# WHY THE COVID-19 DISEASE IS PARTICULARLY DANGEROUS IN ELDERLY PATIENTS?

**Rouatbi Sonia[1,2,3],**

1. Physiology and functional explorations laboratory, Farhat Hached Hospital, Sousse, Tunisia
2. Physiology and functional explorations laboratory, Faculty of Medicine, Sousse, Tunisia
3. Research Laboraory of cardiac failure "LR12SP09"

**Abstracts**: Coronavirus disease 2019 (Covid-19) has so far killed many people; with the majority of deaths occurring in people over the age of 65 years. The severity and outcome of Covid-19 largely depends on a patient's age. The combination of three factors could explain this finding: the first factor is linked to the lung aging, the second is linked to associated comorbidities in elderly subjects and the third is linked to the particularities of Covid-19. Here we emphasize the modifications linked to pulmonary aging and their role in the worsening the covid19 disease.

**Key Words**: Covid-19, lung aging, pulmonary functions, ACE2, co morbidities.

**Author for correspondence:** Dr. .Rouatbi Sonia. Department of Physiology and functional explorations, Farhat Hached Hospital, Sousse, Tunisia. E-mail. Sonia.rouatbi@gmail.com

Among COVID-19 patients, elderly patients have a higher mortality rate and symptomatic infection rate. Approximately 80% and 90% of deaths have occurred in patients aged >70 years and ≥60 years in Korea and Italy, respectively (1, 2).

Why is the high mortality of Covid-19 so strongly associated with age? The answer probably lies in the combination of three factors: the first factor is linked to the aging process especially of the lungs (pulmonary aging), the second is linked to associated co morbidities in elderly subjects and the third is linked to the particularities of Covid-19.

Pulmonary aging can be of intrinsic (genetic) or extrinsic (environmental) origin. The lung is the most vulnerable organ to extrinsic aging since it is in direct contact with environmental factors: tobacco, air pollution, occupational exposure. Indeed exposure to cigarette smoke and other environmental stressors over the life span accelerate biologic processes associated with normal aging. In addition, the elderly are often the subject of several chronic diseases (obesity, diabetes, and cardiovascular conditions) which tend to accelerate the general aging of the individual (3-5).There is a progressive, age-associated decrease in lung function, the forced expiratory volume at the first second (FEV1) declines by ~30 mL per year in men and women, whereas the forced vital capacity (FVC) begins to decline later and at a slower rate (20 mL per year) resulting in a decrease in the FEV1/FVC ratio (6).

The losses in volumes and flow rates due to aging are due to structural and functional changes of the lung: the alteration of the elasticity of thoraco-pulmonary tissues, the kyphosis or curvature of the spine, the decrease in the strength of the respiratory muscles, the changes in the pulmonary circulation, the increase in ventilation-perfusion inequality, the reduction in response to hypoxia and to hypercarbia, the immunosenescence which can cause a low-grade systemic inflammation described as inflamm-aging and the regulation of pulmonary receptors expression (beta2 and Angiotensin converting enzyme-2 (ACE2) (3, 6, 7).

The decrease in the strength of the respiratory muscles with age is related to changes in skeletal muscle structure including the diaphragm (8). Physical inactivity and smoking exposure of many elderly subjects worsens skeletal muscle dysfunction by aggravating proteolysis and inhibiting protein synthesis, leading to loss of muscle mass (9).

Age-related changes in the pulmonary circulation result in an increase in pulmonary artery systolic pressure, increased ventilation-perfusion inequality and a progressive decrease in the diffusing capacity for carbon monoxide (DLCO) in elderly. The reduction in DLCO may be due to declines in the alveolar surface area and, possibly, in the density of lung capillaries (10, 11).

A reduction in response to hypoxia and to hypercarbia is noted in elderly subjects. The hypoxic ventilatory response is substantially reduced in smokers. So aging when associated to tobacco use leads to a loss of potentially protective mechanisms making elderly subjects more vulnerable (12). This effect may delay the diagnosis of the lung disease in elderly subjects (For example infection with Covid19).

The immune system also undergoes an aging process termed immunosenescence which can cause an inflamm-aging. Both innate immunity and adaptive immunity are affected by aging. Declining function of innate immune cells with aging also contributes to the dysregulation of the adaptive immune system via molecular cross-talk (13,14). Humoral immune function also changes significantly with aging. These changes include decreased antibody responses and diminished production of high-affinity antibodies related to defective surface immunoglobulin/B-cell receptor affinity, decreased signaling, and reduced B-cell proliferation. There is also a loss of naïve B-cells and an increase in memory cells with age, resulting in a reduced ability to respond to new antigens (14-16).

The pulmonary receptors' expression changes with age. The main consequences of these modifications are exposure to the risk of infection and poor control of chronic diseases. ACE2 was recently identified as a functional receptor for SARS virus and is therefore a prime target for pathogenesis and pharmacological intervention (17). ACE2 was predominantly expressed in alveolar epithelium (alveolar cells type 2), bronchiolar epithelium, endothelium and smooth muscle cells of pulmonary vessels (17). ACE2 expression is dramatically reduced with aging in both genders (18). This finding could explain the epidemiologic data suggesting that there was an obvious predominance of young adult patients with a slight female proneness in severe acute respiratory syndrome (SARS). Smoking upregulates ACE2: A potential adhesion site for novel coronavirus SARS-CoV-2 (Covid-19) (19). Sina Booeshaghi and Lior Pachter found that the decrease in ACE2 mRNA expression with age in lungs is likely due to two underlying phenomena: a reduction of ACE2 mRNA in ciliated cells, and a shift in ciliated cell abundance with age (20).

