

Stress, Depression and Sudden Cardiac Death: From the Stone Age to Today

Estresse, Depressão e Morte Súbita: da Era da Pedra até Hoje

Carla Alessandra Scorza¹, Helena Maria Calil², Ricardo Mário Arida³, Roberta Monterazzo Cysneiros⁴, Esper Abrão Cavalheiro¹, Fulvio Alexandre Scorza^{1}*

SUMMARY

Stress, depression and cardiovascular alterations are common denominators along human history and we present a historical review of the subject. Psychiatric patients and individuals experiencing acute stressful circumstances are at risk for sudden unexpected cardiac death. Therefore, depression and emotional stress should be evaluated as a potential risk factor for sudden cardiac death. In this way, mental illness should be better and earlier recognized and proper treatment must be provided. Moreover, a closer research co-operation between cardiologists and psychiatrists should be promoted. Understanding the possible role of adverse emotional state as a risk for sudden death in association with psychiatric disorders is of major importance and we hope that this article will shed light to this subject.

Key words: depression, stress, sudden cardiac death and cardiovascular system.

¹Disciplina de Neurologia Experimental Universidade Federal de São Paulo/Escola Paulista de Medicina (UNIFESP/EPM). São Paulo, Brasil.

*Corresponding Author: Prof. Dr. Fulvio Alexandre Scorza - Disciplina de Neurologia Experimental - Rua Botucatu, 862. Ed. Leal Prado - CEP: 04023-900. São Paulo, SP. Brasil - Telefone (0xx11) 5576 4508 - e-mail: scorza.nexp@epm.br

²Departamento de Psicobiologia. Universidade Federal de São Paulo/Escola Paulista de Medicina (UNIFESP/EPM). São Paulo, Brasil.

³Departamento de Fisiologia. Universidade Federal de São Paulo/Escola Paulista de Medicina (UNIFESP/EPM). São Paulo, Brasil.

⁴Programa de Pós-Graduação em Distúrbios do Desenvolvimento do Centro de Ciências Biológicas e da Saúde da Universidade Presbiteriana Mackenzie. São Paulo, Brasil.

RESUMO

Estresse, depressão e alterações cardiovasculares são denominadores comuns ao longo da história humana. O presente artigo apresenta uma revisão histórica do tema. Pacientes psiquiátricos e indivíduos submetidos a situações de estresse agudo são considerados sujeitos de risco para a morte súbita. Portanto, depressão e estresse emocional devem ser avaliados como fatores de risco em potencial para morte súbita. Dessa forma, as doenças mentais devem ser precocemente reconhecidas e devidamente tratadas. Além do mais, a co-operação mútua entre cardiologistas e psiquiatras deve ser promovida. É importante entender o papel dos estados emocionais adversos associados aos transtornos psiquiátricos como fatores de risco para morte súbita e esse artigo objetiva enfatizar o assunto.

Palavras-chave: *depressão, estresse, morte súbita, sistema cardiovascular.*

INTRODUCTION

DEPRESSION

Depression is one of the most common psychiatric disorders affecting approximately 121 millions of people all over the world. According to the National Institute of Mental Health (USA), in a period of a year, approximately 9.5% of the American population or about 20.9 millions people will develop a depression episode¹. Even in ancient times, depression was recognized as an illness. The *Ebers Papyrus*², one of the world's oldest medical documents from ancient Egypt, described a condition of severe despondency that is equivalent to our modern definition of depression. In the 4th and 5th centuries B.C., Hippocrates argued that mental illnesses had biological origins and he described "melancholia" as a manifestation of a brain dysfunction provoked by excessive black bile. Plato believed that the mind was the cause of the mental illness, the result of "a person's ignorance of a psyche, which leads to self-deception"³. Later, in the 2nd century AD, Aretaeus of Cappadocia hypothesized that mania was an end-stage process of melancholia; he described "cyclothymia" as a type of mental disease that alternated between periods of mania and of depression⁴. During the middle Ages, in some Arabic countries, many asylums were opened to care for the mentally ill. Muslim ideology includes the concept that "the mentally ill person is

