Medicine

SOCIAL DETERMINANTS AND OXIDATIVE STRESS AMONG ELDERLY PATIENTS WITH CARDIOVASCULAR DISEASES – TWO FACETS OF THE SAME MATTER

Andreea SERBAN[1]
Minodora IORDACHE[2]
Andreea HODOROGEA[3]
Cristian TOMA[4]
Sean MAHER[5]
Adriana ILIESIU[6]
Ioan Tiberiu NANEA[7]

ABSTRACT:
CARDIOVASCULAR DISEASE (CVD) IS THE NUMBER ONE CAUSE OF DEATH WORLDWIDE.[1] AND ITS PREVALENCE IS PREDICTED TO RISE EXPENDENTIALLY IN THE COMING YEARS. THERE IS A COMPLEX INTERPLAY BETWEEN THE UNDERLYING HEALTH DETERMINANTS THAT COULD TRIGGER ANY PATHOPHYSIOLOGICAL ABNORMALITY LEADING TO THE DEVELOPMENT OF DISEASE[4]. THIS ARTICLE FOCUSES ON THE TWO WAY TICKET THAT IS OXIDATIVE STRESS (OS) AND SOCIAL DETERMINANTS IN THE DEVELOPMENT OF CVD.
IT IS BECOMING INCREASINGLY CLEAR THAT SOCIOECONOMIC FACTORS PLAY A MAJOR ROLE IN THE DEVELOPMENT OF CVD. IN ADDITION, A MULTITUDE OF RESEARCH PAPERS HAVE SHOWN DISADVANTAGEOUS SOCIAL FACTORS CAN TRIGGER AN INCREASE IN ROS PRODUCTION. OUR KNOWLEDGE OF hROS HAS EVOLVED IN THE PAST DECADES TO THE POINT THAT WE NOW HAVE WELL DOCUMENTED EVIDENCE SUPPORTING THE ROLE OF hROS (E.G. PEROXYNITRITE, HYPOCHLORITE, HYDROXYL RADICAL) IN THE MECHANISM OF ENDOTHELIAL DYSFUNCTION, VASCULAR COMPLICATIONS, MYOCARDIAL INFARCTION, CONGESTIVE HEART FAILURE AND STROKE[4].
ON THE OTHER HAND, SOCIAL DETERMINANTS ARE YET ANOTHER FACET OF THE SAME MATTER. RECENT DATA EMPHASISES THE CAPACITY OF SOCIAL DETERMINANTS AND SOCIAL CONFIGURATION TO DETERMINE THE DEVELOPMENT OF CVD[3]. MOREOVER, THE DYNAMIC NATURE OF HOW THE SOCIAL ENVIRONMENT ACTS UPON DISEASE NECESSITATES AN INDEPTH INVESTIGATION.
AS A CONSEQEUNCE, IN ORDER TO PROPERLY ADDRESS THE INCREASE IN CVD, BOTH PATHOPHYSIOLOGICAL AND SOCIAL ASPECTS SHOULD BE TAKEN EQUALLY INTO CONSIDERATION.

KEY WORDS: CARDIOVASCULAR DISEASE, AGING, SOCIAL DETERMINANTS, REACTIVE OXYGEN SPECIES, PREVENTIO

[1] MD, PhD Attending, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania, andreea_liteanu@yahoo.com
[2] MD, Department of Biophysics and Cell Biotechnology, University of Medicine and Pharmacy "Carol Davila"
[3] MD, Cardiology Department, Hospital "Prof. Th. Burghele "
[4] MD, Cardiology Department, Hospital "Prof. Th. Burghele "
[5] MD, Cardiology Department, Hospital "Prof. Th. Burghele "
[6] MD, Cardiology Department, Hospital "Prof. Th. Burghele "
[7] MD, Cardiology Department, Hospital "Prof. Th. Burghele "

INTRODUCTION

1. Cardiovascular Disease Worldwide

Cardiovascular disease (CVD) is the number one cause of death worldwide. Moroever, the prevalence of CVD is projected to rise by 60% from 1990 to 2020. [6]CVD associated morbidity and mortality places tremendous constraints on the health care system. Currently CVD is the leading cause of death among high-income countries[8]. In addition,CVD is now the number one cause of non-transmissible morbidity and mortality amidst low- and middle-income countries, accounting for almost 25% of total deaths[9].

