

## The effect of mirthful laughter on the human cardiovascular system <sup>☆</sup>

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### ARTICLE INFO

#### Article history:

Received 18 February 2009

Accepted 28 February 2009

### SUMMARY

It has become increasingly recognized and more widely acknowledged during the past several decades, that a complex relationship exists between behavior associated with emotion and the human cardiovascular (CV) system. Early studies focused on the interplay between negative emotions and elevated CV risk, an effect that has in large part been attributed to increased adrenergic activity. Thus, a variety of adverse CV effects ranging from sudden cardiac death triggered by natural disasters such as earthquakes to transient myocardial stunning resulting from heightened sympathetic overload have been identified in response to acute emotional distress. In fact, the biologic interplay between emotion and CV health has been greatly enhanced through studies of the vascular endothelium. As the largest organ in humans, the inner blood vessel lining serves as a conduit for the transfer of blood cells, lipids and various nutrients across the lumen to neighboring tissues. Healthy endothelial cells secrete vasoactive chemicals, most notably endothelial-derived relaxing factor or nitric oxide (NO), that effects smooth muscle relaxation and vessel dilation via a cyclic guanosine monophosphate (cGMP) dependent protein kinase signaling pathway. In addition, endothelial derived NO may reduce vascular inflammation by attenuating or inhibiting leukocyte adhesion and subendothelial transmigration as well as decreasing platelet activation via cGMP mediated pathways. Taken together, studying the endothelium provides an exceptional opportunity to advance our understanding of the potentially important interrelationship between emotions and the vasculature. Premised on the identification of physiological and biochemical correlates, the former was demonstrated after intracoronary administration of acetylcholine yielded paradoxical endothelial vasoconstriction in response to mental stress exercises. More recently, the brachial artery reactivity test (BART) has permitted endothelial function to be assessed in a non-invasive manner. In addition to traditional CV risk factors, exposure to negative emotions including mental stress and depression have been associated with reduced endothelial vasoreactivity as measured by BART. Whether mirthful laughter has the opposite effect garnered consideration following the discovery that  $\mu 3$  opiate receptors were expressed in the vascular endothelium. Because mirthful laughter induces the release of  $\beta$ -endorphins which in turn have high affinity for  $\mu 3$  opiate receptors, we hypothesize that such positive emotions lead to the direct release of NO and associated biological consequences. Indeed, our studies have demonstrated opposing effects on endothelial vasoreactivity between those previously established (e.g., mental stress induced by negative visual and/or auditory stimuli) and those induced after mirthful laughter, thereby providing a potential mechanistic link between positive emotions and beneficial effects on the vasculature. This article reviews the relevant physiology and comments on the potentially wider clinical implications in the integration of this process to improve vascular health.

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Laughter is a complex human behavior, with inherent characteristics involving and reflecting participation of almost every functional element of the human organism. Laughter is ubiquitous in the human world population. No human group has been identified as being devoid of laughter.

<sup>☆</sup> Supported in part by the National Heart, Lung and Blood Institute (MM) and National Institute of Mental Health (WFF).

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Psychologically, there are many different types of laughter. Some types are unifying, enhancing rapport and understanding, augmenting communication, and contributing to good will and harmony. Other types of laughter may be viewed as divisive with inherent anti-social properties. The most frequent, most widely recognized and most culturally congenial of all laughter types is that associated with Humor. It is specified as mirthful laughter.

Mirthful laughter is composed of active involvements with many different factors of human biologic functioning, preeminently the respiratory and muscular systems. That axiom arises

in large part from formal scientific consideration of the physiologic nature of this active, dynamic process.

## Background

Scientific study of the physiology of mirthful laughter has been regrettably sparse until recent decades. One of the authors (WFF) initiated and participated in a series of such studies [1–4], primarily with regard to the respiratory/neuro/cardiovascular systems, and their interrelationships. The summary results of these various studies indicated active participation of these identified systems in mirthful laughter behavior. Laughter effects were observed to be generally stimulatory, directed through agencies of various endocrine substances, the central nervous system and/or the autonomic nervous systems.

