and prestige. The following decade, Stewart Wolf, often called "The Father of Neurocardiology", also commented on the constant striving to achieve unrealistic goals and emphasized these were often self-imposed, adding that

even when successful, they were unable to relax and enjoy the satisfaction of their labors. He called this the "*Sisyphus Syndrome*". In Greek mythology, Sisyphus was condemned to roll a huge marble boulder up a hill, which, as soon as it reached the top, always rolled down to the bottom again.

All of these 19th and 20th physicians were describing various aspects of what is now called Type A behavior, a term coined by Meyer Friedman and Ray Rosenman. In 1959, these two friends of mine, who were cardiologists and not psychiatrists, published a paper in the *Journal of the American Medical Association* entitled "Association of specific overt behavior pattern with blood and cardiovascular findings." This and subsequent articles included all these previous observations and added numerous other traits that were characteristic of this complex syndrome, and explained how it promoted coronary disease. Type A was acknowledged by the NIH to be as powerful a risk factor for heart attacks as anything else. In that regard, the MRFIT (Multiple Risk Factor Intervention Trial), a large long-term study designed to show that lowering the standard risk factors of smoking, cholesterol and hypertension, failed to show any reduction in heart attacks or coronary mortality. In contrast, two other intervention trials conducted during this same period were so successful that they had to be halted prematurely so controls would not be denied their benefits. One was a trial designed to modify and lessen Type A traits and the other was administration of Inderal (propanolol), a beta-blocker drug that blocked the damaging effects of stress hormones associated with Type A behavior. (Subsequent attempts to identify the toxic components of Type A are discussed in an interview with Dr. Rosenman, Vice President of The American Institute of Stress. that is available on our web site, www.stress.org)

Type A Behavior, Sudden Death, Stress And Heart Attacks

Type A behavior and stress should not be considered as synonymous. One of the characteristics of Type A is a **lack of anxiety.** Type A's who are in control may not be as coronary prone as those who are constantly frustrated by their self-imposed preoccupation with work in a constant attempt to obtain power and/or fame. Nor is Type A associated with a significant increase in sudden death, with the possible exception of those with high hostility rating scores. In contrast, stress is the major cause of sudden death, which is the leading cause of death in the world. This is particularly true when death occurs within a few hours of a triggering event, and is usually due to a lethal arrhythmia. This can occur in healthy young individuals as well as others without evidence of significant coronary atherosclerosis. Most stress related sudden deaths are due to overwhelming fear, rage, grief, or humiliation, but sudden death can also be caused by intense joy or anything that produces extreme excitement.

The ability of severe fear and psychological stress to cause sudden death is embedded in the folklore of all ethnic groups. Sudden death was particularly common in primitive cultures, following the realization that a taboo had been violated or that a powerful hex had been placed on the victim. Such fatalities represented a punishment by some deity or by a shaman who possessed similar supernatural power. Western medicine tended to dismiss such stories as superstitious "old wives' tales", especially since there was no plausible mechanism to explain how such fear could cause sudden death. Walter Cannon, who described the "fight or flight" response, was fascinated by well-documented accounts of this phenomenon he had collected from all over the globe that he was convinced were not due to witchcraft, "black magic", "devil worship" or voodoo. Most shamans and sorcerers used props along with some special incantation or death decree. African witch doctors had knucklebones, European witches carved wooden dolls, Australian aborigine sorcerers used bones extracted from the flesh of giant lizards and in Haiti, where voodoo was a religion, there were dozens of different dolls and methods of maiming and sticking pins in them to cause harm or death. Yet all these cultures were different, so what did they have in common?