In the past decades there has been a transition from the most common causes of death and morbidity (infectious diseases) to non-transmissible diseases (CVD). There are three possible circumstances that could explain this transition: increasing average life expectancy; economic, social and cultural changes and an increase in CVD risk factors including smoking, overweight, hypertension and diabetes[10].

The vast majority of studies are dedicated to describing the mechanism involved in the development of CVD. Amongst CVD determinants, pathophysiological (e.g. hypertension, diabetes), behavioral (e.g. cigarette smoking, alcohol consumption) and social risk factors (e.g. lowsocioeconomic status, social isolation) were incriminated.

Non-modifiable risk factors of CVD such as age, family history, gender and ethnicity, are also the subject of extensive studies. When considering the percentage of cardiovascular disease induced deaths, there are major differences depending on the age category. CVD mortality and morbidity increases significantly with age. In addition a man is more likely to develop a CVD than a pre-menopausal woman, but the risk equalizes for post-menopausal women (Fig. 1, Fig. 2).[11]

Aside from the non-modifiable risk factors of CVD most others are modifiable risk factors. There are numerous well established risk factors of CVD, but describing them in detail is not the purpose of this paper. However, it is crucial to understand that changes in lifestyle, dietary patterns, physical activity, alcohol consumption and smoke free policies could prevent or reduce the total risk of CVD.

---

[8] Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, Rayner M, European Cardiovascular Disease Statistics 2012, Brussels Sophia Antipolis: European Society of Cardiology, 2012.

[9] Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, Rayner M, European Cardiovascular Disease Statistics 2012, Brussels Sophia Antipolis: European Society of Cardiology, 2012.

[10] *Levenson JW, Skerrett PJ, Gaziano JM. Reducing* the *global burden* of *cardiovascular disease*: the *role* of *risk factors*. *Prev* Cardiol.*5*(2002*):*188-99

[11] N. T. P. S. M. R. Melanie Nichols, "Cardiovascular disease in Europe 2014: epidemiological update," *European Heart Journal* , 2014.

Fig. 1 The major causes of mortality in men, latest available year; adapted after World Health Organization Mortality Database.

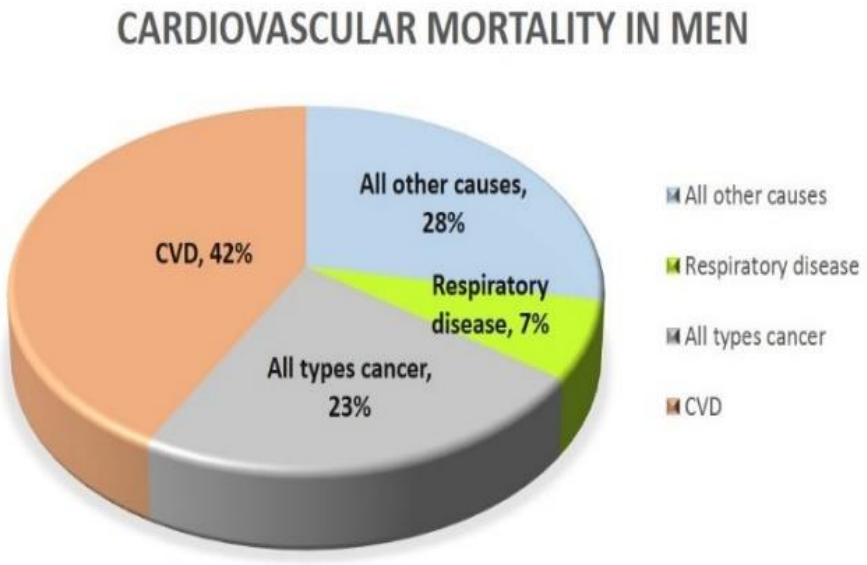
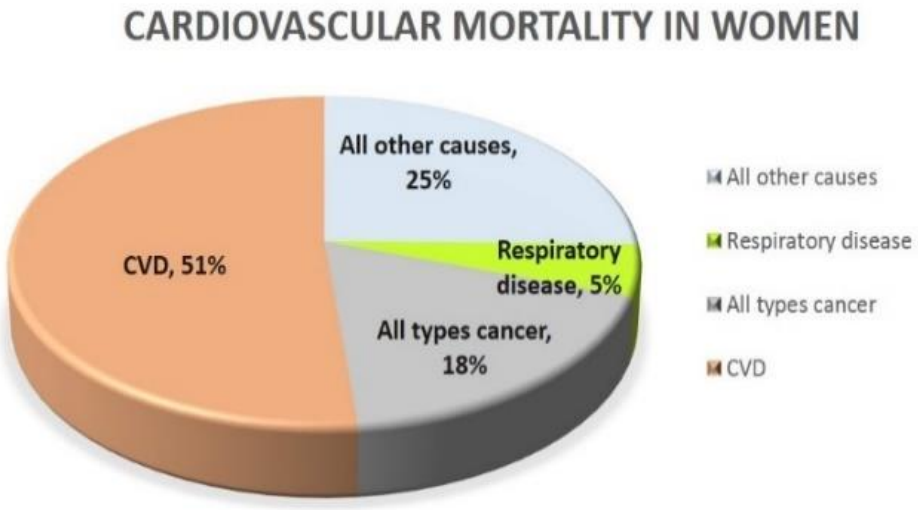