loved and particularly chosen by God to tell the truth". These people were frequently worshipped as saints"³ In Europe at the same time, however, it was an entirely different story. Religious fervor perpetuated the notion that mental illness was a divine punishment for a (known or unknown) misdeed. This persisted well into the 17th century. In 1602, the swiss physician Felix Platter published the first medical textbook to deal with psychiatry. It also contained classifications of mental diseases, which Platter hypothesized to have "organic humoral causation"³. The era of shifting from supernatural explanation to the clinical explanation of mental illness was seen only in the 18th century. Finally, scientific enlightenment was ready to be applied to the field of mental illness as well. In 1756, as a result of the influence of Benjamin Franklin, the Pennsylvania hospital was established as the first public institution in the United States to accept mentally ill patients³. The early psychoanalytic movement happened under the increasing need for the special treatment for the mental illness. Sigmund Freud, with the influence of Jean Martin Charcot and Josef Breuer, formally established the school of psychoanalysis⁵. So this era also had both mind and body issues towards the etiology of mental illness. In the last few decades, researchers had come to understand the importance of both psychological and biological approaches. Our current paradigms were developed throughout the historical argument of mind-body issue.

WAS OTZI SUBMITTED TO A STONE AGE TREATMENT?

In 1991, after five thousand years resting in glacial ice, an iceman body was found by climbers, in Ötztal (Tyrolean Alps) and he was nicknamed Ötzi. In 2000, the iceman was submitted to several medical and scientific studies. Ötzi showed typical signs of aging and had been exposed to severe stress. One of his fingernails showed that he suffered from a chronic disease. What's more, deep furrows across the nail revealed that Ötzi's immune system has been exposed to severe stress around 8, 13 and 16 weeks before his death⁶⁻¹⁰. Interestingly, Ötzi had 57 tattoos on his body, they were not formed by pinpricks but rather by fine cuts and they were located precisely in those areas where Ötzi's skeleton showed signs of wear, presumably causing a great deal of pain. Ötzi's tattoos were probably intended for alleviating pain and not as body ornamentation^{11,12}. However, the therapeutically intended acupuncture was practiced even longer before. Balangoda Man, ancient settlers that inhabited the Hill Country of Sri Lanka beginning 37,000 years ago, developed pointed needles of quartz, flint, bone, chert, antlers and other materials that were almost certainly used for acupuncture type therapies. Acupuncture-related practices have been well preserved in ola leaf manuscripts, ancient Sri Lankan books. These findings raise the possibility that the combination of points selected represents a meaningful therapeutic regimen, a stone age treatment.

STRESS

Stress has been a part of human life since man walked on earth. In the light of a synthetic analysis of traces of violent death observed in Neolithic graves raises the issue of emergence of a real climate of collective violence in the first communities of History¹³. Ötzi's death, for example, was a case of homicide. He died a violent death, probably as a result of a crime or a battle. The

"stress reaction" originally helped prehistoric humans survive dangerous routine. Basically, our bodies are extremely well designed for battle – the only problem is the wrong battle. The enemy has changed and is no longer in the form of prehistoric life, but our stress responses are still programmed for those primitive situation. Modern battles include other pressures and they all take their toll on the body.

