Long-term exposure to climate change levels of atmospheric CO_2 may cause kidney and cardiovascular disease.

P.N. Bierwirth, PhD

Emeritus Faculty

Australian National University

First draft - Web Posted 19 October, 2019

Current Version – 8 Apr, 2022

Web Published: ResearchGate DOI: 10.13140/RG.2.2.30678.80969

Abstract

With the continual increase of atmospheric carbon dioxide (CO_2), there is an associated rise in CO_2 concentration in human blood. The increase in serum CO_2 drives an increase in the activity of carbonic anhydrase, the enzyme involved in the metabolic processing of CO_2 in the body. With increased CO_2, excess CA enzyme converts into templates for the production of calcium carbonate. Calcification resulting from breathing elevated CO_2 has been observed in animal experiments and kidney calcification in humans is also an increasing globally. As climate change proceeds in the future, increasing CO_2-induced calcification of human tissue, causing kidney and cardiovascular disease, may be a serious existential threat although there is no societal awareness at this stage.

Introduction

The average ambient concentration of CO_2 (in fresh air) has been rapidly increasing and is currently around 410 ppm (Scripps Institution of Oceanography 2020; Schmidt 2020) (Figure 1). This increase is due to humanity's activities, largely resulting from the burning of fossil fuels (Eggleton 2013).

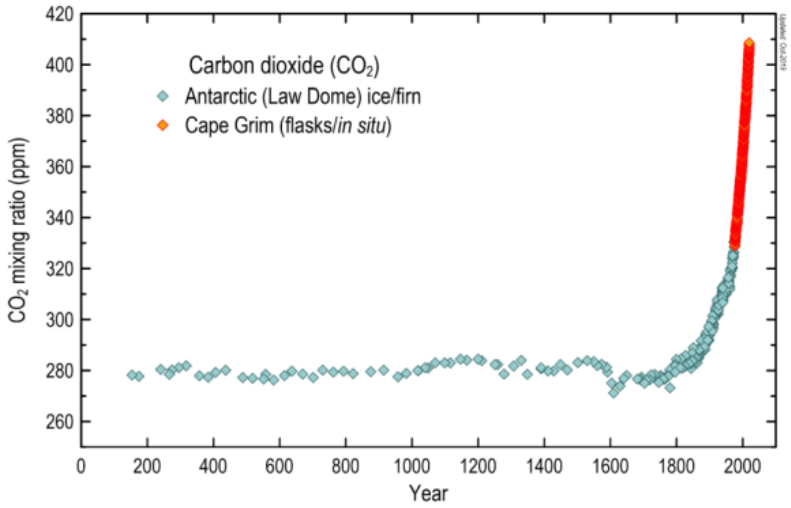

Figure 1. The atmospheric carbon dioxide concentrations (in ppm) over the last 2000 years, based on measurements of air trapped in Antarctic ice, shown in blue-grey diamonds, and the modern Cape Grim, Tasmania direct air measurements, shown in orange. (From Schmidt 2020).

CO_2 breaks down slowly in the atmosphere and there is a large concern in society about climate change effects. So far little attention has been given to the direct impacts of breathing elevated CO_2. This was largely because until recently there was not much evidence or research into the direct impacts of CO_2 at levels relevant to climate change. The toxicity of CO_2 in both outdoor and indoor environments is potentially an issue because (1) CO_2 is highly toxic at high concentrations (OSHA 2012) and (2) CO_2 has likely never been this high throughout human ancestral evolution (Eggleton 2013; Beerling and Royer 2011; Zachos 2001). More recent studies show evidence of a wide range of physiological and cognitive effects from continuous exposures between 900 ppm and 5,000 ppm CO_2 and these levels are highly relevant to both current indoor and future outdoor conditions (Bierwirth 2014; Jacobson 2019). This paper focuses on perhaps the most serious of potential health impacts, calcification of human tissue, that could lead to renal and cardiovascular failure.

Background: The role of carbon dioxide in human physiology

Breathing is one part of physiological respiration and is required to sustain life (Raven et al. 2007). Aerobic organisms like birds, mammals, and reptiles, require oxygen to release energy by cellular respiration, through the metabolism of molecules such as glucose. During aerobic respiration, glucose is broken down by oxygen to release energy, while carbon dioxide and water are the by-products of the reaction. Breathing delivers oxygen to where it is needed in the body and removes carbon dioxide thereby exchanging oxygen and carbon dioxide between the body and the environment. Carbon dioxide (CO_2) is essentially a waste product and needs to be removed from our body. CO_2 from respiring tissues enters the blood plasma and diffuses into the red cells, where it is rapidly hydrated to H^+ and bicarbonate (HCO_3^-) by the carbonic anhydrase (CA) enzyme (Arlot-

Bonnemains et al. 1985; Supuram 2008; Adeva-Andany et al. 2014). This enzyme enables the breakdown of CO_2 which returns to the plasma as bicarbonate and is then transported to the lungs (Adeva-Andany et al. 2014). When the bicarbonate reaches the lungs, CA in the alveoli catalyses the reverse reaction generating water and carbon dioxide which is exhaled as a gas. CA thus allows a large pool of otherwise slowly reacting plasma bicarbonate to be utilized in CO_2 excretion (Arlot-Bonnemains et al. 1985).