Fig. 2 The major causesof mortality in women, latest available year; adapted after World Health Organization Mortality Database.



1. POPULATION AGEING AND SOCIAL HEALTH

1.1 Demographic shift – transition towards a much older population

CVD occurs more frequently in an aging population, which is more advanced in highly developed countries[12]. Population ageing arises from three major demographic effects: increase in average life expectancy, declining fertility and migration[13]. The substantial increase in average life expectancy is a phenomenon that occurs due to the reduction of infant mortality, control of infectious diseases and the enhancement of sanitation, living standards and nutrition. In2050, the number of elderly people is projected to be five times higher than today and will represent 4% of the total population[14]. Elderly people aged 80 and over is the fastest growing segment of the population.

2.1 Demographic shift – transition towards a much older population

CVD occurs more frequently in an aging population, which is more advanced in highly developed countries[15]. Population ageing arises from three major demographic effects: increase in average life expectancy, declining fertility and migration[16]. The substantial increase in average life expectancy is a phenomenon that occurs due to the reduction of infant mortality, control of infectious diseases and the enhancement of sanitation, living standards and nutrition. In2050, the number of elderly people is projected to be five times higher than today and will represent 4% of the total population[17]. Elderly people aged 80 and over is the fastest growing segment of the population.

An ageing populationis in many aspects a matter of international politics. Demographic changes will have major implications for health services. Furthermore, it has the potential to exert substantialburden on the costs of pensions, medical care and long term care services. On the other hand the poor capacity of the health system to directly support vulnerable populations through public health programs, preventive measures and early diagnosis is another reason that leads to physical aging and CVD appearance.

Both CVD and premature aging are closely linked to behavioral risk factors, including alcohol and tobacco use, unhealthy diets and lack of exercise. Old age is marked by changes in health and in social relationships and their impact can be influenced by gender, physical and mental wellbeing, illness, social and economic resources.

---

[12] Kreatsoulas, Catherine; Anand, Sonia S "The impact of social determinants on cardiovascular disease," *Can J Cardiol*, Vols. Vols. 8C–13C- , no. (Suppl C), p. p. 26, 2010. - Aug-Sep.

[13]"http://www.mmuncii.ro/j33/images/Documente/Transparenta/Dezbateri_publice/_Anexa1_ProiectHG_SIA.pdf .," ministerul muncii, 2015-07-15. [Online]. Available: http://www.mmuncii.ro/j33/images/Documente/Transparenta/Dezbateri_publice/_Anexa1_ProiectHG_SIA.pdf.. [Accessed oct 2015].

[14]"http://www.mmuncii.ro/j33/images/Documente/Transparenta/Dezbateri_publice/_Anexa1_ProiectHG_SIA.pdf .," ministerul muncii, 2015-07-15. [Online]. Available: http://www.mmuncii.ro/j33/images/Documente/Transparenta/Dezbateri_publice/_Anexa1_ProiectHG_SIA.pdf.. [Accessed oct 2015].