Hans Selye is recognized as one of the two fathers of the Stress theory. In 1926, as a second year medical student, he noted that the patients studied at rounds all had a strikingly appearance: they were weak, tired, listless, apathetic, often had muscle wasting, diffuse ache and pains, intestinal disturbance and weight loss¹⁴. They even had similar facial expressions. He called this picture "the general syndrome of just being sick"¹⁵. This eventually led him to identify the stress reaction as an underlying cause or major contributing factor to most illness. Selye's theories built on the earlier work of a noted Harvard physiologist named Walter Cannon who had, at the beginning of the century, identified and named the "fight and flight response", which is the body's response to feeling threatened or in danger¹⁶. But whereas Cannon saw the "fight and flight" syndrome as a positive stress reaction that the body uses to protect itself, Selye realized the fact that if the stress reaction goes on for too long, it causes damage and leads to illness. Cannon introduced the term "stress" to medicine but it was Selye who popularised it. In 1936, Selye's¹⁵ experiments on rats showed that various stressors such as cold, heat, infection, trauma, injection of noxious substances, all produced the same effect. When the rats were later examined, they all had swollen and hyperactive adrenal glands, decreased immune response and gastrointestinal ulcers. He had created an experimental model of "the syndrome of just being sick", named General Adaptation Syndrome (GAS). Nowadays, beyond physical stressors as described by Selye, some psychological factors are considered as stressful agents as well (like social problems or even novelty) and they are also capable to

induce important behavioural and physiological alterations^{17,18}. Evidently, the prehistoric man battle in order to survive was uninterrupted, probably provoking a permanent state of tension. In our days, even without eminent death risk, we are exposed to the negative conditions imposed by stress and our organism reacts as if continuously exposed to mortal danger.

SUDDEN CARDIAC DEATH

Although it has been described for at least several centuries, Hippocrates provided a concise, but historically compelling, description of sudden cardiac death in his Aphorisms II, 41: "Those who are subject to frequent and severe fainting attacks without obvious cause die suddenly"¹⁹. This would be the earliest description of sudden cardiac death known. The Aphorism describes recurrent syncope in otherwise healthy individuals. Probably, Hippocrates was very likely describing a group of specific cardiac conditions with a final common pathway of arrhythmic death²⁰. Relying solely on clinical experience based on careful history-taking and keen powers of observation, over 2000 years before the invention of the stethoscope and the electrocardiogram, Hippocrates was the first to describe sudden cardiac death due to a select group of cardiac conditions. In 490 BC, Pheidippides, a renowned Athenian runner, was delivering the news of the Greek victory over the Persians (the first "marathon" in history) but, after running 26.2 miles from Marathon to Athens, immediately collapsed and died. Probably, this was the first recorded incident of sudden cardiac death of an athlete²¹. The association between sudden death and heart disease came with Lancisi's publication *De subitaneis Mortibus* (1706)²². In this work on sudden death, the cause of the demise was not always clear. Although in some of his cases, sudden death was thought to be due to the rupture of an aortic aneurysm, or related to the presence of hypertrophy and dilation of the heart, or to various kinds of valve defects, in many others no apparent cause was found. In the

latter cases Lancisi postulated the possibility of iatrogenic causes. The book on sudden death was dedicated to Pope Clement XI who, in 1706, asked Lancisi to study the strange apparent increase in the number of sudden deaths in the years 1705 and 1706, which had reached epidemic proportions. One year after the pope's request, Lancisi published his *De subitaneis Mortibus*.

PSYCHOLOGICAL STRESS AND SUDDEN DEATH

Psychological stress expresses a situation of imbalance, derived from a real or perceived disparity between environmental demands and the individual's ability to cope with these demands. A situation of psychological stress may include different components: personality factors and character traits, anxiety and depression, social isolation and acute or chronic adverse life events. Studies provide relevant evidence that psychological stress significantly influences the pathogenesis of sudden cardiac death. Furthermore, as well established, stress *per se* exerts important adverse effects on the cardiovascular system²³. Psychological stress acts at both levels: by means of a "chronic" action it contributes to create the myocardial background, while by means of an acute action it can create the transient trigger precipitating sudden death. In the chronic action, two possible mechanisms can be detected: the first is a direct interaction, which contributes to cause a hypertension status²⁴ or to exacerbate coronary atherosclerosis consequent to endothelial dysfunction; the second one acts through adverse health behaviours, such as a poor diet, alcohol consumption or smoking. The mechanisms involved in acute psychological stress, are mainly the ability to trigger myocardial ischemia, promote arrhythmogenesis, stimulate platelet function, and to increase blood viscosity. Finally, some individuals have a sympathetic nervous system hyperresponsivity, manifesting as exaggerated heart rate and blood pressure responses which result in accelerated atherosclerosis, endothelial dysfunction

