SARS-CoV-2 mortality in blacks and temperature-sensitivity to an angiotensin-2 receptor blocker

*Short title:* Physiology of black SARS-CoV-2 mortality

*One sentence summary:* Black vulnerability to SARS-CoV-2 is based on physiological, not sociological, differences, which should guide treatments

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Abstract

Tropical climates provoke adaptations in skin pigmentation and in mechanisms controlling the volume, salt-content and pressure of body fluids. For many whose distant ancestors moved to temperate climes, these adaptations proved harmful: pigmentation decreased by natural selection and susceptibility to hypertension emerged. Now an added risk is lung inflammation from coronavirus. Hypertension and coronavirus have in common angiotensin converting enzyme 2 (ACE2), which decreases blood pressure and mediates virus entry. In keeping with less detailed studies, a long-term case-report shows that decreased blood pressure induced by blocking a primary angiotensin receptor is supplemented, above critical blocker dosage, by a further temperature-dependent fall, likely mediated by ACE2 and secondary angiotensin receptors. Temperature-dependence suggests a linkage with tropical heritage and an influence of blockers on the progress of coronavirus infections. Positive therapeutic results should result from negation of host pro-inflammatory effects mediated by the primary angiotensin receptor, and promotion of countervailing anti-inflammatory effects mediated by ACE2 through other receptors. Black vulnerability is likely based on physiological, not sociological, differences, which should guide treatment.

Keywords: Angiotensin converting enzyme 2, Angiotensin receptor blockers, Complement, Environmental temperature, Glycan shield, Hypertension, Innate immunity, Lectin pathway
Introduction

Humans whose distant ancestors lived in tropical regions can differ biochemically and physiologically from those whose ancestors were in temperate regions. Increased sunlight and heat engender not only evolutionary differences in skin color (1), but also in cooling mechanisms that regulate the volume, salt-content and pressure of body fluids (2,3). This has influenced recommendations for treating hypertension, a disease to which those with dark skins are prone (4-6). To these major differences in responses to sunlight and heat, the coronavirus (SARS-CoV-2) has added another – an increased mortality of those infected, often from inflammatory complications of lung disease.

Thus, at an early stage of the present epidemic (April 12th 2020) the Chicago Department of Public Health reported that, while the percentage mortality in other groups was around 4%, for non-Latino blacks mortality was 22.7%. This extreme difference has been corroborated elsewhere (7, 8). Since those with pre-existing conditions are particularly vulnerable, the higher mortality could be explained in terms of general ill-health or sociological factors (9). However, given the degree of the disparity, specific differences in underlying physiology could play a role.

As a component of the renin-angiotensin system (RAS)(10), angiotensin II (Ang II) is fundamental to the regulation of blood pressure (BP; Fig. 1). The degrees to which countervailing Ang II receptors are activated could influence, not only BP, but also coronavirus therapy. SARS-CoV-2 enters cells by way of angiotensin converting enzyme 2 (ACE2)(11), which is generally protective for lung infections (10). Increased ACE2 gene transcription occurs during SARS-CoV-2 infection (12, 13). Thus, there is a relationship between coronavirus and a host’s physiological mechanisms for the control of the volume, salt-content and pressure of body fluids. Such mechanisms should be most severely tested in hot countries (e.g. sweating with loss of salt and water (14). Thus, it would be expected that, over evolutionary time, just as skin pigmentation became a fixed (non-inducible) adaptation in hot countries, so the fine-tuning of cooling mechanisms by natural selection could have resulted in stable, more extreme, adaptations than in temperate regions.

However, being advantageous at one location at one point in time is not a guarantee of permanence. Adaptations may further evolve in diaspora. Skin pigmentation proved disadvantageous when populations moved to temperate climes and needed to synthesize vitamin
D. Pigmentation was decreased by natural selection, yet it could still be induced to return, albeit at lower levels (tanning), in response to radiation (1). Likewise, cooling mechanisms might prove counter-adaptive when challenged, either less severely by temperate climates, or more severely by pathogenic microorganisms. A combination of the two challenges could be fatal.