Each of those studies referenced above examined a different aspect of mirthful laughter physiology. The encompassing research format consisted of a progression of investigations. After a preliminary study of tolerances of heart/circulation function relating to mirthful laughter, instrumental examination of laughter was carried out to clarify its essential respiratory nature and to establish the verities of respiratory action patterns. It was determined that mirthful laughter, as existing in Nature, consists of an infinite number of mixed patterns of expiration, inspiration and interval pause, each being of varying duration, sequence, intensity. A subsequent research study explored effects of mirthful laughter on circulating arterial blood pressure. Onset of mirthful laughter has a significant impact on blood pressure, almost simultaneously causing intra-arterial pressure to rise. That initial rise subsequently fluctuates at more modest elevation in gross coordination with intensity fluctuations of continuing laughter. Cessation of laughter is followed by brief decrease of pressure to varying levels slightly below the pre-laughter baseline.

## General history

During the past century, general research in human physiology has demonstrated extensive and complex inter-relationships between respiratory activities and functioning of the cardiovascular system. Considerable efforts have delineated details of reciprocal influences between pulmonary functioning (with neuromuscular participation) and blood pressure regulation. It is not scientifically surprising to discover that in many ways these functional networks perform in intricate coordination. That coordination has been demonstrated to be naturally achieved and maintained through biological events mediated by a very busy and very profuse array of monitors and other bio-cybernetic controls, operating according to basic chemical and physical principles [5].

The intensity and complexity of this coordinated respiratory/circulatory network is observed to be wholly consistent with the survival issues of the biologic functions under those controls. That consistency is found in consideration of the inter-relationship of specific respiratory activity (in this case, mirthful laughter) and in vivo arterial blood pressure. Further, parallel consistency of these research findings is observed when results of experimentation with mirthful laughter are matched with results obtained in studies of blood pressure effects of other respiratory-determined behavior – e.g., coughing, talking [6–10].

However, at this point, a larger inconsistency appears and makes it necessary to question the evolutionary logic of this schema. We are forced to question the survival prospects for a creature that is susceptible to damaging, or even destroying the integrity of its vital oxygenation/circulation apparatus at any time that an indiscretion of frequent emotive behavior exceeds relevant tissue threshold.

Such undesirable occurrences could be recognized in an uncontrollable consequence of the sort of consistency described above, between intermittent presence of a certain behavior (mirthful laughter) and consequent damage to the confining walls of tubes that function to circulate life-sustaining fluids. Mirthful laughter is often boisterous and vigorous in its physical behavior. The consistency noted above, between the behavior and the blood pressure effect, leads to the expectation that blood pressure responses to specified behavior could reach similar extremes of intensity and abruptness, thus perhaps severely testing the integrity of the artery walls through which the blood passes. It is not unreasonable to experience concern about prospects of hemorrhagic ruptures or/and reactive spasms of these walls in the presence of such extremes.

Given that this occasional extravagance of laughter is demonstrated to be associated with potential for extravagance of blood pressure excursions; it could be questioned whether health hazards might arise during boisterous laughter. What might be the degree of potential for a hearty laugher to experience, with an intensity of laughter-induced blood pressure, a vascular accident – such as a “stroke” or other breakdown of blood conveyance? Considering the known factors operating, it could be reasonable to expect that a high incidence of vascular accidents might be associated with laughter.

In fact, occurrence of hemorrhagic vascular accidents in association with mirthful laughter is documented in medical archives. However, the incidence of such misfortunes is very low – so low that no specific statistics are tabulated regarding its occurrence. Occasional such episodes may receive public notice, but as an abnormal event – a tragedy, but not a common one. This very low incidence of hemorrhagic disease, etc., is totally appropriate according to survival expectations, but it is inconsistent with the pathologic potentials of the demonstrated physiology. Until recently, the science world had been left with that enigma. What is reasonable to expect, is not taking place. One way to resolve this paradox, is to assume that here is evidence of the existence of an as-yet undelineated “sparing factor” in the biologic formula.