2.2 Social health

It is necessary to mention here that the term "social health" introduced by Donald and Co in 1978, is seen as a dimension of wellness distinct from an individual's physical and mental health. In terms of social support, social health is a component that can alter the effect of one's environment and that of stressful events on the physical and mental health of the elderly.

Social health is a complex term that encompasses the need for a satisfactory social status, good working and living conditions, active and appropriate access to health care and efficacious social support[18]. Available social support for the elderly influences health, happiness and longevity. Seniors with more support and social interaction need less health care and have less need for hospitalization. This theory suggests that health in old age, as well as quality of life, could be significantly improved by managing the social environment.

2. THE DYNAMIC NATURE OF SOCIAL DETERMINANTS OF CARDIOVASCULAR DISEASE

"Social determinants of health" represent an extensive term used for describing how age and conditions in which people are born, live and work have an impact on health[19]. Alongside other social factors, such asmonetary allocations, degree of education and resources, probably the most influential one is the health care system[20]. This system needs to provide solutions for the increase in CVD and for the complex phenomenon behind it, i.e. the interaction between socioeconomic features and pathophysiological features of CVD. Literature data implies that sociallydeprived groups are exposed to more cardiovascular risk factors[21].

3.1 Lowsocioeconomic status and social isolation

In a review from 2009 that linked social factors with cardiovascular disease, C. Kreatsoulas found that the underlying cause of other modifiable CVD risk factors could have a

[15] Kreatsoulas, Catherine; Anand, Sonia S "The impact of social determinants on cardiovascular disease," *Can J Cardiol,* Vols. Vols. 8C–13C- , no. (Suppl C), p. p. 26, 2010. - Aug-Sep.
[16]"http://www.mmuncii.ro/j33/images/Documente/Transparenta/Dezbateri_publice/_Anexa1_ProiectHG_SIA.pdf .," ministerul muncii, 2015-07-15. [Online]. Available: http://www.mmuncii.ro/j33/images/Documente/Transparenta/Dezbateri_publice/_Anexa1_ProiectHG_SIA.pdf.. [Accessed oct 2015].
[17]"http://www.mmuncii.ro/j33/images/Documente/Transparenta/Dezbateri_publice/_Anexa1_ProiectHG_SIA.pdf .," ministerul muncii, 2015-07-15. [Online]. Available: http://www.mmuncii.ro/j33/images/Documente/Transparenta/Dezbateri_publice/_Anexa1_ProiectHG_SIA.pdf.. [Accessed oct 2015].
[18] B. L. A.-C. S. S. L. M. K.-I. Thierry Lang, "Social Determinants of Cardiovascular Diseases," *Public Health Reviews,* vol. 33, no. 2, pp. 601-622
[19] Kreatsoulas, Catherine; Anand, Sonia S "The impact of social determinants on cardiovascular disease," *Can J Cardiol,* Vols. Vols. 8C–13C- , no. (Suppl C), p. p. 26, 2010. - Aug-Sep.
[20] Kreatsoulas, Catherine; Anand, Sonia S "The impact of social determinants on cardiovascular disease," *Can J Cardiol,* Vols. Vols. 8C–13C- , no. (Suppl C), p. p. 26, 2010. - Aug-Sep.
[21] H. Hennekens,Charles, "Increasing Burden of Cardiovascular Disease Current Knowledge and Future Directions for Research on Risk Factors", Circulation, 97(1998):1095-1102

socioeconomic causality[22]. Thus, the review identified the social characteristic of certain disadvantaged groups and highlighted their vulnerability and higher risk for CVD.

Unemployment and low socioeconomic status, a concept first reviewed by GA Kaplan in 1993, are two possible CVD risk factors that are quickly overlooked due to their time-dependent effect.[23] There is a powerfulconnection between various social circumstances, such as destitute working and living settings, limited health education and decreased access to health care.There is substantial evidence of an inverse relationbetween socioeconomic status and almost all the cardiovascular disease risk factors, with the possible exceptionof cholesterol level. Furthermore, prominent evidence implies that people with a low socioeconomic status are more prone to smoking and to have unhealthy dietary habits. [24]Also, it is shown that poverty in early life has a substantial effect on the development of arteriosclerosis.[25]

Makenbach et al highlighted how a lack of education may increase levels of ischemic heart disease, cerebrovascular disease, and total CVD mortality by carrying out a study in the United States and eleven Western European countries that found higher mortality among individuals with lower education in all countries[26].