Fig. 1. Regulation of BP and inflammation by countervailing receptors in the renin-angiotensin system (RAS). The vasoconstrictor/pro-inflammatory pathway (thick grey arrows) is impeded at the level of the primary Ang II receptor by ARBs. Accumulated Ang II then drives the vasodilatory/anti-inflammatory pathway. Having entered by way of ACE2, SARS-CoV-2 causes lung inflammation that should be opposed by the ARB-induced arrest of pro-inflammatory activity and stimulation of anti-inflammatory activity. The dashed arrow indicates an ARB-dependent activation of the secondary Ang II receptor (23). The fine dotted arrow indicates the same result achieved by way of a β-arrestin pathway (26).
Knowledge that a RAS component, ACE2, was the SARS-CoV-2 receptor suggested that existing drugs employed to treat hypertension might be repurposed to treat coronavirus infections. Indeed, reports from China state that angiotensin receptor blockers (ARBs) can mitigate the severity of SARS-CoV-2 infections (15). Their continued in-hospital use is associated with lower mortality risk compared with non-users (16). My earlier study of a temperature-dependent hypersensitivity of BP to an ARB (losartan), was interpreted in terms of a switch from primary to secondary countervailing receptors (17). I argue here that this mechanism supports the views, both that ARBs can mitigate the severity of acute inflammatory lung diseases whatever the etiology (10) and that, rather than “racism” (7), there is a fundamental physiological explanation for the high mortality of those whose distant ancestors lived in tropical regions.

A recent stepwise regression study has identified both African-American origin and environmental temperature as significant variables, and has postulated a marginal vitamin D deficiency to explain the enhanced vulnerability of African-Americans to coronavirus (8). In contrast, my study, while also implicating temperature as a critical variable, has suggested differential evolved responses to heat-stress that might be influenced by ARBs. This has implications for control of SARS-CoV-2 infections in North America and for meeting the growing threat in Africa.

**Environmental temperature and response to ARBs**

Following short-term studies to determine efficacy and minimize adverse side-effects, losartan was introduced in the 1990s for the treatment of hypertension. A case report of its employment by an elderly white male as sole medication over a 12-year period (2003-2014), responded to calls for studies of possible long-term effects (17). There were also accounts, some anecdotal, of seasonal hyperresponsiveness to antihypertensive medications when environmental temperatures were high (17, 18). For the subject of the case report, doses had been adjusted daily with the goal of maintaining home-monitored BP readings (systolic/diastolic) close to 130/80 (mm Hg). Fig. 2 shows that initially (2003-2010) this goal was consistently achieved with approximately 20 mg losartan daily and no relationship to temperature was evident. Then in late 2011 a need emerged to increase dosage close to 50 mg daily. This had been hinted at by small rises in December 2010
and early 2011. From this higher level, a marked and repeatable summer-time dip emerged (2012-2014). This was clearly seen in plots of dosage against temperature (Fig. 3). Indeed, when extrapolated, the plots indicated that no medication would be needed above 34°C – a temperature range more consistent with tropical locations than that of the subject (Canada). Since losartan was used world-wide, if not an individual idiosyncrasy then this result had serious implications for the treatment of hypertension in equatorial regions (19, 20).

![Fig. 3. Environment temperature and monthly losartan requirement for a 12-year period (2003–2014)](image)

**Fig. 2. Environment temperature and monthly losartan requirement for a 12-year period (2003–2014).** 2003, black triangles; 2004, dark yellow triangles; 2005, green circles; 2006, black squares; 2007, blue diamonds; 2008, orange squares; 2009, grey triangles; 2010, red diamonds; 2011, cyan circles; 2012, black circles; 2013, green diamonds; 2014, dark red circles. Data for 2012–2014 include standard errors. [From ref. (17); copyright DRF]

Given that seasonal hyperresponsiveness to anti-hypertensive medications had been the subject – albeit not documented in individual detail – of previous reports, it was hoped that the possibility of individual idiosyncrasy would be discounted by further “crowd sourced” reports (21). Unlike previous accounts that had not considered detailed mechanisms (e.g. (18) and (22)), it was proposed that the reported phenomena could be explained in terms of differential signaling by countervailing Ang II receptors – inhibition of a primary receptor that increased BP
(vasoconstriction), and activation, at a critical ARB concentration, of a secondary receptor that decreased BP (vasodilation)(17). The view that these observations are relevant to current considerations of a role of ARBs in the management of SARS-CoV-2 infections was encouraged by rapid developments in the biomedical literature, as will be set out here.

Fig. 3. Relationship between daily losartan requirements for the 2003-2014 period and corresponding maximum environmental temperatures. Least-squares regression fits to the points (third order polynomial) are shown as continuous lines for each year. Line coloring for different years follows that of Fig. 2. Consecutive $r^2$ values for 2011–2014 were 0.22, 0.38, 0.34, and 0.45. [From ref. (17); copyright DRF]
It should be noted that there is generally little incentive for the pharmaceutical industry to carry out sustained long-term studies; hence, the call for “crowd sourcing” (21). Despite the absence of temperature effects during the first eight years (Figs. 2,3), fortuitously the study was not terminated in 2010.

With primary receptors for Ang II (AT1R subtype) blocked by losartan, there should be an increase in the concentration of Ang II that could then suffice to affect the losartan-insensitive, low abundance, secondary receptors (AT2R subtype). Reaction of excess Ang II with the secondary receptors would greatly amplify the fall in BP resulting from the losartan block of primary receptors (Fig. 1). An extensive literature based on both animal and human studies was cited as consistent with this (17,23).