In his 1942 article entitled "Voodoo Death", Walter Cannon wrote that death was certain for this type of "death by decree" if three criteria were met:

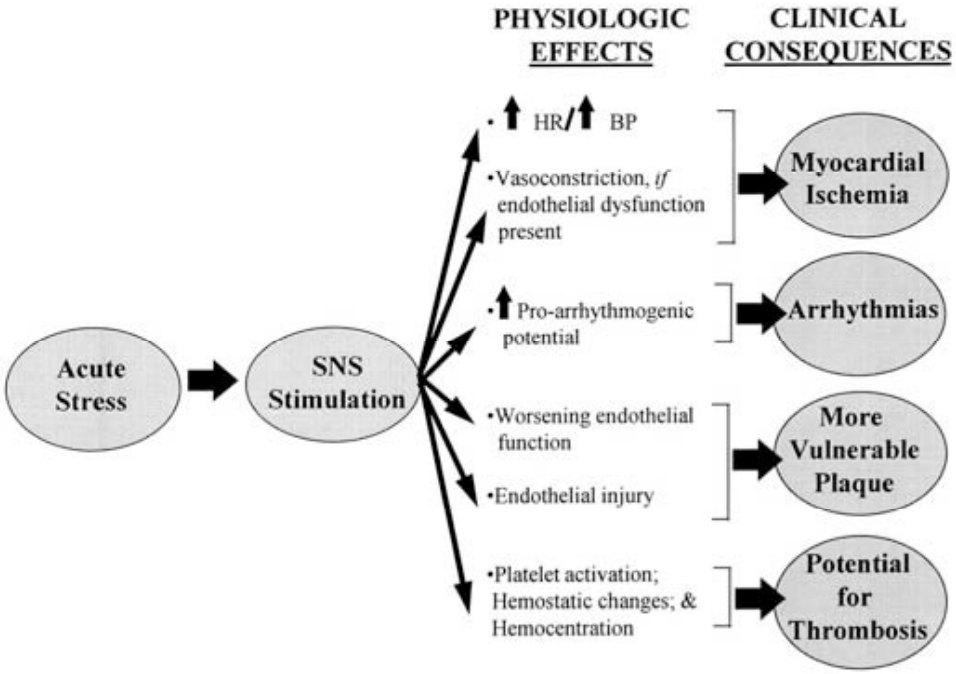
1. The victim and all family and friends must believe that the power of the medicine man or hex is genuine and will cause death.
2. All previously known victims of the hexing or curse must have died unless the spell had been removed.
3. Every person known to the victim must behave as if death in a short period of time was a certainty. This meant that everyone would leave him alone and isolated, including family and friends.

The absence of social support was more important than withholding food, water, or physical aid. The famous psychologist William James had previously emphasized, "the catastrophic emotional effect we all would suffer if everyone around us acted as if we ceased to exist." It is difficult to imagine anything more stressful than such complete and permanent isolation because of the powerful stress busting effects of social support.

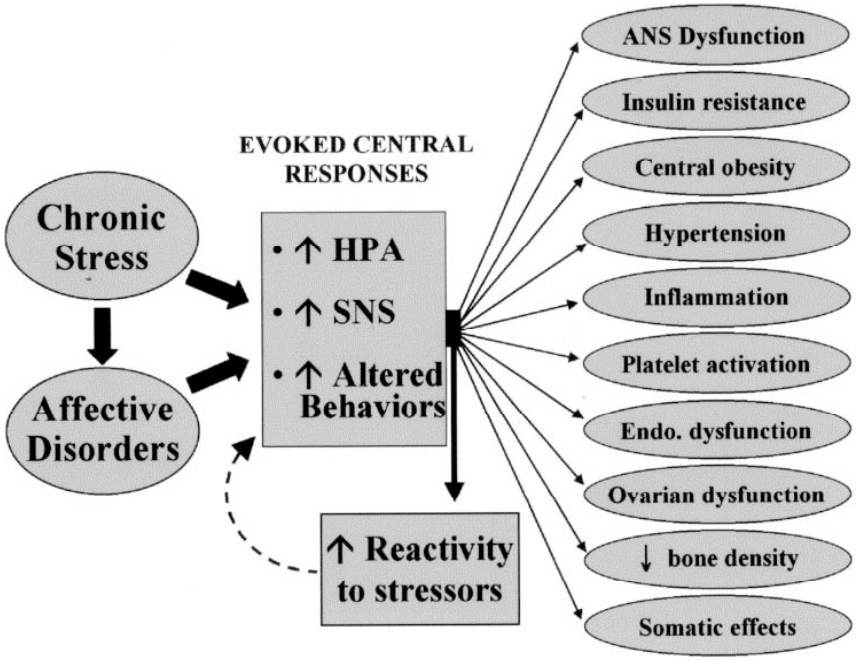
Stress can contribute to heart disease in myriad ways, some of which are subtle but particularly troublesome because they can set up a vicious self-perpetuating cycle. For example, stress is a major cause of insomnia and insomnia is a frequent source of stress. A similar relationship exists between stress and obesity. Some of the other important ways that stress can cause heart attacks and increase coronary mortality are as follows:

1. Stress causes cardiac damage via increased catecholamine secretion that can cause coronary vasoconstriction and increased platelet stickiness and aggregation that promote clot formation.
2. Stress induced catecholamine secretion and sympathetic nervous system stimulation can cause sudden death by triggering ventricular fibrillation. Rebound parasympathetic vagal overdrive in response to sympathetic activities may also cause sudden death from asystole.
3. Severe stress can cause direct heart damage due to increased secretion of norepinephrine at nerve endings in the myocardium.
4. Stress contributes to the traditional risk factors of cholesterol, smoking, and hypertension, as well as diabetes, obesity and others.
5. Stress increases homocysteine, C-reactive protein, and fibrinogen, all of which are associated with greater risk for coronary disease.
6. Chronic stress induced cortisol secretion increases the deposition of deep abdominal fat, which secretes cytokines that contribute to inflammation, insulin resistance, Type II diabetes, hypertension, and lipid disturbances that characterize metabolic syndrome and its deadly cardiovascular consequences.
7. Increased cortisol also lowers immune system resistance to infections that are associated with the accelerated development of coronary atherosclerosis. Heart attack patients have increased antibodies to herpes viruses compared to controls admitted for other diagnoses. Chlamydia, which causes mild flu symptoms, as well as herpes, can remain in the body where they are asymptomatic until activated by stress. Chlamydia has been cultured from atherosclerotic plaque in the carotid and coronary arteries obtained during surgery.
8. Depression, anxiety, hostility, stressful life change events such as loss of a spouse, natural disasters, loss of esteem due to educational failure, loneliness, marital strife, and a host of other psychosocial stresses have all been linked to higher risks of coronary heart disease.
9. Stress increases free radical damage and inflammation, which is increasingly being recognized as a major cause of heart attacks due to unstable plaque.

Acute and chronic stress both damage the heart but via different pathways. Sympathetic nervous system stimulation emanating from acute stress leads to a variety of effects, ranging from heart rate and blood pressure elevation to direct effects on coronary vascular endothelium. The clinical consequences of these effects include development of hemostatic changes, myocardial ischemia, cardiac arrhythmias, as well as fostering the development of more vulnerable unstable plaque. These activities provide a substrate for the development of an acute myocardial infarction and sudden death as depicted below.



Chronic stress and affective disorders like depression activate the hypothalamic-pituitary-adrenal (HPA) axis as well as the sympathetic nervous system (SNS), and also affect behavior, as illustrated below.

