Could long-term exposure to climate change levels of atmospheric CO\textsubscript{2} cause kidney and cardiovascular failure?

P.N. Bierwirth, PhD
Emeritus Faculty
Australian National University

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Abstract

As atmospheric carbon dioxide (CO\textsubscript{2}) increases, there is an associated rise in CO\textsubscript{2} concentration in human blood. The increase in serum CO\textsubscript{2} drives an increase in the activity of carbonic anhydrase; the enzyme involved in the metabolic conversion of CO\textsubscript{2}. This increased enzyme activity is associated with the deposition of calcium carbonate in human tissue. Calcification resulting from breathing elevated CO\textsubscript{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\textsubscript{2}-induced calcification of human tissue, causing kidney and cardiovascular disease, may be a serious existential threat.
Introduction

The average ambient concentration of CO₂ (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).](image)

CO₂ 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 CO₂. This was largely because until recently there was not much evidence or research into the direct impacts of CO₂ at levels relevant to climate change. The toxicity of CO₂ in both outdoor and indoor environments is potentially an issue because (1) CO₂ is highly toxic at high concentrations (OSHA 2012) and (2) CO₂ 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 CO₂ 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, if ongoing, 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 (CO₂) is essentially a waste product and needs to be removed from our body. CO₂ from respiring tissues enters the blood plasma and diffuses into the red cells, where it is rapidly hydrated to H⁺ and bicarbonate (HCO₃⁻) by the carbonic anhydrase enzyme (CA) (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).

The relationship between CO\(_2\) 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.

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.

Discussion

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\(_2\). 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.

Although the mechanism of calcification in human tissues is unclear, one theory is that it may be an adaptation to change or damage (Adeva-Andany et al. 2015). Vascular calcification is 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). One possible causative process is the effect of pH on CA enzyme activity. In blood plasma, where most of the carbon dioxide is transported in the form of bicarbonate (Adeva-Andany et al. 2014), increased acidity (lower pH) can significantly increase the activity of the CA enzyme (Tan 2018). Increased CO$_2$ in the blood caused by breathing higher levels of the gas could lower the pH enough to increase the activity of CA thereby potentially increasing calcium carbonate deposits. 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 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.

So 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 evidence that carbonic anhydrase enzyme activity causes soft tissue calcification in humans by sequestering CO₂ for conversion to bicarbonate which in the presence of Ca²⁺ precipitates as CaCO₃. Increasing levels of CO₂ 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 CO₂. The issue, continually exacerbated with rising atmospheric CO₂ levels, could be an existential threat for humans in the not so distant future.

References


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