A similar scenario would have the excess of Ang II (an octapeptide) converted by ACE2 to Ang (1-7) (a septapeptide). This truncated Ang II fragment, either by way of another receptor (MasR) (24,25), or by selectively influencing the AT1R subtype (26), also lowers BP. Whether acting individually or collectively, these pathways should decrease BP. However, unexplained was the critical dependence on losartan dosage and the relationship to high environmental temperature (Figs. 2, 3). The latter raised the possibility that individuals retaining genetic linkages to ancestors who had adapted to tropical climes, might have particular responses to extrinsic agents, namely to drugs and to the SARS-CoV viruses that bind to ACE2 (27) – but not to ACE1 (generally referred to as ACE, which has its own specific inhibitors referred to as ACEI).

Of possible relevance to this hypothesis are reports that, as latitude decreases towards the equator, populations normally tend to have a lower BP (28), and that sub-Saharan Africans tend to be salt-sensitive regarding increasing BP (14). Furthermore, while experimental hypertension induced in rats by high salt diets does not respond to ARBs, that induced by the combination of salt and high environmental temperature is responsive (29). Although not concerned with the use of anti-hypertensive medications, a new study by Adam Li and his colleagues of black mortality in SARS-CoV-2 infections (8), suggests these results are relevant to humans.

Role of ARBs in SARS-CoV-2 infection
Given the dependence of SARS-CoV-2 on a host’s ACE2 receptor, at issue is whether ARBs can affect, either negatively or positively, the progress of infection (30-32). Thus, it is proposed that the research community should “better outline the renin-angiotensin system and specifically ACE2 in the pathogenesis of COVID-19,” and that clinicians should accumulate more data “to determine if there is a link between the use of ACEIs, ARBs, or both, and COVID-19 mortality and morbidity” (33). In the absence of such information, various authorities have advised against stopping treatment, or switching to a BP treatment that does not involve the renin-angiotensin system (34,35). Furthermore, if administered to non-hypertensive patients, ARBs might provoke dangerous degrees of hypotension (19, 20).

Current studies of SARS-CoV-2 are guided by the pioneering studies of SARS-CoV-1 (usually referred to as SARS-CoV), which also enters cells by way of ACE2. SARS-CoV-1 infectivity correlates with ACE2 expression (36). The Penninger laboratory showed that the lung inflammation responded to anti-hypertensive drugs, with ARBs being particularly effective (37,38). So, as recently recollected (27): “Thus, for SARS-CoV pathogenesis, ACE2 is not only the entry receptor of the virus but also protects from lung injury. We therefore … suggested that in contrast to most other coronaviruses, SARS-CoV became highly lethal because the virus deregulates a lung protective pathway.”

SARS-CoV-2 deaths are mainly associated with respiratory failure association with virus-induced inflammation (10,32,39). The ACE2 receptor (like the secondary Ang II receptor, AT2R) has an anti-inflammatory role and is shed or incorporated with the virus on cell entry, so is lost from the cell surface. Sometimes such receptor down-regulation is a viral strategy to prevent superinfection by another, possibly competing, virus (40). However, this militates against any other roles a receptor may play. While there are indications that SARS-CoV-2 can repress the gene encoding the ACE2 receptor, so that there is no receptor refurbishment (41), detailed transcriptional studies suggest that refurbishment is possible (12). Consistent with the human case history discussed here (17), RAS system-based anti-hypertensive agents (ARBs and ACEI) may stabilize or increase host refurbishment of ACE2 receptors, thus opposing their virus-induced loss (42). However, a study of Butler and coworkers (12) concluded that with ACEI (but not with ARBs) there was “significantly increased risk of intubation and death.”
Innate Immune differences in African populations

Associations of varying strength have been found between certain RAS genes and susceptibility to hypertension. These associations distinguish African-Americans from other population groups (43). The association approach also supports the case that enhanced susceptibility of African-Americans to SARS-CoV-2 is physiologically based. A recent study of various geographical groups shows a higher variation among Africans of genes encoding proteins that play major roles in innate immunity – e.g. mannose binding lectin 2 (MBL2). Thus, in ancestral Africans natural selection may have favoured the explorations of a wider range of responses to environmental challenges than in non-Africans – perhaps so bestowing relative disadvantages on the descendent diaspora. Indeed, it is held that the higher variation “might be relevant for the host response to SARS-CoV-2 infection” (44). The locations of the amino acid changes in three MBL2 variants would be expected to compromise the ability of these proteins to aggregate into functional units (oligomers), so that decreased activity would be expected. Thus, possibly “variants in genes for proteins involved in the innate immunity add some disadvantage to individuals in combating COVID-19” (44). Earlier studies of SARS-CoV-1 also concluded that certain MBL variants might be disadvantageous (45).