Regardless of the approach used to define social status or how society is structured, education has proven to be a useful tool for the measurement of socioeconomic status. Alongside other instruments for the measurement of social class, such as income, occupation and living conditions, education has been the first choice for epidemiologists[27]. It seems that poor-living conditions, a low level of education, social instability, unemployment or low income and reduced access to health care are strongly linked to coronary heart disease, stroke and myocardial infarction[28].

It is therefore crucial that we identify and prevent the social forces that trigger the development of CVD risk factors, by reducing the number of people at risk of poverty or social exclusion[29].

---

[22] Kreatsoulas, Catherine; Anand, Sonia S "The impact of social determinants on cardiovascular disease," *Can J Cardiol*, Vols. Vols. 8C–13C- , no. (Suppl C), p. p. 26, 2010. - Aug-Sep.
[23] K. J. Kaplan GA, "Socioeconomic factors and cardiovascular disease: a review of the literature," *Circulation*, vol. 88, pp. 1973-98, Oct 1993
[24] K. J. Kaplan GA, "Socioeconomic factors and cardiovascular disease: a review of the literature," *Circulation*, vol. 88, pp. 1973-98, Oct 1993
[25] K. J. Kaplan GA, "Socioeconomic factors and cardiovascular disease: a review of the literature," *Circulation*, vol. 88, pp. 1973-98, Oct 1993
[26] K. M. L. T. Leclerc A, "Inégaux face à la santé: du constat à l'action," *La Découverte*, p. 298, 2008.
[27] K. J. Kaplan GA, "Socioeconomic factors and cardiovascular disease: a review of the literature," *Circulation*, vol. 88, pp. 1973-98, Oct 1993.
[28] B. L. A.-C. S. S. L. M. K.-I. Thierry Lang, "Social Determinants of Cardiovascular Diseases," *Public Health Reviews*, vol. 33, no. 2, pp. 601-622.; Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, Rayner M, European Cardiovascular Disease Statistics 2012, Brussels Sophia Antipolis: European Society of Cardiology, 2012.
[29] B. L. A.-C. S. S. L. M. K.-I. Thierry Lang, "Social Determinants of Cardiovascular Diseases," *Public Health Reviews*, vol. 33, no. 2, pp. 601-622.

3.2 Chronic exposure to stress – a time varying risk factor

Chronic stress is usually an environmental factor that affects one'sperceptualcapacity and is consistently associated with a wide range of health morbidities, depending on the duration of the stressor agents. A conflictual home or work environment as well as social isolation, significantly increases the risk of myocardial infarction and premature mortality[30]. Arterial hypertension is more frequently detected in men with negative social interactions and a stressful workplace than in people who have an amicable working realtionship with their colleagues[31]. Consequently, work-related chronic stressor otherstressful events, and their role in cardiovascular disease needs further investigation[32].

3. THE ROLE OF HIGHLY REACTIVE OXYGEN SPECIES IN CVD

4.1 Endogenous and exogenous triggers of oxidative stress

There is an abundance ofstudies and literatureavailable on oxidative stress and its potential triggers. Apart from known reactive oxygen species (ROS)generating factors like infectious, inflammatory diseases, surgery,cancer and drugs (e.g.corticosteroids), there are furtherjob-related and behavioral risk factors worth mentioning.

Oxidative species seem to increase with age[33], cigarette smoking[34], occupational exposure to ionizing radiation [16], and environmental stress like prolonged exposure to UV radiation or heat[35].

4.2 Several mechanisms of reactive oxygen species in CVD pathophysiology

This review paper is not meant to be exhaustive, especially on such a complex chapter of CVD pathophysiology, instead it is meant to stress the importance of developing new specific molecular therapy targets. Our knowledge of highly reactive oxygen species (hROS) has evolved in the past decades to the point that we now have well documented evidence supporting the role of hROS (e.g. peroxynitrite, hypochlorite, hydroxyl radical) in the mechanism of endothelial dysfunction, vascular complications, myocardial infarction, congestive heart failure and stroke[36].