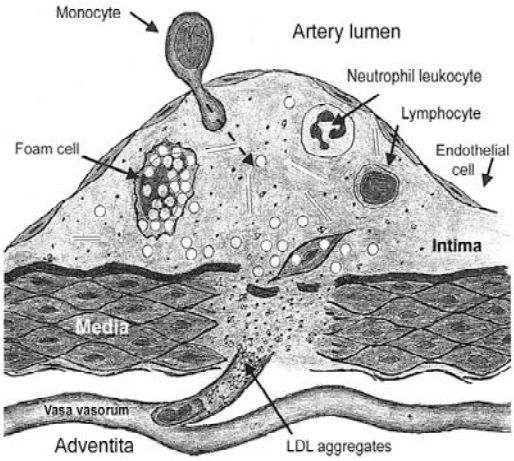


(Rozanski A, et al. *J Am Coll Cardiol* 2995;45:637-651)

This combination tends to trigger a state of heightened responsivity to acute stress that can interact with chronic stressors causing more adverse effects. While acute stress responses are likely to produce significant signs and

symptoms, chronic psychosocial stress from loneliness and poor social support, loss of self esteem from educational failure, chronic marital discord, frequent fights with family, co-workers or customers, poverty and especially depression, are much more insidious and subtle. Chronic stress is also much more pervasive and has more widespread adverse effects that are generally not appreciated, including osteoporosis, central obesity, as well as endothelial and ovarian dysfunction. Many of these damaging consequences feed on each other and create acute as well as additional chronic stress.

The above topics have been discussed in prior Newsletters, but recent advances require that some be updated or emphasized. For example, Uffe Ravnskov and Kilmer McCully have now suggested that unstable plaque might represent a "microabscess" resulting from an infection. They point out that lipoproteins are part of a nonspecific immune defense system that binds and inactivates microbes and their toxins by the formation of complexes.



Is Unstable Plaque A Microabscess?

An accumulation of such complexes can be trapped in the vasa vasorum of major arteries that is furthered by homocysteine, which reacts with the free amino groups of apolipoprotein B to form homocysteinylated LDL. As shown to the left, this LDL complex precipitates out and is engulfed by macrophages to form foam cells that accumulate and eventually obstruct the vasa vasorum. This produces local ischemia in the arterial wall that results in intramural cell death and capillary rupture that allows microorganisms to escape into the intima. The resulting inflammation leads to unstable plaque.

Unstable plaque has all the characteristics of a microabscess, which, by bursting, starts the creation of an occluding thrombus. The presence of homocysteinylated or oxidized LDL stimulates the production of LDL autoantibodies, which may start a vicious cycle by increasing complex formations and aggregation of lipoproteins. This would explain why vulnerable plaque contains microbes and lipids in the arterial wall, why neutrophils are seen in the myocardium following an infarct, as well as the frequent occurrence of fever, diaphoresis, elevated inflammatory markers and even bacteremia in acute myocardial infarction. Mental stress, hyperhomocysteinemia, diabetes, smoking and other risk factors may cause atherosclerosis not by damaging the vascular wall directly, but rather by inhibition of the immune system that facilitates microbial growth, and/or by promoting lipoprotein complex formation and aggregation.

This proposal may seem far-fetched to some since it implies that heart attacks associated with bacteremia might respond to appropriate antibiotics or that vaccines could be used to retard the development of atherosclerosis. There was similar skepticism two decades ago when it was suggested that peptic ulcers were caused by helicobacter infection, rather than stress. However, the vast majority of patients harboring helicobacter have no gastrointestinal complaints. It is only when stress related hormones or non-steroidal anti-inflammatory drugs impair normal protective defenses that ulcer symptoms start to surface. It is well established that stress reduces immune system resistance to bacterial and viral infections. Stress hormones or the administration of cortisol like steroids can often cause the clinical reappearance of previously quiescent tuberculosis because they impair immune system defenses that normally prevent this. Similarly, when healthy young adults were exposed to rhinoviruses, the frequency as well as the severity of subsequent colds were directly correlated with the magnitude of their stress levels.

How Does Stress Reduction Prevent Heart Attacks And Atherosclerosis?