In healthy individuals, endothelial cells help to regulate blood pressure, prevent inflammation, and inhibit clotting, in part through the continual production of nitric oxide (NO); they also serve as gatekeepers for molecules passing in and out of the bloodstream. Some elderly patients who have obesity, diabetes, and cardiovascular conditions have compromised endothelial cells. By attacking those cells, COVID-19 infection causes leaking fluids out of the vessels and blood clotting. Those changes spark inflammation throughout the body and fuel the acute respiratory distress syndrome (ARDS) responsible for most patient deaths (21).

These changes related to age may expose elderly subjects to an increased risk of serious infections by Covid-19, decompensation of chronic diseases, addiction and death.

**References:**

1. Guan WJ, Ni ZY, Hu Y, et al., for the China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382:1708-1720

2. COVID-19 Surveillance Group. Characteristics of COVID-19 patients dying in Italy: report based on available data on March 20th, 2020. Rome, Italy: Instituto Superiore Di Sanita; 2020. https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_20_marzo_eng.pdfpdficon

3. Guénard H, Rouatbi S. Physiological aspects of the decline of pulmonary function with age. Rev Mal Respir 2004 Nov;21(5 Pt 3):8S13-24.

4. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The Hallmarks of Aging. Cell 2013;153(6):1194-217.

5. Lepeule J, Litonjua AA, Gasparrini A, Koutrakis P, Sparrow D, Vokonas PS, et al. Lung function association with outdoor temperature and relative humidity and its interaction with air pollution in the elderly. Environ Res 2018;165:110-7.

6. Culham EG, Jimenez HA, King CE. Thoracic kyphosis, rib mobility, and lung volumes in normal

women and women with osteoporosis. Spine 1994;19(11):1250-5.

7. Cho WK, Lee CG & Kim LK. COPD as a Disease of Immunosenescence. Yonsei Med J 2019;60(5):407–13.

8. Rouatbi S, Ben Moussa S, Guezguez F, Ben Saad H. Muscle dysfunction in case of active tobacco consumption. Science & Sports 2017; 32(4): e119-e126

9. Jackman RW, Kandarian SC. The molecular basis of skeletal muscle atrophy. Am J Physiol Cell Physiol 2004;287(4):C834-843.

10. Levin DL, Buxton RB, Spiess JP, Arai T, Balouch J, Hopkins SR. Effects of age on pulmonary perfusion heterogeneity measured by magnetic resonance imaging. J Appl Physiol 2007;102(5):2064-70.

11. Rouatbi S, Ouahchi YF, Ben Salah C, Ben Saad H, Harrabi I, Tabka Z, et al. Physiological factors influencing pulmonary capillary volume and membrane diffusion. Rev Mal Respir 2006;23(3 Pt 1):211-8.

12. Lalley P.M.. The aging respiratory system - Pulmonary structure, function and neural control. *Respiratory Physiology & Neurobiology* 2013, 187(3): 199-210.

13. Castelo-Branco C, Soveral I. The immune system and aging: a review. Gynecol Endocrinol 2014;30:16-22

14. Baylis D, Bartlett DB, Patel HP, Roberts HC. Understanding how we age: insights into inflammaging. Longev Healthspan 2013;2:8.

15. Solana R, Tarazona R, Gayoso I, Lesur O, Dupuis G, Fulop T. Innate immunosenescence: effect of aging on cells and receptors of the innate immune system in humans. Semin Immunol 2012;24:331-41.

16. Whisler RL, Grants IS. Age-related alterations in the activation and expression of phosphotyrosine kinases and protein kinase C (PKC) among human B cells. Mech Ageing Dev 1993;71:31-46

17. Gheblawi Mahmoud, Wang Kaiming, Viveiros Anissa, Nguyen Quynh, Zhong Jiu-Chang, Turner Anthony J., et al. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System. Circ Res 2020;126(10):1456–74.

18. Xudong X, Junzhu C, Xingxiang W, Furong Z, Yanrong L. Age- and gender-related difference of ACE2 expression in rat lung. Life Sci 2006;78(19):2166–71.

19. Samuel James Brake,Kathryn Barnsley ,Wenying Lu ,Kielan Darcy McAlinden ,Mathew Suji Eapen andSukhwinder Singh Sohal. J Clin Med 2020, 9(3), 841

20. Sina Booeshaghi A. & Pachter L. Decrease in ACE2 mRNA expression in aged mouse lung. : https://doi.org/10.1101/2020.04.02.021451 . Version posted April 5, 2020.

21. Serena Del Turco, Annamaria Vianello, Rosetta Ragusa, Chiara Caselli, and Giuseppina Bastaa. COVID-19 and cardiovascular consequences: Is the endothelial dysfunction the hardest challenge? Thromb Res. 2020 Dec; 196: 143–151.

**Conflict of Interest:** None