Physiological compensation for elevated CO_2

Compensation mechanisms in the body, that regulate for increased acidity in the blood, are employed during times of persistent exposure to elevated CO_2. The lowering of blood pH triggers various compensatory mechanisms, including pH buffering systems in the blood, increased breathing to reduce excess CO_2 in the bloodstream, increased excretion of acid by the kidneys to restore acid-base balance, and nervous system stimulation to counteract the direct effects of pH changes on heart contractility and vasodilation (widening of the blood vessels) (Burton 1978; Eckenhoff and Longnecker 1995). In respiratory acidosis, for a period the kidneys retain bicarbonate helping to normalise the pH of the blood as it passes through them. This occurs within 6 to 8 hours of exposure but achieves full effect only after a few days. With continued high levels of CO_2 in the blood, metabolic acidosis occurs and the kidneys do not respond in producing bicarbonate (Schaefer et al 1979a). After this the body uses the bones to help regulate the acid levels in the blood. Bicarbonate and a positive ion (Ca2+, K+, Na+) are exchanged for H+. The kidneys are involved in a wider array of physiological compensation responses to CO_2 induced pH imbalance (acidosis). The kidney tubule recovers filtered bicarbonate or secretes bicarbonate into the urine to help maintain acid-base balance in the blood and this again involves the CA enzyme (Adeva-Andany 2014).

The relationship between CO2 and calcium carbonate deposits in the body

Carbonic anhydrase (CA) enzymes participate in metabolic reactions that result in the precipitation of calcium carbonate (Adeva-Andany et al. 2015; Kim et al. 2012; Tan et al. 2018; Lotlikar et al. 2019). CA is implicated in calcification of human tissues, including bone and soft-tissue calcification (Adeva-Andany et al. 2015). The enzyme may be also involved in bile and kidney stone formation and carcinoma-associated micro-calcifications. The molecular mechanisms regulating the development of calcification in human tissues and arteries are similar to those that regulate physiological mineralization in bone tissue, being poorly understood (Adeva-Andany et al. 2015). Carbon dioxide conversion by the CA enzyme provides bicarbonate and hydrogen ions that fuel the uptake of ionized calcium which is then deposited in the body tissues as calcium carbonate. With elevated CO_2 in cells there is increased release of calcium from the endoplasmic reticulum (ER), a large dynamic structure within cells that serves many roles including protein synthesis and calcium storage (Kryvenko and Vadasz 2021).

Kidney calcification is known to occur with longer term exposure to elevated CO_2 levels (Schaefer et al., 1979a; Rice 2004). A similar causal link between the activity of CA enzyme, which is mainly responsible for the reversible breakdown of CO_2, and calcium deposits in arteries has also been established (Adeva-Andany et al. 2014). As part of a US Navy experimental program in the 1960's and 1970's investigating impacts of long-term CO_2 exposure, Schaefer et al (1979b) found that, in a study of guinea pigs in an enclosed environment breathing 5,000 ppm CO_2 for 8 weeks, the kidneys

started to calcify along with bone degradation. Schaefer (1982) also indicated that preliminary experiments had found kidney calcification effects in animal studies for CO_2 concentration as low as 2,000 ppm. Although these studies did not identify a mechanism, they established the casual link between CO_2 and kidney calcification. More recent studies have found that tissue calcification is promoted where CA is overexpressed due to increased CO_2 in the body (Song et al 2021; Phelan et al 2021).

Discussion

As discussed earlier, the body compensates for high levels of CO_2, through a combination of increased breathing, blood pH buffering, kidney and bone adaptations depending on the length of continuous exposure, until we can resume breathing lower levels of CO_2 (Bierwirth 2022). In a climate changed world, ambient CO_2 levels will be perpetually high and health consequences are likely from ongoing physiological compensation. Long-term exposure to environmentally relevant levels of CO_2 leads to increases in the levels of CO_2 in human blood (Zheutlin et al. 2014; Hughson et al. 2016; Vehviläinen et al. 2016). This is retention of CO_2 in the human body at greater than normal levels. With higher levels of CO_2, chemical compensation activities increase and the greater the activity of the carbonic anhydrase (CA) enzyme in converting bicarbonate. As discussed earlier, CA activity is related to the process of human tissue calcification.