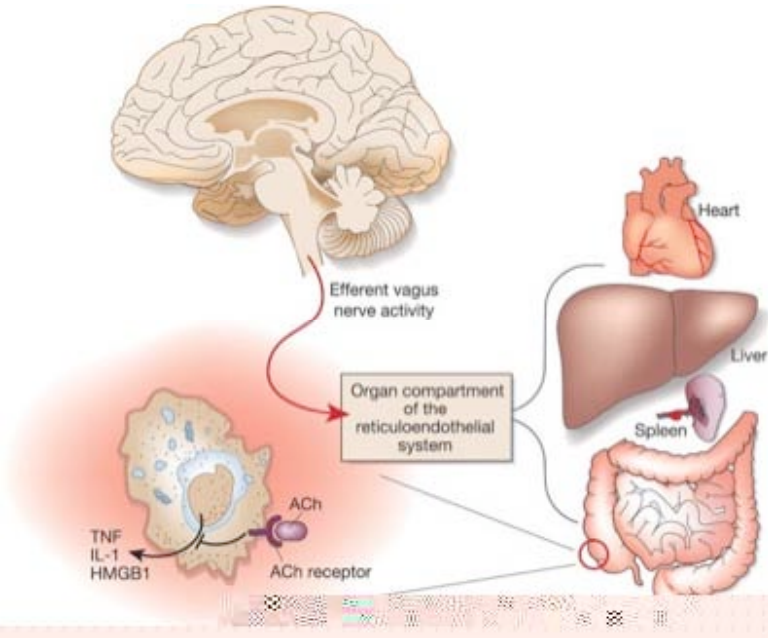
Reducing stress and bolstering immune system function in other ways should help to prevent the development of unstable plaque due to infection. However, coronary atherosclerosis is a multifactorial process and stress also plays a crucial role in the development of metabolic syndrome and its damaging cardiovascular consequences. Stress related cortisol secretion promotes the deposition of deep abdominal fat cells that not only secrete proinflammatory molecules but also stimulate the hypothalamic-pituitary-adrenal axis to produce more cortisol. These visceral fat cells (adipocytes) have increased receptors for cortisol that tend to perpetuate its deposition. Thus, stress-induced increased cortisol contributes to fat cell accumulation and vice versa and both promote insulin resistance and low-grade smoldering inflammation to create another sinister self-perpetuating cycle.

Inflammation appears to be the most important cause of metabolic syndrome based on levels of C reactive protein (CRP). CRP levels in patients with any one of the components of metabolic syndrome (hypertension, lipid disturbances, Type 2 diabetes, increased coagulation etc.) can vary considerably, but a progressive rise in CRP with each additional factor has been clearly demonstrated. It should also be noted that CRP levels correlate very closely with the severity of abdominal obesity, which, as previously emphasized, is largely due to increased cortisol activities that increase fat cell production of inflammatory cytokines.

It has become increasingly clear that heart attacks as well as atherosclerosis are due to inflammation rather than elevated lipid levels. However, this

inflammation is subclinical and can only be detected or measured with crude markers, such as CRP, interleukin-6 and tumor necrosis factor. If stress reduction is effective in preventing heart attacks and atherosclerosis, what evidence is there that it suppresses inflammation? And what is the mechanism of action? Fortunately, Kevin Tracey's ground breaking research on the "anti-inflammatory reflex" have now provided some clues and answers to these questions. It is difficult to explain this in a few paragraphs but key aspects are summarized in the following diagrams and legends.

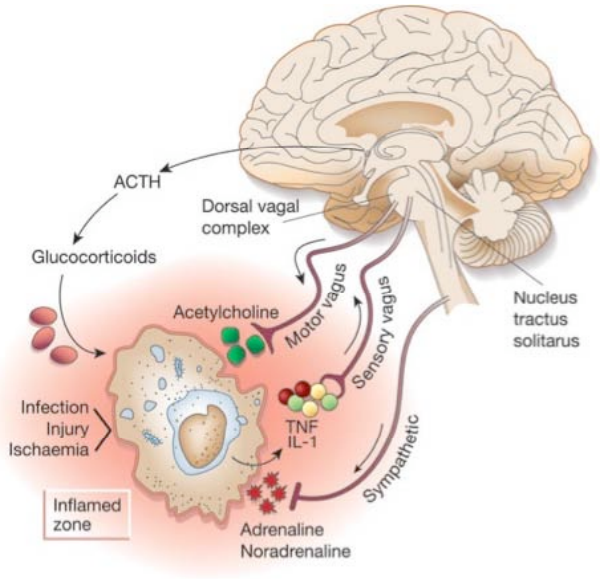
The Cholinergic Anti-inflammatory Pathway