## A “sparing factor”

During the past half-century, a buildup of scientific information has, indeed, contributed to our perception of what is that sparing factor. That perception did not come suddenly like a bursting epiphany, but gradually, building from one insight to another. The result of that process of discovery has been to establish a solid, unequivocal new science of circulation. The core of that new science is recognition of the dynamic character of normal vascular tissues. Arteries are revealed to be functionally far more than passive tubes, affording simple circulatory passage. By means of the participation of chemical effusions, cellular transactions, ad hoc structural modifications, arteries – and to a lesser extent, veins – are in active interactions with the ‘commodities’ they convey, and with the surrounding tissues to which they deliver. As one researcher stated, “It is appropriate in many ways to consider the human vascular tree as another functional endocrine gland.” [11].

An assortment of experimental studies – none having any specific focus onto any possible relationship to mirthful laughter and/or the blood pressure conundrum identified above – have been conducted by several groups of scientists inspired by objectives of creating greater knowledge about intrinsic capacities of entities of the human vascular system, and exploring implications of those capacities. One focus has been to provide greater illumination of functional characteristics of arterial endothelium. Some novel, highly significant data have been revealed during the unfolding of this research. “Endothelial cells regulate vascular tone, hemosta-

sis, inflammation, lipid metabolism, cell growth, cell migration, and interactions with the extracellular matrix through many receptor-mediated mechanisms.”[12].

An interesting view of the change of scientific focus from one era to the next is afforded by a comparison of two review articles published one in 1956 [13], and the other in 1991 [14] that the wide range of effects of the recently discovered, endothelial-derived relaxing factor, or nitric oxide, whose important biological functions were yet to be fully characterized. In the 1990’s the relationship between aerobic activity, coronary vasodilation and improved endothelial vasoreactivity were explored [15–16], with shear stress responsible for the upregulation of both nitric oxide and prostacyclin. These scientific insights provided a conceptual basis for the endothelium serving as an important mediator of vascular tone; subsequent studies extended the evaluation of endothelial function from physical activity to emotional stimuli. Specifically, monkeys and humans exposed to mental stress demonstrated paradoxical vasoconstriction following intracoronary administration of the vasodilator, acetylcholine [17–18], support-

ing the concept that adverse psychosocial factors directly impair endothelial-dependent vasoreactivity, via heightened sympathetic activation [19].

### Effect of mirthful laughter on endothelial vasoreactivity

If negative stressors adversely impact endothelial biology, the question has arisen as to whether positive emotions, such as mirthful laughter would beneficially impact endothelial function. Having previously identified patients with established CV disease to score poorly (as compared to spouses and other family members without CV disease) on a validated questionnaire assessing response to situational-humor [20], we were interested in determining whether mirthful laughter might also favorably affect endothelial dependent flow-mediated vasodilation (FMD). To test this hypothesis, volunteers were randomized to two different phases in a randomized-crossover design. One phase included watching a movie or segment of popular comedies (e.g., Saturday Night Live) whereas a second phase was to view a movie known