The mechanism of calcification in human tissues is unclear and it was thought to be an adaptation to change or damage (Adeva-Andany et al. 2015). Vascular calcification was believed to be a process initiated by primary damage to the artery wall although the original causes have not been identified (Adeva-Andany et al. 2015). In blood plasma, where most of the carbon dioxide is transported in the form of bicarbonate (Adeva-Andany et al. 2014), one possible causative process is the effect of CO_2 and pH on CA enzyme activity. Tan et al. (2018) showed that increased acidity (lower pH) can significantly increase the activity of the CA enzyme although Zheng and Qian (2020) showed that, using CA producing microbes, increases in CO_2 caused highest calcification rates in a weak alkaline environment (pH 9). The latter study suggested that $CaCO_3$ can be kept in balance under normal pH and CO_2 conditions, but increases in CO_2 will increase calcification due to increased CA activity. Increases in CO_2 reduces pH which can dissolve $CaCO_3$, however pH is normalised by physiological compensation and excretion of acid. This leaves increased CO_2 and bicarbonate with active CA resulting in increased calcification. This would occur by CA activity where tissues connect with plasma, e.g. arteries, kidneys. Significant tissue calcification has been observed in animals after 12 weeks exposure with only slight reductions in pH (Schaefer et al 1979b). Another possible cause of tissue damage might be due to the role of Interleukin, a protein involved in regulating immune responses, which causes inflammation and vascular damage when CO_2 levels in the blood increase (Thom et al. 2017). One study demonstrates that some types of bacteria encourage the deposition of $CaCO_3$ which enhances the pathogenic impact of the bacterial organism (Lotlikar et al 2019).

Carbonic anhydrase (CA), a group of isoenzymes that catalyse the reversible hydration of carbon dioxide, participate in calcification processes in a variety of biological systems, including shell formation in shell-forming animals (Adeva-Andany et al. 2015; Lotlikar et al. 2019; Zebral et al 2019). Studies have shown that the calcium carbonate precipitation rate is increased with a strong buffer solution and higher levels of CO_2 (Favre et al. 2009; Lotlikar et al. 2019). It is possible that an increase

in atmospheric CO_2 might result in excessive calcification in humans and animals. This also fits with observations from animal experiments where kidney calcification effects in guinea pigs were documented at 5,000 ppm (Schaefer et al. 1979b) after 8-week exposures and also observed at 2,000 ppm in animals under long-term exposure (Schaefer 1982). There are still few, if any, studies at lower values and longer timeframes although it is highly possible that the calcification effect would be observed for the CO_2 levels and durations (i.e. lifetime) relevant for climate change. Furthermore, the incidence and prevalence of human kidney calcification (i.e. stones) is increasing globally (Romero et al. 2010; Turney et al. 2011; Kittanamongkolchai et al. 2018) and it is possible that rising office CO_2 levels (boosted by increasing ambient CO_2) are the contributing cause.

Perhaps the most informative study about CA behaviour is that of Rodriguez-Navarro et al (2019). CA catalyses the formation of the reactive precursors (i.e., $HCO3^-$ and $CO3^{2-}$ ions) required for mineralization and accelerates the precipitation of metastable amorphous calcium carbonates. Ca^+ and CO_3^{2-} ions promote the partial unfolding and oligomerization of CA, resulting in fibril- and sheet-like supramolecular assemblies that template nanostructured calcium carbonate crystallization. The enzyme then loses its CO_2 hydration catalytic activity and elicits a mechanism for arresting calcium carbonate mineralization. Such a negative feedback mechanism would first help jump-start $CaCO_3$ mineralization and subsequently contribute to the arrest of this process, offering a simple mechanism for organisms to control $CaCO_3$ biomineralization. Otherwise, if CA endlessly remained catalytically active once secreted, it would be difficult for an organism to stop the biomineralization process (Rodriguez-Navarro et al 2019). Despite the significant reduction observed, some enzyme activity remains even after precipitation of calcite. In a future where increasing atmospheric CO2 will potentially result in excess CO_2 in the body, the resulting excess CA may be converted into calcium carbonate production sites creating an ongoing calcification problem.