and even cardiac necrosis²⁵⁻²⁷. A recent study with 3000 individuals of 52 different countries showed that psychological stress corresponds to one of the six major factors of risk to the development of cardiovascular diseases²⁸. The triad stress, cardiac abnormalities and depression cannot be underestimated nor ignored. In this line of evidence, the following question is raised: are people with depression more vulnerable to the occurrence of sudden death?

STRESS, DEPRESSION AND SUDDEN CARDIAC DEATH

Several studies have shown the positive relation among depression, cardiovascular alterations and sudden death since the 80's²⁹⁻³². Sudden death is defined as the occurrence of death shortly after the first symptoms onset (within minutes up to one hour), or even without any clinical previous symptomatology^{33,34}. Furthermore, the depression *per se* can be arrhythmogenic, considering that subjects with depression present reduced parasympathetic tonus, making them more vulnerable to cardiac arrhythmic condition³⁵. Sociologists at UCLA found that 40% of people rejected by their beloved suffered from clinical depression just eight weeks after they separated. Moreover, some of them kill themselves and some simply die shortly thereafter of broken heart, literally³⁶. Sudden emotional stress can result in a condition called stress cardiomyopathy, colloquially known as "broken heart" syndrome: real and potentially deadly. Unfortunately, cardiac alterations and sudden death in depressed people is not so rare as believed. The main factors possibly associated to these phenomena are depression itself, coronary disease, antidepressant therapy, metabolic syndrome and obesity, inadequate lifestyle and smoking³⁷. In this line, studies relate high depression prevalence in patients with cardiac disease. Furthermore, major depressive disorder predicts cardiac events in patients with coronary artery disease³⁸⁻⁴¹. As mentioned, depressed subjects submitted to

antidepressant treatment can be more vulnerable to sudden cardiac death when compared to depressed individuals without pharmacotherapy, probably due to cardiovascular functioning alterations induced by some antidepressants, like the reduction of the intraventricular conduction. This last event is showed in the EEG through QT interval enlargement^{42,43}. In 1990, Ellison et al. related fluoxetine-induced bradycardia and syncope in two patients⁴⁴. This is an important information that should be considered by psychiatrists when dealing with patients with previous history of atrial alterations and/or left ventricular failure.

Stressful life events are known to be predisposing factors for depression. Based on this information, researchers used a stress-induced rodent model of depression to examine the influence of this disorder on ventricular arrhythmias⁴⁵. Chronic mild stress (CMS) is a rodent model of depression that was developed to mimic particular defining features of mood disorders, such as anhedonia (the reduced responsiveness to pleasurable stimuli) and reduced activity level. The researchers found significantly reduced sucrose intake in rats exposed to four weeks of CMS, a specific indication of decreased responsiveness to a pleasurable stimulus. These anhedonic rats displayed elevated heart rate, reduced heart rate variability and reduced threshold for specific ventricular arrhythmias. They concluded that stress appears to reduce the threshold for ventricular arrhythmias, and may signal an increased risk of detrimental cardiovascular outcomes, such as myocardial infarction, heart failure, and sudden cardiac death⁴⁵.

CONCLUSION

Societies along the human history always faced tension, stress and depression. Relationships always seemed tenuous. Modern societies are overcrowded and technologically advanced contributing to increased anxiety and stress. Apparently, stress, depression and cardiovascular alterations are common denominators along human history. Stress

and depression are intimately associated to increased cardiovascular alterations and mortality. Understanding the causes of individual differences and the consequences of variation in vulnerability is of major importance. In this way, a carefully cardiovascular evaluation should be conducted in order to verify the potential effects of the risk factors in the individuals with depression and severe stress, not only due to sudden death risk *per se*, but also in order to provide better quality of life to these individuals.