As illustrated to the left, efferent activity in the vagus nerve leads to the release of acetylcholine (ACH) in compartments of organs of the reticuloendothelial system. ACH interacts with its receptors on tissue macrophages that inhibit the release of tumor necrosis factor (TNF), interleukin 1 (IL-1) and other cytokines. Tracey refers to this as the "cholinergic anti-inflammatory pathway" because acetylcholine is the principle neurotransmitter for parasympathetic nervous system activities. Macrophages that are exposed to acetylcholine are effectively deactivated. In addition to the heart, the vagus nerve (named for its wandering course) also innervates reticuloendothelial sites in the liver, lung, spleen and gut.

The cholinergic anti-inflammatory is only one component of the body's ability to suppress inflammation, as shown below.

Anti-inflammatory Reflex Pathways

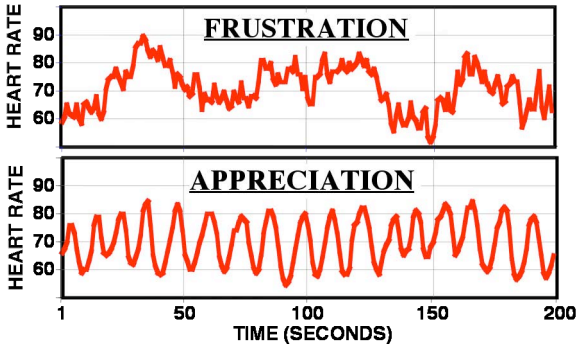


Inflammatory products produced in damaged tissues activate afferent signals that are relayed to the nucleus tractus solitarius. This then activates vagus efferent activity that inhibits cytokine synthesis through the cholinergic anti-inflammatory pathway (‘the inflammatory reflex’). Information can be relayed to the hypothalamus and the dorsal vagal complex to stimulate ACTH that activates humoral anti-inflammatory pathways. Fight or flight responses that stimulate sympathetic nervous system activities can increase local concentrations of adrenaline and noradrenaline, that further suppress inflammation.

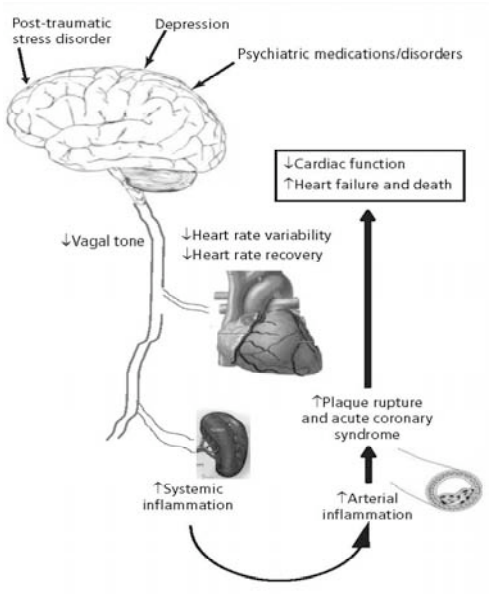
This runs counter to classical teaching that actions of the sympathetic and parasympathetic nervous systems are usually in opposition. But in some situations, as noted above, the two systems function synergistically and their combined action is significantly anti-inflammatory. Similarly, simultaneous stimulation of both sympathetic and vagus nerves produces a higher increase in cardiac output than does isolated stimulation of either alone.