What level of permanent CO_2 will cause significant calcification effects? It has been suggested that blood pH would be reduced to dangerous levels, if there were no physiological compensation, at CO_2 levels as low as about 430 ppm (Robertson 2006) implying that ongoing compensation would occur at this level. Ambient conditions may already be dangerously close to CO_2 levels that cause human tissue calcification, particularly when considering the additive effect of ambient levels on indoor CO_2 concentrations. In the final paper of the US Navy CO_2 research program in the 1960's and 1970's, Schaefer (1982) indicated that this issue had "become the concern of the Department of Energy and other US government agencies" although it appears to have been largely forgotten since.

If allowed to persist, problems such as kidney and artery calcification could lead to cardiovascular failure. In the extreme case lifespans could become shorter than the time required to reach reproductive age. Calcification of kidneys and arteries can be fatal through renal and cardiovascular failure. This could threaten the viability of human and animal species without interventions such as the creation of artificial living environments.

Conclusion

There is growing evidence that carbonic anhydrase enzyme activity causes soft tissue calcification in humans by sequestering CO_2 for conversion to bicarbonate which in the presence of Ca^{2+} precipitates as $CaCO_3$. Increasing levels of CO_2 in the blood, as has been observed in the general population, will likely result in a rise in the incidence of kidney and cardiovascular calcification. This

effect has been observed in animal experiments conducted at environmentally relevant levels of CO_2. The issue, continually exacerbated with rising atmospheric CO_2 levels, could be an existential threat for humans in the not-so-distant future.

References

Adeva-Andany MM, Carneiro-Freire N, Donapetry-García C, Rañal-Muíño E, and López-Pereiro Y. 2014. The Importance of the Ionic Product for Water to Understand the Physiology of the Acid-Base Balance in Humans. BioMed Research International 2014: Article ID 695281, 16 p. https://doi.org/10.1155/2014/695281.

Adeva-Andany MM, Fernandez-Fernandez C, Sanchez-Bello R, Donapetry-García C, Martínez-Rodríguez J. 2015. The role of carbonic anhydrase in the pathogenesis of vascular calcification in humans. Atherosclerosis 241: 183-191.

Arlot-Bonnemains Y, Fouchereau-Peron M, Moukhar MS, Benson AA, Milhaud G. 1985. Calcium-regulating hormones modulate carbonic anhydrase II in the human erythrocyte. Proc. Nati. Acad. Sci. USA 82: 8832-8834.

Beerling DJ, Royer DL. 2011. Convergent Cenozoic CO_2 history. Nature Geoscience 4: 418-420.

Bierwirth PN. 2022. Long-term carbon dioxide toxicity and climate change: a major unapprehended risk for human health. Working paper online at ResearchGate. DOI:10.13140/RG.2.2.16787.48168.

Burton RF. 1978. Intracellular buffering. Respiration Physiology 33: 51-58.

Carbon Dioxide Information Analysis Center. 2014. U.S. Department of Energy. Available: http://cdiac.esd.ornl.gov [accessed 23 December 2014].

Eckenhoff RG, Longnecker DE. 1995. The therapeutic gases. Effects of carbon dioxide. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th Ed (Hardman JG,ed). McGraw Hill, 355-356.

Favre N, Christ ML, Pierre AC. 2008. Biocatalytic capture of CO2 with carbonic anhydrase and its transformation to solid carbonate. Journal of Molecular Catalysis B: Enzymatic 60: 163–170.

Hughson RL, Yee NJ, Greaves K. 2016. Elevated end-tidal PCO2 during long-duration spaceflight. Aerosp. Med. Hum. Perform. 87: 894–897.

Jacobson TA, Kler JS, Hernke MT, Braun RK, Meyer KC, Funk WE. 2019. Direct human health risks of increased atmospheric carbon dioxide. Nature Sust. 2: 691-701.

Kim IG, Jo BH, Kang DG, Kim CS, Choi YS, Cha HJ. 2012. Biomineralization-based conversion of carbon dioxide to calcium carbonate using recombinant carbonic anhydrase. Chemosphere 87: 1091-1096.

Kittanamongkolchai W, Vaughan LE, Enders FT, Dhondup T, Mehta RA, Krambeck AE, McCollough CH, Vrtiska TJ, Lieske JC, Rule AR. 2018. The changing incidence and presentation of urinary stones Over 3 Decades. Mayo Clin Proc. 93: 291-299.

Kryvenko V, Vadász I. 2021. Mechanisms of Hypercapnia-Induced Endoplasmic Reticulum Dysfunction. Frontiers in Physiology 12.

Lotlikar SR, Kayastha BB, Vullo D, Khanam SS, Braga RE, Murray AB, McKenna R, Supuran C, Patrauchan MA. 2019. *Pseudomonas aeruginosa* β-carbonic anhydrase, psCA1, is required for calcium deposition and contributes to virulence. Cell Calcium 84: Article 102080.