REFERENCES

1. National Institute of Mental Health. The numbers count: mental disorders in America; 2006. NIH Pub. No. 06-4584. Available from: URL: <http://www.nimh.nih.gov/publicat/numbers.cfm>.
2. Joachim H. Papyrus Ebers. The first complete translation from the Egyptian. Berlin, G. Reimer; 1890.
3. Mora G. History of psychiatry. In Kaplan HI, Sadock BJ, editors. Comprehensive text book of psychiatry. Baltimore: Williams & Wilkins; 1985. p. 2034-54.
4. Goodwin FK, Jamison KR. Maniac-depressive illness. New York. University Press; 1990.
5. Davidson GC, Neale JM. Abnormal Psychology 7th ed. New York: John Wiley & Sons Inc; 1998.
6. Felisati D. Ötzi, the man who came from ice (the most ancient repair of nasal bone fracture). *Acta Otorhinolaryngol Ital.* 2000; 20:62-5.
7. Mayer BX, Reiter C, Bereuter TL. Investigation of the triacylglycerol composition of iceman's mummified tissue by high-temperature gas chromatography. *J Chromatogr B Biomed Sci Appl* 1997; 692: 1-6.
8. Williams AC, Edwards HG, Barry BW. The 'Iceman': molecular structure of 5200-year-old skin characterised by Raman spectroscopy and electron microscopy. *Biochim Biophys Acta* 1995; 1246: 98-105.
9. Selye H. A syndrome produced by diverse noxious agents. *Nature* 1936; 138: 32.
10. McEwen BS. The neurobiology of stress: from serendipity to clinical relevance. *Brain Res* 2000; 886:172-89.
11. Dorfer L, Moser M, Spindler K, Bahr F, Egarter-Vigl E, Dohr G. "5200-Year-Old Acupuncture in Central Europe?" *Science.* 1998; 282:242.
12. Dorfer L, Moser M, Bahr F, Spindler K, Egarter-Vigl E, Giullen S, Dohr G, Kenner T. A medical report from the stone age? *Lancet* 1999; 354: 1023-25.
13. Beyneix A. Réflexions sur les débuts de la guerre au Néolithique en Europe occidentale. *L'anthropologie.* 2007; 111:79-95.
14. Szabo S. The Creative and Productive Life of Hans Selye: A Review of His Major Scientific Discoveries. *Experientia Basel* 1985; 41: 564-7.
15. Selye H. Inflammation and metabolic disorders. *Nature* 1936;444: 860-67.
16. Cannon WB. Bodily Changes in pain, hunger, fear and rage. Appleton and Co., New York and London; 1929.
17. Anda R, Williamson D, Jones D, Macera C, Eaker E, Glassman A, Marks J. Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of U.S. adults. *Epidemiology* 1993; 4:285-94.
18. Nishi N, Nanto S, Shimai S, Matsushima Y, Otake K, Ando A, Yamasaki K, Soga S, Tatara K. Effects of hostility and lifestyle on coronary heart disease among middle-aged urban Japanese. *J Epidemiol* 2001; 11:243-48.
19. Chadwick J, Mann WN. The medical works of Hippocrates. Oxford: Blackwell; 1950.
20. Mirchandani S, Phoon CK. Sudden cardiac death: a 2400-year-old diagnosis? *Int J Cardiol* 2003; 90:41-8.