---

[30] K. M. L. T. Leclerc A, "Inégaux face à la santé: du constat à l'action," *La Découverte,* p. 298, 2008.
[31] T. Pickering, "Reflections in hypertension: work and blood pressure," *J Clin Hypertens,* vol. 6, pp. 403-405, 2004.
[32] K. J. Kaplan GA, "Socioeconomic factors and cardiovascular disease: a review of the literature," *Circulation,* vol. 88, pp. 1973-98, Oct 1993.
[33] I. H.-F. N. M. E. V. J. M. O. G. M. C. C. A. M. R. M Andriollo-Sanchez, "Age-related oxidative stress and antioxidant parameters in middle-aged and older European subjects: the ZENITH study," *European Journal of Clinical Nutrition,* vol. 59, no. 2, p. S58–S62, 2005
[34] C. A. I. R. Isik B1, "Oxidative stress in smokers and non-smokers," *Inhal Toxicol,* vol. 19, no. 9, pp. 767-9, 2007.
[35] G. A. S. J. D. D. U. J. V. J. Svobodová AR, "Acute exposure to solar simulated ultraviolet radiation affects oxidative stress-related biomarkers in skin, liver and blood of hairless mice," *Biol Pharm Bull,* vol. 34, no. 4, pp. 471-9, 2011.
[36] Sugamura,Koichi and John F. Keaney,"Reactive Oxygen Species in Cardiovascular Disease", Free Radical Biology&Medicine,51(2011):978-992

Research has focused on validating the toxic effects of hROS on the cellular membrane, cellular structure, lipids, proteins and DNA. In vitro experiments demonstrate that all these cumulative effects lead to an interruption in cell signaling, oxidative metabolism and finally, to cell death either through apoptosis or necrosis.

Essentially all CVD are the direct consequence of atherosclerosis. ROS play a very important role in the initiation of the atherosclerotic process, by oxidizing low density lipoproteins (LDL). The transfer of oxidized LDL from the vascular lumen into the media, represents the initiation of atherosclerosis at the site of endothelial damage[37]. Also, ROS maintain the progression of atherosclerosis and support plaque development[38]. Complicated atherosclerotic plaque is a well established risk factor for myocardial infarction. Procedures for resolving an acute myocardial infarction rely mainly on restoring blood flow in the ischemic area. Unfortunately, reperfusion progresses with a burst of ROS, which may persist for hours[39]. In addition, these high levels can lead to structural damage of the heart, capillary leakage and cardiomyocyte metabolism alterations thus, affecting both the systolic and diastolic function[40]. Also reperfusion can lead to cardiac conduction system dysfunction with the occurrence of arrhythmias[41].

Thus, increased concentration of ROS can be triggered by socio-economic factors which in turn may contribute substantially to the development of CVD.

4.3 Desirable new therapeutic approaches

So far, synthetic antioxidants have been examined in human clinical trials with no concluding results. Outcome predictions are difficult to make due to the complex effects of hROS, making it difficult to choose the dosage and type of antioxidant[42]. In order to alter distinct ROS-sensitive pathways we need novel probes suited for the detection of each hROS with high

[37] J. A. B. A. D. W. e. a. M. Navab, "The Yin and Yang of oxidation in the development of the fatty streak: a reviewbased on the 1994 George Lyman Duff memorial lecture," *Arteriosclerosis,Thrombosis, and Vascular Biology,* vol. 16, no. 7, pp. 831-842, 1996.; H. J. T. J. J. C. B. D. J. D. Yannick J., "Reactive Oxygen Species and the Cardiovascular System," *Oxidative Medicine and Cellular Longevity,* 2013.

[38] C. H. Livia, "Reactive oxygen species in cardiac signalling – from mitochondria to plasma membrane ion channels," *Proceedings of the Australian Physiological Society,* pp. 55-61, 2005.

[39] M. O. J. B. S. P. e. a. R. Bolli, "Direct evidence that oxygen-derived free radicals contribute to postischemic myocardial dysfunction in the intact dog," *Proceedings of the National Academy of Sciences of the United States of America,* vol. 86, pp. 4695-4699, 1989.

[40] S. Toyokuni, "Reactive oxygen species-inducedmolecular damage and its application in pathology," *Pathology International,* vol. 49, no. 2, p. 91–102, 1999.