OSHA (Occupational Safety and Health Administration). 2012. Sampling and Analytical Methods: Carbon Dioxide in Workplace Atmospheres. Available: http://www.osha.gov/dts/sltc/methods/inorganic/id172/id172.html [accessed 23 December 2014].

Phelan DE, Mota C, Lai C, Kierans SJ, Cummins EP. 2021. Carbon dioxide-dependent signal transduction in mammalian systems. Interface Focus 11(2):20200033.

Raven P, Johnson G, Mason K, Losos J, Singer S. 2007. Biology. 8th ed. New York. McGraw-Hill.

Rice SA. 2004. Human health risk assessment of CO_2: Survivors of acute high-level exposure and populations sensitive to prolonged low-level exposure. Third Annual Conference on Carbon Sequestration. 3-6 May 2004, Alexandria, Virginia, USA. Available: http://www.netl.doe.gov/publications/proceedings/04/carbon-seq/169.pdf [accessed 13 April 2015].

Robertson DS. 2006. Health effects of increase in concentration of carbon dioxide in the atmosphere. Current Science 90:1607-1609.

Rodriguez-Navarro C, Cizer O, Kudłacz K, Ibañez-Velasco A, Ruiz-Agudo C, Elert K, Burgos-Cara A, Ruiz-Agudo E. 2019. CrystEngComm 21, 7407.

Romero V, Akpinar P, Assimos DG. 2010. Kidney Stones: A Global Picture of Prevalence, Incidence, and Associated Risk Factors. Reviews in Urolology 12: e86–e96.

Schaefer KE, Pasquale SM, Messier AA, Niemoeller H. 1979a. CO_2-Induced Kidney Calcification. Undersea Biomed Res. Suppl 6: S143-S153.

Schaefer KE, Douglas WHJ, Messier AA, Shea ML, Gohman PA. 1979b. Effect of Prolonged Exposure to 0.5% CO_2 on Kidney Calcification and Ultrastructure of Lungs. Undersea Biomed Res. Suppl 6:S155-S161.

Schaefer K E. 1982. Effects of increased ambient CO_2 levels on human and animal health. Experientia 38: 1163-1168.

Schmidt S. 2020. CO2 is trending: See the latest atmospheric concentrations data on Twitter. CSIROscope 28 February, https://blog.csiro.au/co2-data-twitter/

Scripps Institution of Oceanography. 2020. A daily record of global atmospheric carbon dioxide concentration. UC San Diego. https://scripps.ucsd.edu/programs/keelingcurve/

Song X, Li P, Li Y, Yan X, Yuan L, Zhao C, An Y, Chang X. 2021. Strong association of glaucoma with atherosclerosis. Scientific Reports 11: 8792.

Supuran CT. 2008. Carbonic Anhydrases – An Overview. Current Pharmaceutical Design, 14: 603-614.

Tan S, Han Y, Yua Y, Chiu C, Chang Y, Ouyang S, Fan K, Lo K, Nga I. 2018. Efficient carbon dioxide sequestration by using recombinant carbonic anhydrase. Process Biochemistry 73: 38-46.

Thom SR, Bhopale VM, Hu J, Yang M. 2017. Inflammatory responses to acute elevations of carbon dioxide in mice. J Appl Physiol 123: 297-302.

Turney BW, Reynard JM, Noble JG, Keoghane SR. 2011. Trends in urological stone disease. BJU International 109: 1082-1087.

Vehviläinen T, Lindholm H, Rintamäki H, Pääkkönen R, Hirvonen A, Niemi O, Vinha J. 2016. High indoor CO_2 concentrations in an office environment increases the transcutaneous CO_2 level and sleepiness during cognitive work. J. Occupational and Environmental Hygiene 13: 19-29.

Zachos J, Pagani M, Sloan S, Thomas E, Billups K. 2001. Trends, rhythms, and aberrations in global climate 65 Ma to present. Science 292: 5517.

Zebral YD, Fonseca JD, Marques JA, Bianchini A. 2019. Carbonic Anhydrase as a Biomarker of Global and Local Impacts: Insights from Calcifying Animals. International Journal of Molecular Sciences 20: 3092.

Zheng T, Qian C. 2020. Influencing factors and formation mechanism of CaCO3 precipitation induced by microbial carbonic anhydrase. Process Biochemistry 91: 271-281.

Zheutlin AR, Adar SD, Kyun Park S. 2014. Carbon dioxide emissions and change in prevalence of obesity and diabetes in the United States: an ecological study. Environment International: 73, 111–116.