21. Ghosh J. Sudden cardiac death in athletes – what can be done? *Indian Pacing Electrophysiol J* 2006; 6:139-41.
22. McDougall JI, Michaels L. Cardiovascular causes of sudden death in “De Subitaneis Mortibus” by Giovanni Maria Lancisi. A translation from the original latin. *Bull Hist Med* 1972; 45:486-94.
23. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999; 99:2192-217.
24. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001; 345:1473-82.
25. Kaplan JR, Manuck SB. Status, stress, and atherosclerosis: the role of environment and individual behavior. *Ann N Y Acad Sci* 1999; 896:145-61.
26. Pickering TG. Mental stress as a causal factor in the development of hypertension and cardiovascular disease. *Curr Hypertens Rep* 2001; 3:249-54.
27. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004; 364: 937-52.
28. Rodriguez-Font E, Vinolas-Prat X. Sudden death (III). The causes of sudden death. Problems at the time of establishing and classifying the types of death. *Rev Esp Cardiol* 1999; 52:1004-14.
29. Penninx BW, Guralnik JM, Mendes de Leon CF, Pahor M, Visser M, Corti MC, Wallace RB. Cardiovascular events and mortality in newly and chronically depressed persons > 70 years of age. *Am J Cardiol* 1998; 81:988-94.
30. Luukinen H, Laippala P, Huikuri HV. Depressive symptoms and the risk of sudden cardiac death among the elderly. *Eur Heart J* 2003; 24: 2021-6.
31. Sadre-Chirazi-Stark M, Sandmeyer P. Los herederos de Ötzi. *Mente y Cerebro* 2004; 8:86-9.
32. Rollo F, Ubaldi M, Ermini L, Marota I. Ötzi's last meals: DNA analysis of the intestinal content of the Neolithic glacier mummy from the Alps. *Proc Natl Acad Sci USA* 2002; 99:12594-99.
33. Roose SP, Glassman AH, Dalack GW. Depression, heart disease, and tricyclic antidepressants. *J Clin Psychiatry* 1989; 50:12-7.
34. Lett HS, Blumenthal JA, Babyak MA, Sherwood A, Strauman T, Robins C, Newman MF. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. *Psychosom Med* 2004; 66:305-15.
35. Ayuso-Mateos JL, Vazquez-Barquero JL, Dowrick C, Lehtinen V, Dalgard OS, Casey P, Wilkinson C, Lasa L, Page H, Dunn G, Wilkinson G; ODIN Group. Depressive disorders in Europe: prevalence figures from the ODIN study. *Br J Psychiatry* 2001; 179:308-16.
36. Schönberger J, Seidman CE. Many roads lead to a broken heart: the genetics of dilated cardiomyopathy. *Am J Hum Genet* 2001; 69:249-60.
37. Steffens DC, Helms MJ, Krishnan KR, Burke GL. Cerebrovascular disease and depression symptoms in the cardiovascular health study. *Stroke* 1999; 30:2159-66.
38. McKhann GM, Borowicz LM, Goldsborough MA, Enger C, Selnes OA. Depression and cognitive decline after coronary artery bypass grafting. *Lancet* 1997; 349:1282-84.
39. Carney RM, Rich MW, Freedland KE, Saini J, teVelde A, Simeone C, Clark K. Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosom Med* 1988; 50:627-33.
40. Glassman AH, Preud'homme XA. Review of the cardiovascular effects of heterocyclic antidepressants. *J Clin Psychiatry* 1993; 54:16-22.

41. Boehnert MT, Lovejoy FH Jr. Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. *N Engl J Med* 1985; 313:474-79.
42. Ellison JM, Milofsky JE, Ely E. Fluoxetine-induced bradycardia and syncope in two patients. *J Clin Psychiatry* 1990; 51:385-86.
43. Sperling MR. Sudden Unexplained Death in Epilepsy. *Epilepsy Curr* 2001; 1:21-3.
44. Scorza FA, de Mari JJ, Bressan RA. Sudden cardiac death in schizophrenia: should the psychiatrist pay more attention? *Rev Bras Psiquiatr* 2006; 28:339.
45. Grippo AJ, Santos CM, Johnson RF, Beltz TG, Martins JB, Felder RB, Johnson AK. Increased susceptibility to ventricular arrhythmias in a rodent model of experimental depression. *Am J Physiol Heart Circ Physiol* 2004; 286:619-26.