[41] L. L. C. B. G. e. a. R. D. Lopes, "Atrial fibrillation and acute myocardial infarction: antithrombotic therapy and outcomes," *American Journal of Medicine,* vol. 125, no. 9, p. 897– 905, 2012.; A. S. K. S. M. A.-K. e. a. M. Majidi, "Reperfusion ventricular arrhythmia "bursts" predict larger infarct size despite TIMI 3 flow restoration with primary angioplasty for anterior ST-elevation myocardial infarction," *European Heart Journal,* vol. 30, no. 7, p. 757–764., 2009.

[42] Sugamura,Koichi and John F. Keaney,"Reactive Oxygen Species in Cardiovascular Disease", Free Radical Biology&Medicine,51(2011):978-992

specificity and sensitivity[43]. In vitro studies are making progress in understanding the mechanisms of oxidative damage and which species can be more toxic than others. Extrapolated results for parameters in vivo can make relevant contributions to cardiovascular disease therapeutic strategies[44].

Knowing that hROS play a pertinent role in the physiology as well as the pathophysiology of CVD, it is only fair to ask how a more selective, targeted antioxidant therapy would benefit the primary or secondary prevention of CVD. Further research should focus on matching antioxidant therapy to the oxidative stress present in CVD[45].

Only by understanding these specific molecular targets can we propose new effective therapeutic strategies, aside from the desirable correction of the socio-economic risk factors and improved social heath.

CONCLUSION

It is becoming clear that socioeconomic factors play a major role in the development of CVD. As life expectancy increases, the aging population is exposed to a greater number of cardiovascular risk factors. However, in a vicious circle the aging process accelerates when CVD occurs, triggering a cluster of pathophysiological abnormalities.

Disadvantageous social factors can trigger an increase in ROS production which in turn may contribute substantially to the development of CVD. Social circumstances and the health care system hold a key role in the evolution, prevention, prompt diagnostic and treatment of cardiovascular risk factors and cardiovascular disease.

As a consequence, in order to properly address this increase in CVD in elderly patients, both pathophysiological and social aspects should be equally taken into consideration.

Reflecting on health determinants in this way could lead to interdisciplinary strategy sessions to build knowledge, set priorities and improve prevention measures. In light of this data we need to evaluate and address this subject from an interdisciplinary angle, taking into consideration the interrelation of social and pathophysiological determinants of illness.

[43] Sugamura,Koichi and John F. Keaney,"Reactive Oxygen Species in Cardiovascular Disease", Free Radical Biology&Medicine,51(2011):978-992

[44] H. J. T. J. J. C. B. D. J. D. Yannick J., “Reactive Oxygen Species and the Cardiovascular System,” *Oxidative Medicine and Cellular Longevity*, 2013.

[45] H. J. T. J. J. C. B. D. J. D. Yannick J., “Reactive Oxygen Species and the Cardiovascular System,” *Oxidative Medicine and Cellular Longevity*, 2013.