By virtue of reactivity with mannose-rich surface glycans, MBLs promote phagocytosis of particulate pathogens and effect antibody-independent complement lysis of microbial and mammalian cells. This involves what has become known as the lectin pathway (46). Thus, as with other innate immune system components, MBLs should assist antiviral host defenses. Indeed, MBLs can react with the “glycan shield” – glycosylated SARS-CoV-1 spike protein (47). So far this is not found with the oligomannose-rich SARS-CoV-2 spike protein, although other lectins do bind (48).

While these considerations indicate a possible positive role of MBLs in combatting SARS-CoV-2, proinflammatory cleavage products generated in the complement cascade might enhance SARS-CoV-2 pathogenicity. These products have been proposed, from mouse studies, to enhance SARS-CoV-1 pathogenicity (49). Indeed, a highly likely negative scenario involving the lectin pathway is supported by much emerging evidence (50). Ting Gao and colleagues (51) have
implicated the SARS-CoV-2 nucleocapsid N protein – the most evolutionary flexible of the main coronavirus structural proteins (52) – as activating the complement cascade by way of a lectin pathway intermediate. Studies with the complement inhibitor suramin, which has long been employed to treat African trypanosomiasis, have cast an intriguing light on this.

To be effective against protozoal pathogens, suramin requires a functioning host immune system. It has long been known that the complement-dependent inhibition by lectin of cultured mammalian lymphocytes in calf serum is inhibited at an early stage by suramin (50). From recent experiments with susceptible cells cultured in calf serum it is concluded that “suramin inhibits binding or entry” of SARS-CoV-2 (53). Suramin was found to inhibit if added before, or at the time of, adding virus. However, if added one hour later there was no inhibition. Hence it is suggested that suramin inhibits viral binding to ACE2 receptors and cell entry. Suramin is known to interact with various serum proteins, so there is a possible role for MBLs or other lectin pathway components in the calf serum used for culture; this remains to be explored. These considerations suggest there might be circumstances under which MBLs could both facilitate initial infection (inhibitable by suramin) and enhance pathogenicity (due to inflammatory complement cleavage products). Both of these negative functions might be manifest more in African-Americans by virtue of physiological differences. Since the antimalarial drug chloroquine enhances lectin pathway inhibition (54), it would be contraindicated therapeutically.

**Conclusions**

Investigations on possible ARB therapies are in progress (33) and are likely to consider the well-reported age and gender differences. What can be added at this time is that the design and interpretation of clinical evaluations should factor in, not only variables such as tropical heritage (e.g. degree of skin pigmentation), but also ambient temperatures, past and present ARB dosage, the stage of the progression of a patient’s hypertension, and differences in innate immune defenses of various population groups. In other words, ARBs, by decreasing the pro-inflammatory effects of AT1R and hence supporting the anti-inflammatory effects of AT2R and ACE2 receptors, might be remedial under some circumstances, but not others. ARBs would operate, not by way of their ability to lower BP, but by way of their anti-inflammatory activities. Sensitivity to environmental temperature (8, 17) suggests that patients should be kept in warm
environments. Indeed, the case doubling time is longer in tropical regions \((55,56)\), indicating that those with unabridged RAS systems might be helped by higher temperatures.

While much attention is rightly being given to \textit{possibilities} of future effective anti-viral measures (vaccination and drugs selectively affecting viral chemistry), there are pressures to buttress host defenses with what drugs are now available. Thus, “an approach to treating patients with severe COVID-19 infection might be hiding in plain sight;” namely ARBs, perhaps employed in concert with another class of repurposable drug, the statins \((57)\). Others envisage a role for \(\beta\)-arrestins that mediate the desensitization, internalization and ubiquitination of G-protein coupled receptors, such as \(\text{AT}_1\text{R}\). Although it only weakly binds \(\text{AT}_1\text{Rs}\), they point to Ang \((1-7)\) as an “endogenous \(\beta\)-arrestin biased agonist of the \(\text{AT}_1\text{R}\),” which is like other arrestins that can be invoked by \(\text{AT}_1\text{R}\) activation \((\text{Fig. I})\) \((26)\). The repurposing of a drug found to \textit{selectively} modulate \(\text{AT}_1\text{R}\) signaling could activate anti-inflammatory arrestin pathways without the raising of BP or inflammation, which require \(\text{AT}_1\text{R}\) associated G-protein coupled signaling that is controlled by RGS2 \((\text{regulator of G-protein signaling} 2)\) \((58)\). If successful, these approaches would allow humoral and cellular herd immunity to develop without concomitant deaths, and hence could decrease requirements for testing and contact-monitoring.

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