Tracey's research is supported by studies showing that activation of the cholinergic anti-inflammatory pathway by direct electrical stimulation of the efferent vagus nerve inhibits the synthesis of TNF in liver, spleen and heart. Conversely, vagotomy significantly exacerbates TNF responses to inflammatory stimuli and sensitizes animals to the lethal effects of endotoxin. Vagal and parasympathetic nervous system activation blocks stressful fight or flight reactions and produces a "Relaxation Response" that is its antithesis. Heart Rate Variability (HRV) feedback research now confirms this as well as the effect of differing emotions on HRV.

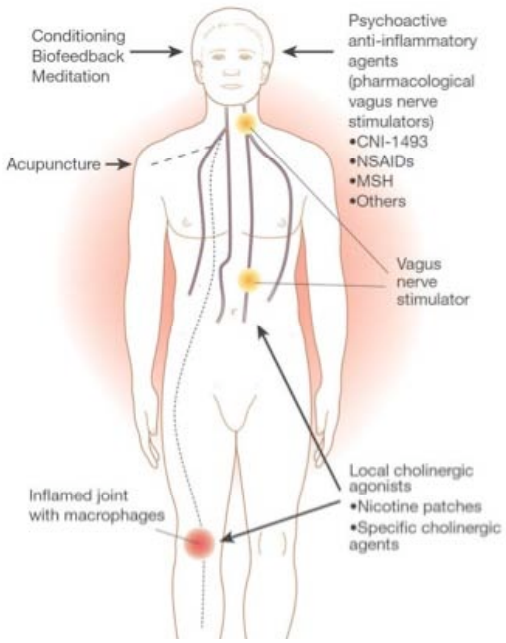
Low HRV is seen in depression, frustration and other stressful states. The reverse is true during relaxation and when feeling positive emotions such as true love and deep appreciation, as shown to the right in this HeartMath study. Low HRV reflects the inability of the heart to adapt to change and a powerful predictor of sudden death. HRV provides the most accurate and objective method of assessing current stress levels.



Heart rate variability can only be measured by complicated ECG analysis but the recent availability of inexpensive hand held devices that convert these ECG patterns to easily understood visual signals. This allows the user to not only immediately get the same information but also to learn how to correct dangerously low levels by altering respiratory patterns to obtain maximal parasympathetic stimulation. In many instances, it is possible to achieve the same degree of relaxation in a week or two that can take months to attain with meditation. In studies of coronary artery disease patients, five or six biofeedback sessions coupled with daily practice resulted in significantly increased heart rate variability, improved symptoms and quality of life. In heart failure patients, eight biofeedback sessions markedly improved performance on a 6-minute walk test and reduced perceived stress levels. There are numerous other examples that could be cited that demonstrate the efficacy of HRV biofeedback in relieving asthma, insomnia and other stress related complaints. HRV biofeedback is also an extremely cost effective way to improve learning skills and various cognitive functions as well as performance and productivity in numerous diverse areas.



Stress→Inflammation→Heart Disease



Potential Therapeutic Approaches

The diagram above to the left shows how stress causes inflammation, low HRV and cardiac damage by suppression of vagal activities. Possible therapies that reduce inflammation by cholinergic stimulation and where they operate are shown on the right. Some of these are consistent with an emerging paradigm of unappreciated subtle energy communication pathways in the body that could explain poorly understood phenomena such as the power of placebos, strong faith, prayer, therapeutic touch and acupuncture. Vagal and cranioelectrical stimulation can relieve depression, and anxiety and are also being used to treat obesity, migraine and other pain syndromes. Weak electromagnetic stimulation has been shown to promote healing and reverse metastatic malignancy and terminal cardiomyopathy.

The heart's electromagnetic field is 6.000 times more powerful than the brain. Can it be harnessed to provide similar therapeutic benefits? I am looking forward to participating in the Prince Sultan Cardiac Center's "The Heart as King of Organs" conference in Saudi Arabia, where this and relevant topics will be discussed. Few of us aware of the great contributions of Islamic physicians, – so stay tuned for more on this fascinating event!

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