REFERENCES

1. **Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, Rayner M**, European Cardiovascular Disease Statistics 2012, Brussels Sophia Antipolis: European Society of Cardiology, 2012.
2. **Kitiching, Angela,** "Health and Social Care Bill Second Reading Briefing",*Age UK,* 2011.
3. **Kreatsoulas, Catherine; Anand, Sonia S** "The impact of social determinants on cardiovascular disease," *Can J Cardiol,* Vols. Vols. 8C–13C- , no. (Suppl C), p. p. 26, 2010. - Aug-Sep.
4. **Sugamura,Koichi and John F. Keaney,"**Reactive Oxygen Species in Cardiovascular Disease", Free Radical Biology&Medicine,51(2011):978-992
5. **Prof Yusuf, Salim and Steven Hawken, Stephanie Ôunpuu, Tony Dans, Alvaro Avezum, Fernando Lanas, Matthew McQueen, Andrzej Budaj, Prem Pais, John Varigos, Liu Lisheng**, "Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries(the INTERHEART study): case-control study,The Lancet,364(2004):937-952,Issue:9438
6. **H. Hennekens,Charles**, "Increasing Burden of Cardiovascular Disease Current Knowledge and Future Directions for Research on Risk Factors", Circulation, 97(1998):1095-1102
7. ***Levenson JW, Skerrett PJ, Gaziano JM***. *Reducing* the *global burden* of *cardiovascular disease*: the *role* of *risk factors*. *Prev* Cardiol.*5*(2002*):*188-99
8. N. T. P. S. M. R. Melanie Nichols, "Cardiovascular disease in Europe 2014: epidemiological update," *European Heart Journal* , 2014.
9. "http://www.mmuncii.ro/j33/images/Documente/Transparenta/Dezbateri_publice/_Anexa1_ProiectHG_SIA.pdf.," ministerul muncii, 2015-07-15. [Online]. Available: http://www.mmuncii.ro/j33/images/Documente/Transparenta/Dezbateri_publice/_Anexa1_ProiectHG_SIA.pdf.. [Accessed oct 2015].
10. B. L. A.-C. S. S. L. M. K.-I. Thierry Lang, "Social Determinants of Cardiovascular Diseases," *Public Health Reviews,* vol. 33, no. 2, pp. 601-622.
11. **K. J. Kaplan GA**, "Socioeconomic factors and cardiovascular disease: a review of the literature," *Circulation,* vol. 88, pp. 1973-98, Oct 1993.
12. K. M. L. T. Leclerc A, "Inégaux face à la santé: du constat à l'action," *La Découverte,* p. 298, 2008.
13. **T. Pickering**, "Reflections in hypertension: work and blood pressure," *J Clin Hypertens,* vol. 6, pp. 403-405, 2004.
14. I. H.-F. N. M. E. V. J. M. O. G. M. C. C. A. M. R. M Andriollo-Sanchez, "Age-related oxidative stress and antioxidant parameters in middle-aged and older European subjects: the ZENITH study," *European Journal of Clinical Nutrition,* vol. 59, no. 2, p. S58–S62, 2005.
15. C. A. I. R. Isik B1, "Oxidative stress in smokers and non-smokers," *Inhal Toxicol,* vol. 19, no. 9, pp. 767-9, 2007.
16. J.-P. J.-G. D. P. Edouard I. Azzama, "Ionizing radiation-induced metabolic oxidative stress and prolonged cell injury," *Cancer letters,* vol. 327, no. 1–2 Oxidative Stress-Based Cancer Biomarkers, p. 48–60, 31 December 2012.
17. G. A. S. J. D. D. U. J. V. J. Svobodová AR, "Acute exposure to solar simulated ultraviolet radiation affects oxidative stress-related biomarkers in skin, liver and blood of hairless mice," *Biol Pharm Bull,* vol. 34, no. 4, pp. 471-9, 2011.
18. M. O. J. B. S. P. e. a. R. Bolli, "Direct evidence that oxygen-derived free radicals contribute to postischemic myocardial dysfunction in the intact dog," *Proceedings of the National Academy of Sciences of the United States of America,* vol. 86, pp. 4695-4699, 1989.
19. S. Toyokuni, "Reactive oxygen species-inducedmolecular damage and its application in pathology," *Pathology International,* vol. 49, no. 2, p. 91–102, 1999.
20. L. L. C. B. G. e. a. R. D. Lopes, "Atrial fibrillation and acute myocardial infarction: antithrombotic therapy and outcomes," *American Journal of Medicine,* vol. 125, no. 9, p. 897– 905, 2012.
21. A. S. K. S. M. A.-K. e. a. M. Majidi, "Reperfusion ventricular arrhythmia "bursts" predict larger infarct size despite TIMI 3 flow restoration with primary angioplasty for anterior ST-elevation myocardial infarction," *European Heart Journal,* vol. 30, no. 7, p. 757–764., 2009.

22. **C. H. Livia**, "Reactive oxygen species in cardiac signalling – from mitochondria to plasma membrane ion channels," *Proceedings of the Australian Physiological Society,* pp. 55-61, 2005.
23. J. A. B. A. D. W. e. a. M. Navab, "The Yin and Yang of oxidation in the development of the fatty streak: a reviewbased on the 1994 George Lyman Duff memorial lecture," *Arteriosclerosis,Thrombosis, and Vascular Biology,* vol. 16, no. 7, pp. 831-842, 1996.
24. H. J. T. J. J. C. B. D. J. D. Yannick J., "Reactive Oxygen Species and the Cardiovascular System," *Oxidative Medicine and Cellular Longevity,* 2013.
25. M. W. RG Marmot, "Social Determinants of Health," *Oxford University Press,* no. 2nd edn, 2006.