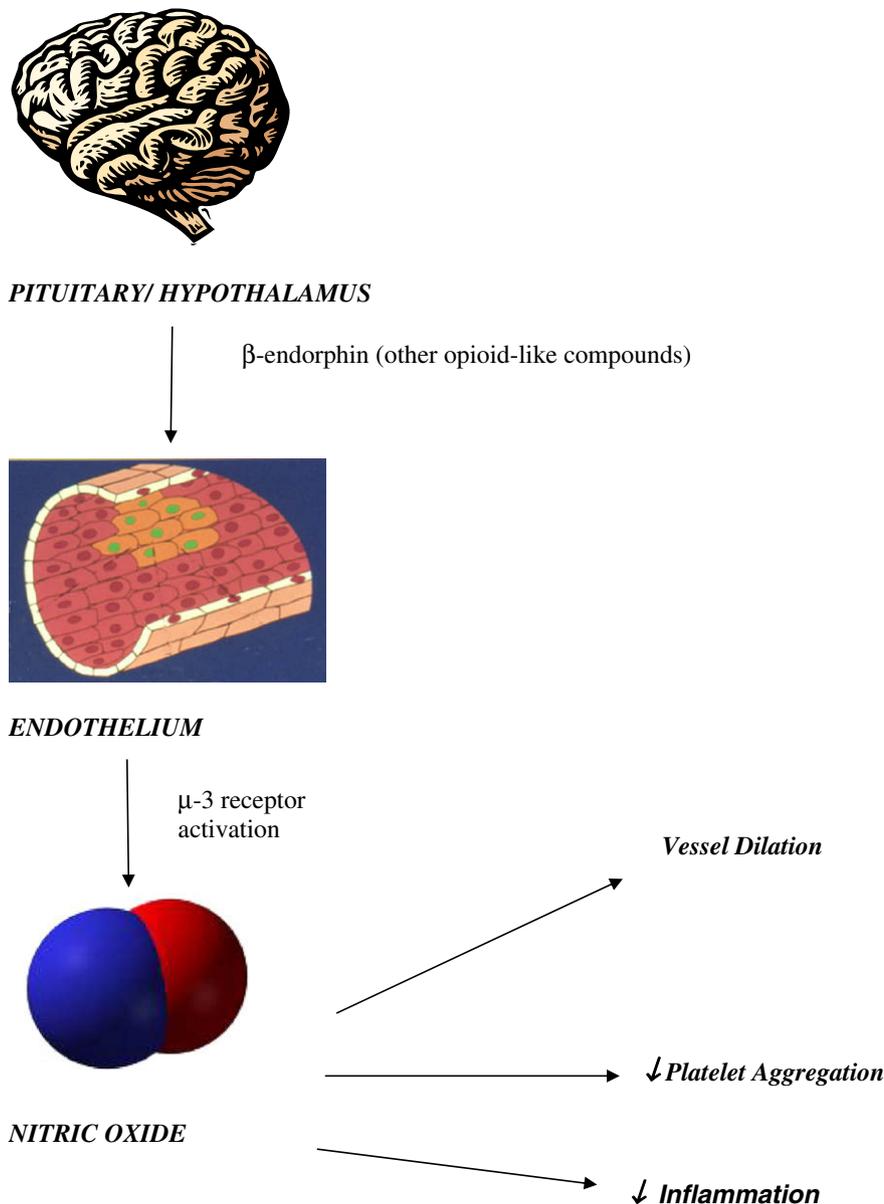


Fig. 1. Postulated effects of mirthful laughter on the vascular endothelium.

to promote mental stress (e.g., the opening segment of *Saving Private Ryan* (DreamWorks, 1998). The assessment of endothelial-dependent vasoreactivity was performed using high resolution ultrasound of the brachial artery. Also referred to as brachial artery reactivity testing (BART), this non-invasive tool has been used in the evaluation of CV risk factors as well as the BART response to therapy [21–24]. A total of 160 BART measurements were performed and demonstrated a divergent effect after watching a movie provoking mental stress as compared to mirthful laughter. Specifically, a 35% reduction in FMD compared to baseline followed mental stress whereas a 22% increase in FMD occurred in response to laughter [25] which was similar to that previously observed with aerobic activity [16] or statin therapy [24].

Based upon these observations, we propose the following schematic representation that may subservise the physiological benefit on the vasculature resulting from mirthful laughter (Fig. 1). In addition to effects on blood pressure and vascular tone described above, we hypothesize that  $\beta$ -endorphins released by the pituitary activate  $\mu_3$  opiate receptors (expressed in the vascular endothelium) that in turn, upregulate nitric oxide synthase to enhance production of nitric oxide (NO) [26]. Nitric oxide exerts a variety of cardioprotective cellular processes via cellular signaling pathways that include a cGMP-dependent pathway responsible for vasodilation and reduced platelet aggregation as well as inhibition of leukocyte trafficking for reduction of vascular inflammation [27]. Taken together, mirthful laughter may serve as a useful and important vehicle for the promotion of vascular health.

### Unresolved issues

Additional research is warranted in order to enhance our understanding of the complex bio-behavioral relationship associated with mirthful laughter and its clinical significance. They include direct assessment of endothelial  $\mu_3$  opiate receptor expression and circulating NO metabolites. In addition, it would be important to comparatively evaluate the extent to which other factors associated with improved endothelial function (and  $\beta$ -endorphin release) [28,29] may impact myocardial blood flow and hemodynamics. Ultimately however, the demonstration that mirthful laughter (practiced on a regular basis) independently reduces CV events, would serve as the most persuasive stimulus for its inclusion as part of an overall program aimed at optimizing CV prevention and vascular health.

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